Ambikanandan Misra
Aliasgar Shahiwala *Editors*

Novel Drug Delivery Technologies

Innovative Strategies for Drug Re-positioning

Springer

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ISBN 978-981-13-3641-6 ISBN 978-981-13-3642-3 (eBook)
https://doi.org/10.1007/978-981-13-3642-3

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

The application of drug delivery is a valuable, cost-effective lifecycle management resource. By infusing drugs with new and innovative therapeutic benefits, drug delivery systems extend products' profitable lifecycle, giving pharmaceutical companies competitive and financial advantages and providing patients with improved medications. Formulation development is being used in the creation of new dosage forms for existing products, which not only reduces the cost and time of new drug development but also helps with patent protection and bypassing existing patents. However, the goal for any new formulation development should be to make a better product rather than patent protection.

During the past few years, research in the field of drug delivery has resulted in bringing out potential innovative drug delivery options. Improved drug delivery systems and access to other mucosal routes of administration provide viable alternatives for reformulating drugs for better patient convenience, improved therapeutic efficacy, and reduced side effects. For example, almost 40% of the population including children and elderly are facing difficulty in swallowing tablets and capsules. Reformulating such drugs in liquid formulations with latest solubilization and taste masking techniques can provide better patient convenience. Mouth dissolving/dispersible tablets, medicated chewing gums, lozenges and lollipops, and mouth dissolving films are recent formulation approaches in this regard. Other examples include formulating drug in prolonged or controlled release formulations with latest polymeric and production technology that helps to reduce frequency of dosing with lesser side effects. Significant progress has been made in transdermal drug delivery and parenteral drug delivery with respect to prolonged or controlled drug release. Yet another example is disease that requires local administration like eye diseases and pulmonary diseases. Systemically administered drugs do not preferentially reach to the eye, while local injection is very painful and stressful, while drug administered as eye drops lost quickly due to mucociliary clearance. Conditions like this and many more can be effectively managed with mucoadhesive formulations. Therefore, there was a need to provide a unique platform that addresses diversity of needs and emergence of different formulation approaches to tackle them.

The purpose of this book is to reposition an old drug in a manner that it falls under classification of new drug specially in terms of favorable change in its pharmacokinetic and biodistribution. Since oral route is the most preferred route of drug administration, the first five chapters describe different formulation approaches

used for this route. The first chapter is focused on solubility- and bioavailability-related issues, which is a major issue with most of the drugs. The second to fifth chapter covers formulation approaches according to descending areas of oral route starting from buccal and intraoral followed by controlled release, Peyer's patch targeting, and colonic drug delivery, respectively. Each of the remaining chapters focuses on formulation approaches to deliver drugs through different routes including parenteral, transdermal, nasal and pulmonary, ophthalmic and otic, and to the brain. The last chapter covers different drug targeting approaches.

We hope this book serves as a comprehensive resource for formulation scientists and researchers with respect to novel and up-to-date formulation approaches that are developed in the field of drug delivery. This book can also be used as a reference to teach in undergraduate or postgraduate pharmacy curriculum.

Our sincere thanks to all the contributors who made this manuscript possible.

Vadodara, Gujarat, India — Ambikanandan Misra
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Editors

Ambikanandan Misra is currently a Professor and UGC-BSR Faculty Fellow at the Faculty of Pharmacy and former Dean of the Faculty of Technology and Engineering (August 2011–December 2015) at Maharaja Sayajirao University of Baroda. He has been associated with the field of pharmaceutical sciences for more than 39 years. He has 8 books, 43 book chapters, and 170 peer-reviewed publications in reputed journals to his credit and holds 9 national and international patents. He has completed 22 research projects funded by the government and pharmaceutical industry and is the recipient of many prestigious awards, including the Best Scientist of the Year Award from the Association of Pharmaceutical Teachers of India (APTI) in 2009. He serves on the Editorial Board of 15 international journals and as a Reviewer for more than 50 international journals.

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Abbreviations

Numerical

3D	Three dimensional
2D	Two dimensional
#Y	Number of years
#M	Number of months
#W	Number of weeks

A

API	Active pharmaceutical ingredient
AR	Alveolar region
Ag	Silver
ACRP	Ascending controlled release preparation
AMD	Age-related macular degeneration
ATR	Antiretroviral therapy
AUC	Area under curve
Anti-PD-1	Anti-programmed cell death-1
AAV	Adeno-associated virus
ACV	Acyclovir
AD	Alzheimer's disease
AMT	Adsorptive-mediated transcytosis
AET	Active efflux transport
APP	Amyloid precursor protein
Aβ	Amyloid B
ApoE	Apolipoprotein E
AuNPs	Gold nanoparticle
ATP	Adenosine triphosphate

B

BCS	Biopharmaceutical Classification System
BDSI	BioDelivery Sciences International
Bn	Billion
bFGF	Basic fibroblast growth factor
BAB	Blood-aqueous barrier
BPLB	Blood-perilymph barrier
BRB	Blood-retinal barrier
BBTB	Blood-brain tumor barrier
BBB	Blood-brain barrier
BCECs	Brain capillary endothelial cells

C

C	Degree celsius
cm	Centimeter
CNS	Central nervous system
CS	Chitosan
CR	Controlled release
CMC	Carboxymethyl cellulose
COER	Controlled-onset extended-release
CS-TGA-PF	Chitosan-thioglycolic acid-pluronic
CYP	Cytochrome
CDDS	Colonic drug delivery system
CD	Crohn's disease
CUR	Curcumin
CAGR	Compound annual growth rate
CPP	Central precocious puberty
CPSP	Chronic post-surgical pain
Cp	Plasma drug concentration
Css	Steady-state drug concentration in plasma
CL_T	Total clearance
Cmax	Maximum plasma drug concentration
Chol	Cholesterol
CPA	Cyclophosphamide
CD	Cluster of differentiation
CV	Coefficient of variance
CoCr	Cobalt chromium
Crisper	Clustered regularly interspaced short palindromic repeats
Cas9	CRISPR associated protein 9
CPT	Camptothecin
ConA	Concanavalin A
CSF	Cerebrospinal fluid

CFTR	Cystic fibrosis transmembrane conductance regulator
CAP	Cellulose acetate phthalate
CD	Cyclodextrins
CMC	Critical micelle concentration
CsA	Cyclosporine A
CMT	Carrier-mediated transport
CED	Convention enhanced delivery
CD71	Cluster of differentiation 71 (transferrin receptor)

D

DOX	Doxorubicin
DOC	Docetaxel
DDP-4	Dipeptidyl peptidase 4
D_M	Maintenance dose
D_L	Loading dose
DNA	Deoxyribonucleic acid
DEPC	1,2-Dierucoyl-sn-glycero-3-phosphocholine
DPPG	1,2-Dipalmitoyl-sn-glycero-3-phospho-rac-(1-glycerol)
DOPC	1,2-Dioleoyl-sn-glycero-3-phosphocholine
DCM	Dichloromethane
DOPE	1,2-Dioleoyl-SN-glycero-3-phosphoethanolamine
DPPC	Dipalmitoyl phosphatidylcholine
DHPC	Diheptadecanoyl phosphatidylcholine
DPPC	1,2-Dipalmitoyl-sn-glycero-3-phosphocholine
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
DPPA	1,2-Dipalmitoyl-sn-glycero-3-phosphate
DPPE	1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine
DSPE	1,2-Dioctadecanoyl-sn-glycero-3-phosphoethanolamine
Da	Dalton
DDS	Drug delivery system
DR	Diabetic retinopathy
DOTAP	Dioleoyl-3-trimethylammonium-propane
DAMGO	[D-Ala^2, N-$MePhe^4$, Gly-ol]-enkephalin
DNA	Deoxyribonucleic acid
DQA	Dequalinium chloride

E

EDTA	Ethylenediaminetetraacetic acid
EEA	European economic area
e.g.	For example
Eq.	Equation

ERL	Eudragit RL
et al.	and others
ER	Extended release
EC	Ethyl cellulose
EVA	Ethylene vinyl acetate
EMA	European Medicine Agency
EAAT	Excitatory amino acid
EPR	Enhanced permeability and retention
ECF	Extra cellular fluid
EGCG	Epigallocatechin gallate
ER	Endoplasmic reticulum

F

FDA	Food and Drug Administration
FDDDs	Fast dissolving drug delivery systems
Fig.	Figure
FDM	Fused deposition modeling
FFEM	Freeze fracture transmission electron microscopy
FPF	Fine particle fraction
FPE	Fluid-phase endocytosis

G

GAS	Gas antisolvents recrystallisation
GERD	Gastroesophageal reflux disease
GIT	Gastrointestinal tract
Gov.	Government
GRT	Gastric retention time
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GnRH	Gonadotropin releasing hormone
GRAS	Generally regarded as safe
GFIG	Glu-phe-leu-gly tetrapeptide
GSH	Glutathione (reduced)
GSD	Geometric standard deviation
GM-CSF	Granulocyte macrophage colony-stimulating factor
GDNF	Glial cell-derived neurotrophic factor
GLUT1	Glucose transporter 1

H

HPH	High pressure homogenization
HPMC	Hydroxy propyl methyl cellulose
Hz	Hertz
HCL	Hydrochloric acid
Hr	Hour
HME	Hot melt extrusion
h	Hour
HIV	Human immunodeficiency virus
HP-β-CD	2-Hydroxypropyl-β-cyclodextrin
HPC	Hydroxy propyl cellulose
HCO	Hydrogenated castor oil
HCV 1	Hepatitis C 1
HPV	Human papilommavirus
HA-SS-DM1	Hyaluronic conjugated emtansine through disulfide linkage
HA	Hyaluronic acid
HC	Hydrocortisone
HEC	Hydroxyethyl cellulose
HMC	Hydroxymethyl cellulose
HPLC	High-performance liquid chromatography
HSA	Human serum albumin
HP-β-CD	Hydroxypropyl-B-cyclodextrin

I

IR	Immediate release
IM	Intramuscular
IER	Ion-exchange resins
ISO	International Standard Organization
IBD	inflammatory bowel disease
IBS	inflammatory bowel syndrome
IVIVC	*In vitro- in vivo* correlation
id	Inner diameter
IC50	Concentration to kill 50% of cells
IND	Investigational new drug
IV	Intravenous
ID	Intradermal
IFR	Inspiratory flow rate
IBU	Ibuprofen
IOP	Intra ocular pressure
IVT	Intravitreal
i.n.	Intranasal
IA	Intra-arterial
ICAM-1	Intercellular adhesion molecule-1

K

Kg	Kilogram
kDa	Kilo dalton
Ke	Elimination rate constant
k_r^0	Zero-order drug release rate constant
KCS	Keratoconjunctivitis sicca

L

L	Liter
Leu	Leucine
Leu-Enke	Leu-enkephalin
LHRH	Luteinizing hormone-releasing hormone
LAART	Long-acting injectable antiretroviral therapy
LA:GA	Lactic acid/glycolic acid ratio
LA	Lactic acid
LVIs	Large-volume injectors
LCST	Lower critical solution temperature
LC MS	Liquid chromatography-mass spectrometry
LUV	Large unilamellar vesicles
LRP	Low-density lipoprotein receptor-related protein
LAT1	Large neutral amino acid
Lf	Lactoferrin
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LMWP	Low molecular weight protamine

M

Min	Minute
mL	Mililiter
μg	Microgram
mg	Miligram
mm	Milimeter
MC	Methyl cellulose
MCG	Medicated chewing gum
MDF	Mouth dissolving film
MCs	Medicated confectioneries
MDTs	Mouth dissolving tablets
mL/min	Milliliter per minute
μm	Micrometer
MTX	Methotrexate

MDDS	Microparticulate drug delivery system
mPas	Milli pascal second
mAb	Monoclonal antibody
MW	Molecular weight
MNPs	Magnetic nanoparticles
MMP	Matrix metalloproteinases
MLVs	Multilamellar vesicles
MVLs	Multivesicular liposomes
mPEG	Methoxy-PEG
MSPC	1-Tetradecanoyl-2-octadecanoyl-sn-glycero-3-phosphocholine
mPEG5000-DPPE	mPEG5000 conjugated DPPE
MoSul	Morphine sulfate
MMAD	Mass median aerodynamic diameter
MDI	Metered dose inhaler
MLV	Multi lamellar vesicles
MRT	Mean residence time
MCT1	Monocarboxylic acid
MDR	Multidrug resistance protein
MTS	Mitochondrial targeting signal
mTOR	Mammalian target of rapamycin
MRI	Magnetic resonance imaging
MN	Microneedle

N

NaGDC	Sodium glycodeoxycholate
NDA	New drug application
NIH U.S.	National Institutes of Health, United State
nm	Nanometer
NP	Nanoparticles
NLCs	Nanostructured lipid carriers
Na CMC	Carboxymethyl cellulose sodium
NSAID	Non-steroidal anti-inflammatory drugs
NMEs	New molecular entities
NBEs	New biological entities
NRTIs	Nucleoside reverse transcriptase inhibitors
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NMT	Not more than
NMP	N-Methyl-pyrrolidine
NFIs	Needle-free injectors
NIPAAM	Poly(n-isopropylacrylamide)
NPR	Nasopharyngeal region
NLC	Nanostructured lipid carrier
NMDA	N-Methyl-D-aspartate

NGF	Nerve growth factor
NPC	Nuclear pore complex
NLS	Nuclear localization signals

O

OA	Oleic acid
ODFs	Orally disintegrating films
ODTs	Orally disintegrating tablets
ODDS	Osmotic drug delivery system
OATPs	Organic anion transport polypeptides
OTC	Over the counter

P

PVP	Polyvinylpyrrolidone
PEG	Polyethylene glycols
PACAP	Pituitary adenylatecyclase activating peptide
PAMAM	Polyamidoamine
PEG	Polyethylene glycol
PG	Propylene glycol
PVA	Polyvinyl alcohol
PSD	Particle size distribution
PEC	Polyelectrolyte complexes
PMMA	Poly(methylmethacrylate)
PEO	Poly ethylene oxide
PEG 6000	Poly ethylene glycol 6000
PVAc	Polyvinyl acetate (PVAc)
PLA	Poly(L-lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
POC	Proof of concept
PMSBS	Prednisolone sodium metasulfobenzoate
PR	Prolonged release
PI	Protease inhibitors
PeP	Preexposure prophylaxis
PK	Pharmacokinetics
PBS	Phosphate buffered saline
PLGA/PLGH/PLG	Poly-lactide-co-glycolide (polylactic acid-co-glycolic acid)
PEG	Polyethylene glycol
PC	Phosphatidyl choline lipid
PCA	Patient-controlled analgesia

PAI	Periarticular injection
PC polymer	Polycarbonate polymer
PEVA	Polyethylene vinyl acetate
PCL	Polycaprolactone
PPG	Polypropylene glycol
PHB	Polyhydroxybutyrate
PPF	Precision particle fabrication
POE	Polyorthoester
PPE	Polyphosphoesters
PBLG	PEGylated poly(γ-benzyl L-glutamate)
PHC	Lipid (N-palmitoyl-L-homocysteine
PEG(2000)-DSPE	PEGylated 1,2-dioctadecanoyl-sn-glycero-3-phosphoethanolamine
PTX	Paclitaxel
PMEEECL-b-POCTCL	Poly(γ-2-(2-(2-methoxyethoxy)-ethoxy) ethoxy-ε-caprolactone)-b-poly(γ-octyloxy-ε-caprolactone)
P-gp	P-glycoprotein
PFS	Pre-filled syringe
PAH	Pulmonary arterial hypertension
PAA	Poly (adipic anhydride)
PGA	Poly (glycolide)
p-HEMA	Poly (hydroxyethyl methacrylate)
PIC	Polyionic complex micelles
POLTF	Post lens tear film
PPDS	Punctal plug delivery system
PPI	Polypropyleneimine
PD	Parkinson's disease
PAI-1	Plasminogen activator inhibitor-1
PSD-95	Postsynaptic density protein
PrP	Prion protein
PBCA	Poly(Butylcyanoacrylate)
PA	Phosphatidic acid
PEI	Poly(ethylenimine)
P-80	Poly(sorbate) 80
Pc 4	Photodynamic agent
PS	Phosphotidyserine

Q

q3W	Once every three weeks
QoL	Quality of life

R

RESS	Rapid expansion of supercritical solutions
RLD	Reference listed drug
RES	Reticuloendothelial system
RSV	Respiratory syncytial virus
RNA	Ribonucleic acid
RNAi	RNA interference
Ri	Rate in
Ro	Rate out
rhuIGF	Recombinant human insulin-like growth factor
rPAA	Reducible poly(amino acid)
RF	Radiofrequency
RPE	Retinal pigment epithelium
RWM	Round window membrane
ROS	Reactive oxygen species

S

SCF	Supercritical fluid
Sec	Second
SD	Solid dispersion
SC	Subcutaneous
sCT	Salmon calcitonin
SDGC	Sodium deoxyglycocholate
SLN	Solid lipid nanoparticles
SA	Sodium alginate
SMEDDS	Self-microemulsifying drug delivery systems
SEDDS	Self-emulsified drug delivery system
SRS	Sigmoidal release system
SP	Succinyl-prednisolone
SA	Sebacic acid
SABER	Sucrose acetate isobutyrate (SAIB) extended release
SAIB	Sucrose acetate isobutyrate
SPIO	Supramagnetic iron oxide
sPLA2	Secretory phospholipase A2
SGLT2	Sodium/glucose cotransporter 2
SLM	Solid lipid microparticle
SCS	Suprachoroidal space
SSNHL	Sudden sensorineural hearing loss
SUV	Small unilamellar vesicles
SPARC	Secreted protein, acidic and rich in cysteine
siRNA	Small interfering ribonucleic acid
STPP	Stearyl tri-phenyl phosphonium

T

Tc	Critical temperature
TMC	N-Trimethyl chitosan
TRH	Thyrotropin-releasing hormone
TIJ	Thermal inkjet
TES	Times controlled expulsion system
τ	Duration to maintain Css
t_d	Duration of drug release
t_{Css}	Time till Css is achieved
Tmax	Time to Cmax
$t_{1/2}$	Half-life
TSNAs	Tobacco-specific nitrosamines
TEM	Transmission electron microscopy
TG	Triglyceride
TaT	Heat-activated cytotoxicity
TDDS	Transdermal drug delivery system
TBR	Trachea-bronchial region
TEOS	Tetraethyl orthosilicate
TPP	Triphenylphosphonium

U

USA	United States of America
UC	Ulcerative colitis
USFDA	United States Food and Drug Administration
UV	Ultraviolet
UN	United Nations

V

PVPK30	Polyvinylpyrrolidone K30
p-CFG	Polyacrylamide-g-corn fiber gum
PVA	Polyvinyl alcohol
VAS	Visual analog scale score
VAS-R	VAS at rest
VAS-A	VAS with activity
Vd	Volume of distribution
Vin	Vinpocetine
VHH	Heavy chain antibodies

W

w/w	Weigh per weight
WGA	Wheat germ agglutinin
w/o	Water in oil
w/o/w	Water in oil in water
WHO	World Health Organization

X

Xp	Plasma drug level

Z

Z-DEVD-FMK	Caspase-3 inhibitor, N-benzyloxycarbonyl-Asp(ome)-Glu(ome)-Val-Asp(ome)-fluoromethyl ketone

Introduction

1

Aliasgar Shahiwala, Ankit Javia, Hinal Patel, and Ambikanandan Misra

Contents

1.1 Introduction

Innovative pharmaceutical companies often look for line extensions for their products as an effective tool toward product life cycle management. Line extensions are incremental innovations that usually enter the market near the expiration of the exclusivity periods of the original product to avoid loss occurring through generic competition. Similarly, other companies changed the profile of patented branded

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_1

products by demonstrating superiority over the available branded product by using innovative new drug delivery technologies. For industry, repurposing or repositioning of already-approved drugs offers a lower-risk strategy that may reduce both cost and time required to carry the drug to the market. Drug repositioning opportunities can be identified through variety of processes or resources including knowledge mining of present scientific databases, in silico tactics, in vitro/in vivo trials, clinical observations, and post hoc analysis [1].

Repositioning of an old drug can be achieved by three different means [2, 3], namely, new indication of existing drug (drug repurposing), using different formulation approaches (reformulation), and new combinations of the drugs in the same dosage unit. Some of the key strategies that innovator employs to delay generic competition are to reformulate already-approved product which is at the verge of getting off patent (product life cycle management or product evergreening), to secure the patent for the same product, and to drive the market toward the reformulated product by promoting its superiority or by discontinuing previous version(s) of reformulated product. Generic players can also consider using reformulation strategy to avoid potentially strong formulation patents of innovator for early market entry and get approval by filling ANDA with Paragraph IV certification under section 505(j)(2)(C) or NDA under section 505(b)(2) of FD&C Act. Generic player can also get its reformulated product patented and keep other competitor generics at bay by preventing them from reformulating in similar way. If generic gets approval under section 505(b)(2), it can also claim market exclusivity from the FDA if criteria for the same is fulfilled [4].

Reformulation is a most promising approach as it allows the drug manufacturer to expand its offerings in a given market while targeting a new, potentially larger demographic that may not have been able to use the medication in its original dosage form [5]. Reformulating old products can not only reduce the cost and time of new drug development but also give benefits of patent protection and bypassing the existing patents. However, the goal for any new formulation development should be to make a better product rather than patent protection.

1.1.1 Drug Repositioning USFDA Regulatory Pathway

The USFDA recognizes the importance of innovation in pharmaceutical formulations and offers truncated regulatory assessment options for the research focused on repositioning of existing drug, unlike new chemical entity (NCE) application which requires detailed assessment.

New drug products are approved and accepted by the USFDA via three key regulatory pathways: 505(b)(1), 505(b)(2) as New Drug Application (NDA), and 505(j) as Abbreviated New Drug Application (ANDA). Branded drugs can be approved either via 505(b)(1) NDA pathway or through 505(b)(2) NDA pathway [6]. The 505(b)(1) pathway is used for drugs which have been newly discovered and developed; these are more often for new molecular entities (NMEs) and NCEs that have not been previously registered/listed in the USFDA [6]. In contrast, a 505(b)(2)

covers reports of safety and effectiveness, along with nonclinical data required for the approval; still, at least some of the information/data which is essential for NDA approval comes from studies not conducted by or for the applicant. The 505(b)(2) regulatory pathway was created, in part, to avoid unnecessary repetition of studies, including the clinical and nonclinical studies, which have already been performed on an existing or earlier approved drug(s) (e.g., orange book listed drugs).

In the recent times, two regulatory pathways are well known for filing products that differ from the approved reference listed drug (RLD) in the US market: one is filing an Abbreviated New Drug Application (ANDA) following the approval of suitability petition (SP) filing under 505(j)(2)(C), and second one is through filing New Drug Application (NDA) under 505(b)(2) of FD&C Act [7, 8].

According to Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA), nonclinical evaluation of previously approved drug substances in new formulation requires additional toxicity data depending on the change in excipients, new route of administration, or change in duration of therapy. New formulation will be used in a substantially different way (e.g., new route, change in dosing frequency) [9]. This document [9] includes route-specific recommendations for all new formulations, whether they are proposed for a new route or the same route as a previous formulation. ICH M3(R2) [10] and ICH S9 [11] guidelines further provide recommendations for the durations of the toxicity studies.

1.1.2 Exclusivity Benefits

Data exclusivities for a newly formulated drug, including new dosage form or new use exclusivity, are granted for 3 years for change described in 21 CFR 314.108 – new drug product exclusivity. This is granted to drug when application or supplement contains reports of new clinical investigations (not bioavailability (BA) studies) conducted or sponsored by applicant and essential for the approval.

Orphan exclusivity is often granted for 7 years. This is granted to drugs selected and approved to treat diseases or conditions affecting fewer than 200,000 in the United States (or more than 200,000 with no hope of recovering costs). This is governed through the Orphan Drug Act and 21 CFR 316.31.

Pediatric exclusivity (PED) is granted for 6 months and added to existing patents/exclusivity as an additional 6 months of market protection at the end of listed patents and/or exclusivity for sponsor's drug products containing the active ingredient, when the sponsor has conducted and submitted pediatric studies on the active ingredient in response to a written request from the FDA.

Note also that under the Generating Antibiotic Incentives Now (GAIN) Title VIII of the FDA Safety and Innovation Act (FDASIA), additional 5-year exclusivity can be granted only for antibiotic products that have been granted a Qualified Infectious Disease Product (QIDP) designation (with some exceptions) [12].

1.2 Promising Reformulation Approaches

Many new drug delivery systems and methods have emerged that provide better efficacy, cost-effectiveness, reduced side effects, and better adherence to the therapy. The main drivers of new drug delivery technologies are increasingly challenging molecules and markets. On molecule side challenges are poor water solubility and bioavailability, poor stability, controlled release of highly water-soluble drugs, etc., while on market side, challenges include patient-preferred dose forms, pill burdens, unpleasant taste, and requirements for specific age groups such as children and elderly. Many drugs may benefit from new and innovative drug delivery technologies that provide conversion from invasive to noninvasive route of administration, targeted and controlled drug delivery, and improved patient convenience.

Improved delivery technologies and options may be the biggest growth industry in reformulation. While there are many diseases and conditions that may have benefited from the reformulated drugs, there are many areas in which there are substantial unmet patient needs that reformulated drugs have the potential to address. Foremost potential areas for reformulating drugs are discussed in the further section.

1.2.1 Solubility, Dissolution, and Bioavailability Enhancement

Through high-throughput screening, thousands of drug candidates are identified as molecular targets; however, difficulty comes when formulating them for preclinical and clinical setting as they tend to be very hydrophobic in nature. Formulation scientists can avail different formulation approaches that can be used to improve solubility and dissolution rates of such drugs on based on properties of drug, route of administration and required dosage form characteristics. These approaches include synthesis of soluble prodrugs and salts, micronization, nanonization, formation of polymorphs/pseudo-polymorphs (including solvates), complexation/solubilization (by means of cosolvency, pH adjustment, hydrotropy, use of surfactants, complexation with cyclodextrins, and an addition of cosolvents), formulation of drug dispersions in carriers (solid solutions, non-molecular solid dispersions, and eutectic mixtures), sonocrystallization, supercritical fluid technology, lipid-based formulation approaches including self-emulsifying or self-micro emulsifying systems, and liquisolid methods [13].

1.2.2 Modified Drug Release

Extended release (XR) or sustained release oral dosage forms are well-established technologies that offer improved patient compliance with lower side effects. Modified release technology platform is often used as a key life cycle extension strategy by many pharmaceutical companies. Such as, for chronic therapies, converting multiple daily doses to a once-daily dosing with an XR dosage form has

been reported to increase patient compliance [5]. The most popular dosing change involves the development of modified release including controlled or extended release (XR) and fixed-dose combination (FDC) versions of the patented drug [14]. In fact, XR formulations have proven so valuable that some manufacturers begin development even before the original formulation of the drug has been approved.

Several antipsychotics have become available as new formulations including an inhalation powder (ADASUVE® (loxapine)) and long-acting intramuscular depot formulations (risperidone LAI, paliperidone palmitate, olanzapine pamoate, and aripiprazole) thought to be particularly beneficial for patients with adherence problems and for those with a history of severe relapse upon medication discontinuation [26]. Another important case is opioid analgesics, where reformulation as extended release tablet (OxyContin (oxycodone)) offers not to target the patient adherence issues but to prevent the abuse of opioid analgesics.

1.2.3 Nanotechnology and Drug Targeting

Nanotechnology, a multidisciplinary field, has revolutionized the medicine in the twenty-first century. It has a vast potential and scope to radically advance the treatment and prevention of many chronic diseases, such as cancer, HIV/AIDS, arthritis, asthma, etc. Pharmaceutical formulations with drug particles, drug-carrier particles or complexes in the range of 10–1000 nm referred to as nanoformulations which includes other terms such as nanocrystals, nanoparticles or nanomedicine. These nano-sized formulations are intended to advance the pharmaceutical properties and drug response by improving the solubility, stability, pharmacokinetics, biodistribution, safety, and efficacy of the drug. Advanced research in nanotechnology leads to fabrication of new therapeutics in cancer treatment with old chemotherapeutic agents. Although nanoparticles are smaller compared to cells, they are large enough to encapsulate many small molecule compounds, and at the same time, due to their relatively large surface area, functionalization with ligands, DNA or RNA strands, peptides, aptamers, or antibodies is possible. These properties allow combination of drug delivery, multimodality treatment, and theranostic action, i.e., combined therapeutic and diagnostic treatment. The physical characteristics of the nanoparticles, like energy absorption and reradiation, can also be used to disrupt diseased tissue, as in hyperthermia and laser ablation applications [15]. For clinical treatment and prevention of HIV, targeted delivery of antiretroviral drugs to CD4+ T cells and macrophages, as well as delivery to the brain and other organ systems which are latent reservoirs, nanotechnology held the most promise [16, 17].

1.2.4 Advances in Transdermal Drug delivery

Presently, oral route has been preferred as the most common route of drug delivery. Though oral route provides ease of administration, it also has limitations, such as poor bioavailability due to first-pass metabolism, limited gastric retention time, and

dose dumping, and often requires high and/or frequent dosing to maintain drug within therapeutic level throughout the treatment period, which can be both inconvenient and costly. On the other hand, transdermal route offers improved patient convenience and compliance, avoiding first-pass metabolism. A well-designed transdermal drug delivery system allows continuous input of drugs in systemic circulation in a controlled manner, eliminating pulsed entry into systemic circulation. The primary barrier to transdermal drug penetration is the stratum corneum [18]. Hence, the compounds suitable for the transdermal penetration must be relatively small ($\leq$ 500 daltons), nonionic, and relatively lipophilic (log P < 2.6). Several physical and chemical approaches for transdermal flux enhancement include application of electricity, microneedle, and ultrasound, and chemical enhancers have been utilized to enhance the drug permeation through the skin [19]. Nowadays, research trend is directed toward the use of microneedles. Recently, influenza vaccine delivered by a dissolvable microneedle patch has shown to generate robust antibody responses and well tolerated in human trial [20, 21]. Disposable thrombin-responsive patch for long-term autoregulation of blood coagulation by integrating thrombin-responsive heparin-conjugated hyaluronic acid matrix with microneedle patch that responds to blood clotting factors by releasing heparin into the blood stream to prevent thrombosis has also been developed [22].

1.2.5 Advances in Pulmonary Drug Delivery

The first commercial inhaled insulin (Exubera®) launched by Pfizer in 2006 was a major breakthrough for the drug administration via pulmonary route for the systemic therapy [23–25]. Unfortunately, this product was withdrawn from the market just after 2 years of its launch due to poor and variable bioavailability of insulin [26]. Despite this, there is growing interest toward development of inhalable products both for local and systemic purpose due to large surface area and highly absorptive mucosa of the lungs [27]. High-dose (> 100 mg) dry powder inhalers with innovative approaches such as swellable microparticles, large particles with high porosity, and nanoparticle aggregate-based porous particles are the new promising approaches for pulmonary administration [28]. Various technologies of particle engineering including micronization, controlled solvent crystallization, supercritical fluid processing, spray drying, spray freeze drying, particle formation from liquid dispersion systems, and particle coating for the development of pulmonary drug delivery systems have emerged [29]. A more recently developed particle engineering technology, iSPERSE™ (Pulmatrix Inc., Lexington, MA, US), has smaller particles with high density (typical tapped densities > 0.4 g/cc) [30]. With increased integration of particle engineering with software-aided digital devices, it is likely that a greater proportion of repurposed drugs are through aerosol formulations.

1.2.6 Ocular Drug Delivery

Ocular disease directly affects human vision and quality of life. The number of visually impaired people globally was estimated to be 285 million, out of which 65% and 82% are over 50 years of age with visual impairment and blindness, respectively [31]. Currently, eye drops and intravitreal injection are common treatment modalities for eye diseases. However, both of these suffer from various issues. Only less than 5% of totally administered drug is reaching the aqueous humor due to the corneal and pre-corneal factors [32]. As a result, frequent administration of eye drops is required, which can result in corneal surface impairment, tear film instability, and inflammation to cornea and conjunctiva [33]. Also, eye drops are proven to be effective in anterior eye diseases such as corneal diseases, dry eye, keratitis, conjunctivitis, cataract, and glaucoma; they are less efficient in treating posterior eye diseases which are most commonly in the retina and choroid [34]. Therefore, intravitreal injections are given vitreous cavity through a 27- or 30-gauge needle to treat posterior eye diseases [35]. However, intravitreal injection is an invasive technique which can result in series of side effects such as retinal detachment, uveitis, cataract, endophthalmitis, iritis, and intraocular hemorrhage, and repeated injections further increase the incidence of these complications [36]. Therefore, there is a tremendous scope in reformulating the drug in order to improve drug permeation and to prolong the drug retention in the eye. Considerable interest is being directed toward viscosity enhancement, in situ gelling systems, nanotechnology, ocular inserts, and implants [37].

1.2.7 Routes of Administration for Biologics and Reformulation Options

Biologics are becoming more dominant in the current pharmaceutical market. Moreover, there are currently more than 150 biologic license applications approved in the United States. Biologics are typically manufactured in living systems that may produce similar but not necessarily identical products. System contaminants and structural alterations such as changes in glycosylation can lead to immunogenicity problems which may not be associated with the original ones. Product differences may even be present within the same batch. Therefore, there are both prospects and challenges for pharmaceutical companies interested in reformulating the biological products.

Most biologics are administered through parenteral routes (e.g., intravenous infusion and subcutaneous or intramuscular injection). Biologics are commonly administered by IV infusion because of the need to deliver safe concentrations, maintain stability, avoid aggregation and undesirable viscosity properties, and limit degradation in the digestive tract due to short half-life. Recently, a number of non-injection technologies are being developed for delivery of biologics through oral, transdermal, nasal, and pulmonary as major routes of administration. However, there are failures associated with some reformulation strategies. The famous case was Exubera®, an

inhaled insulin product launched by Pfizer that failed to gain market share and made substantial loss of at least $2.8 billion to Pfizer [14]. PEGylation or polymer conjugate is another reformulating strategy for biologicals that are based on improved safety and potency. It may be eligible for new exclusivity period as well as any new patent term. For example, pegylated filgrastim (Neulasta, Amgen) has a human half-life of 15–80 h compared to 3–4 h half-life of filgrastim (Neupogen, Amgen) allowing for a single-dose administration for each cycle of high-dose chemotherapy. On the contrary, Neupogen is given in several injections (as many as ten) on a daily basis until neutrophil counts come back to normal levels [38].

A new oral powder formulation of Norvir (ritonavir), an HIV protease inhibitor which was originally approved in tablet and oral solution forms in 1996, has been recently approved by the FDA. This new oral powder formulation does not contain ethanol or propylene glycol and can be mixed in soft foods. It provides safer and more palatable alternative, reduced pill burdens, elimination of the food effect, and patient-preferred dose forms for children [39].

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2 Poorly Water-Soluble Drugs and Formulation Strategy to Improve Oral Bioavailability

Mo. Rahil G. Bhura and Aliasgar Shahiwala

Contents

Abstract

Poor water solubility of a drug is a tough and difficult task for researchers and pharmaceutical scientists during the formulation and development of dosage forms. Poor drug solubility often leads to inadequate and variable bioavailability. The properties of drugs cause problems in drug dissolution and its rates are solubility, particle size, polymorphism, salt form, complexation, wettability, etc. The improvement of drug solubility there by its oral bioavailability remains one of most challenging aspects of drug formulation process mostly for oral drug

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_2

administration and the oral bioavailability will be governed by various parameters including dissolution rate, aqueous solubility, drug permeability, pre-systemic metabolism and susceptibility. To improve solubility and rate of dissolution, there are many approaches available like pH adjustment, particle size reduction, sono-crystallization, inclusion complexation, liquid solid methods, solid dispersion methods, self-emulsifying method, supercritical fluid processes, freeze drying method, spray drying method, hot melt extrusion method etc. Selection of right technique is the key to improve the drug dissolution and bioavailability and it helps to avoid the rejection of recent chemical entities because of low solubility.

Keywords
Solubility · Dissolution · Bioavailability · Approaches

2.1 Introduction

Out of various means of administering drug into body one may find the oral route delivery is the most universal and practical route of drug administration due to the ease of administration [1]. The absorption of the drugs from solid dosage form is governed by mainly two parameters:

(a) Drug should get solubilised in biological in GIT.
(b) Transportation of dissolved drugs through membrane [2].

Dissolution within the gastrointestinal fluids is a rate determining step before absorption when the medicaments are administered orally in solid dosage forms like tablet and capsule. It is important to mention that there are some drugs with a slow rate of dissolution that could call for the absorption in an insufficient manner leading to low bioavailability. Because of limited solubility and poor dissolution rates, there is a less concentration gradient between the gut and blood vessels, resulting in restricted transport of drug and that consequently affects the oral absorption of poorly water soluble drugs. With rising frequency of less dissolvable drugs, development of new products particularly for the oral route of administration poses notable risk of less and irregular bioavailability which affect safety and efficacy. Bioavailability is restricted by dissolution rate for many poorly soluble drugs. Thus, escalating the solubility and dissolution velocity is a right key for poorly water soluble drugs [3]. Many different technologies like micronization, solid dispersion, co-solvency complication, hydrotrophy, sono-crystallization, reduction in the size of particle, micro emulsion, use of surfactant, nano suspensions and other techniques of cryogenic are extensively used for the enhancement of solubility and thus providing new edge to the existing product [4]. List of patented technologies used for solubility enhancement are provided in Table 2.1.

Table 2.1 Patented technologies used to enhance drug solubility

Sr. no	Patent number	Drug used	Patented technology used	Reference number
1	US5202129	Chloramphenicol	Micronization	[5]
2	EP2768485B1	Flubendazole	Co-crystal formation	[6]
3	US8497303B2	Ibuprofen	Micronization	[7]
4	WO2013040187A1	Lovastatin	Solid dispersion	[8]
5	US9511078B2	Finofibrate	Self nanoemulsion	[9]
6	US8722091B2	Ibuprofen	Dispersion Lyophilization	[10]
7	US7607596B1	Ketoprofen	Twin screw extruder	[11]

2.2 Techniques for Solubility Enhancement

2.2.1 Micronization

There are number of formulation strategies employed to target the poor aqueous solubility of pharmaceutical compounds. Micronization is one of the widely explored strategies used for particle size reduction and thus providing improved dissolution rates of poorly water-soluble drugs by increasing their surface area.

Micronization is performed by milling techniques and instruments which are used for milling is rotor stator colloid mills, jet mills etc. This technique has been used for griseofulvin, progesterone, fenofibrate, and spironolactone. For individual drug, micronization improved their absorption and simultaneously their bioavailability and clinical efficiency. Micronized fenofibrate showed more than 10-fold (1.3–20%) rise in dissolution in 30 min in biorelevant media [12, 13]. Size reduction of the drug particle can also be done by recrystallization of the solute particles from the solutions, which use liquid antisolvents, along with labour intensive techniques like crushing, milling, grinding, freeze drying and spray-drying. However, some drugs may degrade because of mechanical or thermal stress as well as solvents are toxic in nature [14].

(a) *Jet Milling*

Ultra fine grindings of pharmaceutical powders can be obtained through energy of the fluid (air with elevated pressure) by a fluid jet mill (Fig. 2.1). Being a dry process, there is no contamination involved. This method is also appropriate for drugs that are sensitive to heat. Drawbacks of traditional micronization such as low bulk density, agglomeration, no dissolution improvement, poor flexibility and loss of the expected surface area can be solved by using jet milling technology [15]. In one of the research, Ibuprofen powder was micronized in the size range of 5–10 μm via using a process that utilize micronization and Jet milling at the same time. The dissolution behaviour was found to increase with the increase in the surface area for drug particles in accordance with Noyes–Whitney equation [16]. In another research done by Jinno et al. demonstrated that bioavailability and dissolution of Cilostazol which is poorly soluble in nature was accelerated by jet milling process [17].

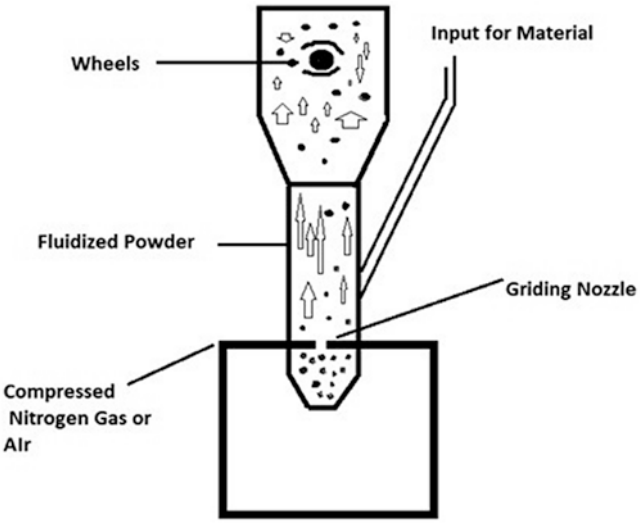

Fig. 2.1 Schematic diagram of a jet mill

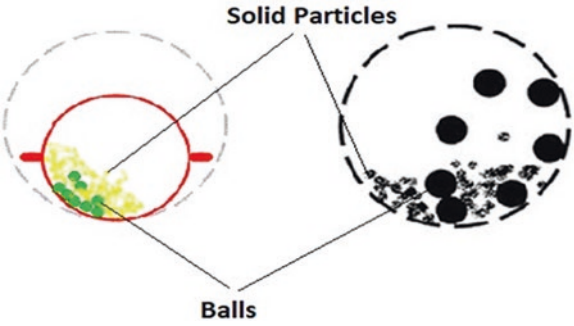

Fig. 2.2 Schematic diagram of a ball mill

(b) *Ball Milling*

Ball mill is beneficial for grinding of pharmaceutical powders. Powder rotates around a horizontal axis in a cylindrical grinding tool. The instrument is half part filled with the material to be ground and the medium used for grinding is mostly stainless steel balls, solid pebbles or ceramic balls (Fig. 2.2). Particle size reduction to less than 200 nm was achieved for poorly water soluble drug danazol by ball milling in the presence of polyvinylpyrrolidone K-15 as a stabilizer. The resultant nanosuspension of drug shown better bioavailability in beagle dogs compared to that of conventional aqueous suspension of the drug [18]. The effect of ball milling on physical dispersions of Nimesulide in presence of carrageenan or polyethylene Glycol (PEG) 4000 was studied for its solubility enhancement [19]. The results revealed that both the polymers (Carrageenan, Polyethylene Glycol (PEG) 4000)

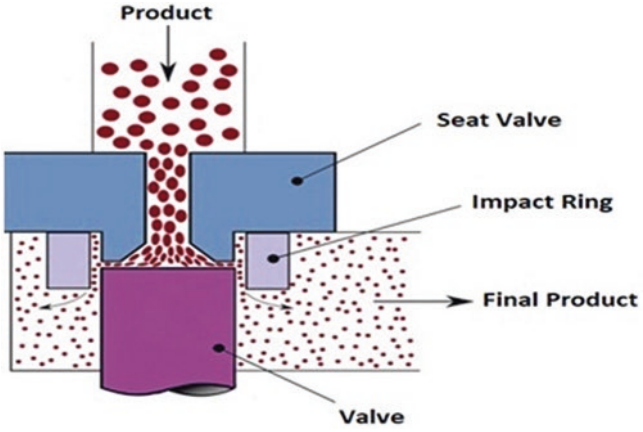

Fig. 2.3 Schematic diagram of High pressure homogenizer

help in increasing the solubility of Nimesulide. However, ball milling with PEG 4000 had a better effect than milling with carrageenan.

(c) *High pressure homogenization*

High pressure homogenization is a top down technique, which is extensively used techniques for making nano suspension of drug which has the poor water solubility. Use of this technology can be use for improving the rate of dissolution as well as bioavailability for poorly water soluble drugs like omeprazole, budesonide and spironolactone. This can be done reducing the size of the particle nano size range [20]. Schematic figure of HPH is shown in Fig. 2.3.

2.2.1.1 In Situ Micronization

This is the latest particle engineering method in which produced micron sized crystal during its manufacturing without the need any more reduction of particle size. On the contrary, different techniques which are used for external processing condition such as pressure, temperature and mechanical force are necessary; during crystal formation of the drug micron size particle is obtained. Therefore, above method is called as in situ micronization. The following sections where this practices can be seen to cover various aspects of micronization [21].

It is the simplest method to produce microcrystal which involves single stage process that need common equipment while, other micronization processes such as supercritical fluid (SCF) milling and spray drying, having issues including costly processing conditions as well as material loss, intensive labour and dust explosion risks etc. [21, 22]. J. Varshosaz et al carried out the in situ micronization process on Gliclazide with the use of solvent change method in existence of HPMC as stabilising agent. The particle size was reduced about 50 times and the efficiency of dissolution for gliclazide was enhanced about 4 times.

2.2.1.2 Super Critical Fluids

Supercritical fluid (SCF) can be defined as a dense non-condensable fluid whose temperature and pressure are greater than its critical pressure (Pc) and critical temperature (Tc). The SCF processing is a novel nanosizing and solubilization technology and its application has increased in particle size reduction. Rapid expansion of supercritical fluids such as supercritical carbon dioxide leads to reduction of the size particles quickly and naturally for the various drugs [23, 24]. The most helpful methods of SCF applied for particle size reduction are quick expansion of supercritical solutions and gas anti solvents recrystallisation (GAS). Both the methods are applied by the pharmaceutical industries using carbon dioxide as the supercritical fluid [25] due to its significant handling properties such as its low critical temperature (Tc = 31.1 °C) and pressure (Pc = 73.8 bar) [26, 27].

2.2.2 Nano sizing

Micronization is commonly used approach for particle size reduction to improve the dissolution rate for water insoluble drugs. Though, the extent of dissolution rate needed to increase in vivo drug absorption for such kind of poorly soluble drug compounds is greater than that which can be achieved by micronization. Also, for drug with high dose number micronization method is not appropriate because it does not alter saturation solubility of drug [28, 29]. Therefore, the reduction in the size of particle in the range of nanometer which could enhance the oral absorption of such type of drugs. Many research reports revealed that the nano particles have the capability to increase the absorption of the drug that are poorly soluble in nature, in addition it provides enhancement in other biopharmaceutical characteristics (e.g. variable absorption in the fed vs. fasted condition) Nanosizing as a certain process which could reduce the size of the active pharmaceutical ingredients to the submicron range. Nano suspensions are aqueous dispersions which include mixture of stabilizers like a surfactant and/or a polymer and API, in water [30]. Nano suspensions can be prepared by means of wet media milling [31], homogenization with high pressure [25], it can combination of the two methods mentioned before [32]. Since Sucker et al formulate nano particles in the 1980s, nanonization has attracted much attention, especially for enhancing the bioavailability of poorly soluble drugs. Nano Crystal Technology utilizes attrition process where the large micron size drug crystals are media blended in stabilizer solution which is aqueous-based [33]. The process makes physically acceptable dispersions consisting of nano-sized drug crystals. This nano crystalline particles are suitable delivery system for all routes of administration, such as, topical, injectable and oral uses. Moreover, these nanoparticles aqueous dispersions are processed in the form of capsules, tablet rapid-melts and sterile lyophilized form for usage. In all stages of the drug progression cycle from recognition of new chemical molecules to reproducing marketed products to enhance their performance and value by utilizing these methods.

2.2.3 Crystal Engineering for Solubility Enhancement

Reduction in particle size often leads to prospective for increased Vander Waals interactions and electrostatic attraction between particles, results in to reduction of effectual surface area for dissolution. Crystal engineering methods are used to wide range of crystalline materials to design molecular components in crystalline phase with specific physical or chemical properties in order to enhance the solubility and/or rate of dissolution. Different approaches in crystal engineering are applied such as crystal habit modification, polymorphism, solvation, co-crystal formation and surface modification to change the surface and molecular assembly in equilibrium with a solution. These approaches are capable of producing drugs having appropriate dissolution qualities while maintaining their suitable physical and chemical integrity [34]. This is one of the successful methods for tailoring the characteristics of a solid state dosage form at the molecular level can be performed by incorporating co formers (pharmaceutically allowable) into a different crystal lattice without changing the covalent bonding of the API. Therefore, this form of engineering has been appeared into the pharmaceutical field with the design of new multi component solid-state assemblies based on synthon approach [35].

Jia-Mei Chen et al, found out the co-crystallization performance of Mebendazole by approach of crystal engineering having the aim of forming the new crystals that could improve the water solubility of Mebendazole. Mebendazole, is having a very less bioavailability (<10%) because of low water solubility. In order to enhance its solubility, Jia-Mei Chen et al combined mebendazole with a group of dicarboxylic acids via liquid-assisted grinding and crystallization techniques [36]. In other study done by Childs et al., Fluoxetine HCl succinic acid cocrystal was found to show approximate two-fold enhancement in aqueous solubility only after 5 min [37]. Carbamazepine-saccharin co-crystal was appearing to be superior to crystal forms of carbamazepine alone with regards of its dissolution, stability, oral absorption profile of dogs, and suspension stability [38].

There is a method of crystal engineering which is used for preparing hydrates as well as solvates that could enhance the rate of dissolution. This process of crystallization cause entrapping of solvent molecules inside the lattice. When water is used as solvent, the obtained crystal is a hydrate; when any other solvent is used as a solvent, it is known to as solvate. The solubility and dissolution rate of a drug can show different benefit for Different solvates. For e.g., Glibenclamide have been isolated as toluene and pentanol solvates, and these solvates shows increased solubility and dissolution rate when compare to two non solvated polymorphs [39].

2.2.4 Solid Dispersions (SD) a Strategy for Solubility Enhancement

Solid dispersion technique is another promising strategy to improve the solubility, dissolution and bioavailability of poorly soluble drugs. In SD the drug exists in molecular or amorphous or microcrystalline state. The solubility and wettability of

drug is improved in amorphous state, which also increases the dissolution rate of drug. Disulfiram is hardly absorbed from the cornea but its SD with polyvinylpyrrolidone (PVP) prepared by the spray drying method improves its ocular bioavailability [40]. The physical and chemical stability of Fluvastatin was increased by making SDs of drug with different polymers like PVP, Eudragit RS100 and chitosan [41].

SD can be prepared by using numerous processes and methods. Along with process diversity the wide range of carriers/polymers also strengthen the concept of SDs. In recent years, binary, ternary and quaternary SDs have been formulated to improve the stability of dispersions, and also to prevent recrystallization of drug in the carrier. Apart from conventional applications, the SDs also have been explored for making controlled- or sustained-release products [42].

SD work through different mechanisms. The mechanism depends on the type of SD, interaction between drug, carrier and other carriers used to prepare it.

- High-energy metastable state/amorphous form.
- Reducing particle size up to molecular level.
- Presence of carrier prevents aggregation of drug particles.
- Carrier material also prevents crystal growth.
- Intermolecular hydrogen bonding between drug molecule and carrier.
- Wetting properties are increased.
- Co-solvent or solubilisation effect of water-soluble carriers [43].

First generation SDs made by using crystalline carriers such as sugar and urea, that have been considered as very first carriers which are used in the dispersion of solids. However, the first generation SDs are thermostable and may not releases the drug in a quicker manner as the amorphous forms.

Second generation solid dispersions use amorphous carriers instead of crystalline carriers which are generally polymers. The carriers used in these SDs are synthetic polymers such as polyethylene glycols (PEG), poly vinyl pyrrolidone (PVP), and polymethacrylates copolymers as well as natural product-based polymers like hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose (EC), and hydroxyl propyl cellulose (HPC) or starch derivatives.

It has been recently discovered that the dissolution profile can be increased when the carrier has self-emulsifying properties or surface activity. Thus, third generation SD appeared. The utilization of surfactants such as Compritol 888 ATO, Poloxamer 407, Inulin and Gelucire 44/14 as carriers were proved to be effective in improving *in vivo* bioavailability and creating high polymorphic purity [44].

2.2.4.1 Methods for Preparing SDs

Depending on the problem of solubility and requirements, SDs can be made by various approaches. If one approach fails to obtained stable SD, then other approach can be used [45]. The methods and process for preparing SD can have great impact on dispersion characteristics. Along with process parameters (solvent system, friction force, attrition, shear, temperature, rate of cooling), the carrier composition also influences the characteristics of SD [46].

2.2.4.1.1 Kneading Method

The physical blend of drug and carrier is triturated with a small amount of solvent into a thick paste. The solvent used may be organic (alcohol, dichloromethane, acetone) or aqueous (water) or mixture thereof. The kneaded paste is dried in vacuum oven or oven and the dried mass is pulverized and stored in desiccator [47]. Kneading technique is an economic process, but residual solvent can be a problem.

2.2.4.1.2 Spray Drying Method

Spray drying is a form of technique which has been established greatly and can be used for the purpose of formulating amorphous SDs and an effective strategy for delivering drugs that are poorly water-soluble [48]. One may find spray drying technology in the form of an operation of unit where liquid (solution, suspension or emulsion) seems to be flowing and sub divided into various droplets. It is shifted into a glass compartment and it comes into contact with hot gas. It is later dried in the form of fine particles that are separated out of the drying gas by means of a bag-filter and cyclone separator [49]. Spray drying is a moderate drying method (which uses mild temperatures and low exposure times compared to other SD method such as melt extrusion) which produces powder with reasonable particle size [50].

2.2.4.1.3 Solvent Wetting

In this technique, a poorly water-soluble drug is dissolved in organic solvent (ethanol, isopropyl alcohol), and this solution is added drop by drop to the carrier material and properly mixed. The solvent is evaporated, and the dried mass is grounded and pulverized after proper mixing [51].

2.2.4.1.4 Solvent Evaporation

The drug and carriers are dissolved or dispersed in common solvent (or solvent mixture) and solvent then is evaporated with the help of heat, with or without vacuum. The dried solid mass is crushed, pulverized and stored in desiccator. The dispersion characteristic may be affected by several factors, some of which are listed as: drug-to-carrier ratio, carrier type, solvent composition, evaporation rate and evaporation temperature [52]. Sharma and Jain developed the Carvedilol SD using the solvent evaporation method with PVP K30. They found that the SD developed by solvent evaporation technique with PVP K30 is a promising way to improve the solubility and dissolution rate of carvedilol [53].

2.2.4.1.5 KinetiSol Dispersing

Kinetisol is a novel fusion-based process for the production of amorphous SD systems that has been adapted from the plastics recycling industry to pharmaceutical processing. KinetiSol technology rapidly transit drug by using frictional and shear energies to achieve an amorphous single- phase SD. The typical time of processing can be considered fewer than 20 s having a temperature which is elevated that lasts usually for fewer than 5 s. The process is monitored by a computer control module and molten material is immediately ejected when the user reaches the defined

endpoint. On a commercial scale, it seems to be operated by achieving the product throughput that can be high at the rate of 1000 kg/h.

With its unique process attributes, KinetiSol offers new solutions for water insoluble compounds that are difficult to process. These unique characteristics include short processing times, low temperatures, high intensity of mixing and high torque output. These process aspects offer unique abilities for the production of amorphous dispersion with thermally sensitive pharmaceutical materials, high melting point pharmaceutical active ingredients (APIs) and highly viscous polymers. In addition, KinetiSol offers non-solvent processing operational, environmental and economic advantages [54]. Justin R. Hughey et al. used hot melt extrusion (HME) and KinetiSol ® Dispersing (KSD) to prepare SDs for Roche Research Compound A (ROA), a BCS class II drug, and found that KSD provided a threefold increase in HME ROA recovery for Eudragit ® L100-55 compositions without the need for plasticizers or micronized ROA [55].

2.2.4.1.6 Fusion

In this method, a mixture of carriers and drugs is melted at temperature closed to the point of melting with constant stirring. The uniformly mixed melted mass is allowed to cool at room temperature or rapidly in an ice-bath with vigorous stirring. The cooling rate can influence the characteristics and stability of a solid dispersion greatly. The solidified mass is then crushed pulverized and sieved [56]. The final solid mass is crushed, pulverized and sieved. The cooling process has undergone different changes like the homogenous melt is poured in the form of a thin layer onto stainless steel plate or ferrite-plate which is continuously getting cooled by means of water or air on the opposite side of the plate. Carrier to drug ratio should be high specially for low water soluble drugs in order to deliver the drug in a solubilized state, any attempt to reduce carrier-to-drug ratio may lead to supersaturation and drug precipitation and hence further leads to stability issues and product failure [57]. These conditions can be seen to causing the process of solidification which is done instantly by making use of a solvent matrix. This method of quenching is capable of producing a dispersion with is finer in nature and could cause certain crystallites that are used in the case of eutectic mixtures.

2.2.4.1.7 Fluid Nozzle Spray Drying

Conventional spray drying requires a solvent in which both excipient and drug should be dissolved. However, due to hydrophilic nature of the excipient and lipophilic nature of the drug, finding a common solvent is often difficult for the formulation scientist. Also, large amount of solvent is required, the removal of which is time and energy consuming and also not considered eco-friendly [58]. Moreover, toxic solvents like dichloromethane are used and the choice of matrix former is often limited.

In order to improve some of the limitations of conventional spray drying process, a spray drier having 4-fluid nozzle, two nozzles for liquid and two nozzles for gas passages that could cause emitting of liquid and gas passages. Using this technique, several drugs processing were carried out [59]. This 4-Fluid nozzle spray drying

generates more uniform particle size than conventional spray drying. According to this technique, two different solutions can be sprayed at same time that allows drug to be dissolved in different solvents thus restricting the use of a common solvent has been utilized. The machine is equipped with two routes for gas supply and two routes for liquid-feed. The gas and liquid are instantaneously mixed; liquid extended by the gas is atomized in the shock waves that arise from the collision focus of the edge tip [60].

2.2.4.1.8 Twin Screw Extruder

Twin screw extruder is one of the most common methods used for SD preparation. One may find several benefits where Twin-screw extruder is used because of the manufacturing process that is done continuously and has a certain speed associated with it. Moreover, solvent is not required during the extrusion process [61]. The Twin screw extruder consist of hopper, kneading screw, barrel, a die and heaters. Heaters are used to control temperature inside the barrel. Uniformly mixed composition (drug and carriers) is introduced into the hopper of Twin-screw extruder. This mixture from hopper is carried forward by feed screw into the barrel and kneaded under high pressure with the help of kneading screw. Water can be supplied through an injection port into the mixture. The kneaded mixture is extruded through dies. The extrudes are then dried, pulverized and stored [62]. This machine is shown in Fig. 2.4.

2.2.4.1.9 Microwave Irradiation

It is a process in which one may find is relatively new and can be used for improving the solubility as well as improving the level of bioavailability of drying and thermostable materials. This specific technology seems to be differing itself from the heating which is conventional in nature. Here, one may find the material's surface to

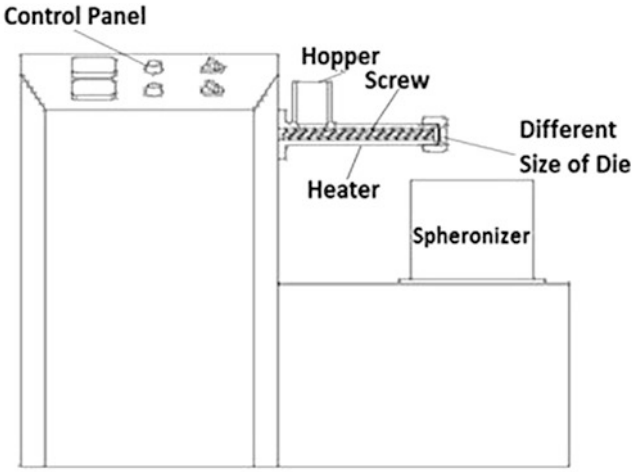

Fig. 2.4 Schematic diagram of Extruder and Spheronizer

be heating where this heat seems to be moving inwards. Here in microwave irradiation method. This heat is produced within the material and can passed to the entire volume with the constant heating rate. Microwave irradiation energy helps to converting to the amorphous form of drug from the drug which has crystalline form and thereby progresses the rate of dissolution of drug, which could lead to increased bioavailability of the drug [63]. This form of irradiation has the capacity to cause penetration in to the material which could lead towards the production of heat everywhere in the material. Microwave irradiation has several benefits also that cannot be compared with other form of techniques including low operating cost, non-contact heating, energy saving, fast start-up and stopping, portability of equipment and no form of overheating at the surface [64]. The microwave irradiation formulates the product which is virtually free of residual solvents.

2.2.4.1.10 Spray Freeze Drying

There is a process of spray freeze dying which is a great technique for generating micro powders. One may take into consideration liquid feed that consists of a solution of aqueous nature. It also consists of a suspension that contains Active Pharmaceutical Ingredients along with other carriers. This form of spray freeze dying technique has combined features which includes spray drying and freeze drying. In the first step atomization of a solution into liquid nitrogen generates the globules or droplets. This form of particles that are frozen in nature can be transferred in the freeze dryer where the particles are made to dry that could give rise to the production of a free-flowing powder. The spray-freeze-drying technology provides high process yield, fine particle control, better compatibility with various biopharmaceuticals excipients and less biopharmaceutical stresses in contrast to other particle formulation technologies. Maa et alhas demonstrated the ability of the spray-freeze-drying process to produce aerosol powders [65]. So far, only few studies have been conducted on the production of spray-freeze-drying pharmaceutical formulations for the poorly water-soluble drugs [66] like Ciprofloxacin [67], Phenytoin [68] and Carbamazepine [69] and Azithromycin [70].

2.2.4.1.11 Freeze Drying

The freeze-drying process which is associated with the phenomenon of physical phenomenon, has the potential of establishing a place for the stabilization of substances which are labile to heat [71]. This process of freeze dying also consists of producing an industrial method that could maintain chemical and physical qualities and long-term stability [72]. Freeze drying or lyophilization is a convenient but time consuming unit operation to made dry solid dispersions for thermolabile or biological materials. Lyophilization consists freezing, primary drying (ice sublimation) and secondary drying. The uniform drug carrier mixture dissolved in an appropriate solvent system is frozen under controlled conditions. This frozen material is subjected to freeze drying in appropriate freeze dryers. Primary drying obtained under low vacuum, chamber pressure is kept below the vapor pressure of ice and the ice is transferred from frozen material to the condenser by the processes of sublimation. The secondary drying takes place at high temperature and low pressure to remove

the water from the dried material. All three stages are very important and should be properly optimized. Lyophilized products are predominantly amorphous and sensitive to moisture and can crystallise if exposed to moisture. Although the technique is costly and time consuming, but it is always preferred for the preparation of solid dispersion of thermolabile materials [73].

2.2.5 Self-Emulsifying Drug Delivery Systems

There are many challenges in the world of science today in improving the oral bioavailability of drugs with poor and inconsistent absorption. Self emulsifying drug delivery system (SEDDS) is highly useful technological innovations to overcome the bioavailability of poorly water soluble drugs. SEDDS can be used to hiccups the bioavailability due to their smaller globule size, higher solubilization tendency for hydrophobic drugs, easier scalability in the pharmaceutical manufacturing and robust formulation advantages [73]. SEDDS are ideally isotropic mixtures of oils and surfactants, sometimes containing co-solvents that spontaneously emulsify to obtained fine oil-in-water emulsions when introduced into the aqueous phase under gentle agitation [74]. SEDDS typically produces emulsions with a droplet size of between 100 and 300 nm, while SMEDDSs form transparent microemulsions with a droplet size of less than 50 nm [75]. However, liquid SMEDDS are usually filled in capsules, and many times, this lead to leakage and softening of the shell. To avoid this, liquid SMEDDS were converted to solid SMEDDS using different approaches like adsorbing, lyophilization, and spray drying.

2.2.5.1 Solid Self-Microemulsifying Formulation Prepared by Spray-Drying

Spray drying is used to prepare dry emulsions by removing water from a common emulsion consisting a water-soluble solid carrier. The initial emulsion consisted mainly of oil, water and an ordinary emulsifier, and the droplet size of reconstituted dry emulsions usually exceeded 1 μm [76]. This technique involves the preparation of formulations by mixing lipids, surfactants, drugs, solid carriers and mixture solubilization before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The volatile phase gets evaporates as the droplets introduced in a drying chamber, forming dry particles under controlled temperature and air flow conditions. For the preparation of S-SMEDDS, a variety of solid carriers were used, including Dextran 40 (water soluble solid carrier and Aerosil ® 200 (non – porous and hydrophilic solid carrier) [77]. Critical parameters should be controlled during spray drying: air intake temperature, air outlet temperature, viscosity, solid content, surface tension, feed temperature, solvent volatility and nozzle materials.

2.2.5.2 Melt Extrusion

Melt extrusion is a solvent-free process that allows high drug loading of approximately 60%. Extrusion is a method by which a raw material with plastic properties

is changed in to a product of uniform shape and density by forcing a die under controlled temperature, product flow and pressure. This method is most widely used method in the pharmaceutical industry which can use to make uniform sized spheroids. It requires the following steps: mixing of excipients and dried drug to get a uniform powder; wet binding massage; extrusion into a extrudate; spheronization from the extrudate to form a uniform size of spheroids; sifting, drying to achieve the required size distribution. After the application of this technique, self-emulsifying pellets of diazepam and progesterone have been formulated to obtain a better in vitro drug release [78].

This Method utilizes the technique in which powder agglomeration is produced by adding a binder that melts or softens at relatively low temperatures. As a one step operation, melt granulation offers many applications over conventional wet granulation, as the addition of liquid and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation method are the speed of the impeller, the time of mixing, the particle size of the binder and its viscosity. A wide range of semisolid lipids and solid can be utilized as meltable binders. Gelucire, a family of vehicles derived from the mixture of polyethylene glycols esters and mono/di/tri/-glycerides of fatty acids, is able to further enhances the rate of dissolution compared with PEG typically used before, probably owing to its SME property [79].

2.2.5.3 Lyophilization Technique

In this method, after optimum SMEDDS is obtained, lyophilization was carried out in the presence of suitable cryoprotectant. A study by Fei L et al made use of lyophilization methodology where formulation of solids is designed successfully through using a system of self-emulsifying powder. Significant improvement in Lornoxicam S-SMEDDS dissolution behaviour through self-emulsification in aqueous media was obtained [80]. Some Patented Technologies used to improve drug solubility are shown in Table 2.1

2.3 Conclusion

Molecular modelling and screening of drug discovery having significantly enhanced the number of poorly water-soluble drugs. Therefore, choosing an appropriate solubility improvement technique or combination of techniques is crucial to produce a good formulation with superior oral bioavilability, reduced frequency of dosing and better patient compliance combined with a less cost during production. Selection of approach for solubility improvement can be dependent upon the properties like chemical nature, solubility, melting point, physical nature, absorption site and pharmacokinetic behavior of drugs. By studying drug properties, we can select the right approach to improve dosage form in the form of capsule or tablet for immediate release. In this regard, regulatory requirements could be fulfilled by means of approved excipients.

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Buccal and Intraoral Drug Delivery: Potential Alternative to Conventional Therapy

3

Bazigha K. Abdul Rasool and Aliasgar Shahiwala

Contents

Abstract

Repositioning an old drug through intraoral drug delivery system benefits the pharmaceutical manufacturer by imparting unique product differentiation and enabling its use as line extensions for existing commercial products. Although the needs for these systems are real, and many classes of drugs could benefit from intraoral drug

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_3

delivery, turbulent and changing nature of the oral cavity, less surface area, and contact time pose significant formulation challenges. This chapter discusses all these challenges and different approaches that can be adopted in formulating an intraoral dosage form. This chapter further provides details of approved marketed products, products that have recently completed or in ongoing clinical trials, and regulatory requirements for bioequivalence for intraoral dosage forms.

Keywords
Intraoral · Buccal · Drug delivery · Bioavailability · Proteins · Mucoadhesive

3.1 Introduction

Many drugs suffer from poor bioavailability through peroral route due to the harsh acidic conditions of the stomach, enzymatic degradation, and extensive first-pass metabolism. Traditionally, these drugs have been administered through parenteral route, which invariably leads to patient discomfort, difficulty in self-administration, and patient incompliance. All these issues lead pharmaceutical companies to look for alternative routes of drug delivery. One such route is oral cavity with buccal and sublingual which are important sites of drug absorption in oral cavity. Repositioning an old drug through intraoral drug delivery system benefits the pharmaceutical manufacturer by imparting unique product differentiation and enabling its use as line extensions for existing commercial products. Although the needs for these systems are real, and many classes of drugs could benefit from intraoral drug delivery, turbulent and changing nature of the oral cavity, less surface area, and contact time pose significant formulation challenges. Intraoral drug delivery not only protects the drug from acidic and enzymatic degradation and first-pass metabolism but also offers convenient way of dosing medications, not only to special population groups with swallowing difficulties but also to the general population. With our increased understanding of oral mucosal drug delivery, and emergence of sophisticated drug delivery technologies, many drugs including old and new can be formulated as intraoral delivery systems. These systems generally fall into one of the four broad categories: mucoadhesive buccal patches and tablets, quick disintegrating solid dosage forms, solid intraoral delivery systems, and aerosol intraoral drug delivery systems. For the purpose of this chapter, these delivery systems are discussed as buccal drug delivery systems and other intraoral drug delivery systems.

3.2 Anatomic Structure of the Oral Mucosa

Oral cavity is lined with a mucosal membrane which is comprised of four distinct regions, namely, buccal, sublingual, gingival, and palatal mucosa. Oral mucosa is a multilayered, thick, and dense mucous membrane and highly supplied with of blood vessels. It is normally covered with a lubricating layer of saliva, creating a moist

surface which is important for food digestion and at the same time influences drug absorption from the oral cavity. The tissue of the oral mucosa generally consists of three different layers: the stratified squamous epithelium, the basement membrane, and the connective tissue known as the lamina propria.

Buccal mucosa is the most commonly used site for drug administration among other mucosae mentioned above. It represents the floor of the mouth and the internal lining of the cheeks. The thickness of the epithelium in the buccal area in adult humans is about 500–800 μm and of 100 cm^2 an average surface area [1]. Buccal epithelium turns over into almost complete new tissue every 5–6 days which is probably the same of the oral mucosae as a whole. Sublingual mucosa has a structure similar to buccal mucosa but is thinner and with less layers of stratified and nonkeratinized epithelial cells. Sublingual mucosa in human adult is approximately 100–200 μm in thickness; hence it is expected to be more permeable than buccal mucosa [1]. The gingival mucosa is a part of the oral mucous membrane that is attached to the necks of the teeth and alveolar bones. It attaches the buccal mucosa at the gingivobuccal sulcus.

The epithelium covers buccal and sublingual regions, and the floor of the mouth is nonkeratinized, while in the hard palate and gingiva regions, epithelium is keratinized similar to the epidermis of the skin. The keratinized epithelium acts as a waterproofing layer and is composed of tightly packed dead cells filled with the protein filaments known as keratin. Light microscopy examination reveals that the keratinized and nonkeratinized areas of the oral epithelial layer differ from each other in terms of cellular lipid structure. The keratinized epithelium contains mainly neutral lipids such as ceramides and acylceramides which are the main cellular components associated with providing a barrier function. In contrast, the nonkeratinized epithelial cells have few but polar lipids, mostly glucosylceramides and cholesterol sulfate [2]. Therefore, the nonkeratinized epithelia have been considered to be significantly more permeable and subsequently more attractive for drug administration compared to other regions of the oral cavity.

3.3 Permeability of Oral Mucosa

In general, permeability of the oral mucosae arranges in the order, where the sublingual mucosa occupies the first rank followed by the buccal mucosa and lastly the palatal region depending on their thickness and the degree of cellular keratinization [3]. Galey et al. studied the in vitro permeability of buccal mucosa and the skin in humans and pigs to certain test drugs, and they concluded that skin dermis and buccal mucosa are similar in their permeability characteristics and the permeation process through these tissues is diffusion limited [4].

Nowadays, it is believed that the membrane-coating granules, saliva, mucous, and basement membrane are the main barrier components to drug penetration through the buccal mucosa. The predominant permeability barrier property is due to membrane-coating granules which are small granules (1–5 nm in diameter) present in the cell cytoplasm and form within the differentiating epithelial cells. The granules move toward the apical surface of the cell then fuse with the plasma membrane

and extrude their contents into the intercellular spaces at the upper part of the epithelium. The content of these cells spread at the cell surface and form a thickened cell envelope that prevents the action of keratinolytic agent. Permeation studies had been conducted to evaluate the permeability of the oral epithelia in mammals by injection of horseradish peroxidase, an intercellular water-soluble tracer, under the keratinized and nonkeratinized epithelial cells. Results revealed that the extent of the tracer's penetration was mainly decided by the level of the permeability barrier, membrane-coating granules, near to external plasma membranes of the epithelial cells. Since the granules were found in the same location of all nonkeratinized and keratinized oral tissues, this indicates that the cell keratinization is not expected to play the predominant role as barrier function in oral drug absorption [5].

Another barrier that hinders buccal permeation is the saliva secretion. The main functions of saliva are moistening of the mouth cavity, teeth protection against decay [6], regulating the normal flora of the oral cavity, helping in food digestion, and mineralization/demineralization of the tooth enamel due to its high contents of calcium and phosphate. Saliva fluid consists mainly of water with small amount (1%) of inorganic and organic materials. Saliva is a very dilute aqueous solution; the high amount of water (99%) in saliva plays a key part in the selection of the polymers for the formulation of buccal drug delivery systems. Many of the natural and synthetic hydrophilic polymers (e.g., sodium alginate, gelatin, carbomers, and cellulose derivatives) were incorporated as vehicles in buccal dosage forms due to their compatibility with the aqueous nature of saliva [7]. The volume of daily salivary secretion in healthy people ranges between 0.5 and 2 l, while the normal range of salivary flow rate is between 0.1 and 0.2 mL/min depending on the degree of the stimulation of saliva secretion; however below this range is considered as salivary gland hypofunction [8]. Salivary flow rate depends on three main factors, namely, the degree of salivary stimulation, the time during the day, and the type of the stimulus. Saliva is slightly acidic; the normal salivary pH is 5.5–7.8 based on its composition and flow rate. At peak flow rate, the pH of saliva increases due to the increase in sodium and bicarbonate concentrations [9]. Physiological washing effect of saliva and mechanical removal of the oral cavity lead to the inability of the conventional buccal dosage forms to retain the drug for enough time at the site of absorption and subsequently inadequate transmucosal drug permeation into the circulation. Moreover, saliva is equipped with some hydrolytic enzymes like carbohydrases, esterases, and phosphatases [10] which act as a metabolic barrier and deter buccal drug bioavailability. Saliva does not contain proteases though some of them have been found in the epithelial cells of the buccal mucosa, e.g., carboxypeptidases, aminopeptidase, and endopeptidases [11]. The detailed effect of these proteolytic enzymes on the systemic absorption of protein and peptide drugs from intraoral delivery systems has not yet clarified [12].

On the other hand, the existence of mucus at the surface of the epithelial cells also forms a potential barrier to buccal drug delivery. Mucus is an intercellular ground substance that forms a viscoelastic gel with shear-thinning behavior that can provide lubrication and protection to mucosa. The thickness of the mucus layer ranges from 40 to 300 μm and highly affected by the balance between secretion and degradation processes. In the oral cavity, mucus is a part of saliva which is produced

and secreted by both major and minor salivary glands, while in the epithelia of the mucosal membrane found elsewhere in the body, mucus is produced by specialized mucus-secreting cells like the goblet cells in the stomach [13]. The principle components of mucus are water and mucins combined with electrolytes, proteins, and lipids [14]. Mucins are composed of carbohydrate (70–80%), protein (12–25%), and up to 5% ester sulfate. The dense carbohydrate portion is responsible for the high water holding capacity and proteolysis resistance of mucin, while the gelatinous characteristics of mucin are owed to the big protein core. Due to the presence of sialic acid and sulfate ions in its composition, mucus carries a negative charge at the physiological pH. Therefore it can form a firmly cohesive gel-like matrix and adheres to the surface of the epithelial cells [15].

According to the mentioned properties of mucus, it is evident that it possesses several barrier characteristics including (a) a steric barrier due to its viscosity and the unstirred water layer; (b) a dynamic barrier because of its continuous secretion and shedding from the surface of the epithelium; and (c) an interactive barrier due to the hydrophobic interactions between the protein core of mucin and the lipid components of mucus with hydrophobic diffusing compounds, hydrogen bond formation between the carbohydrates of mucin and permeates, and since mucus carries the negative charge as explained in the previous paragraph, thus ionic interactions is also possible [16]. The bioadhesiveness of the mucus is a crucial factor behind the effectiveness of the novel mucoadhesive drug delivery system; this property will be later discussed in details.

In addition, the basement membrane acts as a mechanical barrier and may contribute to buccal permeation resistance. Actually, the basement membrane is a fibrous extracellular matrix of tissue that partitions the oral epithelium from the connective tissue, the lamina propria. The main function of this membrane is to anchor down the oral epithelium deeply into the underneath connective tissue. It also prevents cancer cells from invading the deeper tissue and remains limited to the epithelial layer at the early stages of oral malignancy [17]. Normally, it contains glycoproteins, glycosaminoglycans, type IV collagen, and reticular fibers. It was proposed that the electron dense constituents of this membrane, type IV collagen, can limit the penetration of lipophilic compounds through oral mucosa. However it is still believed that the superficial epithelium represents the rate-limiting step to mucosal permeation.

3.4 Pathways of Drug Absorption

The drug permeation across the squamous stratified epithelium of the buccal mucosa involves two major pathways, transcellular (intracellular, permeant travels through the cell) and paracellular (intercellular, permeant travels between the cells), as shown in Fig. 3.1. Since the oral epithelium is stratified, the permeants can utilize both paths to diffuse through the buccal mucosa simultaneously; however the route that provides the less amount of hindrance to permeation becomes the predominant one. The magnitude of compound permeation across these routes is greatly affected

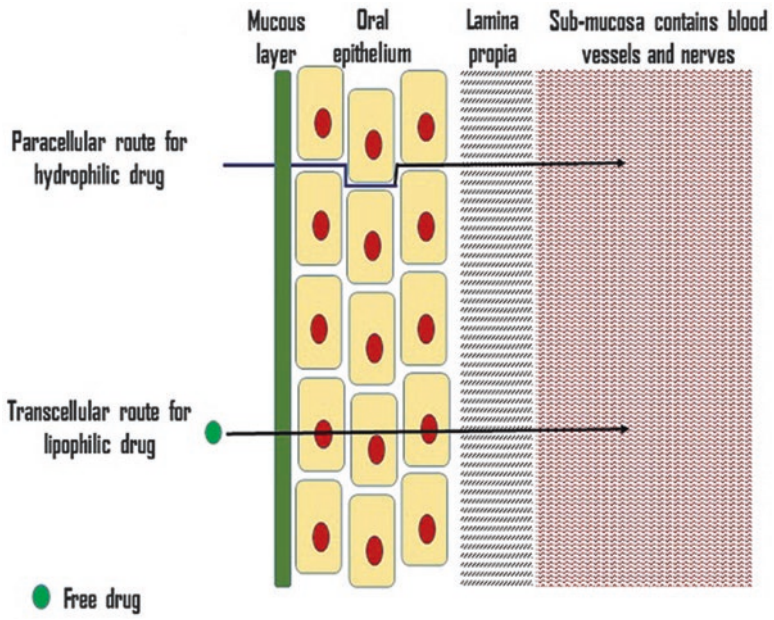

Fig. 3.1 Permeation routes of drug molecule through oral mucosa

by the physicochemical properties of the permeant such as partition coefficient, solubility, and molecular weight of the permeant. Since the intercellular spaces and cell cytoplasm are hydrophilic in nature, thus lipophilic molecules would have low solubilities in this medium. On the other hand, the cell membrane has relatively lipophilic character; thus hydrophilic compounds face difficulty to permeate through the cell membrane due to their low partition coefficient. Therefore, the paracellular spaces can be considered as the rate-limiting step for the permeation of lipophilic compounds, while the lipophilic cell membrane acts as the main barrier for hydrophilic molecules. Furthermore, previous studies suggested that large molecules such as proteins [5] and dextrans [18] permeate buccal mucosa by passive diffusion and mainly through via the intercellular spaces.

The primary transport mechanism of drugs through oral mucosa is passive diffusion of the unionized species through the lipid membrane. Similar to other biological mucosal membranes, buccal mucosa is known to be a lipophilic barrier to the permeation of drug molecules. Most of the drugs are weak acidic or weak basic compounds and can exist as ionized and unionized form; therefore the pH of the medium and drug ionization constant, pKa, play a crucial role in buccal absorption. Since the unionized form of a drug is lipid-soluble, therefore it diffuses easily by dissolution in the mucosal lipid layer. Lipophilic drugs dissolve in the membrane and move along with the concentration gradient through the membrane, i.e., from the medium of high concentration to one of low concentration, and no energy is required. Moreover, in the buccal absorption of large molecules such as peptides and protein factors, cytokine absorption occurs commonly by passive diffusion

transport mechanism. The major pathway is probably via the paracellular route where the principal permeability hindrance is represented by organized array of neutral lipids in the superficial layers of the epithelium [19].

The kinetics of buccal drug absorption can be described by first-order rate process where the rate of drug absorption depends on the initial concentration of the drug. Equation 3.1 represents the differential form of first-order kinetics [20]:

$$\text{Rate} = -d[A]dt = k[A] \tag{3.1}$$

where the "rate" is the absorption rate (in units of molar/time), k is first-order rate constant (in units of 1/time), and $[A]$ is molar drug concentration.

Dearden and Tomlison [21] reported that salivary secretion changes the kinetics of buccal drug absorption from solution dosage form by altering the drug concentration in the dissolution medium of the mouth. Equation 3.2 depicts the relationship between salivary secretion and time [22]:

$$-dm / dt = kC / Vi\,Vt \tag{3.2}$$

where m is the mass of a drug in the mouth at time t, k represents the drug absorption constant, C is drug concentration in the dissolution medium, Vi is the dose volume of the oral solution, and Vt is the volume of salivary secretion.

3.5 Buccal Drug Delivery

Buccal mucosa becomes recently a very attractive site for the administration of various pharmaceutical dosage forms due to the potential benefits offered by this route [23] such as:

- Good accessibility and painless administration.
- Effective route for both local and systemic actions.
- Offers direct drug delivery to the systemic circulation and bypass gastrointestinal tract and hepatic portal system, thereby improving drug bioavailability.
- Buccal drug administration is easy, and therapy termination in emergency cases is possible.
- Relatively immobile buccal mucosa and presence of smooth muscle, hence it is convenient for administration of sustained release dosage forms.
- The buccal lining is strong and can resist environmental extremes like change in temperature and pH. It is characterized by fast cellular healing and recovery after exposure to local stress or damage.
- Buccal mucosa rich with blood supply therefore manifests fast drug absorption and rapid onset of action.
- Advanced buccal formulations can be designed to modify tissue permeability, inhibit local enzyme activity, or reduce the immunogenic response; therefore it becomes an attractive alternative route for delivery of peptides, proteins, and other large molecules unsuitable for the oral route.

However, the buccal route of drug administration manifests many benefits; nevertheless, some problems associated with this route formulation scientist must consider are:

- Buccal mucosa is characterized by low permeability especially when it is compared to the sublingual membrane; thus it permits low drug flux and subsequent low drug absorption.
- Relatively small surface area since the nonkeratinized buccal mucosa available for drug absorption represents almost one third (~50 cm^2) of the total surface area of the oral cavity.
- Drug absorption from buccal dosage forms is highly affected by presence of food and drinks.
- The continuous daily secretion of saliva (0.5–2 L/day) in the mouth results in drug dilution and consequent change of the dose. In addition, the involuntary removal of the dissolved or suspended drug is possible due to swallowing of saliva.
- Over hydration of the mucoadhesive polymers present in the formulation can also potentially lead to formation of a slippery surface and affect the integrity of the formulation.
- Buccal drug delivery is limited only for the administration of drugs which are stable at the buccal pH (6.28 ± 0.36), are nonirritant to the mucous membrane, have pleasant taste and odor, are potent and administered in small doses, and predominately are absorbed by passive diffusion.

3.5.1 Permeation Enhancers

Due to the barrier characteristics of the buccal epithelium permeation, the use of permeation enhancers had been studied extensively to enhance buccal bioavailability. The ideal permeation enhancer has to be nontoxic, nonirritant, rapidly working, pharmacologically inert, reversibly effecting buccal mucosal lining, compatible with the drug and excipients, and of acceptable taste. Permeation enhancers improve buccal absorption via various mechanisms of action including reducing mucus viscosity, increasing fluidity of lipid components in cell membrane, increasing drug partitioning into the buccal mucosa, buccal enzyme inhibition, increasing drug retention at the site of absorption, and interaction with protein domains in buccal epithelium. Several examples on oral mucosal permeation enhancers and their categorization and mechanism of action are described in Table 3.1 [24–28].

Permeation enhancers were investigated for the buccal delivery of drugs over a wide range of physicochemical characteristics and molecular weight including large molecular weight peptides, e.g., interferon, insulin, LHRH, and octreotide; low molecular weight ionizable and neutral drugs; and small molecules such as butyric acid and butanol. Table 3.2 lists some of the drugs for which absorption

Table 3.1 Permeation enhancers and their categorization and mechanism of action

Permeation enhancer	Category	Mechanism of action
Synthetic polymers: Polyacrylic acid, polyethylene oxide, polyvinylpyrrolidone, polyvinyl alcohol, polyhydroxy ethyl methyl acrylate *Natural polymers*: Chitosan, sodium alginate, pectin, xanthan gum, guar gum, gelatin	Mucoadhesive	Increase retention time of drug in contact with mucosa and disruption of intercellular lipid organization
Chitosan-4-thiobutylamide, chitosan-cysteine, poly(acrylic acid)-homocysteine, polycarbophil-cysteine, polycarbophil-cysteine/GSH, chitosan-4-thioethylamide/GSH, chitosan-4-thioglycolic acid	Thiolated mucoadhesive polymers (thiomers)	Reversible opening of the tight junctions and the role of glutathione as permeation mediator
Cationic: lysine and histidine Anionic: glutamic acid and aspartic acid	Amino acids	Ion pairing with proteins and formation of non-covalent complexes that could exploit the amino acid-mediated transport
Chitosan, trimethyl chitosan	Cationic mucoadhesive polymers	Ionic interaction with negative charge on the mucosal surface
Oleic acid, caprylic acid, lauric acid, phosphatidylcholine	Fatty acids	Increase fluidity of phospholipid domains
Sodium glycocholate, sodium deoxycholate, sodium glycodeoxycholate, sodium taurodeoxycholate, sodium taurocholate	Bile salts	Lipid extraction from the mucosa
Ethylenediaminetetraacetic acid (EDTA), sodium salicylate, methoxy salicylates, citric acid	Chelators	Interfere with Ca^{2+} ions
Cyclodextrins	Inclusion complexes	Solubilization of poorly water-soluble drugs and inclusion of membrane compounds
Poloxamer, Brij, Myrj, tweens, spans	Surfactants	Lipid extraction from the mucosa and increasing drug partitioning into the buccal mucosa
Aprotinin, puromycin, bestatin	Enzyme inhibitors	Overcome enzyme activity by changing the conformation of the peptides or proteins and/or rendering the drug less accessible to enzymatic degradation
L-lysine, poly-L-arginine	Cationic compounds	Ionic interaction with negative charge on the mucosal surface

enhancement technologies have been proposed and tested to promote the transbuccal drug delivery from different dosage forms.

3.5.2 Bioadhesive Micro-/Nanoparticles

The application of nano-/microtechnology became very attractive in pharmacy and received significant attention in the last decades. Nano-/microparticulate carriers were applied in a wide range of the pharmaceutical formulations since they can be targeted to various biological tissues and organs by modifying in their physicochemical characteristics, for example, particle size and shape, degree of hydrophobicity, surface properties, and ionic charge. The nanoparticulate delivery systems are usually delivered into the oral cavity as an aqueous dispersion or to be incorporated in various pharmaceutical dosage forms such as gel, cream, paste, aerosol, and foam. These formulations are more likely to be acceptable by the patients than oral tablets due to their smaller particle size and less frequency of administration. For example, atenolol-loaded microspheres were prepared by using poloxamer 407 alone and in combination with Gelucire 50/13 for buccal administration. The microspheres were evaluated in vivo, and atenolol pharmacokinetics were determined and compared to the reference marketed product, oral tablets. The microsphere formulations were found to be successful in controlling atenolol plasma level over a prolong period of time along with higher drug bioavailability than the reference product in spite of using lower dose of atenolol in the microspheres [46].

More interesting, bioadhesive micro-/nanoparticles were also prepared to offer intimate contact of the drug over a large area of the mucous membrane and for long duration, therefore consequently improving drug bioavailability and therapeutic activity. The bioadhesive particulate delivery systems were prepared from mucoadhesive polymers, e.g., chitosan, sodium alginate, Carbopol, poloxamers, and polyacrylic acids. In a previous study, Suh JW et al. produced buccal mucoadhesive nanoparticles comprised of natural bioadhesive polymers dextran sulfate and chitosan by ionic gelation method. The mucoadhesive characteristic of dextran sulfate/chitosan nanoparticles was found five times greater than that of the control, nanoparticles of chitosan alone [47]. In another interesting study, Hazzah et al. evaluated the feasibility of using mucoadhesive sponges loaded of curcumin solid lipid nanoparticles (SLN) for local drug delivery to the oral mucosa. The lyophilized SLN were prepared from Gelucire and poloxamer 407 polymers. Results revealed the considerable interaction between the mucoadhesive polymers and the mucous membrane. Subsequently, long in vivo residence time of the formulation on the buccal mucosa and significant amount of curcumin into saliva were achieved. The bioadhesive sponge provided a promising approach for the delivery of curcumin SLN in form of solid dosage [48].

The bioadhesive nanoparticulate formulations were applied for both local and systemic drug delivery. For local drug delivery, chitosan-silver (CS/Ag) nanocomposites were synthesized in the forms of nanoparticles and as ionic dendritic structures. Both forms were prepared as films to be applied locally inside the oral cavity.

Table 3.2 Examples on drugs investigated for buccal delivery by using permeation enhancers

Drug	Permeation enhancer	Dosage form	Comments	References
(a) *Small-molecule drugs*				
Salbutamol sulfate	Oleic acid (OA)	Buccal patches	Drug's flux with OA is more than eightfold compared to patches without OA	[29]
Didanosine (antivirus nucleoside analogue)	Oleic acid derivatives	Buccal gel	Bicephalous dianionic surfactant showed the highest in vivo buccal enhancement ratio (1.72) compared to the parent OA	[30]
Salicylic acid	Azone	Emulsion	Drug's permeation through azone-pretreated cheek pouch was approximately 2.7 times larger than in the non-treated one	[31]
Barbaloin (C-glucoside of aloe emodin anthrone)	Polyvinylpyrrolidone (bioadhesive polymer)	Buccal films	Barbaloin accumulation into buccal mucosa is tenfold more than the control (aloin solution)	[32]
Prochlorperazine maleate (antiemetic)	Bile salts: sodium glycholate, sodium taurocholate, sodium deoxycholate	Buccal bioadhesive bilayer tablets	Sodium glycholate enhanced drug's permeation by an enhancement factor of 1.37	[33]
Mannitol, caffeine, diazepam	Levulinic acid, propylene glycol, sodium dodecyl sulfate	Solutions	All enhancers increased mannitol permeation but not caffeine or diazepam across porcine buccal mucosa	[34]

(continued)

Table 3.2 (continued)

Drug	Permeation enhancer	Dosage form	Comments	References
Ropinirole hydrochloride (a non-ergot dopamine agonist)	N-trimethyl chitosan (TMC), sulfobutyl ether-β-cyclodextrin, HP-β-cyclodextrin	……	All enhancers tested particularly TMC increased the transport of ropinirole across buccal epithelium	[35]
Fenretinide (a synthetic retinoid derivative)	Propylene glycol (PG), menthol	Mucoadhesive patches	The highest ex vivo permeation of fenretinide was achieved with 2.5 wt % PG + 5 wt % menthol	[36]
Acyclovir (ionized antivirus drug)	HP-β-cyclodextrin, mucoadhesive polymers	Mucoadhesive buccal patch	Acyclovir inclusion complex was able to enhance drug released from the patches	[37]
(b) *Macromolecule drugs*				
Insulin (peptide hormone)	Amino acids: lysine, histidine, glutamic and aspartic acid	……	Possible amino acid-mediated transport of insulin across in vitro buccal cell layers via ion-pairing mechanism	[25]
Salmon calcitonin (sCT, polypeptide hormone)	Sodium deoxyglycocholate (SDGC), ethanol, N-acetyl-L-cysteine	……	The combination of SDGC with electrical assistance showed significant enhancement of sCT delivery through swine buccal tissue	[38]
Alpha interferon and insulin	Lysalbinic acid (a product of the alkaline hydrolysis of egg albumin)	……	Lysalbinic acid increased the mucosal permeability for alpha interferon and insulin through hamster cheek pouch	[39]

(continued)

Table 3.2 (continued)

Drug	Permeation enhancer	Dosage form	Comments	References
Luteinizing hormone-releasing hormone (LHRH), Leu-enkephalin (Leu-Enke), pituitary adenylate cyclase-activating peptide (PACAP)	Glutathione, GSH (aminopeptidase N enzyme inhibitor)	……	In the presence of 2% (m/v) GSH, Leu-Enke, LHRH, and PACAP remained stable after 5 h of incubation	[40]
Leu-enkephalin calcitonin	Chitosan-EDTA conjugate	Bioadhesive gel	The bioadhesive polymer conjugate was able to overcome enzymatic degradation by aminopeptidase N	[41, 42]
Insulin	Poly(L-aspartic acid) and chitosan	Redox-responsive submicron capsules	The capsules were bioadhesive and of good cytocompatibility. Amount released of insulin could be regulated by the levels of GSH	[43]
Thyrotropin-releasing hormone (TRH)	Bioadhesive polymers	Adhesive buccal patches	The combination of polycarbophil AA1 with HPMC or sodium alginate was the most suitable for drug loading and in vitro release of TRH	[44]
Opioid peptide DPDPE	Sodium glycodeoxycholate (NaGDC)	Polyamidoamine dendrimer nanoparticles	Coadministration of NaGDC enhanced the permeability of dendritic nanoparticles by multiple folds through porcine buccal mucosa	[45]

The antimicrobial activity of the resultant formulations was studied against two bacteria: Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. The bactericidal activity of both CS/Ag nanocomposite films increased by increasing the concentration of silver. Nevertheless the antimicrobial activity of chitosan-silver nanoparticles found the double of that of silver ions [49]. Another new approach is the application of nanotechnology in treatment of oral tumors by the development of tumor-targeted nanoparticulate drug delivery systems. The key advantage of these delivery systems over the conventional dosage forms is to reduce the undesirable side effects and enhance therapeutic activity of chemotherapeutic drugs. Nanoparticles tend to target tumor cells with less distribution to normal healthy tissues because of their small particle size which enhance their intracellular permeation and retention impact. For example, solid lipid nanoparticles (SLN) were suggested as a viable strategy for local delivery of unstable poorly water-soluble chemo-preventive drugs in human oral tissues. The drug-loaded nanoparticles could penetrate deeply into the basal layer cells of oral epithelium and also be internalized by the oral squamous cell carcinoma cells to enhance drug penetration into the target cells [50]. Furthermore, doxorubicin is one of the most effective antineoplastic agents in the treatment of squamous cell carcinomas and other oral malignancies. However, the dangerous dose-dependent cardiotoxicity of doxorubicin [51] and other side effects like low blood count, hair loss, nausea, vomiting, and pain resulted in its usage limitation. Abbasi et al. encountered this problem by developing a combined chemotherapy of doxorubicin and methotrexate loaded into nanoparticulate carrier DOX-MTX NP which was given to oral squamous cell carcinoma-induced rats in form of IV and oral dosages. Results showed that both dosage forms of DOX-MTX NP were safe and exhibited potent anticancer therapy, possibly by reducing gene expression responsible for tumor metastasis and invasion. The antitumor activity of the combined nanoparticulate therapy was 12 times more than of the control, free doxorubicin [52]. In the same context, polymeric micelles loaded with cisplatin, cytotoxic agent, were developed and evaluated in oral carcinoma-induced mice. Cisplatin-loaded nanoparticles and the control, free cisplatin both showed equivalent anticancer activity; however the nephrotoxicity side effect was significantly less with the cisplatin nanoparticles [53].

Literatures described the buccal mucosa as a convenient route for the administration of macromolecules (e.g., proteins, peptides, antibodies, or nucleic acids) to achieve rapid drug absorption into the systemic circulation, bypass the GIT conditions, and sustain drug delivery. Various strategies were used historically to improve the bioavailability of macromolecules such as the mucoadhesion, the use of permeation enhancers, and/or enzyme inhibitors. More advanced trends include the development of macromolecule-loaded nanoparticulate systems to further enhance drug targeting and bioavailability. In recent studies, insulin-loaded nanoparticles were prepared and embedded into films produced from mucoadhesive polymers and triad as potential peptide delivery systems [54, 55]. Morales et al. prepared insulin-coated nanoparticles embedded into bioadhesive films for insulin buccal delivery. The films were fabricated from either cationic polymethacrylate derivative ERL alone or in combination with hydroxypropyl methylcellulose. Results showed that ERL

loaded with insulin-coated nanoparticles offered excellent bioadhesive characteristics and high permeation enhancement through human buccal mucosa model comparing to the control and other film formulations [56].

A novel insulin delivery system based on a colloidal liquid formulation was developed in form of aerosol. Oralin® oral insulin spray (Generex Biotechnology Corp., Toronto, Canada) was developed in the form of micellar preparation applying a mixture of surfactants as formulation stabilizers and permeation enhancers. A metered-dose inhaler is used to deliver a precise dose of insulin in form of fine aerosolized droplets directly to the site of absorption inside the oral cavity. This technique is simple and painless and was found to be effective for rapid oral absorption of insulin and postprandial glucose level control and more compliant to diabetic patients in comparison to the SC insulin injection [57]. This system had also been utilized to develop products for pain management, vaccination, and weight loss for intraoral administration [58]. In another study, gelatin/PEG mucoadhesive film enriched with polyamidoamine (PAMAM) dendrimer nanoparticles was developed and evaluated as a targeting drug carrier to the central nervous system (CNS). The nanoparticles were loaded with opioid peptide drug and grafted with either PEG alone or a combination of transferrin receptor monoclonal antibody OX26 and PEG. Sodium glycodeoxycholate, bile salt, was incorporated as permeation enhancer, and drug permeation was studied through porcine buccal mucosa. Their results revealed that significant enhancement of the peptide permeation was obtained from the grafted dendritic nanoparticles as well as from the coadministration of the bile salt indicating that buccal transmucosal delivery is a candidate route for administration of therapeutic nanoparticles targeted to CNS [45]. Morsi et al. proposed a new flushing resistant platform for sublingual drug delivery comprised of drug-phospholipid complex in mucoadhesive polymers. The first step in the platform production was the preparation of the nano-sized solid particles of mosapride citrate-phospholipids (phosphatidylcholine or phosphatidylinositol/soybean lecithin) complex. The second step was the lyophilization of the prepared complex with the mucoadhesive polymers, sodium carboxymethylcellulose and sodium alginates at different molar ratios. They found that the optimized sublingual platform significantly improved the bioavailability of mosapride citrate in human comparing to the market fast dissolving sublingual tablets. The extended sublingual drug release profile and flushing resistance time were mainly controlled by the polymer concentration [59].

Liposomes were studied as one of the advanced approaches for enhancement of intraoral mucosal delivery of peptide and protein therapeutics [60]. Later a novel drug carrier of highly deformable structure known as transfersomes was found more effective than liposomes in enhancement of insulin buccal absorption. Therefore, transfersomes were considered as better carrier than the conventional vesicles, liposomes for intraoral delivery of protein drugs [61]. Liposomes were found to be alternative carrier for poorly soluble drugs, since solid dosage forms do not efficiently deliver these drugs via buccal mucosa. For example, silymarin is a natural pharmacological agent, used in the prevention and treatment of hepatic diseases. It is a very lipophilic drug; thus it exhibits low oral bioavailability. Silymarin

liposomes showed controlled permeation profile across chicken cheek pouch for 6 h; therefore they were capable to improve the buccal absorption of silymarin [62]. Till now research still continue in the same field by employing liposomes to increase the intraoral (buccal and sublingual) bioavailability and therapeutic activity of various drugs such as antibiotics [63], anticancer therapy [64, 65], immunotherapy allergens [66], and vaccines [67].

3.5.3 Films and Patches

Film/patch technology is one of the innovative dosage forms for intraoral drug delivery. This technology has emerged as an alternative to the conventional types of dosage forms to enhance drug efficacy, safety, and patient compliance. Practically, buccal mucosa is the most convenient region in the oral cavity for the administration of films due to its physiological characteristics, as discussed previously. Films provide several merits for the buccal administration: (1) they are thin and flexible and hence can be adjusted easily to the oral mucosa; (2) they can be applied for local and systemic effect; (3) films can remain in place for optimal duration of absorption due to their bioadhesiveness; (4) their manufacturing process is reproducible and practical; and (5) films offer advantages in delivering a precise measured dose of the medication to the site of application compared to semisolids such as creams and ointments.

Furthermore, the construction of multilayer buccal film is also possible in which two or more drugs could be included into one system and the layers may be designed to have the same or various rate of dissolution. Films can be designed as immediate drug release formulations or as sustained release films depending upon the combination of the film-forming polymers and film characteristics such as film thickness.

The primary disadvantage of the buccal film is the relatively low dose of the active pharmaceutical ingredient (API) that can be incorporated within the film matrix. However, recent research in the development of the production techniques were conducted and could solve this problem [68, 69]. Generally, buccal films are produced by several techniques including solvent casting, hot-melt extrusion, and inkjet printing.

(i) *Solvent casting technique*

In this technique, the API is either dissolved or dispersed in the polymer solution. Plasticizers and other excipients are also dissolved in the polymer solution to form a mixture which is known as a film dope. The film dope is spread over a rolled release media, using the classical solvent casting technique. The release medium like plastic-impregnated paper acts as backing or support layer to the dope. The coated release media is then passed through a drying oven or chamber to evaporate the volatile solvent such as ethanol or water. After the solvent drives off, a thin layer of the dried film is formed over the media that is later cut into strips, sealed, and

packaged in atmospherically resistant pouches. Solvent casting technique is more suitable for heat-sensitive drugs since relatively lower temperature for film dying is required, comparing to the hot-melt extrusion process. However, the main limitations in this technique are the following: (i) special manufacturing equipment and safety measures are required if any of the solvents used is flammable, and (ii) trace amount of the residual solvent(s) may remain in the dried film which is not compliant with the pharmacopoeial standards [70].

Many studies explored solvent casting technique to prepare buccal films for local effect and systemic absorption because it is easy, fast, and economical technique and can be even applied for lab-scale production [71].

(ii) *Hot-melt extrusion technique*

Hot-melt extrusion has been recently explored as an alternative manufacturing technique and produced promising results where an extruder machine to produce films is needed [72]. A solid mixture of the active pharmaceutical ingredients and other excipients is heated and homogenized with the molten polymer by the action extruder screw. The molten mixture is then forced through a flat extrusion die and pressed into a desired film shape. The hot film is further passing over elongation rollers to adjust its strength and thickness. The film is then dried, cut, and packaged. This process has many advantages over other traditional techniques such as the following: lower temperature for polymer heating is required, absence of organic solvents, optimized operating conditions, minimum product loss, drug content uniformity, and possibility of yield scale-up. The polymer can act as a drug reservoir and control its release over a sustained period of time. In addition to that, dispersion or solubilization of the drug in the melted polymer significantly improved drug dissolution and bioavailability from buccal films prepared by this technique. Nevertheless, this technique is still believed to be unsuitable for the production of films containing volatile substances and heat-sensitive biological drugs such as proteins, peptides, nisin, and lysozyme [73].

(iii) *Inkjet printing technique*

Another promising strategy for the production of oral films is inkjet printing method. Drug-loaded ink is delivered from the printer cartridge in form of droplets over a flat surface of a substrate. The dose of the drug is controlled by the printed area of the substrate, and flexible drug doses in a single unit can be produced by printing several consequent layers over the already printed ones, using thermal inkjet printer [73]. Furthermore, personalized dosage forms to patients can be provided by the printing concept. Various printing substrates, namely, porous copy paper sheets, water impermeable transparency films, and orodispersible films, were evaluated for the preparation of inkjet-printed drug delivery systems. Drug crystallization did not occur with the copy papers like other substrates due to complete penetration of the ink into the matrix of the substrate. However, edible substrates that possess the same absorption characteristics of the copy papers are more favorable for the

production of buccal films by inkjet printing method due to safety and biocompatibility issues [68]. Thermal inkjet printing system was proved as a reliable process for buccal administration of proteins since it is an economical, simple, and reproducible method and can effectively enhance protein absorption without affecting their structure and biological activity [74]. Future studies are going on to develop new printing materials that are able to stabilize and control the release of protein and peptide drugs.

In recent years, extensive research have been conducted in the field of development of mucoadhesive buccal films. Polymers with different characteristics were used for the preparation of the mucoadhesive films. Broadly, mucoadhesive polymers can be categorized into three main groups including (i) nonionic polymers, e.g., cellulose derivatives, Eudragit analogues, polyvinyl alcohol, and polyethylene oxide; (ii) anionic polymers, e.g., sodium alginate, Carbopol, polyacrylates, and sodium carboxymethylcellulose; and (iii) cationic polymers, e.g., chitosan. Mucoadhesive buccal films are comprised of the API (5–30% w/w), mucoadhesive polymer (45% w/w), plasticizers (0–20% w/w), saliva-stimulating agents (2–6% w/w), sweetening agent (3–6% w/w), and sufficient quantity of penetration enhancers, colors, and flavoring agents [75].

3.5.4 Buccal Tablets

Tablet dosage form has been widely studied for buccal drug delivery since they exhibit high level of patient acceptability, good stability, and relatively low cost. Tablets are also convenient for self-administration, can be easily produced, and can be used for accurate unit dosing. However, possible obstacles that patients may experience by the administration of buccal tablets such as potential discomfort due to the unpleasant taste and local irritation. Swallowing of the tablets and separation of the tablets from the buccal mucosa into the saliva are also possible. Certainly there is a big difference between orally disintegrating tablets (ODTs) and buccal tablets since the latter deliver the drug for buccal transmucosal absorption, while ODTs rapidly disintegrate and release the drug into the oral cavity to be absorbed later from other parts of the GIT.

From the technological opinion, ideal buccal tablets need to have three properties: (i) should stay in the mouth at the same position for enough time; (ii) sustain the drug release an extended period; and (iii) deliver the drug into the buccal mucosa rather than into the saliva. Several buccoadhesive tablets have been prepared by direct compression technique either for systemic or local drug effect [76, 77]. Two systems of tablets, namely, monolithic tablets and bilayer tablets, were used for buccal drug delivery. Their formulations were designed to release the drug into two different patterns: either directly toward the buccal mucosa (unidirectionally drug release) or into the oral cavity (multidirectionally drug release) [78]. The unidirectional drug release is usually achieved by including an impermeable backing layer to the tablet components to ensure that the drug is directed to the buccal mucosa. Monolithic tablets are prepared by the incorporation of the API and the excipients

into the tablet matrix. The swelling matrix consists of one or combination of the bioadhesive polymers (e.g., Carbopol, polycarbophil, and polyacrylic acid). A second impermeable layer is probably included into the formula in case unidirectional drug delivery is desired.

Bilayer tablet technology was also proposed for buccal drug delivery. This novel dosage form is composed of two layers of granulation compressed together in a single dosage form. In general, the bilayer design of tablets can be applied to achieve consecutive release of two or more drugs in combination and to separate between incompatible materials in the same dosage form. This will also beneficial to control the drug release over a prolonged time by loading one layer of the tablet with an initial dose for immediate drug release and the second layer with a maintenance dose for the continuous drug release. However, various problems are associated with the manufacturing process of bilayer tablets such as inadequate tablet hardness, separation of the tablet layers, and difficulty in weight control and low yield. Several techniques are available nowadays in the market for the production of bilayer tablets including OROS® push pull technology; L-OROS® technology; EN SO TROL® technology (Shire laboratory); Duros® technology; and DUREDAS® technology (Dual Release Drug Absorption System by Elan Corporation). Buccal bilayer tablets are designed in a specific manner in which the inner layer is formed of a bioadhesive matrix and the outer layer contains the drug for a bi-directional release profile to exhibit local effect. On the other hand, for systemic effect, the drug is incorporated into the inner bioadhesive layer, and the outer layer is drug-free and acts as a protective layer so that the rate of drug release is mainly controlled by the bioadhesive layer [79].

Historically speaking, prochlorperazine buccal sustained tablets (Buccastem®) were produced by Reckitt and Colman and marketed in Europe and other countries like Japan for the treatment of nausea and vomiting with migraines in adults aged 18 years and over. Later prochlorperazine buccal tablets (Emezine®) were introduced in the USA by BioDelivery Sciences International (BDSI). However, in March 2006 the FDA sent a non-approval letter to BDSI for the application of the new drug Emezine [80]. The FDA decision was due to the slower absorption in the first 1–2 h and higher C_{max} values of prochlorperazine from the Emezine buccal tablets comparing to the oral tablets. The difference in the drug pharmacokinetics between Emezine tablets and the reference product caused the FDA to be concerned about the drug's effect on older patients, and, therefore, the FDA had requested a study in this group of patients. In addition, Loramyc® bioadhesive buccal tablets (by BioAlliance Pharma SA) containing miconazole 50 mg were approved in October 2006 for the local treatment of oropharyngeal fungal infections due to *Candida* in patients with reduced immune system, particularly those who have undergone anticancer chemotherapy and radiotherapy and those infected with HIV. This medicine is authorized in the member states of the EEA (France, Germany, Italy, and the UK). Loramyc tablet is to be applied on the buccal mucosa once daily in the morning and preferably after brushing without swallowing or chewing [81]. Acyclovir Lauriad(®) is a new buccal tablets that was approved by the USFDA in 2013 for the treatment of recurrent herpes infections. This new product can deliver high concentration of acyclovir directly to the site of the viral infection, and data from the clinical trials

proved its therapeutic efficacy for the treatment of patients with recurrent herpes labialis [82].

3.5.5 Iontophoretic Drug Delivery

Iontophoresis is a noninvasive and safe technique that was employed to enhance drug delivery by the application of a voltage gradient on cell membrane. It was found efficient to increase the penetration of both charged and neutral drugs across the membrane. Although the absorption of large molecules such as proteins, peptides, and hormones by this procedure has demonstrated to be effective, hydrophilic drugs with relatively low molecular mass are still the candidates for iontophoresis. Three mechanisms are included in iontophoresis, namely, electroosmosis (electroosmotic solvent flow), electrophoresis (direct field effect), and electropermeabilization (electroporation) [83]. In electroosmosis, molecules are transported along the bulk solvent flow that is created by the electrical currency across the membrane. This method was applied to enhance the penetration of both ionic and nonionic drug molecules. The second method is electrophoresis where a direct electrical current is applied so the negatively charged ions are repelled from the cathode and attracted to anode and positively charged ions from the anode to cathode. Thus ionic drugs are the potential candidates for electrophoresis rather than neutral drugs. While in the last technique, electropermeabilization, the mechanism of working differs from the former methods, it can increase the membrane permeability by altering the intrinsic properties of the permeation routes (e.g., membrane pore size and charge) of the cell membrane [84].

Iontophoresis generally had been approved as a safe and efficient drug delivery system by the US Food and Drug Administration (FDA) for many drugs through transdermal and ocular routes of administration. As example, sumatriptan iontophoretic transdermal patch (Zecuity® by NuPathe; Teva Pharmaceutical Industries) was approved by the FDA in January 2013 for the treatment of migraine headache [85]; fentanyl iontophoretic transdermal system (Ionsys® 40 micrograms per dose, by Medicines Co. Parsippany, NJ, USA) was approved in 2015 for the management of acute postoperative pain in patients requiring opioid analgesia [86]. In addition, a novel ocular iontophoresis devise, the EyeGate® II system (EyeGate Pharmaceuticals, Inc., Waltham, MA), was utilized to deliver drugs directly into the targeted ocular tissue [87]. Iontophoresis was also used as a reliable laboratory diagnostic tool such as a reverse iontophoresis for glucose monitoring [88] and pilocarpine iontophoresis neonatal sweat analysis device (Nanoduct®, ELITechGroup, Italy) for the diagnosis of cystic fibrosis [89].

Recently, intraoral iontophoresis drug delivery was extensively investigated in human and animal studies for local and systemic effects on the oral mucosa as well as for dental care purposes on enamel and dentin tissues. The physiological conditions of the intraoral mucosa including blood supply, the barrier properties, and pH of the environment are the main reason behind making this area attractive for iontophoretic drug administration. Electrophoresis and electroosmosis were the main

two mechanisms that were used for buccal iontophoresis. Studies had reported that iontophoretic devices enhanced drug flux significantly via buccal mucosa and other intraoral tissues, but still there is inadequate knowledge of the mechanisms of drug transport. The application of the electrical field generally found to be more efficient in buccal drug transport comparing to the passive diffusion for different drugs.

Buccal electrophoresis was basically employed as alternative way for the systemic drug administration particularly (i) drugs that extensively undergo first-pass metabolism, e.g., atenolol [90] and diltiazem [91]; (ii) drugs irritant to the gastric mucosa, e.g., sodium salicylate and naproxen [92]; and (iii) drugs of low oral bioavailability such as salmon calcitonin [38]. Solutions and hydrogels were the common formulations used in these studies. Further in vivo trials were also performed by combining the effect of the chemical penetration enhancers with iontophoresis to improve buccal absorption of medications such as ondansetron [93], sumatriptan succinate, lidocaine, diltiazem, and nicotine [91].

Wei et al. examined the effect of the enhancer pretreatment prior to iontophoresis administration on the buccal absorption of nicotine and lidocaine and found enhancer pretreatment improved iontophoresis significantly [94]. The results from these studies confirmed the feasibility and safety of oral iontophoresis for the enhancement of drug bioavailability and therapeutic effect. Some electrophoretic devices are currently being tested in clinical trials, e.g., IntelliDrug® which is a novel device capable of delivering drugs continuously and directly to the blood circulation. The device is fitted to a molar tooth and releases the drug to the buccal mucosa over a prolonged duration of time. The built-in software and electronics enable the communications for patient monitoring and dose control via a wireless remote.

The hard palate and sublingual were less interesting for intraoral iontophoresis due to the limited space and difficulty in placing the bulky iontophoretic device; therefore limited studies were found. Ren et al. investigated the iontophoretic transport of chlorhexidine, fluoride, dexamethasone, and salicylate across the palate mucosa. It was found that electroosmosis is the dominant iontophoretic method of both ionic and nonionic species of permeates, while the direct field effect was more convenient for ionic compounds. In addition, the rate-limiting step for iontophoretic transport through the palate was found to be the cornified epithelium [95].

In dentistry, iontophoresis was mainly used on enamel and dentin to treat tooth decalcification and hypersensitivity and to produce local anesthesia. Fluoride and lidocaine were the most common drugs used in oral iontophoresis procedure. The potential application of the device for remineralization of early caries lesions was also investigated [96]. In addition, iontophoresis was found to be effective drug delivery through the intact and caries-affected dentin of naproxen, salicylate, and metronidazole [92]. Low-voltage operating iontophoretic toothbrush is currently available in the market (e.g., HyG-2, Dyna-Dental Systems). It provides effective teeth cleaning due to the ionic repulsion of negatively charged bacteria on the tooth surface; however the efficacy of the ionic brush is brushing time-dependent device [97].

In conclusion iontophoresis is an advanced approach of intraoral drug delivery system alternative to conventional dosage forms in local treatment of periodontal diseases such as gingivitis and periodontitis and for tooth decalcification and hypersensitivity. The iontophoretic device also succeeds in drug delivery to the circulation for systemic treatment. The limited space of the oral cavity is the main drawback of the bulk iontophoretic device. Furthermore, oral cavity is the place for the frequent normal functions as eating, drinking, and talking; therefore it is more suitable for short-term iontophoresis application rather than long-term treatment.

3.6 Other Intraoral Drug Delivery Systems for Intraoral Application

Most common approaches used in intraoral drug delivery are fast dissolving drug delivery systems which include tablets and films, solid intraoral delivery systems which include medicated chewing gums, and other medicated confectionaries.

3.6.1 Fast Dissolving Drug Delivery Systems (FDDDs)

The oral cavity (intraoral route) is known to be the most popular site of drug delivery as well as one of the most favored routes of administration due to its safety, convenience, low economic burden, ease of administration, as well as increased patient compliance when compared to other routes of administration such as IM, SC, rectal, etc. [98]. FDDDs were developed as an alternative to conventional tablet, capsule, and syrups and increasingly becoming popular and rapidly gaining interest in pharmaceutical industry. Furthermore, the pharmaceutical industry favors the formulation of orally administered tablets, due to the relative ease of production [99]. As the name suggests, FDDDs dissolve or disintegrate within 60 s, without needing water or chewing and hence offer enhanced patient convenience and compliance especially in pediatrics and geriatric patients, who have difficulty in swallowing tablets or liquids. Therapeutic categories that have greatest potential for market success with FDDDs include migraine, nausea, sleeping aids, gastroesophageal reflux disease (GERD), pain, schizophrenia, and other CNS diseases, Parkinson's disease. FDDDs/MDT/ODT key advantage over other format of dosage forms is its enhanced patient compliance. These dosage forms are highly recommended for the patients who have trouble in swallowing the pills/tablets/capsules.

FDDD administration may give a faster onset of action; also it can circumvent the problem of swallowing which is specially seen in dysphagia patients, also in pediatric as well. Table 3.3 highlights important characteristics of intraoral dosage forms. Common excipients used in these dosage forms are provided in Table 3.4.

Table 3.3 Characteristics of intraoral dosage forms

	Mouth dissolving/dispersible tablets	Mouth dissolving films/wafers	Medicated lozenges/ lollipops/pastilles	Medicated chewing gums
Description	Tablets designed to disintegrate and dissolve rapidly in the saliva within 15 s–3 min	Water-soluble polymer matrices with or without a plasticizer	Lozenges are flavored medicated dosage forms with sweetened base intended to be sucked and held in the mouth	API contained in masticatory gum base
Typical composition	Drug, superdisintegrants, diluents, and lubricant optional excipients may include swelling agents, cryoprotectants, permeability agent, sweeting, and flavoring agents	Drug, hydrophilic low molecular weight polymers, plasticizers, and coloring, sweeting, and flavoring agents	Drug, candy base (sugars and/or sugar-free vehicles); fillers; binders; lubricants; flavoring, coloring, and whipping agents; humectants	Drug; gum base; plasticizers; bulking; coloring, sweeting, and flavoring agents; opacifiers; antioxidants
Manufacturing technologies	Freeze-drying, molding, spray-drying, sublimation, wet and dry granulation, direct compression, melt granulation, mass extrusion, cotton candy process	Solvent casting method, hot-melt extrusion, semisolid casting method, rolling method. Wafers are made by freeze-drying	By heating a candy making admixture of corn syrup, sucrose syrup, compression	Conventional/traditional method (melting); freezing, grinding, and tableting; direct compression method. Direct compression
Common quality control parameters	Weight variation, content uniformity, friability, hardness, disintegration time, dissolution test, wetting time, water absorption	Weight variation, content uniformity, folding endurance, tensile strength, surface pH, texture analysis, disintegration time, dissolution test	Moisture analysis, determination of sugar and corn syrup ratios, percentage of reducing sugars, hardness and friability, in vitro drug release, microbial check	Weight variation, content uniformity, texture analysis, in vitro drug release
Packaging	Single pouch, blister card with multiple units, multiple unit dispenser	Single or multiple pouch with barrier films, rapid card™	Paper or plastic wraps, blister pack, glass and plastic containers	Airtight containers, strips, wraps, aluminum foil

(continued)

Table 3.3 (continued)

	Mouth dissolving/dispersible tablets	Mouth dissolving films/wafers	Medicated lozenges/ lollipops/pastilles	Medicated chewing gums
Examples of marketed products	Examples of marketed products	Feldene Fast Melt, Claritin RediTab, Maxalt MLT, Zyprexa, Pepcid RPD, Zofran ODT, Zomig ZMT, Zeplar TM, Tempra Quicklets, Febrectol, Benadryl Fastmelt, Propulsid Quicksolv, Nurofen FlashTab, Zomig Rapimelt, Cibalgina DueFast, Ralivia Flash Dose, Allegra ODT, Aricept ODT	MDF: Klonopin Wafers, Listerine Cool, Sudafed PE, Suppress®, Orajel, Theraflu, Gas-x Wafers: Triaminic, Theraflu, Gas-x, Sudafed, Benadryl, Chloraseptic, Listerine	Aspergum, Nicorette, Nicotinell, Travell, Go-Gum, Chooz, Endekay Vit C, Brain, Stay Alert, Stamil Vit C, Café Coffee, Buzz Gum, Chroma Slim

Table 3.4 Excipients used in intraoral dosage forms

Category	Function	Examples
Diluent/fillers	Provide bulkiness	Mannitol, dicalcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose, sorbitol, xylitol, calcium carbonate, magnesium carbonate, pregelatinized starch, magnesium trisilicate, aluminum hydroxide
Superdisintegrants (MDT)	Provide lesser disintegrating time	Croscarmellose sodium, crospovidone, sodium starch glycolate, calcium silicate (wicking agent), microcrystalline cellulose, pregelatinized starch
Gas-forming agents (MDT)	Aid in disintegration	Citric acid, tartaric acid, sodium bicarbonate
Flavoring agent	Improves palatability, patient appeal	Menthol, cherry menthol, cinnamint, spearmint, peppermint, orange flavor, natural, vanilla, cocoa, coffee, chocolate, fruit flavors including citrus, raspberry, strawberry, pineapple, cherry, apple, tangerine, etc.
Coloring agent	Improves appearance	FD&C colors, natural colors
Water-soluble lubricants (MDT)	Lower friction between tablet and die wall during ejection	Polyethylene glycol (PEG 4000 and PEG 6000), boric acid (1%), DL-leucine (3–10%), sodium benzoate (5%), sodium acetate (5%), sodium lauryl sulfate (1–5%), magnesium lauryl sulfate
Water-insoluble lubricants	Help to avoid sticking of candy to the teeth while chewing	Metallic stearates (0.25–1%) (magnesium and calcium stearate), Hydrogenated Cottonseed Oil (Sterotex®), vegetable oils and fats, waxes, Sterowet (mixture of calcium stearate and sodium lauryl sulfate), glyceryl behapate, liquid paraffin
Binder (MDT)	Provides binding to the tablet mass	PEG-6-stearate, PEG 1000, gelatin
Glidant (MDT)	Improves flowability of powder blend	Colloidal silica, pyrogenic or fumed silica, sodium stearyl fumarate, hydrated sodium silicoaluminate, corn starch
Film-forming polymers (MDF)	Film formers to achieve rapid disintegration and good mouth feel and provide good mechanical strength to the film	Lycoat NG73 (granular hydroxypropyl starch), HPMC, hydroxypropyl cellulose, hydroxyethyl cellulose, methylcellulose, sodium alginate, gelatin, pectin, Eudragit RD-10, polymerized rosin, xanthan gum, gum arabic, tragacanth, acacia, carrageenan, guar gum, locust bean gum, alginates, polysaccharides (polydextrose, dextrin, and dextran), pullulan, starch gelatin, malt dextrin, amylose. On the other hand, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, carboxymethylcellulose, polyethylene oxide, Kollicoat, hydroxypropyl cellulose, hydroxyethyl cellulose

(continued)

Table 3.4 (continued)

Category	Function	Examples
Plasticizers (MDF)	Provide mechanical strength and improve flexibility of films	Glycerol; propylene glycol; low molecular weight polyethylene glycols; phthalate derivatives like dimethyl, diethyl, and dibutyl phthalate; citrate derivatives (tributyl, triethyl, acetyl citrate, triacetin); castor oil
Humectants	Improve chew and mouth feel properties	Glycerin, propylene glycol, and sorbitol
Antiadherants	Avoid sticking of dosage form to the punches	Talc, corn starch
Surfactants/ surface-active agents	Help in faster dissolution/ disintegration	Sodium lauryl sulfate, benzalkonium chloride, benzethonium chloride, tweens, spans
Elastomers and elastomer solvents (MCGs)	Gum base	Complex mixture of elastomers either natural or synthetic such as polyisobutylene or styrene-butadiene, natural and synthetic resins such as polyvinyl acetate
Candy base (MCs)	Provides body to the lozenges and lollipops	Sugars, sugar alcohols (polyols), sugar such as dextrose and sucrose, sugar-free vehicles such as mannitol, sorbitol, and polyethylene glycol (PEG) 6000 and 8000. Directly compressible sugar-based vehicles such as Emdex, Nu Tab, SweeT.Rex, Mola Tab, Honey Tab, Sugartab
Whipping agents	Incorporate air to obtain the desired degree of soft chew	Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin, and carrageenan
Saliva-stimulating agents	Generally acidic in nature, stimulating production of saliva in oral cavity, used in MDFs/wafers	Citric acid, malic acid, tartaric acid, ascorbic acid, and lactic acid

3.6.1.1 Formulation Considerations

The first FDDDs were orally disintegrating tablets, which is commonly known as ODTs, FDTs, MDTs, orally disintegrating tablets, orodispersible tablets, fast dissolving tablets, mouth without the need of drinking water, or chewing. They disintegrate and dissolve rapidly in mouth within a few seconds; FDT usually dissolves in the saliva within 15 s–3 min, generally less than 1 min. After the launch of first ODT based on Zydis, door to new intellectual property in form of new technologies has emerged, which gives significant marketing benefits to pharmaceutical companies.

Selection of Drug Candidates

Despite its increased patient compliance, presence of hydrophobic moieties and sometimes an increased amount of dose provide a tough challenge and limiting factor for FDDDs, because with such a large dose and active nature, it's very challenging to meet the quality target profile of FDDDs. Also, drugs required for sustained action, drugs with highly disagreeable taste, and drugs with very short half-life and require frequent dosing are not suitable candidates for FDDDs. The future of FDDDs thus require much more formulation strategies that lie in consideration of incorporating large doses and at the same time meeting the quality target profile that can eventually make the ODT suitable for a conventional packaging.

Palatability

Taste masking is an important factor while developing FDDDs, as this remains the prime acceptability criteria for healthcare providers. Unacceptable taste of a drug is one of the major challenges while formulating FDDDs as many drugs poses this problem. Nowadays, many efficient technologies are present in the market for effective taste masking of bitter APIs; however every taste masking technology does not fit every API, so it really depends on the API's physicochemical characteristics, indented action, and desired dosage forms. Taste masking technologies vary from use of flavors and sweeteners to much more advanced technologies like sol gel, lyophilization, etc. Formulation scientists have mask the bitter taste of the drugs by using different approaches like granulation (thus reducing surface area), suitable taste masking agents, or encapsulating the drug in polymer system or through complexation, thus preventing the direct exposure of drug to the tongue. Details of different taste masking approaches are well reported in the literature [100–107].

Moisture Uptake

Also, ODTs' key physical attribute is moisture absorption. This is how ODTs disintegrate in oral cavity; they tend to absorb saliva/moisture present in the external environment and got swelled and easily disintegrate and hence release APIs. Majority of the ODTs were formulated by cellulose-based excipients or functionalized excipients which are soluble in water or can absorb enormous amount of water. Protection of ODTs from external environment is a forthcoming challenge and on which major pharmaceutical giants are working on. Not only the rationale thinking and selection of excipients for the design of ODTs are important, but primary packaging also contributes to its shelf life. Hygroscopicity is another issue rendered by many FDTs as they are made from water-soluble excipients, and as a result their physical integrity is difficult to maintain.

Mechanical Strength

First-generation ODTs are extremely porous, soft, and especially sensitive to moisture, making them brittle and difficult to handle. Only FDTs produced with Wow Tab and DuraSolv technologies are sufficiently hard and durable which allow them to be packaged in multidose bottles.

3.6.1.2 Approaches to ODT Development

In order to allow rapid disintegration of the ODT, generally they are manufactured as highly porous matrix tablet. This is usually achieved by the use of superdisintegrants or highly water-soluble excipients in the tablets. Different intellectual properties in the field of ODTs include ZYDIS®, LYOC®, QUICKSOLV® involving freeze-drying approach, ORASOLV®, DURASOLV® EFVDAS®, FLASHTAB® involving alterations to conventional tableting, and FLASHDOSE® using floss formation [108, 109] are available. Common methods of manufacturing are discussed here.

Direct Compression

Direct compression method is the most preferable method in ODT development as it has high-dose incorporating capacity and involves less number of processing steps and disintegration time can be controlled by type and concentration of disintegrants, water-soluble excipients, effervescent agents, and volatile agents. Other ingredients commonly used are lubricants, antistatic agents, plasticizers, binders, colors, and flavors (Table 3.4).

The low porosity of compressed tablets even after using highly water-soluble ingredients results into slower dissolution. Therefore, the use of superdisintegrants is the basic approach in development of FDTs. A less common approach to improve porosity of compressed tablets is by using volatile inert solid ingredients like urea, camphor, and hexamethylenetetramine or volatile solvents such as cyclohexane and benzene that will evaporate leaving the porous matrix behind [110].

Spray-Drying

Spray-drying of drug with other hydrophilic excipients generally produces highly porous, fine, free-flowing solid dispersions with improved dissolution properties. Tablets compressed from the spray-dried powder disintegrates very fast when immersed in an aqueous medium.

Molding

Molding is an another method to prepare ODTs in which a hydroalcoholic solvent is molded into tablets under lower compression pressure. The solvent is then removed by air-drying. This process produces porous structure that enhances dissolution [63].

Freeze-Drying

Lyophilization or freeze-drying is commonly applied for both MDTs and MDFs as lyophilized products are having very high surface area due to their high porosity that imparts faster water intake and rapid dissolution. However, hydrophilic drugs may form eutectic mixtures with the polymers that lower the freezing point depression (eutectic temperature), which leads to collapse or shrinkage of dosage form after drying. Therefore, complete lyophilization cycle for MDT/MDF containing water-soluble drug should be performed below the eutectic temperature of the formulation mixture [111].

3.6.1.3 Oral Films and Wafers

Oral films can be designed as fast release or sustained release and also as mucoadhesive patch depending on their disintegration time and design. Usually, fast dissolving films are usually placed onto the tongue, while mucoadhesive patch is placed onto the cheeks. This section focuses on oral soluble films/orodispersible films only, and details on mucoadhesive and sustained release films are provided in Sect. 3.5.3.

Fast dissolving films, also called mouth dissolving films (MDFs), are new, innovative DDS for the fast delivery of medication via the oral cavity. These systems were formulated based on the transdermal patch technology as it consists of an oral strip that is very thin thickness positioned on the patient's oral mucosal tissue or tongue.

MDFs are water-soluble polymer matrices with or without a plasticizer. As this film gets hydrated by the oral wet saliva, it gets adhered on the site of application followed by rapid disintegration leading to the dissolved medication to be release for faster oromucosal absorption [112]. These films are produced by many different film formers such as PVP, chitosan, hydroxypropyl cellulose (HPC), methylcellulose (MC), maltodextrin, polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (Na CMC), and some natural gums. A typical film thickness ranges from 12 to 100 μm [113]. Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. Unlike MDTs, MDFs are flexible but still robust to mechanical forces [114].

Manufacturing techniques for ODFs include solvent casting method, semisolid casting method, hot-melt extrusion method, rolling method, solid dispersion extrusion, and printing technologies such as inkjet printing and flexographic printing technology. Various production technologies are patented and used nowadays for wafer production. ODFs produced by lyophilization, generally called freeze-dried wafers, are porous sponge-like matrix that further facilitates the imbuement of saliva into their structure and provide faster disintegration [115] such as SOLULEAVES™, WAFERTAB™, FOAMBURST™, Micap, and XGEL™. Common methods for manufacturing ODFs are based on the technology for producing transdermal patches, which is less expensive than lyophilization [116]. However, packaging will be an issue for such systems as in case of ODTs.

Products based on ODF/wafers are, though approved by the USFDA, EU, not yet official in the pharmacopoeias; typical evaluation tests, besides content, content uniformity and impurity profile, and disintegration or dissolution properties, include mechanical profiling, microbial evaluation, surface pH, texture analysis, in vivo disintegration test, taste evaluation, etc. The detailed information is available in published literature [117].

3.6.2 Medicated Chewing Gums

By formulating the drugs in a MCG composition, revitalization of old products and reformulation of new patented products are possible to distinguish them from future

generic competition in the market. However, traditional method of chewing gum manufacturing involves softening of gum components with the aid of heat and mix with other ingredients such as sweeteners, syrups, active ingredients, and other excipients. The molten gum mass is then molded through a series of rollers to convert into a thin, wide ribbon and applied with a light coating of finely powdered sugar or sugar substitutes. The gum is allowed to set for up to 48 h in a controlled room environment to set and finally cut into desired size and packed. However, this process is not suitable for pharmaceutical industry, and many drugs are unsuitable to process at high temperatures due to their heat liability.

Development of blending with direct compression as a generalized platform technology made the manufacturing process easier, faster, and adaptable by the pharma industry. Many directly compressible chewing gum excipients have been invented and are classified as generally regarded as safe. Availability of directly compressible gum materials, a mixture of polyols (sorbitol/xylitol/mannitol) and of sugar with gum, plasticizers, and anticaking agents, enables the rapid development of gum delivery system at low cost using a pharmaceutical in house tablet compression machine. For regulating flow of powdered blend during compression, glidant, antiadherant, and lubricants such as flow promoters are added in the formulation [118]. Standardization of quality control parameters of MCG required by the regulatory bodies opens the door for pharma industries to work on MCG-based products which are relatively unexplored area which can grant generic line extension for the existing products. Pharmagum® M and Cafosa's Health in Gum are directly compressible gum base and made the production of medicated chewing gum easier and suitable for pharma industry. However, temperature and humidity should be kept low during the production to avoid issues of sticking to punches and dyes.

3.6.3 Lozenges

Hard boiled candies, lozenges, hard or soft gums, tablets, and chewing gums are all confectionary products and when medicated are called pharmaceutical confectionaries. Confectionaries are usually made from sugars. Various carbohydrates used in these confectionary products are sucrose, dextrose, glucose syrup, modified starch, mannitol, maltitol, sorbitol, xylitol, and isomalt. Recently, sugar-free excipients commonly known as polyols such as sorbitol, mannitol, erythritol, isomalt, maltitol, and xylitol allow the formulation of sugar-free lozenges. Medicated confectionaries can be made by different methods. In classical method, candy base is heated at 95–125 °C and transferred to planetary or sigma blade mixer, followed by addition of whipping agent and active ingredients below 105 °C, followed by addition of color dispersed in humectant at a temperature above 90 °C. Then seeding crystals and flavors and lubricants are added between 80 and 85 °C, and candy shape is formed by rope forming. However, these classical boiling techniques are usually not suitable for formulations of medicated confectionary products.

Alternatively, lozenge tablets can be prepared in a manner similar to conventional tablet by direct compression or wet granulation and differs only in terms

of organolepticity, non-disintegrating characteristics, and slower dissolution profiles [119].

Lozenges tablets are compressed at greater compression force in order for it to dissolve slowly in the mouth. Ingredients in tablet lozenges include sugars such as dextrose and sucrose and/or sugar-free vehicles such as mannitol, sorbitol, and PEG 6000 and 8000 along with fillers, binders, lubricants, and coloring and flavoring agents. Soft lozenges can be made from middle molecular weight grade of PEGs between PEG 1000 and PEG 1500, chocolate, carrageenan, gums such as gum acacia and xanthan gum, and sugars or sugar-free vehicles, along with flavors and colors by heating at about 50 °C, followed by molding [119]. Further reading on medicated confectionaries is available in literature [120].

3.6.4 Bioequivalence of FDDDs

FDDDs, in general, can be formulated as a line extension of an existing oral dosage form. However, unlike conventional oral dosage form where absorption of drug occurs in post-gastric segments, in case of ODT, varying degrees of pre-gastric absorption is observed; thus the pharmacokinetic profiles will vary. Hence bioequivalence to oral dosage form is difficult [121]. Therefore, drugs (log $P > 1$ or preferable > 2) like selegiline and buspirone with substantial absorption in oral and pre-gastric areas are considered to be good candidates for NDA application [122]. Also, the design of clinical trials for MCG is difficult as drug release is variable due to individual differences in chewing time and rate. Generally, minimum chewing time of 30 min with chewing rate of one chew per second is reported. Particle size of drug also affects the release of the drug as finer particles are more tightly embedded in the gum base; thus their contact with the saliva is delayed. Other strategies to retard the drug release include making the drug complex with resin or cyclodextrin or applying the release retard coating of polymers on the drug particles.

Bioequivalence studies should be conducted according to the recommended use of the product [123]. If the FDDDs test product is an extension to conventional oral formulation, a three-period three-treatment crossover study is recommended in order to evaluate administration of the FDDDs both with and without water intake. However, if bioequivalence between FDDDs taken without water and reference product with water is demonstrated in a two-period study, bioequivalence of FDDDs taken with water can be assumed [108].

If the FDDD is a generic/hybrid to an approved FDDDs reference drug product, the following recommendations regarding study design should apply:

- If the reference product is taken only with water, the bioequivalence should be demonstrated for test product in similar condition (i.e., with water) using a conventional two-way two-period crossover design.
- If the reference listed drug can be taken with or without water, bioequivalence studies should be performed without water according to intended use of the formulation. This is especially important if the drug is partly absorbed in the oral

cavity. If bioequivalence is demonstrated without water, also bioequivalence is assumed with water also. However, in certain cases this assumption is unlikely. For example, when either the test or the reference FDDDs contain excipients such as mannitol that exerts osmotic effects, it may result in different drug absorption when taken with or without water [124].

- When the test product is intended for both the ways of administration, i.e., with and without water, and RLD is taken only with water, the test product should be compared both with and without water against RLD only with water in a three-period, three-treatment crossover design.

In some cases, BCS-based biowaiver is also being considered when substantial evidence available which states that drug is only absorbed in post-gastric segments like in case of conventional tablet in comparison. Otherwise, bioequivalence must be demonstrated via in vivo human studies. In designing bio-relevant dissolution test conditions, the physiological conditions of the mouth such as pH, volume, and flow rate of the saliva and targeted population should be considered. However, dissolution test parameter such as volume of the saliva to simulate oral cavity conditions has not yet been established.

3.7 Current Status and Further Challenges in Intraoral Drug Delivery

In spite of the global evolution and prosperity in the development of innovative intraoral formulations, the challenges are still enormous due to the wide variations in the physicochemical properties of the API, biological factors, producing process, etc. Though various technologies have been utilized over the last decades, only a handful of the commercially available intraoral drug delivery systems have been marketed, as shown in Table 3.5.

Table 3.6 represents recently completed studies (2015 onward) along with ongoing clinical trials of intraoral drug delivery systems compiled from ClinicalTrials.gov, NIH US National Library of Medicine.

We should realize that there is no magic process or formulation for developing all drug entities in intraoral dosage forms. For example, over 60% of the new drug molecules are lipophilic and poorly water soluble; therefore they provide obstacles as well as opportunities to scientists working in the field of intraoral drug delivery. Therefore, there is a continuous need to have a special strategy to enhance the absorption of the drug without causing unwarranted side effects. Several conventional techniques are utilized to enhance drug solubilization such as micronization, surface alteration of the active ingredient, or micromilling but mostly lead to a limited improvement in drug solubility and dissolution. Furthermore, nonconventional approaches were also introduced and employed effectively for the enhancement of drug solubility and their release pattern, including solid dispersions, inclusion complexes, micellization, supersaturation, cocrystallization, nanotechnology approaches,

Table 3.5 Examples on commercially available intraoral dosage forms

Brand Name	Active ingredient(s)	Dosage form	Producer
Suscard	Glyceryl trinitrate	Buccal tablets	Forest Laboratories
Nitromist	Glyceryl trinitrate	Buccal spray	NovaDel
Fentanyl Oralet	Fentanyl citrate	Buccal lozenges	Lexicomp
Corlan pellets	Hydrocortisone	Buccal tablets	Auden Mckenzie
Buccastem M	Prochlorperazine maleate	Buccal tablets	Reckitt Benckiser
Emezine	Prochlorperazine maleate	Buccal tablets	BDSI
Striant SR	Testosterone	Buccal tablets	Columbia Pharmaceuticals
Aphtac	Triamcinolone	Buccal tablets	Teijin Ltd
Corsodyl dental gel	Chlorhexidine	Oromucosal gel	GlaxoSmithKline
Loramyc	Miconazole	Buccal tablets	BioAlliance Pharma
Onsolis	Fentanyl citrate	Mucoadhesive film	Meda Pharmaceuticals
Abstral	Fentanyl	Buccal tablets	ProStrakan
Subutex	Buprenorphine HCl	Buccal tablets	Reckitt Benckiser
Suboxone	Buprenorphine HCl naloxone HCl	Buccal tablets	Reckitt Benckiser
Actiq	Fentanyl citrate	Buccal lozenges	Cephalon
Fentora	Fentanyl citrate	Buccal tablets	Cephalon
Orabase-B Gel	Benzocaine	Gel	Orabase
Nicorette	Nicotine	Chewing gum	GSK consumer health
Nicotinell	Nicotine	Buccal lozenges	Novartis Consumer Health
Maxalt	Rizatriptan	Rapidly dissolving wafers	Merck & Co. Inc.

and high pressure homogenization. Another point to be considered is the dose of drugs, since the low dose may present formulation difficulties especially in drug content uniformity issues. Attaining optimum drug release from the formulation is another challenge for the formulation scientists, i.e., different formulation designing for rapid drug release than that of sustained release and mucoadhesive dosage forms. Another factor is the organoleptic properties of the drug entity which may be a problem for the patient acceptability and compliance.

On the other hand, greater challenges are associated with the formulation of buccal delivery systems of biologics such as protein and peptide drugs due to their undesirable physiochemical properties [125], such as:

1. Most of the therapeutic proteins and peptides are macromolecules and hydrophilic in nature with a log $P < 0$ [126]. The large molecular weight and the presence of both hydrophilic and hydrophobic appendages in their structure are a major hindrance in their transmucosal absorption into systemic circulation.

Table 3.6 List of recently completed/ongoing clinical trials for drug brain targeting (accessed on December 08, 2018)

Official title	Study identifier	Condition	Current status
Study of the Safety and Efficacy of tropicamide Thin films to Reduce hypersalivation in Parkinson's Patients	NCT01844648	Sialorrhea (excessive drooling)	Phase 2 completed December 2015
Oral Potassium Acid Phosphate Supplementation for Preterm Neonates; a Comparison of oral Thin films and Standard Oral Therapy	NCT01676844	Hypophosphatemia osteopenia of prematurity	Phase 2, unknown
Fentanyl Buccal Tablets for Exercise Induced Breakthrough Dyspnea	NCT01856114	Advanced cancers	Phase 2, ongoing
The Effect of CanChew® Cannabidiol (CBD) Containing Chewing Gum on Irritable Bowel Syndrome	NCT03003260	Irritable bowel syndrome	Phase not applicable, recruiting
A Double-Blind, Randomized, Placebo Controlled, Clinical Trial of an Antiplaque Chewing Gum (30 mg) - Phase 2 Proof of Concept in a Generally Healthy Patient Population	NCT02864901	Plaque regrowth	Phase 2, ongoing
A Bioequivalence Study of Three, 2 mg Nicotine Chewing Gums (Two Tests and One Reference) in Healthy Adult Smokers	NCT02688374	Tobacco use disorder	Phase 1, completed June 2016
Clinical Effect of *Lactobacillus Reuteri* in Treatment of Gingivitis	NCT02801773	Gingivitis	Phase 2, ongoing
The Efficacy of Acetium Lozenges in Intervention for Smoking Cessation	NCT02758743	Smoking cessation	Phase not applicable, completed May 2017
Effect of Probiotic Lozenges on Halitosis in Patients With Chronic Periodontitis	NCT02789436	Halitosis	Phase 4, ongoing
The Salivary and Faecal Microbiome of Recurrent Aphthous Stomatitis Patients Before and After Treatment With Probiotics	NCT02976922	Recurrent aphthous ulcers	Phase not applicable, recruiting
A Comparative Clinical Trial to Evaluate the Safety and Clinical Equivalence of Clotrimazole Troche/ Lozenges USP, 10mg (Unique Pharmaceutical Laboratories, India) With Clotrimazole Troche 10mg (Roxane Laboratories Inc., USA) in Subjects With Oropharyngeal Candidiasis	NCT02635438	Oropharyngeal candidiasis	Phase 3, ongoing

(continued)

Table 3.6 (continued)

Official title	Study identifier	Condition	Current status
Crossover Study to Evaluate the PK Effects of Two Different Wafer Administration Protocols	NCT02857361	Pain	Phase 2, completed August 2016
Tumor Resection and Gliadel® Wafers, Followed by Temodar® With Standard Radiation or GammaKnife® for New GBM	NCT02085304	Glioblastoma	Phases 1 and 2, ongoing

2. Many protein and peptide drugs are pharmacologically effective mainly because of their 3D structure, which can be lost or changed under different physical and chemical environments, resulting in their degradation or denaturation, thereby making these molecules unstable in vivo and consequently lose their biological activity.
3. Commonly proteins and peptides own very short biological half-lives due to their rapid hepatic metabolism by proteolytic enzymes and other clearance mechanisms in other body tissues.
4. A precise dosing of the therapeutic proteins and peptides is extremely important since they are highly potent biological compounds and deliver specific clinical actions.
5. Some posttranslational modifications are required for proteins and peptides to be physiologically active such as glycosylation, phosphorylation, and proteolytic cleavage. The modification of protein drugs like insulin may need the use of specific types of cells; thus, recombinant proteins can be produced in large quantities by genetically engineered cells (e.g., bacteria or yeast) in large bioreactors.
6. Biological immune response against protein and peptide drugs is possible which may neutralize the protein and even cause a harmful reaction in the recipient.
7. High cost is required for developing protein and peptide drugs due to the expensive requirements and intermediate technologies utilized in their formulation designing [127].

In addition, there is a difficulty in convincing the regulatory agencies to accept a new product when a novel formulation and route of administration is introduced. The agency may show more circumspection, in keeping with their aim of protecting the public.

According to the previous discussion, we can conclude that numerous challenges are associated with the development of innovative buccal delivery systems. Logically, this may explain the difference between the extent of research activity and the number of buccal dosage forms actually reaching the marketplace and why it is so difficult for the small pharmaceutical companies of limited resources to undertake research and develop oral transmucosal delivery systems.

3.8 Conclusion

Repositioning an old drug through intraoral drug delivery system benefits the pharmaceutical manufacturer by imparting unique product differentiation and enabling its use as line extensions for existing commercial products. There is no doubt that the need for these systems is real and many classes of drugs could benefit from this noninvasive type of drug delivery; turbulent and changing nature of the oral cavity, less surface area, and contact time pose significant formulation challenges. However, with significant advancement in the field of pharmaceutical technology and polymer science, it is now feasible to manufacture variety of dosage forms including films, tablets, wafers, chewing gums, buccal patches, and bioadhesive tablets and deliver both small and peptide-based drugs. Medicated confectionaries such as lollipops, lozenges, troches, and pastilles have also opened the door for pharmaceutical market. Overall, authors feel that intraoral route is the most promising route for reformulating drugs. However, a good knowledge and understanding of the underlying biological factors and permeability problems is required. Besides, verification of the validity and accuracy of the in vivo studies and quantitative analysis of the drug is a fundamental issue.

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Oral Controlled Release Systems: Current Strategies and Challenges

4

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_4

Abstract

Oral drug delivery route is the widely favored and adaptable for all as it is endowed with a maximum surface area when compared to the other routes of drug administration. The conventional dosage form leads to a wide range of fluctuations in plasma drug concentration with subsequent unwanted toxicity and poor efficiency. Maintaining a steady concentration of the drug in the plasma within the therapeutic index is critical for efficient treatment. By optimizing the biopharmaceutic, pharmacokinetic, and pharmacodynamic properties of drugs, improvement in conventional formulation can be achieved. The reduction of dosing frequency is an extent that single daily dose is enough for the management of uniform plasma concentration to achieve the maximum utility of a drug. Controlled release formulation acts on several mechanisms such as osmotic pressure, matrix system, reservoir system, and altered density system to control the drug release rate. This chapter summarizes the formulation designing approaches, release kinetics, strategies, technologies, recent advancements, and challenges in the development of oral controlled drug delivery systems.

Keywords

Oral controlled release system · Pulsatile drug delivery · Ion-exachange system · Three dimensional printing · In-vivo testing

4.1 Introduction

Currently, greater emphasis has been given to develop novel drug delivery systems to overcome the drawbacks of existing drug delivery systems. The drug delivery system involves that a technology has been used to bring a drug to the desired site with a predetermined rate of drug release. Among the several improvements, the oral controlled release (CR) drug delivery is the most commonly used in the pharmaceutical industry. Major drawbacks of conventional dosage are more fluctuations in systemic concentration of drug and tissues with resulting unwanted toxicity and deprived effectiveness, especially for those drugs that are potent and have dose-dependent toxicity. It is crucial to maintain the concentration of drug in plasma within therapeutic index for effective treatment. Oral route is a widely explored and successful route for delivering active pharmaceutical ingredients such as drugs, peptides, macromolecules, and nanostructured formulations, which offer many advantages like convenience and ease of administration, greater flexibility in designing of dosage forms, large active surface area, providing of uniform delivery, ease of production, and low cost.

Several factors can influence the designing of oral controlled release formulation. Many physicochemical properties of drug such as pH-solubility profile, pKa, drug permeability, particle size distribution (PSD), thermal properties, hygroscopicity, and drug-excipient compatibility can impact on the development of oral CR formulation. Conversely, the major parameters such as solubility, permeability, and stability of drugs may affect in vivo process of drug release to drug absorption. Improvement of facts on drug and their pharmacological actions and specific information such as onset of action, duration of action, therapeutic window, dose-response profile, and pharmacokinetic and pharmacodynamic correlations have encouraged awareness in delivering drugs at predefined rates and to predefined locations, which in turn optimize its effectiveness. Motivating forces for the improvement of controlled release formulation are the human need, challenging drugs, personal medication, avoidance of adverse reactions, minimizing variability, prolonging action and reducing dosing frequency, commercial advantage, and overcoming barriers. Several types such as delayed release, sustained release, and repeat action formulations are major considerations for the development of controlled release formulations. Controlled release drug delivery system works on many different mechanisms to control the release rate of drugs. Various approaches such as coating, osmotic pressure, matrix system, reservoir system, microencapsulation, gastroretentive controlled release systems, pulsatile system, layer-by-layer formulations, extrudable technology, lipidic formulations, and 3D printing have been discussed along with recent examples. Factors affecting and challenges involved in the development of oral controlled release formulation and in vitro and in vivo evaluations have also been discussed further in this chapter. The development of controlled drug release formulations progresses as a multidisciplinary science, demanding knowledge of gastrointestinal conditions, polymer science, engineering technologies, etc. This chapter outlines the designing, release kinetics, strategies, technologies, recent advancements, and challenges in the development of oral controlled drug delivery systems.

4.2 Designing of Oral Controlled Release Systems and Consideration of Factors

The various factors affecting the design of oral controlled drug delivery systems are as follows.

4.2.1 Physicochemical Property of Drugs

(A) *Molecular weight*

The molecular weight of the drug affects its diffusibility across gastrointestinal (GI) membrane, and drugs up to 600 Dalton are suitable for oral controlled drug delivery [1, 2].

(B) *Aqueous solubility of drug*

A drug with high water solubility and pH-independent solubility is a good candidate for oral controlled drug release, because absorption of drug with low water solubility is dissolution rate limited and the formulation does not control the absorption process [1, 2].

(C) *Partition coefficient of drug*

A drug should have optimum lipid as well as aqueous solubility, because if drugs have low partition coefficient (high aqueous solubility, low lipid solubility), then they will be accumulating in aqueous phase; if drugs have high partition coefficient (low aqueous solubility, high lipid solubility), then they do not partition out from lipid membrane [3].

(D) *Drug pKa*

Only unionized form of drugs can be absorbed. So for, sufficient absorption drug should be in unionized form at the absorption site at least up to 0.1–5%, Thus, pKa value for acidic drugs should be 3–7, and for basic drugs 7–11 is required for controlled drug delivery; drugs which are existing in ionized forms are poor candidates for controlled drug delivery [3, 4].

(E) *Drug stability*

A drug should be stable in the GI environment [3].

(F) *Drug protein binding*

Drugs with high plasma protein binding are poor candidates for controlled release, because drug protein binding can act as a reservoir for controlled release [4].

4.2.2 Pharmacokinetic Property of Drugs

(A) *Absorption rate*

Controlled release formulation is designed in such a way that it will control the release of drug from formulation. Drugs having good absorption rate are suitable candidates for oral controlled release as their release rate is lesser than absorption rate [1, 3, 4].

(B) *Elimination half-life*

Drugs having half-life in the range of 2–4 h are suitable candidates for oral controlled release, because large amount of dose is required for them, which is hard to incorporate in formulation, but if half-life is>4 h, there is no need to formulate controlled release formulation [1, 4].

(C) *Metabolism*

If a drug is able to induce or inhibit enzymes or change in plasma drug concentration due to hepatic metabolism or metabolism through any tissue of GI tract, then it is a poor candidate for controlled release, because it is difficult to maintain constant plasma drug concentration [1, 5]. For example, metabolism of levodopa occurs through gut micro flora; hence, there is less availability of drug for absorption from controlled delivery systems. Therefore, sustained release formulation of levodopa has no benefit over conventional formulation of levodopa [5].

4.2.3 Pharmacodynamic Characteristic of Drugs

(A) *Therapeutic range*

Therapeutic drug range should be wide enough that variation in drug release does not reach toxic level of drug [1].

(B) *Therapeutic index*

Formulation of oral controlled release system for drugs, which have narrow therapeutic index, is difficult because the drugs which are very potent need to maintain their plasma concentration for safety purpose [1, 3].

(C) *Plasma concentration-response relationship*

Drugs whose pharmacological activity is dependent on its concentration are good candidates for controlled release [1]. Figure 4.1 shows the comparison of release profiles of three different delivery systems.

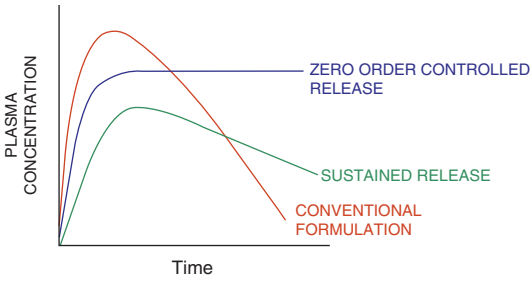

Fig. 4.1 Comparison of release profiles between controlled release formulation and conventional formulation

(D) *Disease state*

Some diseases are affected by circadian rhythm; for instance, myocardial attack occurs in early morning and asthma attack occurs before bedtime. Therefore, design of controlled release system is in accordance with the circadian rhythm [6].

4.2.4 Anatomical Factors

(A) *Buccal mucosa*

The design of controlled drug delivery is to absorb the drug directly into systemic circulation through buccal mucosa, and by this route hepatic metabolism and gastric acid–induced degradation can be avoided [6].

(B) *Stomach*

Controlled drug delivery in the stomach is advantageous in some of the cases where the site of absorption is the stomach; hence, local effect is required in stomach and drug degrades in the intestine. The success of controlled drug delivery in the stomach depends on the anatomical factor of the stomach. The stomach has a small surface area; hence, less absorption of drug occurs in the stomach. Change in blood flow affects absorption of drugs. Gastric volume also affects dissolution of drugs. Drug's absorption occurs only in an unionized form, and the degree of drug ionization depends on gastric pH. The mucus and the parietal and peptic cells are present in the lining of stomach, which act as a barrier for the absorption of drugs. Acid, pepsin, gastrin, mucous, and enzymes are contents of stomach secretion, which affect the absorption of drug. If the absorption site of drug is the stomach, then delay gastric emptying is favorable. If the absorption site is the intestine, then fast gastric emptying is favorable. The gastric motility of the stomach also affects the performance of controlled drug delivery (Fig. 4.2) [6].

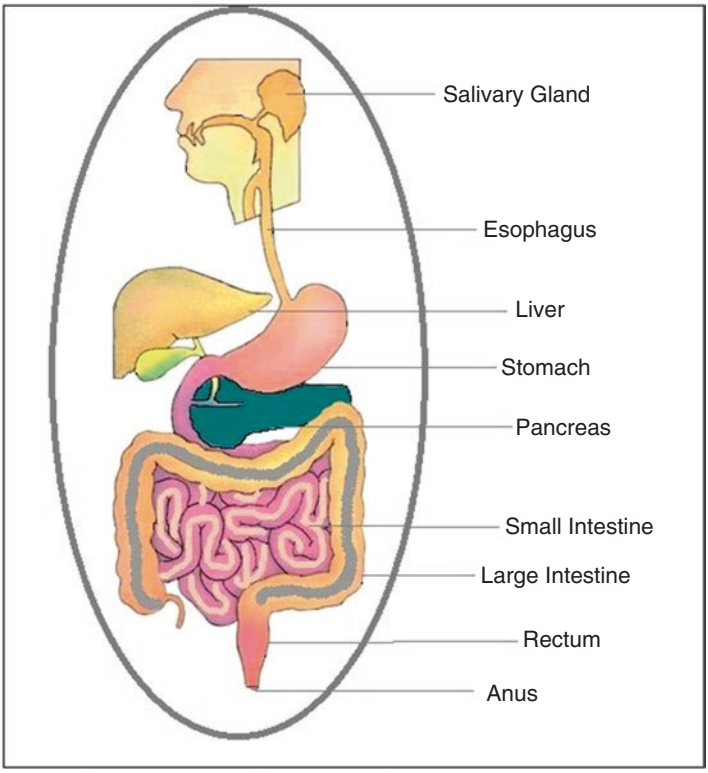

Fig. 4.2 Anatomical sites of GI tract

(C) *Small intestine*

The design of controlled drug delivery in the intestine has advantages like decreased hepatic metabolism, lymphatic targeting, suitable for drugs that are unstable in the gastric environment [6].

(D) *Colon*

Colon environment properties such as pH, mucoadhesion, large surface area, longer transit time, and enzymes are considered during the design of controlled drug delivery to the colon [6].

4.3 Oral Controlled Release Systems: Release Kinetics

The following are various release kinetic mechanisms for the release of a drug from different formulations. Figure 4.3 shows the release pattern of five different kinetic models, and Fig. 4.4 describes the types of release systems.

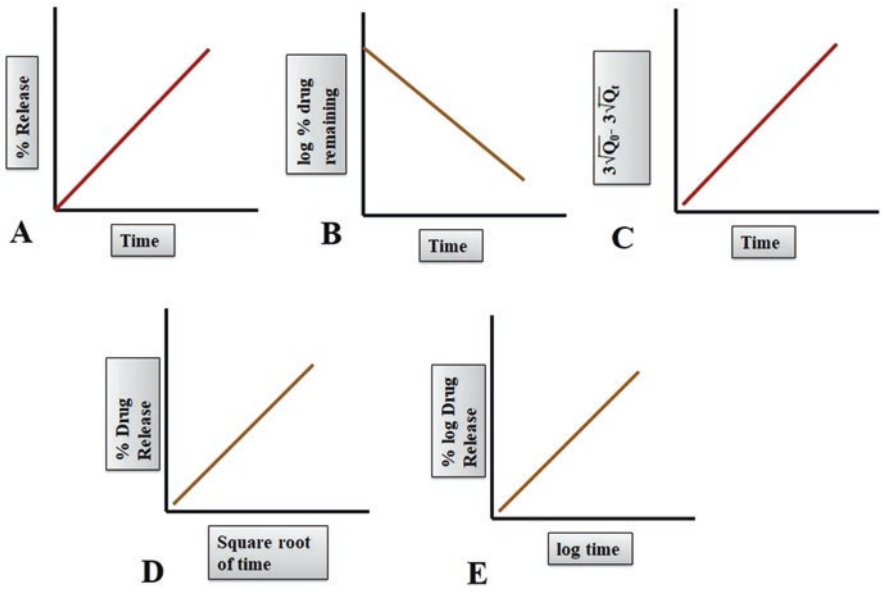

Fig. 4.3 (**a**) Zero-order release kinetic, (**b**) first-order release kinetic, (**c**) Hixson-Crowell release model, (**d**) Higuchi release model, (**e**) Korsmeyer-Peppas release model

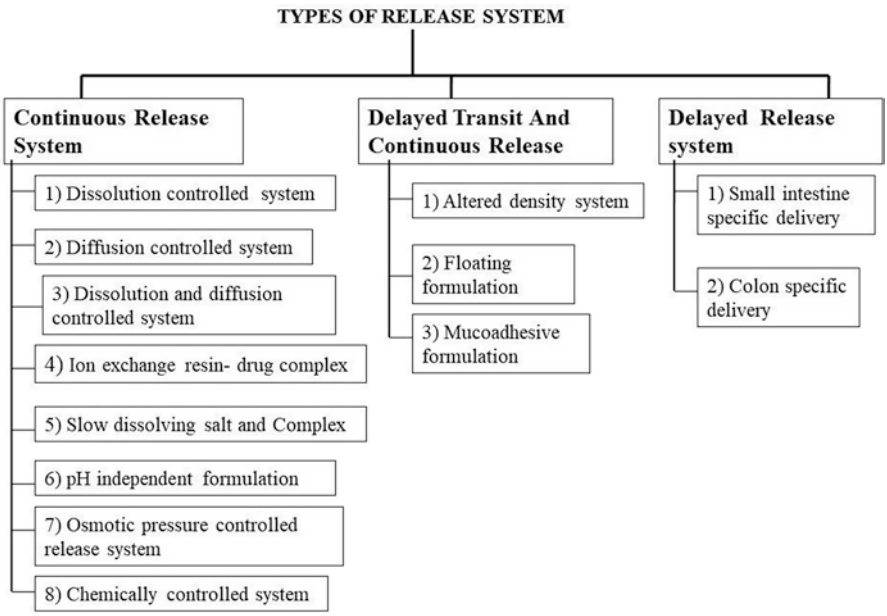

Fig. 4.4 Classification of drug release mechanisms

1. *Zero order* [7]: Drug release is independent of concentration.

$$\mathbf{Q_t = Q_0 - Kt}$$

2. *First order* [7]: Drug release is dependent on concentration.

$$\mathbf{\log Q_t = \log Q_0 - Kt / 2.303}$$

3. *Hixson-Crowell release model* [7]: Drug release occurs by dissolution and change in the surface area and diameter of the particle.

$$\mathbf{3\sqrt{Q_0} - 3\sqrt{Q_t} = Kt}$$

where for all abovementioned three equations Q_t = amount of drug release at time t, Q_0 = initial amount of drug, K = zero-order release rate constant, t = time.

4. *Higuchi release model* [7]: Drug release from matrix system.

$$\mathbf{C = \left[D\left(2qt - Cs\right)Cst\right]^{1/2}}$$

where C = total amount of drug release per unit area of matrix (mg/cm^2), D = diffusion coefficient of drug, qt = total amount of drug in unit volume of matrix (mg/cm^3), Cs = dimensional solubility of drug in matrix of polymer (mg/ cm^3), t = time.

5. *Korsmeyer-Peppas release model* [7]: Drug release from polymeric system.

$$\mathbf{C_t / C_\infty = Kt^n}$$

Ct/C∞ = fraction of drug release at time t, K = rate constant, t = time, n = release exponent (if n = 0.5 – Fickian diffusion, n = 0.5 < n < 0.89 – non-Fickian transport, n = 0.89 – case 2 transport, n = >0.89 – super case 2 transport) [8].

6. *Wiebull release model* [7]

$$\mathbf{C = C_0[1 - \exp\left[-\left(t - T\right)^b / a\right]}$$

where C = amount of dissolved drug at time t, C_0 = total amount of drug release, T = lag time measured as a result of dissolution process. a = scale parameter that describes time dependence, b = shape of dissolution curve.

7. *Baker and Lansdale model* [7]: Drug release from spherical matrix.

$$\mathbf{F1} = \mathbf{3/2}\left[\mathbf{1} - \left(\mathbf{1} - \mathbf{C_t}/\mathbf{C}\infty\right)^{2/3}\right]\mathbf{C_t}/\mathbf{C_\infty} = \mathbf{Kt}$$

where C_t = drug release at time t, C_∞ = amount of drug release at infinite time, K = rate constant, t = time.

8. *Hopfenberg model* [7]: Drug release from eroding surface of polymer.

$$\mathbf{C_t}/\mathbf{C_\infty} = \mathbf{1} - \left[\mathbf{1} - \mathbf{K_0 t}/\mathbf{C_L a}\right]^{\mathbf{n}}$$

where C_t = drug release at time t, C_∞ = amount of drug release at infinite time, K_0 = zero-order rate constant, CL = initial drug loading, a = thickness (radius for sphere or cylinder), n = exponent (n = 1,2,3 for slab flat, cylindrical, and spherical geometry, respectively).

9. *Gompertz model* [7]

$$\mathbf{C_t} = \mathbf{C_{max}}\exp\left[-\alpha \mathbf{e}^{\beta \log \mathbf{t}}\right]$$

where Ct% drug dissolves at time t divided by 100, C_{max} = maximum drug dissolution, α = undissolved portion of at time, β = dissolution rate per unit time.

10. *Sequential layer model* [7]

Model used for study of swelling and release behavior from hydrophilic matrix and determine effect of system's geometry on drug release.

4.4 Oral Controlled Release Systems: Strategies and Technologies

4.4.1 Coating as a Means to Impart Controlled Release

Certain materials such as polymers, plasticizer, pore former, and anti-aggregation agents are generally used to coat the formulation that controls the release of drug in the body due to formulation. Coating materials dissolve, erode, break down, swell, melt, or permeable in the body to provide controlled release. By changing the thickness of coating material, the desired dissolution profile of the drug can be achieved [9]. Methods used for coating are pan coating, fluidized bed coating, melt coating, compaction coating, microencapsulation, dip coating, electrostatic coating, and vacuum film coating. In pan coating, the coating solution is applied on the core material in the pan, followed by the evaporation of the solvent. Examples of pan

coating are sugar and film coating. In fluidized bed coating, the solution is sprayed on the suspended core material in warm air stream in coating chamber with drying air. Controlled release materials having low melting point and thermostability such as carnauba wax, ethylene glycol and polymers are suitable for melt coating, while in compaction coating, the core material is placed within die of tablet compression machine, which has been filled with half of the coating material after placing of core material die is filled with the remaining part of coating material and formulation is then compressed.

Compression coating is a simple technique in which the core material is surrounded by the coating material. Ethyl cellulose is the commonly used coating material; however, it is brittle and can easily breakdown in stress conditions leading to premature release of drug. Qi Xiaole et al. have recently reported self-assembled polyelectrolyte complex films as efficient compression coating layers for controlled releasing tablets using paracetamol as a model drug. The conventional formulation of paracetamol has a short half-life, and so there was a need to design controlled release formulation. To achieve controlled release, Qi Xiaole et al. have used polyelectrolyte complexes (PEC) films consisting of chitosan (CS) and sodium alginate (SA) to control the release of the drug. PEC films are a resultant of the interaction between two oppositely charged polymeric chains and are nontoxic, slowly degraded, safe, and biocompatible. Chitosan and sodium alginate form PEC film in the GI fluid to achieve zero-order drug release (Fig. 4.5) [10].

Siling W et al. have developed multilayer encapsulated mesoporous silica nanospheres so as to sustain the oral delivery of poorly water-soluble drug felodipine. Design of controlled release formulation of felodipine by using mesoporous silica nanospheres as a carrier for drug and polyelectrolyte multilayer consists of chitosan and acacia adsorbed onto drug-loaded mesoporous silica nanospheres by layer-by-layer self-assembly technology. Mesoporous silica is nontoxic, has a large specific surface area; has a tunable pore size; is inert; has easily modified surface properties; and increases dissolution of poorly water-soluble drug (Fig. 4.6) [11].

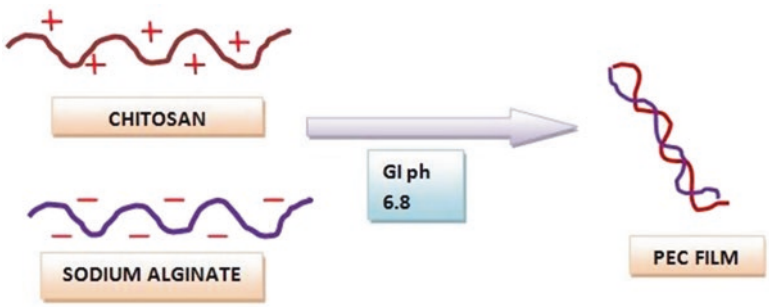

Fig. 4.5 In situ film formation by chitosan and sodium alginate to controlled release

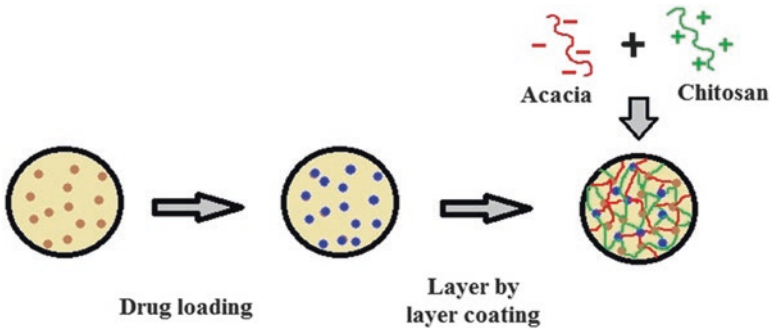

Fig. 4.6 Layer-by-layer coating of chitosan and acacia onto drug-loaded mesoporous silica nanospheres

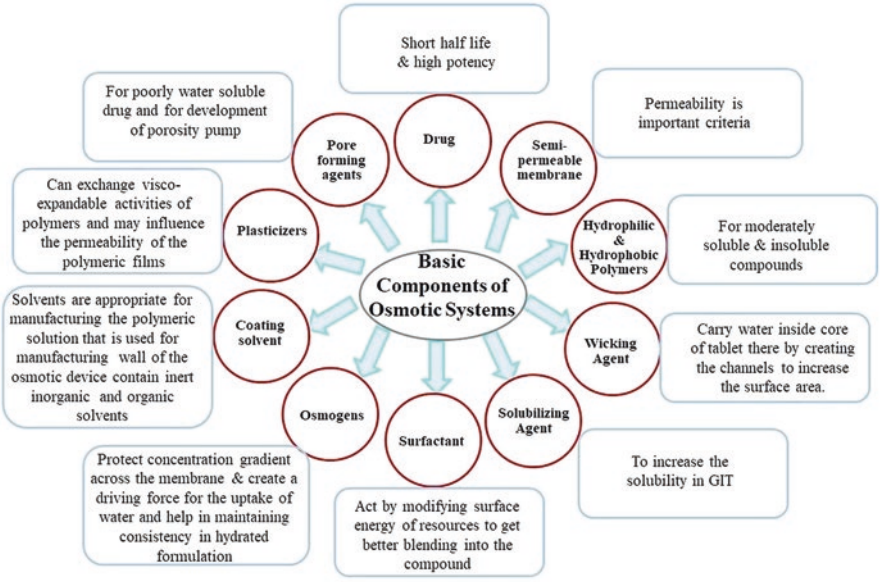

Fig. 4.7 Graphical representation of basic components of ODDS

4.4.2 Osmotically Controlled Drug Release

Osmotically controlled drug release depends on osmosis [12]. Osmotic drug delivery system (ODDS) has been developed for drugs having low oral bioavailability because of poor permeability and solubility issues. It can release the drug with zero-order kinetics and does not depend on either of factors such as initial concentration of drug or the physiological factors of the gastrointestinal tract (GIT) [13]. Figure 4.7 is a graphical representation of basic components of ODDS, while Fig. 4.8 describes oral osmotic delivery technologies [14].

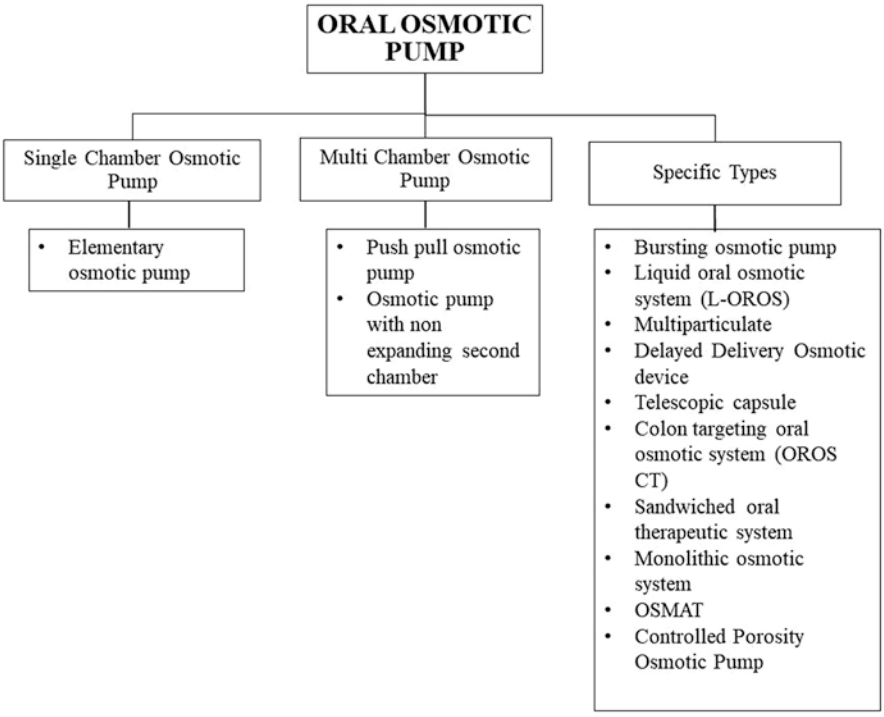

Fig. 4.8 Oral osmotic delivery technologies

OSMODEX® ID delivery for insoluble drug technology offers first-order, zero-order delayed release for insoluble drugs with full release over a fixed period of time. While OSMODEX® SD delivery for soluble drug technology offers the advantage for targeted drug delivery and even for drugs that are soluble but have low bioavailability. OSMODEX® IR/CR combination technology offers an advantage of providing both immediate and controlled release of either one or two drugs. According to the pharmacokinetic and pharmacodynamic needs of the product, it allows the immediate release profile combined with programmed release. OSMODEX® Double CR combination allows the delivery of two drugs from a single osmotic tablet, where each drug release pattern can be designed independently with the desirable release profile. OSMODEX® triple combination technology involves compressed drug layer around an osmotic core. This combination provides an advantage of immediate and controlled release delivery with unique advantage of an osmotic controlled release to achieve three different release rates in the single tablet.

Chulei Yang and colleagues reported that the absolute oral bioavailability of paliperidone ER is 28%, and the mean time to peak plasma concentration is approximately 24 h, possessing terminal elimination half-life of approximately 23 h and also steady-state plasma levels is achieved after 4 daily doses. They also developed

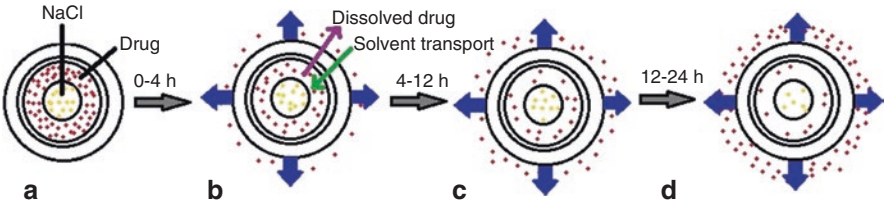

Fig. 4.9 Graphical representation of ACRP. (**a**) ACRP, (**b**) delayed stage, (**c**) accelerated release stage, (**d**) decelerated release stage

ascending controlled release preparation (ACRP) that has a similar release pattern of INVEGA® but with improved safety profile. The release mechanism of ACPR depends on controlled-membrane and osmotic pressure. It can also help in the delivery of drug uniformly along the gastrointestinal tract, and as a result, it causes less local irritation, maintains a stable drug concentration in blood, reduces medication frequency, and improves the patience compliance. However, single pellet has less effect on the whole release profile upto certain levels. It provides low initial release rate that can avoid initial tolerance but also the desired concentration can be achieved rapidly due to the ascending release (Fig. 4.9) [15].

The marketed tablet of metformin hydrochloride (MH) and repaglinide (RG) possesses multidrug therapeutic effect on type-2 diabetes. But due to short half-life of the drugs, the tablet has to be administered 2–3 times a day, which leads to patient incompliance and also there is fluctuation in concentration of drug in plasma. Chao Qin and coworkers have developed sandwiched osmotic pump tablet, which is used to deliver two drugs together and follow zero-order release. They have separated two drug layers using push layer, and each drug layer is surrounded by the semipermeable membrane with two orifices on each side. As metformin is a highly water-soluble drug, it gives burst release and 90% of drug is released in 2 h. Thus, in order to retard the drug release, hydrophilic polymer such as PVP K90 has been added to the drug powder and because repaglinide belongs to BCS class II, solid dispersion has been prepared using PVP K30 to increase the solubility [16].

The conventional tablet of prazosin HCl has to be administered 3 times daily for the management of congestive heart failure and hypertension. Longxiao Liu et al. have tried to prepare an osmotic pump system in which the core tablet was coated with an indentation during the compression of needle punch. The orifice was formed for drug release. As the laser drill is eliminated, the preparation of osmotic pump tablet was simple. They have compared the release profile of both commercial conventional tablet and osmotic pump tablet and concluded that the conventional tablet released 90% of the drug within first half hour, while the osmotic pump tablet released the drug at a constant rate up to 24 h [17].

The commercially available conventional tablet of atenolol to reduce blood pressure has to be taken 2–3 times daily. The two-layer osmotic tablet of atenolol is already available, but it had imbedded side effects. Thus, Liu et al. have developed a three-layer core osmotic pump tablet eliminating the side effects. Its core tablet

consists of a push layer, and there is a two-drug layer attached to it. As atenolol is sparingly soluble, its solubility was increased by converting it into salt using tartaric acid, and then the tablet was coated using ethyl cellulose with PEG 400. They reported once-a-daily osmotic pump tablet, which showed zero-order release rate for 24 h [18].

4.4.3 Rate-Controlling Matrix Systems

One of the controlled drug delivery systems is matrix tablets, which normally release the drug in a continuous manner. It contains a drug substance that is dispersed in the rate-controlling material and releases the drug via dissolution-controlled and/or diffusion-controlled mechanisms [19]. The formulation of matrix tablet is simple and involves direct compression of blend of drug, rate-controlling material, and other additives to formulate a tablet in which the drug is embedded in a matrix core of the rate-controlling material. In addition, the drug and the rate-controlling blend may be granulated prior to compression [20]. Figure 4.10 shows the classification of matrix tablets.

The oral bioavailability of atenolol is 50% and is absorbed from GIT. The longer gastric retention time (GRT) leads to increased absorption and improved bioavailability of the drug. Sanjay Sey et al. have prepared a floating matrix tablet using atenolol, xanthan gum, and guar gum alone, and even in combination to improve floating and sustain release capacity of tablets [21]. Tramadol HCl is a centrally acting analgesic that has an half-life of only about 5.5 h, and the conventional oral dosage is 50–100 mg every 4–6 h with a maximum dosage of 400 mg/day. Hydrophilic matrix tablet is prepared by granulation technique using HPMC, hydrophobic matrix tablet is prepared by melt granulation technique using hydrogenated castor oil (HCO) and ethyl cellulose, and a combination of hydrophilic and hydrophobic polymer was explored by melt granulation technique. From the release data, it was concluded that hydrophilic matrix tablet could give effective release upto

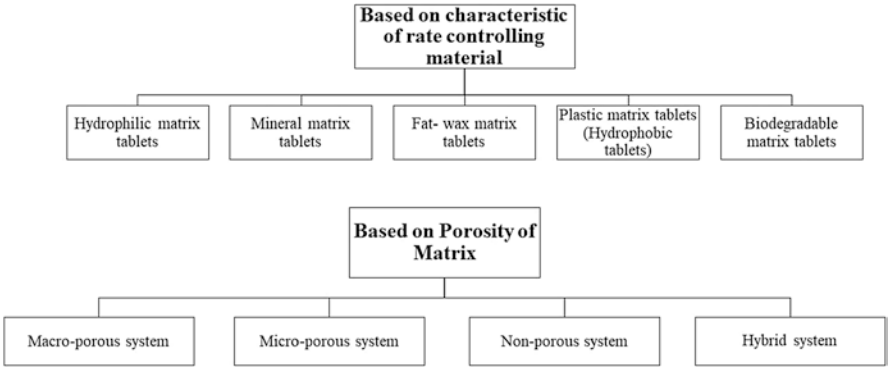

Fig. 4.10 Classification of matrix tablets

12 h for water-soluble drug, while hydrophobic matrix tablet using HCO was a better system for controlled release of water-soluble drug such as tramadol HCl [22]. Metoclopramide HCl is another drug whose matrix tablet is prepared using HPMC, CMC, and EC by direct compression, and dry granulation showed combined mechanisms such as diffusion and polymer chain relaxation for release up to 8 h [23].

4.4.4 Microencapsulation Approach for Controlled Release

Microencapsulation is a process in which tiny particles or droplets of solid or liquid material are coated or surrounded with a continuous film of polymeric material. Generally, the microencapsulated product size ranges from 1 μm in diameter to 1000 μm [24]. Morphologically, two types of structure exist: microcapsules and microspheres. Microcapsules are a reservoir type of system in which the core can be solid, liquid, or gas and which is encapsulated with porous, continuous, or nonporous polymeric phase maybe one or more. Microsphere is a monolithic type of system in which the continuous phase with one or more miscible polymers makes the structure, and the drug is dispersed all over the matrix (Fig. 4.11) [25].

The major mechanisms of drug release from microencapsulated product are diffusion, dissolution, osmosis, and erosion. From various studies, generalized characteristics of microcapsules for the release are as follows:

(a) The drug release from the microcapsules is often zero order.
(b) Microcapsules of monolithic type, which contain dissolved drug, have $t_{1/2}$ dependent release for first half of total drug release and then decline exponentially.
(c) Microcapsules of monolithic type having excess of dissolved drug, the drug release rate is t1/2 dependent through entire release [25]. Figure 4.12 shows various microencapsulation technologies.

Floating delivery systems in a single unit form are not reliable in increasing gastric retention time (GRT), as they have "all or none" concept in the emptying process and which may cause varied bioavailability and also local irritation due to the large amount of drug delivered at a specific site of GIT in order to multiple-unit

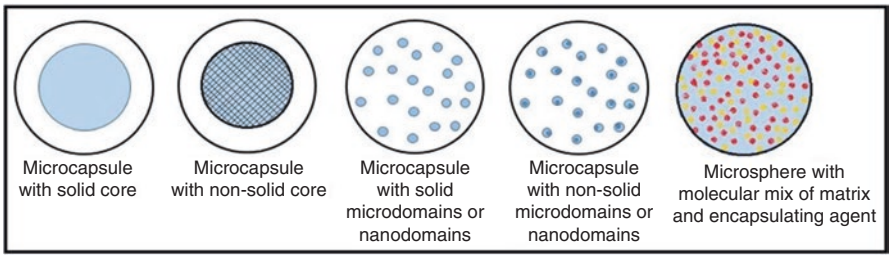

Fig. 4.11 Different structures of microcapsules and microsphere

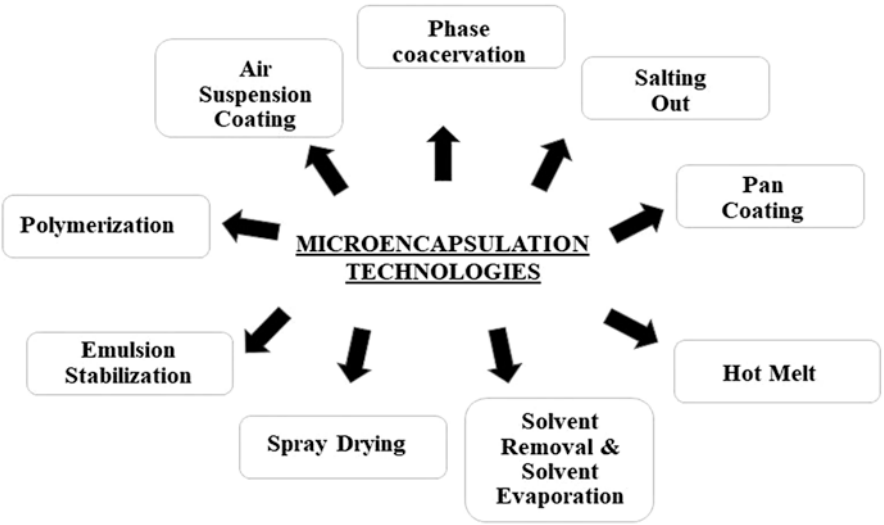

Fig. 4.12 Different microencapsulation techniques

dosage form (e.g., microsphere) pass uniformly through the GIT which avoid variation in absorption and even lessen the local variation in absorption and even lessen the local irritation. Ting Li Lu and coworkers have developed amifostine polylactide-co-glycolide microsphere using double emulsion solvent evaporation technique. In vitro release data showed burst release up to 6 h followed by slow release up to 144 h with diffusion-controlled release [26]. Microencapsulation technique is generally used for lipophilic drugs, but pregabalin, a hydrophilic drug, was encapsulated within anionic acrylic resin, that is, Eudragit S 100 microsphere by water-in-oil-in-oil double emulsion solvent diffusion method. In vitro studies showed initial burst release because of the presence of drug particle on the microsphere surface followed by 93% of the drug released within 10 h. During in vivo studies, pregabalin-loaded microsphere and conventional pregabalin capsule were given orally to rats for 3 days, which showed significant serum pregabalin level in rats with microspheres [27].

4.4.5 Multilayered Tablets

Multilayered tablets are made by compressing granulation fed into a die in sequence, one on top of another, in layer or multilayered tablets consisting of a hydrophilic matrix core mixed with an active ingredient and on both faces presence of impermeable or semipermeable polymeric coatings. Multilayered tablet is suitable for sequential release of two drugs in combination and also for sustained release of the tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. Bilayer tablets had been developed to attain controlled

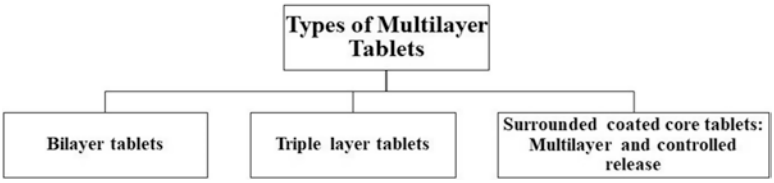

Fig. 4.13 Classification of multilayered tablets

delivery of unlike drugs with predefined release profiles. The main objective of multilayered tablets is to use different APIs in combination, which are administered separately earlier, to obtain biphasic release profile for reducing dosing frequency and to combine compatible and incompatible drugs, which are having different release profiles to enhance the stability of the dosage form [28]. Designs for different release profiles like bimodal, delayed, pulsatile, and multimodal delivery are as follows: (1) zero-order sustained release, (2) quick/slow delivery system, (3) time-programmed delivery system, and (4) bimodal release profile. The classification of multilayered tablets is given in Fig. 4.13.

Chowdary A et al. have formulated a multilayered tablet of pioglitazone HCl and metformin HCl to sustain the release of drug from formulation. Pioglitazone solubility decreases as the pH increases and metformin is freely soluble; therefore, pioglitazone was formulated as an immediate release layer by direct compression using crosspovidone and AVICEL PH 102 as combined disintegrants. Metformin was formulated as a controlled release layer for controlled release using hydrophilic polymer (HPMC K4M) by direct compression and guar gum by wet granulation method. Pioglitazone showed the drug release of 99.97% within 2 h in 0.1 N HCl, and metformin showed 98.81% drug release at 10 h of dissolution in 6.8 pH phosphate buffer. Hence, multilayered tablets of pioglitazone HCl and metformin HCl could be a better alternative way to conventional dosage forms [29]. Similarly, Harika Ryakala et al. have formulated bilayer tablets having immediate layer of nebivolol HCl and sustained release layer of nateglinide. Immediate release layer of nebivolol HCl was formulated by direct compression method using sodium starch glycolate as super disintegrant and sustained release layer of nateglinide was formulated by wet granulation method using HPMC and xanthan gum. From the in vitro release studies, it was found that 97.43% of nebivolol was released within 30 min following Higuchi model, and 97.22% of nateglinide was released up to 12 h with zero-order kinetics [30]. The main importance of biphasic delivery is rapid availability of the drug at the site of action followed by extended release. Similar work was done by Ehab Mostafa et al. using Eudragit RL/RS for both immediate release layer and sustained release layer containing diclofenac potassium for the patient suffering from acute or long-lasting pains [31].

4.4.6 Gastroretentive Approach for Controlled Release

Over the last few decades, many approaches have been frequently developed worldwide to improve the bioavailability of the drug after oral administration [32]. Gastroretentive drug delivery systems are designed to be retained in the upper gastrointestinal tract for a longer period of time, during which they release the drug on a controlled basis [33]. These systems have many advantages, for instance, (i) an increase in solubility of drug (acyclovir, ofloxacin, verapamil, etc.), which are less soluble in a high pH environment; (ii) an improvement of bioavailability of many drug molecules that have the stomach or a proximal part of the small intestine as the site of absorption (atenolol, ranitidine, metformin HCl, etc.); (iii) an enhancement in therapeutic effectiveness; (iv) a perfect target site for many drugs (e.g., captopril, metronidazole, ranitidine HCl, etc.) that are unstable in the colonic environment; (v) the gastric retention property can avoid the problem associated with drugs having short half-life (cefixime, gabapentin, itopride, metoprolol succinate, etc.) as they have the tendency of getting eliminated quickly from the systemic circulation [34–36]; (vi) a reduction in drug loss; and (vii) benefits due to the delivery of drugs (amoxicillin, metronidazole, etc.) that act locally in the stomach and the duodenum, for example, treatment of gastric and duodenal ulcers, including esophagitis. Various approaches for gastroretentive approaches for controlled delivery are given in Figs. 4.14 and 4.15.

4.4.6.1 High-Density (Sinking) Systems

Sinking systems remain in the stomach for longer period of time due to high density. Such systems have a higher density close to 2.5 gm/cm^3, are retained in the bottom of the stomach, are capable of withstanding its peristaltic movements, and can be retained in the lower part of the stomach [37]. Denser materials showed a slower gastric transit time through the gastrointestinal tract. For preparing such formulations, the drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder, and oxide. These materials can increase the density by up to 1.5–2.5 g/cm^3; thus, the system remains at the bottom of the stomach for a longer period of time and releases the drug in a controlled manner. Garg R and Gupta G. reported that small high-density pellets possess the capacity to resist gastric peristaltic movements and increase the gastric residence time from 5.8 up to 25 h [38].

4.4.6.2 Floating Systems

These systems can remain buoyant in the stomach via gas generation mechanisms; thus, two distinctly different technologies have been utilized in the development of FDDS: noneffervescent systems and effervescent systems. Noneffervescent systems further classified as (i) low density due to swelling and gelling capacity and (ii) inherent low density of polymer. In the foremost, the most commonly used excipients are gel-forming or highly swellable polymers, for instance, cellulose type hydrocolloids, polysaccharides, matrix forming material, as well as bioadhesive polymers such as chitosan and carbopol [39–41]. Upon coming into contact with gastric fluid,

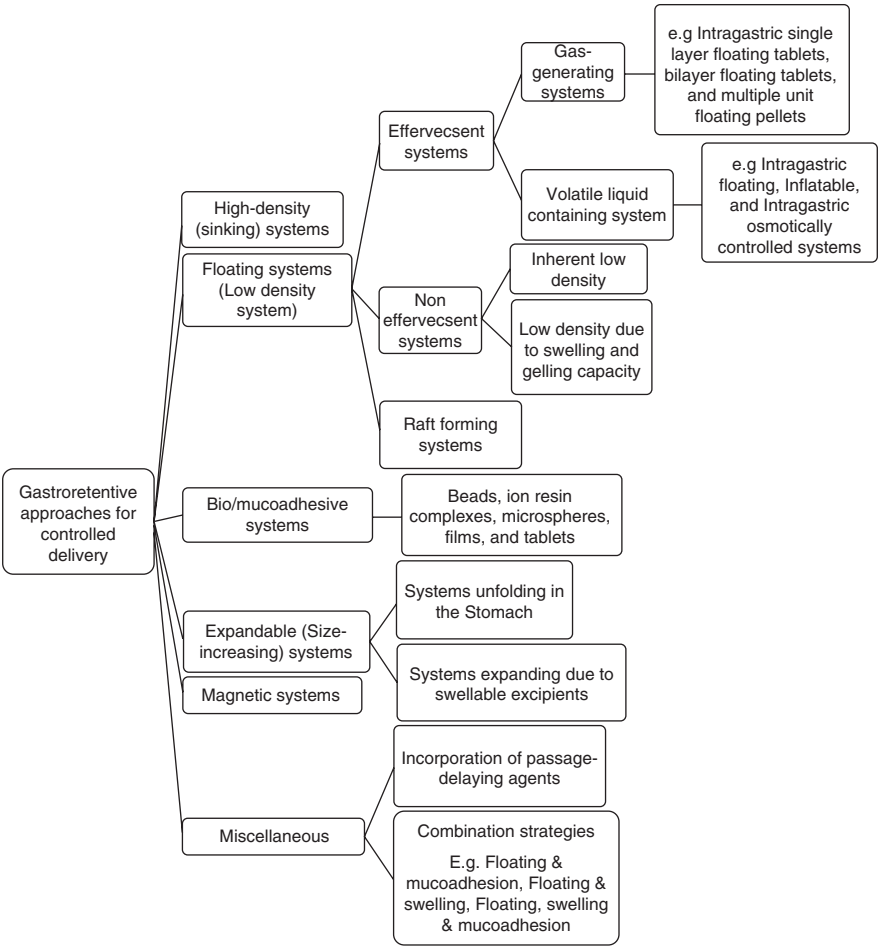

Fig. 4.14 Various approaches for gastroretentive controlled delivery

polymers hydrate and form colloidal gel layers with entrapped air around the system core that can control the rate of fluid penetration and the drug release from the system. In the later one, the system initially settles down and then remains buoyant after a specific lag time. In the multiple-unit systems, porous matrix beads using enteric polymer, Eudragit® L and various amounts of waxes (0, 0.1, 0.5, 1, 2 and 3% w/w), were developed. The effects of cetyl alcohol and white petrolatum on floating behavior and drug release in gastric fluid were investigated [42].

In the gas generating systems, the reaction between carbonates and bicarbonates presents in the formulation with gastric acid or externally added acids (e.g., citric or tartaric acid) produce the gas (CO_2) [43]. Sethi S et al. developed a prolong buoyant tablet of cinnarizine using polyacrylamide-g-corn fiber gum (p-CFG) as a bioadhesive polymer. Interestingly, bioadhesive strength of p-CFG tablet was 2.4 times

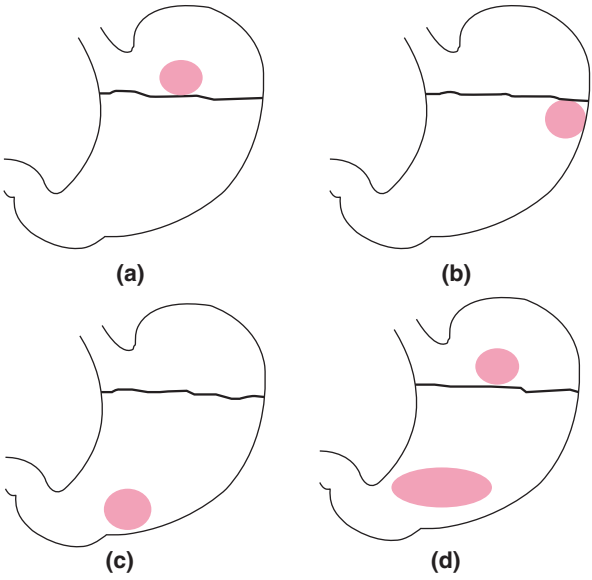

Fig. 4.15 GRDDS approaches. (**a**) Floating system, (**b**) mucoadhesive system, (**c**) high-density system, (**d**) swellable system

higher than HPMC K4M containing tablet and demonstrated more absorption in vivo [44].

For volatile liquid or vacuum containing systems, Hwang K-M et al. prepared tablets by compressing granules and excipients with a sublimating agent and observed the effects of hydroxypropyl methylcellulose (HPMC) content, porosity, and surfactant concentration in dissolution media on release kinetics [45].

4.4.6.3 Bioadhesive/Mucoadhesive Systems

As suggested by its name, a dosage form can adhere to the mucosal surface due to the presence of bioadhesive material, resulting in effective absorption and increased bioavailability of the drug. Different mucoadhesion theories such as electronic theory, adsorption theory, wetting theory, and diffusion theory are invoked to explain the adhesion mechanisms [46]. This approach involves the use of bioadhesive/mucoadhesive polymers and can be divided into cytoadhesive or mucoadhesive, which can adhere to the epithelial surface in the GIT. Commonly, for the interaction between drug and carrier molecules with the mucus membrane, contact stage and consolidation stage play a significant role. However, the exact mechanism for mucoadhesion/bioadhesion is not yet described properly. Mucoadhesion process also includes the chemical interaction such as covalent bond, hydrogen bond, ionic bond, Van der Waals bond. Polymers used for bioadhesion include carbopol, hydroxy propyl methyl cellulose, chitosan, cholestyramide, tragacanth, sodium alginate, polyethylene glycol, dextran, etc. Currently, many research studies focus on the combination of mucoadhesion and floating to enhance the gastric retention (Fig. 4.16). Ofloxacin-loaded gellan/polyvinyl alcohol (PVA) nanofibers were fabricated and showed mucoadhesion and gastric retention in rat's gastric mucosal membrane [47].

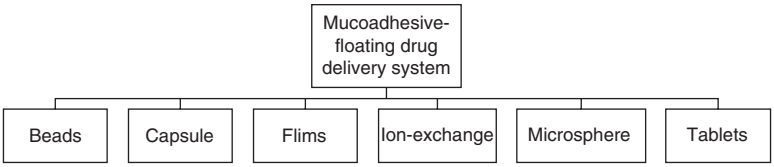

Fig. 4.16 Various types of mucoadhesive-floating drug delivery systems

4.4.6.4 Expandable (Size-Increasing) Systems

This system has the capacity to expand and trap in the stomach for a prolonged period through increase in its volume or shape, leading to sustained drug release and subsequent controlled absorption in the stomach. Expandable systems are categorized into two systems based on modification in volume and shape, which consist of swelling and unfolding systems [48].

Swellable systems are maintained in the stomach due to their mechanical properties. These swellable systems enhance in size after approaching into contact with gastric fluids and it is only promising as they employ hydrophilic polymers, which absorb water from the gastric fluids. Few examples of swellable polymers include polyacrylate polymers, HPMC, polyvinyl acetate, polycarbonates, polyethylene oxides, carbopol, sodium alginate, agar, and calcium chloride. Mamajek RC and Moyer ES [49] patented a matrix system, which contains a swellable polymeric membrane that allows the diffusion of the drug and liquids, which controls the drug release. Unfoldable systems are made of biodegradable polymers that are encapsulated or folded into the carrier. The compressed system expands and releases the drug in the stomach. Various geometric forms of this system are tetrahedron, ring, planar, lobed, disc, etc. Commonly the drug molecule disperses into the polymer matrix comprising of erodible polymer (e.g., HPMC, Eudragit) and nonerodible polymer (e.g., polyamides, polyurethane). In the 1980s, Krumme M. patented a device for controlled release of medicament that comprises a component which expands upon contact with the gastric juice and a polymer coat which is permeable to liquids and drugs [50].

4.4.6.5 Superporous Hydrogels

Another strategy to improve gastric retention time is increasing pore size in hydrogel. This system comprises of cross-linked hydrophilic polymers, which imbibe water rapidly and swell to equilibrium size. The mechanism is when the system comes in contact with aqueous media, it absorbed water and expanded, consequently, opened up the closed capillary channels in the superporous hydrogel that allowed it to swell quickly. To prepare effective gastric retention device, the hydrogels should have properties like high swelling capacity, high mechanical strength, biocompatibility, biodegradability, and stability [51]. El-said IA et al. developed Baclofen-extended release SPH systems, comprising of different polymers such as gellan gum, guar gum, polyvinyl alcohol, and gelatin [52].

4.4.7 Pulsatile Drug Delivery

In the field of drug delivery, pulsatile drug delivery system is the most interesting delayed release and site-specific system, thus increasing patient compliance. Pulsatile drug delivery is defined as the rapid and transient release of active ingredients within a short time period immediately after a lag time (predetermined off-released period). The release of the drug from the pulsatile system is due to (i) response to external signals, for example, chemical, electric, thermal, and magnetic stimuli, and (ii) response regulated by inherent mechanisms, for example, time-controlled devices that are regulated by physiological variables such as pH, temperature, and ionic strength [53]. In this respect, various pulsatile techniques such as delivery systems based on release-controlling coatings, delivery systems based on release-controlling plugs, and delivery systems based on osmotic pumping have been employed according to the type of materials involved and the desired features.

4.4.7.1 Release-Controlling Coating Systems

For the pulsatile delivery, various coating techniques such as spray coating, double-compression, dipping, and powder-layering are used to coat the single- or multiple-unit dosage forms that are used as core materials [54]. The composition of the coating layer plays an important role in release mechanism and based on coating composition, the system can be divided as erodible, rupturable, permeable, and semipermeable systems [55].

When erodible systems are exposed to body fluid, there would be swelling, dissolution, and/or erosion of the system, which leads to a delayed release of active ingredients from the core material [56]. Hydrophilic cellulose derivatives are widely used because they exhibit advantages like excellent swelling property, safe for use, ease of handling, and affordable cost.

Rupturable coatings are formulated as core materials coated by a water-insoluble, although moderately permeable, polymeric layer liable to timed disruption when coming in contact with biological fluids [57]. Ethyl cellulose (EC), with plasticizers and channeling excipients, is extensively used as the film-forming agent.

The permeable coating system is the device comprising of the drug core coated by insoluble polymeric films and diffuses the drug outward once aqueous medium penetrates into a core material [58].

Semipermeable coating systems are made up of insoluble coating layer that is selectively permeable to water and impermeable to other solutes. Cellulose acetate and cellulose acylate derivatives are most commonly used as film-forming agents [59].

4.4.7.2 Release-Controlling Plug Systems

A general design of such systems consists of an insoluble capsule body housing a drug and a plug. Upon contact with biological fluid, the plug swells, erodes, or dissolves and pushes itself out of the capsule body after a lag time, thus allowing the drug to be delivered [54, 60]. Polymers used for designing plug include the following: (i) insoluble but permeable and swellable polymers (e.g., polymethacrylate);

(ii) erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide); (iii) congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate); and (iv) enzymatically controlled erodible polymer (e.g., pectin).

4.4.7.3 Osmotic Pumping Systems

Osmotic pumps were originally conceived in pursuit of zero-order release kinetics and developed a once-a-day controlled-onset extended-release (COER-24) formulation of verapamil hydrochloride for cardiovascular disease [54, 61]. Another known technology is OROS® used for poorly water-soluble drugs. The systems have been developed such as Procardia XL®, Ditropan XL® and Concerta®, and L-OROS® SOFTCAPTM for controlled release of active ingredients and bioavailability enhancement [60].

Current research works on pulsatile systems are shown in Table 4.1. Commercially available products include UNIPHYL®, RITALIN, CODAS®, DIFFUCAPS®, PULSINCAPTM, THREE-DIMENSIONAL PRINTING®, OROS®, IPDAS®, GEOCLOCK®, RITALINA®, and OPANA®ER.

4.4.8 Ion-Exchange Approaches for Controlled Release

Ion-exchange-controlled release systems extensively use ion-exchange resins (IER), which are defined as cross-linked, water-insoluble polymeric materials holding ionic functional groups [71]. Resins with more open structures showed better regeneration properties, and larger pore size leads to less diffusion resistance [72]. Few properties of IER are important during the selection such as functional group, particle size of resin, concentration of the exchangeable group in the resin, degree of cross-linking in the resin matrix, swelling ratio, biocompatibility, and biodegradability. IER can be classified based on the charge of the functional component (cationic or anionic) and the affinity of the functional group. General classification of IER includes charge and functional group or acidic and basic drugs are given in Fig. 4.17. The most important characteristic is the exchange capacity, which is defined as the number of chemical equivalents available for exchange per unit and expressed in milliequivalents per dry gram of resin. Commercially available ion-exchange resins used in pharmaceutical formulations are shown in Table 4.2.

Ion exchange resins are unique in offering the possibility to design controlled release oral dosage forms. Moreover, the IRE systems have more flexibility for designing of variety of delivery systems such as simple matrices, granules, beads, tablets, liquids, microparticles, nanoparticles, fibers, and films. These systems are exemplified in the following novel research.

Jeong SH and Park K. [73] prepared complexes of ion-exchange resins and dextromethorphan. There were use of a batch and a column process with different functional groups, ion-exchange capacity, degree of cross-linking, and resin particle size. The major finding was that cross-linking ratio and particle size are inversely proportional to the drug loading and release rate due to reduced effective diffusion coefficient and surface area.

Table 4.1 Recent research work of pulsatile systems

Pulsatile strategy	Methods used	Major findings	Polymers used	References
Coating	Solid dispersion, solution layering technique	Multiparticulate pulsatile systems for the treatment of angina pectoris by programmed release	Eudragit L100 and RS100	[62]
Rupturable pulsatile	Layering	Fabrication of more robust formulation for pulsatile release system by incorporation of cassava starch nanocrystals (CSN) as a filler in rupturable ethylcellulose film	Swellable layer: croscarmellos; rupturing layer: ethylcellulose	[63]
Biphasic pulsatile: rupture and osmotic system	Compressed coating	Understanding the mechanism behind the biphasic pulsatile release	Poly (DL-lactic acid)	[64]
Implantable pulsatile device	CO_2 laser	In vivo experiments showed the tissue around the implanted device was biopsied and analyzed histologically for a safety evaluation	Poly (methylmethacrylate) (PMMA)	[65]
Coating	Spray method by pan coater	Coating burst is due to osmotic pressure inside the core and the lag time is dependent on the dose and the physicochemical properties of the active material	Ethyl cellulose and calcium pectinate	[66]
Rupture pulsatile coating	Spray coating	The relative bioavailability was 85.01%, and study showed that test formulation had a good in vivo-in vitro correlation	EC and Eudragit L100	[67]

(continued)

Table 4.1 (continued)

Pulsatile strategy	Methods used	Major findings	Polymers used	References
Electrical stimulations	Chemical-oxidative polymerization	Amoxicillin was released in sustained manner from composite hydrogel in response to application of cathodic electrical stimulation	Polyacrylamide, polyaniline	[68]
Coating by swellable polymers	Compression coating	Pharmacokinetic parameters showed pulsatile double-compression coated tablets managed to negligible drug release in the stomach and the small intestine but significant release in the colon	Sodium alginate and hydroxypropyl methylcellulose K 15 M	[69]
Coating by swellable polymers	Compression coating	Investigated low MW HPMCs are efficient than higher MW HPMCs for developing robust EC-based press-coated pulsatile release tablets	Hydroxypropyl methylcellulose, ethylcellulose	[70]

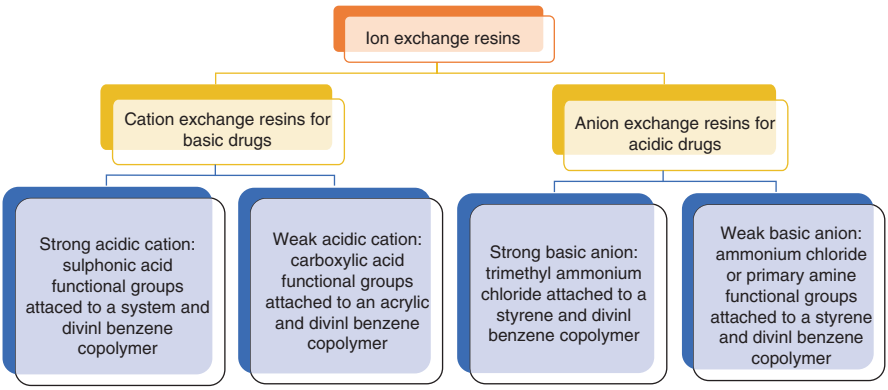

Fig. 4.17 Classification of IER

Table 4.2 Commercially available ion-exchange resins used for pharmaceutical formulations

Trade name	Component name	Producer	Matrix	Pharmaceutical applications	Ionizable group
AMBERLITETM IRP64	Polacrilex resin	Dow Chemical	Methacrylic acid/ divinylbenzene polymer	Taste masking, carrier for cationic drugs, drug stabilization (vitamin B12), controlled/sustained release (nicotine)	Weak acid – COO– H+
AMBERLITETM IRP69	Sodium polystyrene Sulphonate USP	Dow Chemical	Styrene/divinylbenzene	Taste masking, sustained/controlled release, drug stabilization, an active ingredient	Strong acid – SO3- Na+
AMBERLITETM IRP88	Polacrilin Potassium NF	Dow Chemical	Methacrylic acid/ divinylbenzene	Tablet disintegrant	Weak acid – COO- K+
DUOLITE APTM143/1083	Cholestyramine resin USP	Dow Chemical	Styrene/divinylbenzene	Taste masking, modified release, and as excipients	Strong base–N+(R)3Cl-
DUOLITE APTM143/1093	Cholestyramine resin EP				
INDION® 254	Sodium polystyrene Sulphonate USP/NF	Ion Exchange India	Cross-linked polystyrene	Taste masking, sustained release	Strong acid – SO3- Na+
INDION® 294	Polacrilin potassium USP/NF	Ion Exchange India	Copolymer of methacrylic acid and divinylbenzene	Tablet disintegrant, sustained release	Weak acid – COO– K+
Purolite® C100CaMR	Calcium polystyrene sulphonate BP/JP	Purolite	Styrene cross-linked with divinylbenzene, sulfonic acid, calcium form	Reduce serum potassium	Strong acid – SO3-Ca1/2 2+

It is known that very few studies have been developed to prepare oral films using IER. Molecular mechanism for IER is well explained, but still its use in developing pharmaceutical dosage form is unclear. IER film of betahistine hydrochloride and Amberlite® IRP–69 (IER) was prepared by batch method and used five different concentrations of solutions (the ratio of drug to resin ranging from 1:2 to 4:1(*w/w*). The finding summarizes that the prepared film gives the sustained release effect along with masking bitter taste and improving the stability of API [74].

Coating of ion-exchange resins with different polymers controls the release of drug from the system. Polymers used to coat the exchangers are hydroxypropyl methyl cellulose, Eudragit RS, Carbopol, polyethylene imine, ethyl cellulose, poly(methyl methacrylate), gellan gum, and xanthan gum [75]. Racovita S et al. [76] used gellan gum to cover the surface of acrylic ion exchanger to enhance the biocompatibility of the microparticles. The radical suspension copolymerization technique was used to synthesize the acrylic ion-exchange resin. The release of cefuroxime sodium followed diffusion controlled mechanism from acrylic ion-exchange resin microparticles coated with gellan.

4.4.9 Ordered Mesoporous Silica for Drug Delivery

Ordered mesoporous silica has found many applications in drug delivery systems, imagining catalysis, sensors, separation, etc. Mesoporous silica possess many advantages such as inert, outstanding textural and structural properties ,namely, large surface area and high pore volume, facile cellular uptake, biocompatibility, minimal toxicity, amenability for diverse fictionalization, and high physicochemical stability [77]. Moreover, mesoporous silica materials have been designed distinctively; thus, upon exposure to internal (pH, enzymes, reductive species, etc.) or external (light, magntetic fields, ultrasounds, etc.) stimuli triggers, the drug release rate can be controlled at the target site [78]. In 2011, silica nanoparticles were approved by the US FDA for phase I human clinical trials.

4.4.9.1 Controlled Release Novel Technologies for Specific Benefits

In the last decade, the combination of silica-based mesoporous materials was employed for controlled drug delivery. In one of the studies, biomimetic chiral mesoporous silica was synthesized by chiral anionic surfactant for the controlled release of poorly water-soluble drug indomethacin. Formulation controlled drug release without burst release and based on SEM study indicated that pH factor and stirring rate were the more dominant factors to determine particle length [79]. Soto RJ et al. [80] designed mesoporous silica using aminosilane surfactant ion-exchange reaction. Aminosilane-CTAB ion-exchange approach was used to prepare nitric oxide-releasing mesoporous silica nanoparticles with a range of sizes of 30, 150, 450, and 1100 nm. They reported the structure of the pores and the identity of the precursor aminosilane were important for release kinetics.

At the present time, mesoporous material approach in combination with the osmotic pump technology is being applied to develop the controlled release

formulation. Recently, a novel core-shell dual mesoporous silica nanoparticle comprising of core material (fenofibrate, PEO), push layer (PEO, sodium chloride, red iron oxide), and coating material (cellulose acetate, PEG6000) was developed. Prepared tablets, processing a high specific surface area, mesoporous structure and high pore volume which improve the solubility as well as provide controlled release due to used solid dispersion technology combined with the osmotic pump technology [81]. Shariatinia Z and Zahraee Z [82] developed controlled release mesoporous MCM-41 chitosan nanoparticle containing film. This novel delivery film included blended chitosan and poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) and carried metformin and MCM-41. The study derived 4% MCM-41 film revealed the least hydrophilicity and water uptake. Moreover, the greater swelling observed in acidic than alkaline media.

The combination of silica-based mesoporous material and polyelectrolyte-coated film was developed to control the release rate of a poorly water-soluble drug and for sustained release effect. Felodipine (BCS class II drug) was loaded into the pores of mesoporous silica, and polyelectrolyte multilayer shell was adsorbed onto the core layer. Chitosan and acacia were encapsulated through layer-by-layer mechanism and release rate–controlled mechanism [11]. Another new approach, surface-modified MCM-41 and SBA-15 nanoparticles of prodrug sulfasalazine were developed, and Eudragit polymers were used as modifying agents for oral controlled delivery [83], [84].

Most anticancer drugs have poor oral bioavailability. The mesoporous silica nanoparticles comprising nanostructure have shown promising targeting and controlled functionality. The pH-responsive polymer poly (acrylic acid) capped mesoporous SBA-15 (PAA/SBA-15) exhibited a high doxorubicin loading capacity and good biocompatibility. In addition, high solubility in colonic environment is present because of the removal of the capping layer [85]. Anirudhan TS et al. [86] developed layer-by-layer technique for the controlled delivery of 5-fluorouracil. The surface-functionalized mesoporous silica was coated with polyelectrolyte and prepared as biocompatible and biodegradable mesoporous silica nanoparticles.

4.4.10 Extrudable Technologies

Hot-melt extrusion (HME) is a continuous process where, the drug is dispersed into a carrier matrix to manufacture the quality drug products. As the name suggests, molten raw materials are pressed through a die under controlled condition to give uniform shape to the product [87]. Extrusion can be prepared using single- and twin-screw extruders. In hot-melt extrusion process, thermoplastic polymers such as polyethylene oxide (PEO), polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), Kollidon VA®, Eudragit®, and Soluplus® are used for immediate release formulations; ethylcellulose (EC), ethylene vinyl acetate (EVA), polyvinyl acetate (PVAc), poly(L-lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone, silicone, Eudragit ® (RS/RL), and lipid matrices are used for sustained release

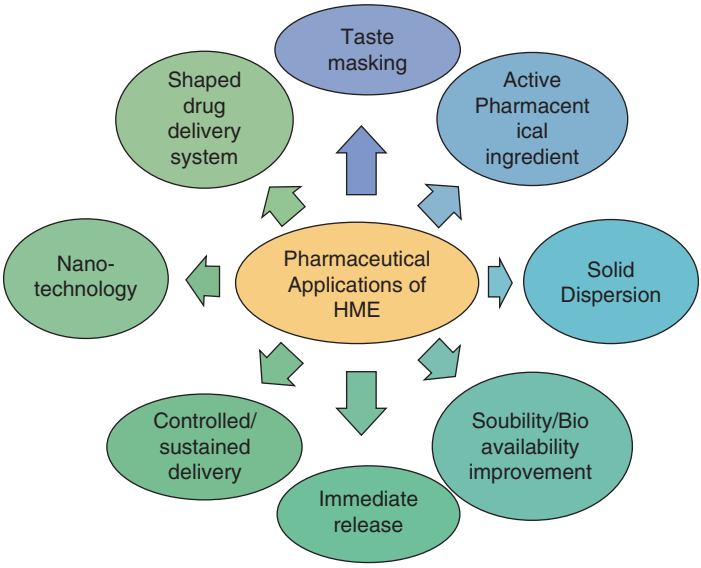

Fig. 4.18 Pharmaceutical applications of HME

formulations; citrate esters, sebacate esters, phthalate esters, and low MW PEGs are used as plasticizers [88, 89. Various applications are depicted in Fig. 4.18. A general hot-melt extrusion (HME)-based manufacturing process for solid oral dosage form is divided into four sections: (i) feeding of the extruder, (ii) conveying of mass and entry into the die, (iii) flow through the die, and (iv) exit from the die and downstream processing.

4.4.10.1 Applications of HME in Controlled Release

To our knowledge, many research works have been carried out to improve solubility/dissolution [90, 91] of drugs, but only a few research studies have been carried out for controlled release by preparing solid dispersion using melt extrusion method. Solid dispersion comprises of venlafaxine hydrochloride and Compritol® 888 ATO as the drug and hydrophilic polyethylene glycol (PEG 6000) and polyvinylpyrrolidone (PVP K30) as carrier excipients were fabricated using melt extrusion. Porosity of carrier has the capacity to control water transport and can release the drug in controlled manner out of the carrier [92].

Hot-melt extrusion (HME) has gained less attention in its application for the development of solid self-emulsifying drug delivery systems (SMEDDS). Silva LAD et al. [93] developed enteric solid-SMEDDS by HME and optimized using Box-Behnken design. The prepared HME showed complete reconstitution and drug release in pH 6.8, whereas it reduced drug release and showed no reconstitution in acidic conditions.

Multiparticulate systems, such as pellets, possessing a spherical shape and a small diameter are rapidly emptied from the stomach. Extrusion technique is very

popular for the production of pellets with high drug loading and high productivity. Several research studies indicated the use of extrusion method to prepare pellets for stomach or colon targeting. A novel floating bioadhesive pellet loaded with amorphous solid dispersion containing felodipine and polymers were developed by utilizing a single step of HME. The prepared system can possess many advantages such as the synergistic effect due to floating and mucoadhesion and enhance bioavailability and controlled release of drug [94].

Novel pharmaceutical manufacturing processes, combination of HME and other technology as a continuous process, provides many benefits. HME and injection molding [95], HME and high-pressure homogenizer, 3D printing with HME [96], electrospinning and melt extrusion are a few examples that were already developed by researchers. Solid-dispersion filaments containing drug-polymer matrix is fabricated via HME technology. Scientists demonstrated that coupling 3D printing with HME offers better controlled release profiles due to HPMC matrix [97].

4.4.11 Lipids and Oral Controlled Release Systems

The most important innovation made up until now is lipid-based systems. Owing to their remarkable hydrophobic nature, oral delivery of lipids has relatively poor bioavailability. The oral lipid system has earned significant attention due to many advantages such as biocompatibility and finer the particle size leading to more bioavailability, intertness, and nontoxicity. BCS class II drugs with high permeability and less solubility are suitable drug candidates for lipid-based oral formulations [98].

Solubilizing agents present in commercially available lipid-based oral formulations are water-insoluble excipients (oleic acid, propylene glycol esters of fatty acids, soy fatty acids, beeswax), triglycerides (corn oil, olive oil, hydrogenated vegetable oil, hydrogenated soybean oil, coconut oil, or palm seed oil), surfactants (tween 20, tween 80, span 20, glyceryl monooleate, PEG 1500 lauric glycerides, PEG 300 linoleic glycerides) [99]. Lipophilic drugs in lipid-based oral solid dosage may be classified as solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLCs), liposomes [100], self-emulsifying drug delivery systems (SEDDS), oily liquids, and mixed micelles.

4.4.11.1 Formulations of Lipid-Based Oral Controlled Systems

SLNs are colloidal nanocarriers that contain core of lipids with a particle size between 150 and 300 nm. The solid matrix of SLNs provides greater stability, no use of organic solvent, accessible scalability, and suitable system for both hydrophilic and lipophilic drugs. Oral bioavailability of drug can be enhanced by preparing drug-lipid conjugate via a disulfide linker. Furthermore, conjugation of drug-palmitic acid SLN expressed great cytotoxicity toward different cancer cell lines and showed greater bioavailability [101].

Nanostructured lipid carriers (NLC) contain unsaturated solid and liquid lipids with surfactants, which result in a partially crystallized lipid system [102]. Fabrication techniques of NLCs include high-pressure homogenization (HPH),

solvent injection method, phase inversion, microemulsion, multiple emulsion, ultrasonication emulsification, and membrane contractor technique. However, the widely used method is HPH. Formulation, particle size, and surface properties influence in overcoming gastrointestinal barriers on the oral drug delivery of lipid-based nanoparticles. The smaller nanoparticle (NLC-100 nm) showed higher uptake efficiency in Caco-2 cell ($P < 0.05$) as well as higher permeation ability in Caco-2 cell monolayer ($P < 0.01$) [103].

Liposomes are bilayer structures that contain enclosed vesicles of concentric self-assembling lipid bilayers composed of phospholipids and cholesterols. Physical stability of liposomes in the GIT is a common topic of discussion. The intestinal mucus adhesion and penetration are enhanced by the chitosan-thioglycolic acid-Pluronic F127 (CS-TGA-PF) liposome system for the delivery of paclitaxel [104]. Modified liposomes absorbed a threefold amount of mucin compared with that of unmodified liposomes, which have increased the residence time in the intestinal tract.

In the recent years, oral bioavailability of poorly soluble drugs has been improved by lipid-based self-emulsifying drug delivery systems (SEDDS). The system is made up of isotropic mixtures of oils (natural or synthetic), surfactants, and cosurfactants, which upon contact with gastrointestinal fluid, form emulsion by self-emulsification. Alayoubi A et al. [105] optimized the formulation variables of self-emulsifying drug delivery system (SEDDS) of a BCS class II drug nimodipine. They proved droplet size significantly affected on lipase activity absorption mechanism.

Mixed micellar systems consist of more than one molecular species, which represent a disk-like structure and look like a lipid bilayer. Oral delivery of vitamin K using mixed micellar system was developed. Stability of mixed micelles was improved using saponins at low pH [106].

4.4.12 Three-Dimensional Printing Technologies

According to International Standard Organization (ISO), "three-dimensional printing" is described as "fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology." In the current scenario, three-dimensional (3D) printing is one of the quickly evolving technologies whose applications in pharmaceutical industries are expanding day by day. 3D printing has become one of the most groundbreaking, influential, and versatile technologies for precise manufacturing of individually developed dosage. This includes multifunctional drug delivery systems with controlled release characteristic, complex inner geometries and structure, predesigned surface texture, incorporation of multiple drugs, and adjustable personalized dosage forms [107–110]. 3D printing technology has been proven as a revolutionary and powerful technology for manufacturing oral controlled drug delivery systems.

One such solid freedom fabrication technology based on 3D printing is TheriFormTM. In a layer-by layer fashion, a dosage form is fabricated using inkjet

printing technology that allows fine spatial placement of specific substances inside the body of the dosage form, which in turn provides control over the release of active pharmaceutical drug from the assembled structure of a dosage form. The individual layer of the dosage form printed here is considered as two-dimensional slice, and motion-controlled print head dispenses liquid into a thin powder layer. At the same time, a powder bed is lowered after each printing pass and the additional powder is spread. The whole printing process is repeated with a new two-dimensional slice until the dosage form is completely built. The process allows placement of one or more active substances within selected locations inside the dosage form, along with other pharmaceutical materials that control the release properties of these activities [111]. Various approaches for 3D printing have been investigated so far such as inkjet printing, direct-write, zip dose, thermal inkjet (TIJ) printing, desktop 3D printing, and fused deposition modeling (FDM) (Table 4.3). Another most widely used method for 3D printing is fused deposition modeling (FDM). To create a 3D dosage form, FDM printers use a thermoplastic filament that is heated to its melting point and then extruded, layer by layer.

4.5 Oral Controlled Release Systems: In Vitro Testing

Dissolution of the drug from the controlled release dosage is an important feature of oral controlled release dosage and is a well-defined process before the drug gets absorbed. It can be illustrated as a procedure in which solid solute gets dissolved in the solvent according to its affinity toward the solvent to develop the solution system. While drug release generally agrees with the release of drug from dosage form into specific release medium in line with the properties of different dosage forms such as immediate release, controlled release, and prolonged or extended release dosage forms, etc. The release kinetics of the drug from specific formulations and its dissolution mainly take place in the determination of in vivo rate and the extent of availability of drug from the dosage form. In vitro dissolution is normally performed to determine the release pattern and the profile of the drug from the formulations. Release of the drug from oral dosage form and its dissolution is generally controlled by a number of factors such as dosage form types, diffusion profile of drug, partitioning of drug, and osmotic pressure. In vitro drug dissolution study plays a vital role in quality control process as well as to predict in vivo performance of oral controlled release formulation. Currently, to demonstrate bioequivalence between the testing and reference formulation product and to get approval of most generic drugs, in vitro studies are recommended by governing agencies. Compendial methods are mainly developed for oral (USP type 1 and 2 apparatus) formulations. The in vitro drug dissolution apparatus commonly comprises a vessel, release medium, a lid and paddle, or basket for agitation. The release medium can be maintained at specific temperature conditions and agitation to mimic the physiological conditions and to avoid wobble. The in vitro drug release from controlled, sustained, extended, and pulsatile release tablets is largely carried out using paddle-type tablet dissolution apparatuses maintained at 37 °C comprising of 900 ml of

Table 4.3 Some examples of 3D printing technology in research

3D printing technology	Dosage form	Active ingredient	References
Desktop 3D printer	Controlled release tablet	Guaifenesin	[112]
A laboratory-scale 3D printing machine	Near zero-order release capsule	Pseudoephedrine HCl	[113]
3D printing technology	Zero-order release oral dosage form	Pseudoephedrine hydrochloride	[113]
3D printing technology	Zero-order drug release complex tablets	Acetaminophen	[114]
FDM 3D printing	Modified-release tablet	5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA)	[115]
Extrusion 3D printing	Controlled release tablet	Captopril with nifedipine and glipizide	[116]
Thermal inkjet printing	Personalized-dose oral films	Salbutamol sulfate	[117]
Extrusion 3D printing	Extrusion printed polymer structures	Dexamethasone-21-phosphate disodium salt	[118]
Hot-melt 3D inkjet printing	Controlled release tablets with bespoke geometries (honeycomb architecture)	Fenofibrate	[119]
3D printing	Immediate-extended release tablets	Chlorpheniramine maleate	[120]
3D printing of the outer structure, followed HME	Oral dual-compartmental dosage unit with controlled release	Rifampicin (RIF) and isoniazid (ISO)	[117]
FDM 3D printing	Channeled tablets	Hydrochlorothiazide	[116]
FDM 3D printing with HME	Double-chamber device composed by a tablet embedded within a larger tablet (DuoTablet)	Glipizide	[115]
FDM 3D printing with HME and fluid bed coating	Capsule-shaped tablets	Budesonide	[114]
Inkjet printing technology with flexographic printing	Solid dosage forms	Riboflavin sodium phosphate (RSP) and propranolol hydrochloride (PH)	[121]
FDM 3D printing	Oral solid dosage forms	Hydrochlorothiazide	[122]
3D printing HME	Tablets	Acetaminophen	[123]

dissolution medium with agitation rate of 50–75 rpm. To mimic gastrointestinal (GIT) conditions, 0.1 N HCl buffer solutions with a pH around 1.2 is used as the dissolution medium for the first 2 h that mimics the pH conditions of the stomach. For next 6 h, dissolution medium can be changed with phosphate buffer pH 6.8 to

mimic in vitro pH conditions of the intestines [124]. At a prefixed time interval during the study, the solution is withdrawn and analyzed spectrophotometrically after a suitable dilution. Similarly, the in vitro characterization of tablet floating behavior, such as floating lag time (the time the tablets took to emerge on the water surface) and the duration of floating, is evaluated in a paddle-type dissolution apparatus mimicking the GIT conditions [125]. For formulations containing poorly soluble drugs or low-dose formulation with sustained release, a flow-through cell apparatus is a broadly accepted dissolution test. For testing of powders, tablets, soft and hard gel capsules, semisolid formulations, various types of cells are available [126]. Thus, though there is one apparatus used to carry out an in vitro drug release test or in vitro dissolution test, several modifications can be done based on pharmacopeial monographs. The apparatus is simple and easily available commercially; however, there is a need to develop and validate a specific methodology for particular formulation. Depending on the formulation components, physicochemical nature of drug and physical attributes of the product, a particular condition of the test to mimic GIT conditions, selection of the apparatus, and composition of release media can be decided. Even the hydrodynamics of releasing media has been affected by dimensions and total geometry of the apparatus and consequently impacts drug release from the formulation [127, 128]. Only a small change can lead to larger differences in the release profiles of drugs and hence in pharmacopeias, accurate explanations of all the features with their dimensions are given. The ultimate objective of the dissolution is to collect data that can be able to prove the drug release mechanism from the dosage. Moreover, information collected from the abovementioned measurements can facilitate the quick optimization and development of a rationale controlled release formulations. The external variables, which can affect drug dissolution, are alignment and centering of the stirrer, type of stirrer, agitation rate, vibration of the apparatus, composition of medium, media pH and ionic strength, dissolved gasses, composition of media, temperature, and evaporation flow pattern of the media, sampling time and position, interference of drug detection process, sorption of drug onto the equipment, and blockage of filters. Additionally, the type of dosage form and its composition are crucial factors for a formulation scientist, and accordingly the method is developed and validated [84, 129]. Solubility of the drugs in release media, chemical or physical changes during the release of a drug from formulation, and development and validation of analytical method are also crucial to know before doing in vitro studies and to confirm the mechanism of release.

4.6 Oral Controlled Release Systems: In Vivo Testing and Animal Models

Drug discovery and development process normally take around 10–15 years. Depending on specific therapeutic field, around one billion US dollars is required to fetch a single drug molecule in the market. Various new therapeutic agents are approved by the Food and Drug Administration (FDA). Many dosage forms

sometimes entered officially in the market for public survey, before approval [130]. After ensuring it based on standard methods of characterization of the new drug, its pharmacokinetics and pharmacodynamic determination ensure its efficacy and toxicity. The abovementioned steps continue to play the most important role in drug discovery and development process of new drug molecules. Validation methods are sorted from in vitro evaluation on cells and tissues isolated from living organisms and in vivo evaluation by taking sampling from suitable animals. In vitro determination is an economic method because it ensures to "fail fast, but fail cheap" if the drug does not give expected results. Moreover, in vitro evaluation is not accessible to living organisms to reduce cost, which in turn also reduces ethical problems and experimental constraint. These cost-effective and ethically straight method gives a source for the predictability of a drug's accomplishment or failure for in vivo studies and at later stage of clinical evaluation. In vivo evaluation is crucial in drug development practice because it offers to assess a drug's parameters, such as its side effects or adverse effects, in vivo drug-drug interaction normally it cannot be determined using in vitro methods. Several confrontations adjoining in vivo determination can be met by selecting a suitable animal model that best exemplifies the human body, where the drug will affect. Any perfect animal model recognizes the availability of drug in the GI tract due to its physiological state such as pH and fasted or feed condition and can mimic possible reticuloendothelial system (RES) uptake. A new in vivo method has conceded to less enveloping use for gathering data vital to metabolism and drug-drug interactions before USFDA approval [131–133].

4.6.1 Role of Animal Model

The ability of the researchers to improve and enhance the welfare of humans and animals normally depends on the modification made in research by adopting the animal models. Usually to study the drug pharmacokinetic parameters, animal models play a crucial role in testing drug characteristics in vivo. Because of various physiological variations between humans and animals, even with the closely similar human and monkey, these animal models do not allocate one to predict totally same results if the therapeutic agent arrives at the assessment of clinical trials. For instance, the bovine stomach is more complex than a human's as it comprised of specific microflora and pH ranges from 3 to 6 [134]. Usually, human studies are crucial to access the drug's behavior in humans since animal models do not envisage with sufficient faith what will occur in humans. It is a chance of diminished exterior power of animal testing, when the new drug executes in clinical trials owing to the evaluation of the result on homogenous groups of animals versus heterogeneous humans. Moreover, the drug characterization in an animal is effectively used to access toxicities, adverse effects, and drug-drug interactions with ADME, before it attains clinical trials to make sure the drug safety [135].

4.6.2 Animal Model Used to Study Absorption

The drug concentration, drug receptors, and the pH of the gastrointestinal tract normally effect on drug absorption process [136]. For this reason, dogs are most widely used for the assessment of in vivo absorption, specifically pH-dependent drugs [137]. Dogs have the most identical pH surrounding to human changes overall. Dogs have a high initial pH which makes them great animal models for drugs especially those drugs whose drug absorption is influenced by the fasted/fed condition. Furthermore, multidrug resistance protein 2 mRNA distributions are identical in dogs and humans, which are conclusively related with resistance except their contraction and expulsion times are dissimilar [136]. In addition, some drugs show inherent effects on GI motility and can significantly affect the other drug absorption. Some errors in animal model, in association to different type, may be disregarded if they are not supposed to be difficult at the stage of human studies [134, 138]. The pH-sensitive drugs normally access on rats and other rodents. The GIT pH and its pH variation are not particularly similar to those of humans, not like dogs. The resemblance of transporters of therapeutic agents offers access of absorption of drug orally, but not bioavailability testing, as it may be determined successfully in the rat model. Exclusion of P-glycoprotein, multi-drug resistance protein 3, and glucose transporters 1 and 3, the rat gives the similar distribution of drug transporters and its expression in the intestine. Rabbits are the only lab-scale animals used to access absorption and permeation using buccal mucosal route that has normally mucosal lining (non-keratinized) same as human tissue, and they are majorly adopted in investigational studies [136]. Existing information advocates that no solitary animal can imitate the GI uniqueness of a human. However, monkeys are the adjoining in like uniqueness to humans in their GIT anatomy and physiology [139].

4.6.3 Animal Models Used to Study Distribution

The foremost characteristics of drug distribution are normally according to the extent of efflux by canalicular membrane and the carrier-mediated transport of drug in the liver. For distribution studies, majorly mice and rats are used. The organic anion transport polypeptides (OATPs) use in rodents should be similar to the application of OATPs in humans. Moreover, the identification of drug-drug interaction by rodents can be relevant to humans [136]. For instance, rifampin's inhibition of hepatic uptake by OATP1a4 diminishes the volume of distribution, which is the same for individuals and rodents. Furthermore, early in drug discovery, ADME characterization using different dose treatments and administration routes in animals permits quick removal of drug, which assists the assembly of an applicant that is more likely to achieve something in the preclinical stage [140].

4.6.4 Animal Models Used to Study Metabolism

Assessment of metabolism on the suitable animal model has a tendency to focus on the alteration of activity or metabolizing enzymes expression. In vivo metabolism study on animal models normally highlight the CYP450 groups in the liver, which is exclusively factual for the assessment of drug-drug interactions. Various cytochrome (CYP) P450 enzymes can catalyze the similar activity, so supplementary data are necessary to determine the animal species most similar to man with respect to the different CYP450 activities [141]. The almost similar relationship between enzyme kinetics and activities can be found in various higher animals, such as dogs (beagle), monkeys (cynomolgus/rhesus monkeys). To study the metabolism, rodents are inadequate as a model animal because not much information related to the CYP enzyme kinetics and different effects of drugs on said enzymes stays unidentified [142]. Different isoforms of CYP enzymes are found in rats that are normally not found in humans. For the abovementioned reason, the prediction specifically based on data is more likely to difficult. Regarding the CYP enzymes, monkeys (rhesus and cynomolgus) acquire the most metabolic resemblance with individual. Around eleven family members of CYP enzymes such as CYP1A, CYP2A, CYP3A, CYP2C, CYP2D, CYP2E, and its subfamilies are around almost ninety percentage homologous in amino acid order. The CYP2C76 is exception and it has about seventy percentage homologous to individuals that may report for variation in metabolism of a number of therapeutic agents. This highlights the significance of indulging the metabolism of a therapeutic agent when selecting an animal model [136].

4.6.5 Animal Model Used to Study Excretion

To determine the rate of excretion, the major parameters such as glomerular filtration rate (GFR), renal flow of blood, tubular secretion, and reabsorption are considered for the study [143]. The GFR is related to the quantity of nephrons; normally it differs extensively all over the accessible animal models. Those genus that utilizes passive absorption and GFR as the main system for renal excretion would be a superior animal model for an excretion study in vivo. However, the rate and extent of drugs excreted through tubular secretion and reabsorption differ crossways in a variety of animal models. The Food and Drug Administration endorse the recognition of drug metabolism differences between animals employed in safety evaluation and humans at the early phase of development. Based on the data acquired from excretion studies on animal models, the dosing should be customized by considering its renal excretion rate and the quantity of nephrons [144]. The enzyme groups of organic cationic transporters (OCTs) and organic anionic transporters (OATs) are the foremost renal uptake transporters in the renal tubules with the variety of OCTs and OATs in unlike genus. For instance, OCT2 and OAT2 are the mainly universal types with OCT2 measured as transporters of the kidney and OAT2 recognized at the basolateral membrane of proximal tubules in human. The OCT1, OAT1, OCT2,

and OAT2 are the key enzymes implicated in renal metabolism in rats. Encouraging associations subsist for OAT1 in rats, monkeys (cynomolgus), and humans, while OAT3 associations subsist only for humans and monkeys (cynomolgus). The drug will be excreted renally, when the alternative of animal model should replicate resemblance among the animal and humans in their transport enzymes [136].

4.6.6 Canine Biorelevant Dissolution Method

Controlled release solid oral dosage forms are a fast-growing formulation option used in drug products to resolve a number of pharmacological challenges. These challenges include allowing for once-daily dosing of active pharmacological ingredients that reveal unfavorable pharmacokinetic properties, blunting and delaying of the maximum concentration of the drug in the plasma for particular indications, or even avoiding adverse events associated with high maximal concentrations of drug in the plasma. Dissolution is the best in vitro methodology available for rank ordering and estimating the in vivo drug release rate of controlled release oral formulations. Standard QC dissolution methods do not accurately mimic the physicochemical environment or the forces inflicted on the dosage form within the GI tract due to the media used and the agitation methodologies. In recent times, dissolution testing performed in biorelevant media, also referred to as biorelevant dissolution, has made a great impact on the development of more predictive dissolution models. Development of a biorelevant dissolution method simulates the conditions experienced by a dosage form within the GI tract of the beagle dog, which can be used to predict the in vivo performance in beagle dogs of controlled release matrix tablets as compared to standard dissolution methodologies or human biorelevant dissolution. This method can be useful when the dog is being used as the preclinical proof of concept (POC) model to recognize the differences in how the dosage form will perform in dogs as compared to humans, or can be helpful in choosing a formulation for pharmacodynamic studies or for sustained or controlled release formulation.

4.7 Challenges and Recent Advancements

Oral controlled release formulations are endowed with the constant drug delivery through oral route with reproducible and predictable drug release kinetics for a predetermined period right through the route of gastrointestinal transit phase. Moreover, the system also targets the drug delivery to a particular area within the GIT for systemic/local action. Majorly, the drug dosage forms invented for systemic action through oral administration route, irrelevant of the method of drug delivery in different forms such as sustain release/controlled release, immediate, and the dosage for design such as liquid/solid/ dispersions, must be built up inside the intrinsic attributes of gastrointestinal physiology [145, 146]. The key areas of possible challenge in the oral controlled release formulation are as follows:

- *Drug delivery system development*: To formulate a feasible oral controlled release drug delivery system that can be able to deliver a drug at a desirable site within the required duration effectively for favorable action.
- *Modulation of GTI transit time*: By altering the GTI transit time, dosage form can be directed to a target site/at the absorption location and exists there for a longer time to improve the drug delivery from the dosage form.
- *Reduction of hepatic first-pass effect*: If the drug has extensive hepatic first-pass metabolism, the precautionary actions should be invented to bypass the degree of hepatic first-pass effect.

At present, technical improvements have been done in the research to control the rate of drug release via oral route by defeating physiological difficulty, such as shorter gastric residence times (GRT) and irregular gastric emptying times (GET). Various advancements are presently employed in the extension of the GRT using different approaches such as hydrodynamically balanced systems (floating drug delivery), swellable and expandable systems, bioadhesive systems, high-density systems, altered-shape systems, and other time-dependent gastric emptying devices. The purpose of development of the oral controlled release system is mainly for: (1) enhancement of the drug residence time in the stomach and to achieve extended period of drug release in order to improve drug bioavailability and [2] reduction of dosing frequency and patient compliance improvement. In the past decade, consideration in the direction of development of controlled and sustained release dosage forms has improved significantly. In some of specific fields, it is possible to utilize quite sophisticated methods that can be able to offer tremendous drug release rate control, e.g., a self-determining insulin delivery using osmotic drug delivery. Advancements in oral controlled release formulation of hydrophobic drug molecule and biological drugs are expected to have a major impact on the industries. Moreover, the constant improvements of current dosage forms are also crucial, when it becomes cost-effective and more efficient to deliver the drug in a controlled manner. Those progresses include modified and novel excipients, improved processes, and advanced equipment as tools for the development of controlled release dosage forms for oral administration [145, 146]. Several technologies that are patented on controlled release dosage form are given in Table 4.4.

Table 4.4 Patented technologies of controlled release formulation

Sr. no.	Patent no.	Title of patent
1	WO2013098831A2	Controlled release formulations of nisoldipine
2	US12064687	Controlled release formulation
3	WO2007103200A3	Oral controlled release formulation for sedative and hypnotic agents
4	US6893661B1	Controlled release formulations using intelligent polymers
5	WO2014147526A1	Tofacitinib oral-sustained release dosage forms
6	US20060275367A1	Extended release formulations
7	US4167558A	Novel sustained release tablet formulations
8	PCT/ US2008/014080	Controlled release formulations of levodopa and uses thereof

4.8 Conclusion

Nowadays, research progress toward the modern technologies primarily emphasizes on the target concept for successful oral controlled delivery. Oral controlled release formulations provide benefits over conventional formulations by customizing the biopharmaceutic, pharmacokinetic, and pharmacodynamic properties of the drug thereby reducing dosing frequency to an extent that single daily dose is enough for the management of uniform plasma concentration and to achieve maximum utility of drug. Controlled release formulation acts on several mechanisms such as osmotic pressure, matrix system, reservoir system, and altered density system to control the drug release rate. Advancements in oral controlled release formulation of hydrophobic drug and biological drugs are expected to have a key impact on the industries, especially pharmaceutical- and biotechnological-based industries. Furthermore, the steady improvements of existing formulations are also crucial, when it becomes economic and more efficient to deliver drug in controlled manner. From the present discussion, it can be concluded that the oral controlled release drug delivery system has been commonly adopted and most convenient route for drug delivery. Additionally, reasonable cost has led ease of market penetration as a replacement of oral conventional formulations.

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Peyer's Patch: Targeted Drug Delivery for Therapeutics Benefits

5

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_5

Abstract

Specialized microfold cells (M cells) within the follicle-associated endothelium of intestinal Peyer's patches play a key role in body's defence mechanism by endocytosing macromolecules. Particulate uptake by the Peyer's patch offers a very attractive avenue for delivering drugs through the peroral route. This review describes the pathway of drug delivery by Peyer's patch targeting and its associated advantages. Disorders affecting the function of the lymphatic and immune system can be treated by targeting the active moieties at the Peyer's patch. Drugs have been delivered to the Peyer's patch for autoimmune disorders like HIV/AIDS, rheumatoid arthritis, chronic inflammatory disorders, tuberculosis, psoriasis and cancer. Several drug delivery systems like nanoparticles, dendrimers, microspheres, SMEDDS and liposomes have been reviewed for oral lymphatic delivery of small-sized drugs as well as macromolecular drugs like vaccines for immunogenic response. Factors such as surface charge, size, hydrophobicity, surface modification and conjugation have been found to be important determinants in modulating the targeting of these drugs to Peyer's patches. These novel drug carriers are particularly useful in improving the oral bioavailability and efficacy of the drugs by selective utilization of lymphatic absorption avoiding the portal circulation. Further research in the direction of elucidating the mechanisms of drug transport to the intestinal lymphatic system specifically the cellular and intracellular events may help in delivering a greater number of drugs through the Peyer's patch.

Keywords

Peyer's patch · Targeting · Nanoparticles · Dendrimers · Microspheres · Nano-/microemulsions · SEDDS/SMEDDS · Liposomes

5.1 Introduction

Mucosal surfaces of the respiratory, gastrointestinal and urogenital tract are the first line of defence system as they are the most probable areas of the body through which majority of the antigens enter into the internal sterile environment. The intestine contains high numbers of microorganisms which are normal residents of the system. The mucosal immune system is constantly challenged by pathogenic microorganisms ingested with food or fluids into the gastrointestinal (GI) tract. Immunity at these mucosal surfaces is essential in preventing many types of infection. These

mucosal surfaces have acquired specialized innate and adaptive defence mechanisms which are functionally different from the systemic immune system. The immune system of the gut is capable of an appropriate response characterized by either ignorance or active suppression against non-pathogenic antigens, whereas for pathogenic antigens, it is able to prevent their attachment and colonization at epithelial surfaces and prevent possible damage of mucosal tissues.

Differentiation between normal resident flora and pathogens in the gut is achieved once the lymphoid cells interact with the intestinal epithelial cells. One of the main lymphoid organs (70% of the body's immunocytes) is the gut-associated lymphoid tissue (GALT) majorly made up of isolated and aggregated lymphoid follicles. Marco Aurelio Severino first described aggregated lymphoid follicles in 1645 in Italy. Later in 1677, the Swiss pathologist Johann Conrad Peyer gave detailed account of these follicles and hence are named as Peyer's patches (PPs). PPs are made of aggregated lymphoid nodules surrounded by a particular epithelium and are found all through the ileum part of the small intestine.

PPs are mainly scattered on the antimesenteric side of the gut and are roughly oval or rectangular lymphatic tissue nodules that are similar to lymph nodes in structure, except that they are not surrounded by a connective tissue capsule. Majority of PPs with larger size are found in ileum, with some of small size in the adjoining jejunum and a few extending as far as the duodenum. PPs also vary with respect to the age, wherein they are maximal at puberty and decline thereafter.

The PPs are organized into three major regions: (1) the follicular and interfollicular area, (2) the follicle-associated epithelium (FAE), and (3) the associated subepithelial dome (SED) which lies between follicles and the FAE.

PP lymphoid follicles make up the follicular and interfollicular areas. The germinal centre (GC) which forms the core of each follicle has proliferating B lymphocytes, follicular dendritic cells (FDCs) and macrophages. As GC forms the core of each follicle, the PPs have curved appearance.

The follicle is covered by SED containing various types of cells such as B cells, T cells, macrophages and dendritic cells (DCs).

FAE is outlined by a high population of infiltrated B cells, T cells, macrophages and DCs. FAE shows the presence of enterocytes, goblet cells and modified epithelial cells termed M (microfold) cells which are specialized enterocytes. These M cells are a unique feature of FAE and bind with many luminal antigens and transfer them to the underlying immune cells, which then ignore or trigger the immune response depending on the antigen being processed, causing either tolerance for self-antigens or systemic immune cell response for non-self-antigens. These same M cells hence offer a challenge for targeting of drugs at the PPs [1]. M cells differentiate from the enterocytes, due to the presence of membrane-bound lymphotoxin ($LT\alpha1\beta2$) on regional lymphoid cells, mainly B cells. Bacteria in the lumen regulate the ratio of enterocytes and M cells in the FAE. For example, patients with typhoid or pneumonia will have a greater number of M cells due to the presence of *Streptococcus pneumoniae* or *Salmonella typhimurium* which are pathogenic.

PPs have a rich supply of lymph and blood. Naive lymphocytes enter into the PP through endothelial venules and escape the PP by lymphatic vessels.

5.2 Pathway of Drug Delivery by PP Targeting and Its Benefits

Soluble proteins, antigens, bacteria and viruses like extracellular materials are transported across the intestinal wall by M cells using various mechanisms such as endocytosis, phagocytosis, pinocytosis and micropinocytosis and deliver it at the basolateral side by exocytosis. At this site these macromolecules/microorganisms interact with lymphocytes and macrophages or are drained in the lymphatic system. Targeting of PP is a convenient route for lymphatic delivery of drugs via oral route [2].

In a manner similar to the one described above, the nano- and microparticles or vaccines can be taken up by M cells and delivered to the gut-associated macrophages or dendritic cells. However, the endocytosis by M cells depends on the particle size, zeta potential and surface modifications of the particulate system. Delivery of vaccines is possible only after the vaccine particulate is coated with appropriate ligand for targeting the M cells [3]. Nonionized, hydrophobic nanoparticles (below 1 μm) coated with M-cell-specific lectins/IgA/antibodies against M cells will form an ideal system for delivery of vaccine/drugs via PPs as shown in Fig. 5.1.

Coating the vaccine or drug with antibodies targeting the apical surface molecules of M cells will help in developing the desired delivery system [4]. M-cell targeting is possible if the receptors on their apical surface are identified; unfortunately very few of these receptors are known, and they are also expressed on the neighbouring enterocytes. The identified receptors include Toll-like receptors (TLR), platelet-activating factor receptor (PAF), apical glycoprotein (GP2) and α5β1

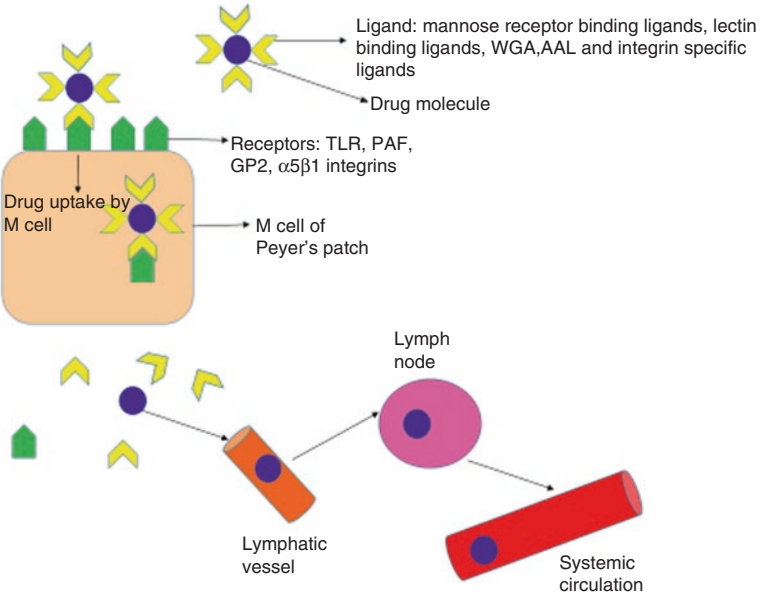

Fig. 5.1 Schematic presentation of drug uptake by M cells

integrins which bind to pathogenic molecules like lipopolysaccharides, peptidoglycan and some proteins like flagellin.

Major ligands used for targeting PPs are mannose receptor-binding ligands, mannose, mannan and mannosamine; lectin-binding ligands, *Ulex europea* agglutinin I (UEAI), wheat germ agglutinin (WGA) and *Aleuria aurantia* lectin (AAL); and integrin-specific ligands, RGD peptide, RGD peptidomimetic (RGDp), LDV derivative (LDVd) and LDV peptidomimetic (LDVp). Of all these, the RGD ligand which targets the α5β1 integrins and increases the transport via M cells is the best one to target PPs [5, 6]. However, binding to M cells is not always necessary for transcytosis as is evident by the fact that PLGA nanoparticles are easily absorbed by M cells in spite of not binding to them [5]. However, one needs to keep in mind that drug delivery can be unsuitable by this route due to higher amount of drug required to elicit pharmacological response and the difficulty in incorporating this high amount in the nano- or microparticulate system [7].

5.3 Types of Conditions/Disease that Requires PP Targeting

PPs being a part of the gut-associated lymphatic tissue, any disease that affects or modifies the functioning of the lymphatic and immune system can be treated by targeting the said drug at the PPs. Autoimmune diseases are the major conditions that will need PP targeting followed by infectious diseases, chronic inflammatory disorders and cancer.

Let us now have a look at these conditions and discuss the benefits of PP targeting.

5.3.1 Autoimmune Conditions

(a) HIV/AIDS

HIV is a retrovirus, which affects the CD+4 helper T cells. The cells may remain affected for a chronic time without revealing any symptoms, but as soon as the cells get activated, the virus activates and very soon starts depleting the host helper T cells. Since the helper T cells are key mediators of the immune system, as soon as this number goes down, the immune system weakens. Mucosa of the alimentary tract is one of the sites for HIV reservoir apart from the respiratory and genital mucosa, brain and lymph nodes. The virus can also affect the stem cells and macrophages at these sites. The current treatment for AIDS is antiretroviral therapy. However, targeting these drugs at the abovementioned reservoir sites and reducing metabolism of the drug are some challenges to be conquered through effective drug delivery systems. Antiretroviral targeting of the M cells of PPs could be a solution to the challenges mentioned above. This will not only target the virus residing at the mucosa of the GIT but also those residing at the lymph nodes, since uptake by M cells of PPs drains into the lymphatic system [8].

The gastrointestinal tract has long been identified to play a vital part in the pathogenesis and transmission. Due to breakdown of the mucosal barrier and infection of the memory CD+4 T cells, disease progresses. Local immunization with the help of vaccines could be a possible option for prevention and subsequent eradication of this deadly human immunodeficiency virus [9].

(b) Rheumatoid Arthritis
Rheumatoid arthritis (RA) is one of the autoimmune disorders that affects the joints and gradually affects the other vital organs including the lungs and heart. PPs harbour immune cells like macrophages and dendritic cells, of which the dendritic cells are crucial in the development of oral tolerance by enhancing the mucosal immune response. Administration of oral vaccines comprising of antigens similar to autoantigens can cause local and systemic priming resulting in gradual induction of systemic tolerance and hence a cure for many autoimmune disorders. A new subset of DCs, namely, CD 11C+ and CD 11 B+, play an important role in inhibiting the progression of rheumatoid arthritis by inducing tolerance [10].
A second mechanism for oral tolerance which may work for rheumatoid arthritis is suppression of immunity. CD4+ T cells and CD8+ T cells reside in PPs. In RA, it is observed that increased CD4+ T cells in periphery and reduced CD8+ T cells in PPs are responsible for the progression of arthritis. These numbers can be modified by targeting the PPs and bringing about an immunosuppressive effect for the treatment of rheumatoid arthritis [11, 12]. The same approach is applicable to treat other T-cell-mediated autoimmune diseases such as multiple sclerosis and type 1 diabetes.

5.3.2 Chronic Inflammatory Disorders

(a) Atopic Dermatitis
Atopic dermatitis is a chronic inflammatory ailment of the skin. It starts with modification of the filaggrin gene expression that codes for a skin protein to form a barrier. Due to inability of the body to form this protein, the skin becomes leaky causing enhanced penetration of allergens as well as microbes into the skin. The body reacts to the presence of these antigens by activating T cells in the skin, which in turn cause production of IgE responsible for the pruritus. Topical steroids, topical calcineurin inhibitors, antibiotic therapy and immunosuppressive agents form the treatment regimen for this condition [13]. Since the disease involves systemic inflammatory response, one can think of targeting the systemic immune system via the PPs which will deliver the immunosuppressive agent to the target tissue, i.e. lymphatic tissue.

(b) Psoriasis
Psoriasis vulgaris and psoriasis arthritis are diseases that have a similar pathology as atopic dermatitis involving defects in the skin barrier function and immune system—both innate and adaptive. Currently phototherapy and therapy

with immunosuppressive agents/TNF-alpha inhibitors are instituted for the patients with psoriasis. Akin to atopic dermatitis, one can postulate PP targeting of immunosuppressive agents/vaccines for treating psoriasis, although no such studies have been conducted till date.

(c) Infectious Diseases

(a) Tuberculosis

PPs are common entry points for the tubercle bacilli. These bacilli are engulfed by the M cells and presented at the basolateral side to the antigen-presenting cells—macrophages and dendritic cells. The phagocytosed bacilli are then transported to other organs by the lymphatic system [14]. The same route could be followed by tubercle antigen upon oral delivery and help in the induction of mucosal and systemic tolerance.

(b) Cancer

Cancer is a disease which can affect any organ. It happens due to uncontrolled growth and multiplication of cells which evade other cell types and induce tissue injury, causing organ dysfunction gradually.

Chemotherapy, radiation therapy and surgery are the options available for controlling cancer. However, till date there is no definitive therapy for curing cancer, and also the incidence of relapse is more. Cancer vaccines developed against particular antigen could be an alternative to treat cancer, but they fail to elicit a strong tumour-targeted immune response. To overcome this problem, vaccines targeting M cells via the PPs can bring about not only mucosal but also systemic immune response. Again, the reason being M cells drain the contents in the lymphatic tissue, which then stimulate the T and/or B lymphocytes against the antigen delivered by the vaccine. These activated lymphocytes then aim at the cancerous cells and cause apoptosis, resulting in complete remission of the cancer.

Most of the anticancer medicines are to be given for a chronic period, and patients suffer from many side effects due to the prolonged therapy. M-cell targeting will help to enhance bioavailability of anticancer drugs and subsequent reduction of the dose, and hence the incidence/severity of the side effects can be reduced. It will also help to deliver the drug at the site of tumour for a prolonged period [15].

5.4 Types of Drugs that Can Be Delivered Through PP Targeting

Drugs which undergo extensive first pass metabolism could be the choice for targeting the M cells, in order to increase their bioavailability. Few M-cell-targeted drug delivery systems are shown in Table 5.1 and discussed in brief as below:

Rifampicin a preferred drug in the therapy of tuberculosis has shown a high lung: plasma concentration ratio when delivered as a nanoparticle using glyceryl monostearate and Gantrez as lipid and mucoadhesive polymer respectively. This system targets the M cells of PPs for absorption. Thus, drugs delivered in this manner could

Table 5.1 Approaches to target PP in various diseased condition

Name of the drug	Disease targeted	Delivery to PP
Rifampicin	Tuberculosis	Nanoparticles of glyceryl monostearate and Gantrez as lipid and mucoadhesive polymer
Isradipine	Hypertension	Nanoparticles using Dynasan 114 as a lipid and Poloxamer 407
Felodipine	Hypertension	PLGA nanoparticles
Agomelatine	Antidepressant	Nanostructured lipid carrier using Dynasan 118, Labrafil 2125 Cs and tween 80 as surfactant
Docetaxel	Cancer	Hydroxypropyl trimethylammonium chloride chitosan-modified solid lipid nanoparticle
Doxorubicin	Cancer	Sodium dodecyl sulphate-modified chitosan-lipid nanoparticle
Epirubicin	Cancer	Styrene maleic acid nanomicelles
Resveratrol	Oxidative stress	PLGA nanoparticles
Insulin	Diabetes	Nanoparticles prepared from Eudragit and poly(-ε-caprolactone)
Calcium	Hypocalcaemia	Microspheres using bovine serum albumin
Iopinavir	AIDS	PLGA-based nanoparticles
Atazanavir	AIDS	Nanoparticles using Eudragit RL100
Diphtheria toxoid	Diphtheria	Alginate-coated microparticle
Ag85 A, an antigen from *M. tuberculosis*/*M. leprae*	Tuberculosis	Guar gum-coated nanoparticles, lectin-coupled microspheres
Legumain DNA vaccine	Breast cancer	Alginate-coated chitosan nanoparticles
Vaccine of ovarian cancer cell line	Ovarian cancer	Eudragit FS30D and hydroxypropyl methyl cellulose acetate succinate and *Aleuria aurantia* lectin
DNA vaccine comprising of secretory chemokine CCL21 and survivin	Lung cancer	Attenuated *Salmonella typhimurium*

be effective for treatment of tuberculosis with no additional increase in dose and less side effects as the portal circulation is bypassed [16].

Isradipine, one of the calcium channel blockers used for the treatment of hypertension, has low bioavailability because of the first pass metabolism. Isradipine-loaded solid lipid nanoparticles using Dynasan 114 as a lipid and Poloxamer 407 as surfactant are selectively transcytosed by M cells due to higher lipid solubility of the nanoparticles which also enhance the bioavailability of Isradipine [17]. Felodipine, another calcium channel blocker, on similar lines targets the M cells when formulated as PLGA nanoparticles, thus showing improved bioavailability and extending the blood pressure-lowering effect [18].

Agomelatine, an antidepressant with a novel mechanism of action, was formulated as a nanostructured lipid carrier using Dynasan 118, Labrafil 2125 Cs and

Tween 80 as surfactant. Due to their nanosize and lipoidal nature, these particles target the PPs and increase the bioavailability of agomelatine [19].

The uptake of docetaxel, an anticancer drug with low solubility and low permeability, was enhanced by targeting the PPs when formulated as hydroxypropyltrimethylammonium chloride chitosan-modified solid lipid nanoparticle [20].

Similarly, the absorption of oral doxorubicin was enhanced when formulated as sodium dodecyl sulphate-modified chitosan-lipid nanoparticle. These nanoparticles were preferentially absorbed from the M cells, causing an eightfold increase in bioavailability; thus, it could be an alternative for formulating drugs with poor bioavailability used to treat chronic disorders [21].

Styrene maleic acid nanomicelles of epirubicin also target the M cells, thereby not only increasing the bioavailability but also protecting the gastrointestinal mucosa from the toxic effects of the anticancer drug [22].

Resveratrol a powerful anti-oxidant undergoes extensive first pass metabolism and enterohepatic recycling reducing its bioavailability. Formulating resveratrol as PLGA nanoparticles overcomes these problems as these particles are preferentially absorbed by the M cells [23].

Insulin-loaded nanoparticles prepared from Eudragit and poly(-ε-caprolactone) are majorly absorbed via lymphatic uptake through the M cells, which also shows an improved glycaemic response; however, with varying type of insulin, the dose optimization studies need to be performed [24].

Absorption of calcium, when formulated as microspheres using bovine serum albumin, is greatly enhanced via M cells, and this may serve as an alternative to parenteral therapy in case of acute hypocalcaemia [25].

M cells offer a path for lymphatic delivery of drugs followed by systemic delivery. Iopinavir, an anti-HIV drug when incorporated in PLGA-based nanoparticles, shows improved permeability as well as bioavailability via absorption through M cells. It also offers an advantage of targeting the lymphatic tissue, the reservoir of AIDS virus, with the antiviral drug offering an easy way to AIDS therapy [26].

Atazanavir, an HIV protease inhibitor, also shows enhanced absorption via M cells when formulated as nanoparticles using Eudragit RL100 [27].

Oral delivery of vaccines has always been a fascination amongst formulation scientist as it offers many challenges, which begins with the disruptive pH of the stomach, enzymes in the GIT, presence/absence of mucus and entrapment/exclusion by intestinal cells. These vaccines if targeted at M cells can be directly presented at their site of action, i.e. the lymphatic tissue. Efforts have been done to develop oral vaccines, protect them from the gastrointestinal environment and target the M cells. Diphtheria toxoid formulated as alginate-coated microparticle had an excellent uptake and was able to bring about systemic and mucosal immune response by IgG and IgA formation, respectively [28].

A naturally occurring guar gum which is rich in mannose residues helps in effective delivery of Ag85 A, an antigen from *M. tuberculosis*/*M. leprae* to the lymphatic tissue via uptake by M cells. It induces strong systemic as well as mucosal immune response, thus paving way for development of oral delivery of tuberculosis vaccine

[29]. Lectin-coupled microspheres loaded with *M. tuberculosis* antigen have higher affinity for M cells and prefer binding to PPs [30].

Effective delivery of DNA vaccines at the PPs is achievable by using chitosan nanoparticulate system for delivery of DNA plasmids. The same was proven by incorporation of legumain DNA vaccine in alginate-coated chitosan nanoparticles. This system not only delivered the vaccine effectively and safely but also improved the autoimmune response and protected against breast cancer [31].

Microparticulate vaccine of ovarian cancer cell line made using Eudragit FS30D and hydroxypropyl methylcellulose acetate succinate, targeted to M cells using *Aleuria aurantia* lectin, triggers the humoral as well cellular immune response and may be effective vaccine for people with residual tumour or higher probability of relapse [32]. Similarly, prostate cancer vaccine and melanoma vaccine which use the same lectin and target M cells can stimulate the overall immune response, i.e. humoral as well as mucosal [33, 34].

Another DNA vaccine comprising of secretory chemokine CCL21 and survivin, a protein-inhibiting apoptosis, has been successfully developed for the complete eradication of lung cancer. Survivin is expressed by tumour cells, thus differentiating them from terminally differentiated normal cells. The delivery of this vaccine by attenuated *Salmonella typhimurium* is targeted to the M cells which in turn brings about T-cell-mediated suppression of angiogenesis [35].

5.5 Formulation Strategies that Can Be Used for PP Targeting

5.5.1 Nanoparticles

In the recent years, nanotechnology-based drug delivery systems are gaining widespread attentions. Currently, many substances such as proteins, peptides and nucleic acids are under investigation for various disease conditions especially cancer. These potent pharmacologically active agents can be delivered in such chronic disease conditions in the form of nanoparticle with site specificity, more accuracy, reduced toxicity and side effects of drugs. Various unique features of nanoparticles like smaller size, customizable surface, improved solubility and multifunctionality make them most promising carriers to deliver these potent and delicate active molecules [36].

Delivery of the drugs through oral route would be the most preferable in comparison to any other route due to its high levels of patient acceptance and long-term compliance, which increases the therapeutic value of the drug. However, the delivery of various macromolecules like proteins and nucleic acids through this route is challenging due to several factors such as sensitivity to enzymatic degradation, large molecular size, brief plasma half-life, ion permeability, immunogenicity and inclination to cause aggregation, denaturation and adsorption. Delivering such delicate molecules in intact form across the mucosal membrane needs a carefully defined carrier system. Recently, absorption of particulate drug carriers such as micro- and nanoparticles has been demonstrated through the gut-associated

lymphoid tissue (i.e. PPs due to presence of M cells). M cells facilitate the transcytosis of particulate materials from the GIT [36–39]. As macromolecules remain protected from hydrolytic and enzymatic degradation inside the polymer matrix of particulate carriers and delivery of such drugs is possible through the PPs, repositioning of macromolecular drugs through oral route has become possible. Further sections describe different formulation strategies along with control parameters that can be used to effectively deliver macromolecular drugs through PPs.

Transport Mechanisms of Nanoparticles across the intestinal barrier. Basically, movement of particles after ingestion, into and across the mucosal membrane of GIT, can happen by four distinct routes which are described as follows:

(a) Endocytosis of very tiny particles with diameter of less than 50–10 nm via 'regular' epithelial cells ([40]).
(b) Transcytosis (M-cell uptake) at the uppermost layer of intestinal lymphoid aggregates. Gut particles, specifically large nanoparticles (20–100 nm) and small microparticles (100–500 nm), are taken up by this quintessential pathway and is very well illustrated ([41–45]).
(c) Persorption. Volkheimer's concept of movement across 'gaps' present at the tip of villous subsequently loss of enterocyte(s) to the gut lumen. This route is probably approached by small and large nanoparticles, but, quantitatively, it is less likely to be competent ([46–48]).
(d) Putative paracellular uptake [49].
Very large molecules with size greater than 1 μm are transferred using the paracellular passage between enterocytes. However, paracellular space occupies <1% of intestinal mucosal surface. This spaces are sealed with junctional complexes having a diameter of <10 A° which restricts the entry of even the smallest of nanoparticles, but changes in this situation, under influence of certain drug and disease conditions, allow the entry of very small nanoparticles [50].

5.5.1.1 Delivery of Macromolecules Using Nanoparticles

Polymeric nanoparticles, amongst many delivery systems have been reported to improve transport of such molecules across the mucosal barrier. They encapsulate the macromolecules inside the polymeric network and prevent enzymatic degradation. As the particles are in the nanosize range, they are absorbed as such by the intestinal epithelium, specifically by PPs, and travel to sites such as the liver, spleen and other tissues.

The rate and extent of uptake of nanoparticles by PPs from the GI tract are affected by several factors such as the particle size of particulate, the surface charge of the particles, hydrophobicity, coating with the adhesion factor and the dynamic nature of particle interaction in the gut. In addition to size, shape and surface chemistry, cellular uptake and effectiveness of the therapy can be greatly affected by factors related to the physiology GI tract, species, ages and pathophysiological state [36]. Hence, during the development of nanoparticulate formulations, these parameters need to be considered and carefully evaluated.

5.5.1.2 Parameters to Be Considered in Formulating Nanoparticles for PP Targeting

5.5.1.2.1 Particle Size and Shape

Uptake of nanoparticles by PPs is greatly influenced by the particle size of the nanoparticles. Many authors have reported that particles with size in nanorange (< 1000 nm) can be efficiently taken up by PPs [51–54].

To learn the effect of shape, size and chemistry of surface on their uptake and movement across intestinal cells, Banerjee et al. [36] have formulated various shaped nanoparticles like sphere, rod and disc and attached them with targeting ligands EZ-link®amine-PEG2-biotin. Caco-2 cells and different coculture model of intestinal cells Caco-2/Raji-B, Caco-2/HT-29 and Caco-2/HT-29/Raji-B were used in the study to more precisely represent the intestinal epithelium. Finding of this study established that the size of the particle reversibly influences the uptake by Caco-2 and Caco-2/HT-29 cells, with uptake of 50 nm > 200 nm > 500 nm > 1000 nm. Transfer of smaller particles with size of 50 and 200 nm was more efficient than bigger particles of 500 and 1000 nm through Raji-B-based cocultures. In the coculture, regardless of the attached active targeted ligands, rod-shaped nanoparticles showed higher transportation and cellular uptake than sphere-shaped nanoparticles. Transfer of rods and disc-shaped nanoparticles (20% by 5 h) was higher in comparison to sphere-shaped nanoparticle (14% by 5 h). The study precisely demonstrated that the rod-shaped nanoparticle showed significantly improved cellular uptake by targeting via biotin receptor in Caco-2 and Caco-2/HT-29 cells in comparison to non-targeted rod-shaped or targeted/non-targeted sphere- and disc-shaped nanoparticles. The outcome of this work clearly depicts that particle size, shape and surface have a strong influence on oral uptake and transport of nanoparticles.

5.5.1.2.2 Nature of Surface

The nature of nanoparticle surface is having significant effect on the uptake of nanoparticle uptake by PPs. Hydrophobic nanoparticles made up of polystyrene, poly(methyl methcrylate), PLA, PLGA, etc. have been reported to be better transported by M cells than hydrophilic particles. Some bioadhesive and hydrophilic particles, made of chitosan, for instance [55], are known to be largely taken up by enterocytes.

Charge

The transport of nanoparticles across the barrier of the mucus and mobility of nanoparticles are also strongly dependent on the surface charge. The overall anionic behaviour of PPs due to the M cell and the mucus gel layer (mucin and glycocalyx) has tendency to interact with oppositely charged particles. Crater and Carrier demonstrated that anionic particles have significant 20–30 times faster diffusion compared to cationic particles. Particle surface potentials negatively affect the transport rates as transport rates of particles with negative charge was higher in comparison to particles with neutral or positive charge having limited transport, because of the

probable aggregation of particle and interactions of electrostatic adhesive with mucin fibres.

The positive charge provided by chitosan and its derivatives has been reported to increase the interaction with the cell surface negative charges, leading to increased nanoparticle internalization and greater transport [56–58].

Polymers such as chitosan and its derivatives being cationic in nature can coat nanoparticles with cationic groups or with mucin-interacting groups which can form nanoparticles that ensure longer connection time with the intestinal layer. This leads to a large surface for absorption and afterwards improved absorption [59].

Beside electrostatic interactions, muco-adhesion is affected by other factors such as Van der Waals interactions, hydrogen bonding, lipophilic forces, polymer chain interpenetration and ionic interactions which cause prolonged retention at the mucosal surface [60].

Surface Conjugation

For initiation of mucosal immunity in the intestine, transepithelial movement of pathogens and antigens through the epithelial wall by M cells may be essential. Attachment to M-cell apical surfaces is needed for effective transport of antigens and pathogens. Chemical modification using specific ligands of M-cell surface receptor can be done with nanoparticle to improve its uptake by M cells. These ligands include M-cell-specific lectins, secretary IgA and anti-M-cell mAbs [61].

Several studies have been done with the idea of specific M-cell targeting to promote the mucosal transport. Selective binding capability of lectins for carbohydrate residues of glycocalyx of epithelial cells have become good candidate on particle surface for specifically M-cell targeting [62, 63]. Lectins, obtained from *Lycopersicon esculentum* (tomato lectin), *Ulex europaeus* (UEA-I), *Canavalia ensiformis*, *Bandeiraea simplicifolia* I, *Aleuria aurantia* lectin (AAL) and *Triticum vulgare* (WGA), have been promoted for targeting at intestinal cell; however, as reviewed by Clark et al. [64], they have difference in their specificity for the different intestinal cell type.

The lectin-binding characteristics of the M-cell apical membranes exhibit considerable species and site-related variations, and there is also evidence of heterogeneity amongst M cells within individual domes. The site-related variations in the M-cell glycocalyx offer the potential for site-specific lectin-mediated M-cell targeting [65–70].

Prompt and efficient delivery of mucosal Ags from the lumen to underlying leukocytes was possible due to the unique characteristic of the apical and basolateral sides of M cells. M-cell apical membranes are more accessible to the particles, bacteria and viruses than adjacent enterocytes as they lack well-developed bush border and thick glycocalyx present on enterocytes [71].

Mantis et al. have demonstrated selective adherence of IgA to murine's PP M cell. The finding of this study suggested that the presence of IgA-specific receptor on the apical wall of M cell facilitates transepithelial transport of secretary IgA from the intestinal lumen to underlying gut-associated organized lymphoid tissue [71].

Yoo et al. have studied chitosan nanoparticles for targeting to PP employing M-cell-homing peptide identified by phage display technique. In this study, a M-cell-homing peptide ligand, CKS9, was identified by the use of phage display screening in combination with human in vitro M-cell model and developed a model oral vaccine carrier for PP targeting, CKS9-CNs, by chemical attachment of CKS9 to the chitosan nanoparticles. The CKS9-CNs have demonstrated improved efficiency for the binding affinity and transcytosis property to the M cells in vitro. In addition to this, the FAE of PP showed increased specific localization of CKS9-CNs in vivo [72].

5.5.2 Dendrimers

Dendrimers are treelike structure and have size range in nanometre. As branched monomer units are used in a stepwise fashion for the synthesis of dendrimers, it is likely to have unique control over surface functionality and size. Recent applications related to systems based on dendrimer include as nanomedicines [73, 74], gene-delivery vectors [75], biological adhesives [76] and imaging agents [77]. Modifications in the nature of the core and the scaffold and variability in the functional group on the dendrimer surface permit targeting of various functional groups or bioactive agents.

To improve the oral absorption of encapsulated drug and to decrease enzymatic susceptibility in the intestine tissue, it was recommended to use colloidal drug carriers like dendrimers which could be taken up by way of the PPs [78]. Experimental finding indicated that lymphoid tissue in the small intestine exhibited preferred uptake of dendrimers than the large intestine. In the small intestine, the lymphoid tissue showed comparatively greater absorption of the percentage of the initial dose than nonlymphoid tissue. These findings suggested improved absorption of poorly permeable drugs in the small intestine tissues by the dendrimers [78].

5.5.2.1 Parameters to Be Considered in Formulating Dendrimers for PP Targeting

5.5.2.1.1 Particle Size and Charge

To develop PAMAM dendrimers as potential oral drug carriers, Wiwattanapatapee and his research group methodically evaluated the effect of dendrimer charge, size and concentration on uptake by the adult rat intestine and studied the dendrimers for absorption mechanisms in intestine tissues [79]. It was indicated that overall uptake of dendrimer was greatly influenced by dendrimer size which was considered as a critical factor [80]. Permeation of macromolecules with diameters up to 3 nm across intestinal membranes can occur either through the paracellular or transcellular routes [81]. Therefore, penetration across the intestine though these routes could be possible for G2.5 and G3.5 PAMAM dendrimers. However, G4 and higher-generation PAMAM dendrimers could conjugate to the invaginating plasma membrane and infiltrate cells by specific or nonspecific adsorptive endocytosis [79].

G5.5 PAMAM dendrimer showed more tissue accumulation compared to G2.5 and G3.5 dendrimers. Tissue uptake ability of G2.5 and G3.5 PAMAM dendrimers was particularly low. Furthermore, cationic dendrimers indicated a contrasting accumulation pattern from anionic dendrimers. The greater tissue binding and lower transport rate of cationic dendrimers were found because the anionic charged cell membrane could interact more profoundly with positively charged molecules. These results suggested that the transport mechanism across the intestine is significantly affected by size, conformation and charge sensitivity of dendrimers [79].

Dendrimers with considerable cationic charge have the most significant effect on the surface charge. For example, at physiological pH dendrimers with amine termination normally have a positive-charged surface and are capable to interact greatly with cell surfaces and membrane that generally bears an overall negative charge. Systems having amine terminations have surface with more cationic charge due to increasing generation leading to increased numbers of surface amine functional group [82].

5.5.2.1.2 Surface Conjugation

Dendrimer permeability can be improved by increasing lipophilicity of dendrimer through attachment of lauryl [83] or polyamino acid (arginine and ornithine) [84] chains to the dendrimer surface. Florence and co-workers studied biodistribution properties of lauroyl-conjugated G4 polylysine dendrimers after oral administration to rats and suggested that PPs in the small intestine are responsible for the absorption instead of transcytosis across the enterocyte [80].

The targeting ability of a tetragalloyl derivative, the tetragalloyl-D-lysine dendrimer (TGDK), to M cells in both in vivo nonhuman primate and in vitro human M-like cell culture models was studied by Misumi S. et al. [85]. TGDK was effectively moved into rhesus PPs from the lumen of the intestinal tract by M cells and later on concentrated in germinal centres. Cyclopeptide derived from rhesus CCR5 and conjugated to TGDK when administered orally to rhesus macaque showed statistically significant increase in stool IgA response against rhesus CCR5-derived cyclopeptide and resulted in neutralizing effect towards SIV infection. Moreover, in the M-like cell model, TGDK also showed specific binding at human M-like cells and effectively transcytosed from the apical side to the basolateral side. Thus, this approach of vaccine delivery system through TGDK indicates effective means for facilitating mucosal vaccines which are targeted to M cell in primates [85].

5.5.3 Microspheres

Microspheres are tiny particulate drug delivery systems of spherical shape ranging in size from 1 μm to few thousand μm [86, 87]. Fabrication of microspheres can be done using polymeric materials of natural origin or synthetic polymers. Few inorganic materials may be employed for the fabrication [86]. Several methods are available to the pharmaceutical scientist for manufacturing the microspheres. Based on the method, formulator can produce microspheres varying in size, morphological

symmetry and porosity. These novel delivery systems can be administered via different routes to provide actives in therapeutic concentration at the appropriate site in the body. These multiunit particulate systems (MUPS) can also be suitably designed to (a) reduce the dose at the non-target sites and (b) achieve desirable pharmacokinetic parameters. Several researchers have employed microspheres in delivering macromolecules like vaccines to PP.

Microspheres provide (a) protection to the labile vaccines due to the wall material during transit through gut, (b) efficient targeted delivery of a high concentration of antigen into the PP and (c) sustained release of the vaccines. A formulator must consider the following points while developing antigen-loaded microspheres [88].

The particle size of microspheres is crucial in absorption across the PP. It has a significant impact on the amount of uptake of the particles as well as on the site of location of the particles. Particle size is also an important determinant in the type of immune response elicited by vaccine-containing microspheres [89].

Hydrophobicity of the particles is crucial in determining their absorption in PP, whereby the hydrophobic particles have higher uptake than their hydrophilic particles. The surface charge on the microparticles also influences the uptake of microparticles into the PP, whereby the non-ionized particles were seen to have greater uptake as compared to negatively charged particles [65].

Desai et al. [52] formulated microspheres of a model protein-bovine serum albumin using w/o/w emulsion solvent evaporation technique with the help of polylactic-polyglycolic acid (50:50) copolymer. The gastrointestinal uptake of the biodegradable microspheres of different sizes (100 nm, 500 nm, 1 μm and 10 μm) was studied in rats. Uptake of microparticles of 100 nm size in the PP was significantly higher as compared to higher-sized particles. The small-sized particles were found distributed in the submucosal layers, whereas the larger-sized particles were majorly aligned at the epithelial linings.

Eldridge et al. [90] prepared poly(DL-lactide-co-glycolide) biocompatible and biodegradable microspheres of staphylococcal enterotoxin B. BALB/c mice were administered in the enterotoxoid encapsulated microspheres. Their results suggested that microspheres <5 μ would extravasate the PP within macrophages to stimulate the systemic immunity, whereas the microspheres in the size range of 5–10 μ stimulated mucosal immunity through the release of antigen in the PP.

In another study, Eldridge et al. [91] prepared staphylococcal enterotoxin B-encapsulated microspheres employing ten different polymers by the solvent evaporation technique. Based on the results from the studies involving oral administration of microspheres to BALB/c mice, the authors concluded that tissue penetration was limited to microspheres of 10 μ in diameter. Microspheres below 5 μ induced circulating antibody response; those above 5 μ exhibited predominantly mucosal response. Polystyrene, polymethyl methacrylate and polyhydroxybutyrate microspheres were absorbed more readily in comparison to poly(DL-lactide), poly(L-lactide) and poly(DL-lactide-co-glycolide) microspheres, whereas cellulose microspheres were not efficiently absorbed.

Jenkins et al. studies the PP targeting of polystyrene particles of different sizes. Their results suggested that greater number of particles of size 0.5 μ and 3 μ was found in the PP of rat in comparison to 0.15 μ (smaller) and 10 μ (larger) particles [92].

Jani et al. prepared nonionic as well as carboxylated fluorescent polystyrene monodisperse microspheres having diameters of 100 nm, 500 nm, 1 μm and 3 μm in diameter. Sprague-Dawley rats were administered the microspheres and their uptake was studied in PP. There was a substantial evidence of these microspheres being localized in the PPs. Nonionic microspheres exhibited greater uptake as compared to carboxylated microspheres. 3 μm particles were not at all taken up by the PP, whereas 1 μm microspheres were taken up less efficiently than smaller particles suggesting the impact of particle size on the uptake of particles [93].

Le Ferve et al. showed that macrophages of PP may be responsible for the uptake of particulate matter in the 2 μ size range [94, 95].

Keljo and Hamilton carried out ex vivo experiments in using chambers by employing piglet jejunum with and without PPs. They quantitatively determined the macromolecular transport rate across intestinal PP by studying the rate of transport of horseradish peroxidase. Their results suggested a sevenfold increase in the rate of transport of horseradish peroxidase across segments containing patches as compared to segments without patches. The authors attributed the increased transport to the active cellular process [96].

Thus, microspheres could prove to have potential applications in oral delivery of vaccines due to their efficient uptake by GALT and also to improve the oral bioavailability of these agents. Additionally, the antigen-loaded microparticles could provide sustained release because they can be trapped in the microvilli, thus prolonging their transit time. The slow breakdown of the polymer would provide sustained release of the therapeutic agent over a prolonged period of time. With the availability of biocompatible and biodegradable polymers, the microspheres are an efficient oral drug delivery vehicle for vaccine antigens. The increased uptake of antigens can broaden the application of microspheres for delivery of peptides/proteins and DNA/RNA.

5.5.4 Nano-/Microemulsions/SEDDS/SMEDDS/SNEDDS

Oral route of drug delivery has been the most appealing from the patient as well as physician point of view. However, many drugs suffer from the solubility issues, which limit their bioavailability. Recent approach to improve the bioavailability involves the utilization of lymphatic circulation upon oral delivery as it bypasses the first pass metabolism in the liver. Avoidance of pre-systemic hepatic metabolism enhances the absorption and bioavailability of orally administered drugs. Actives with characteristics like poor solubility, higher lipophilicity and poor oral bioavailability are a promising candidate for lymphatic targeting. Such actives can be transported in an effective manner through the intestinal lymphatics via the thoracic

lymph duct to the systemic circulation. Large-sized colloidal particles enter into the lymphatics directly, due to intercellular junctions between endothelial cells of lymphatic capillaries. Since such junctions are absent between the endothelial cells of the blood capillaries, their entry is restricted in the blood. This property of lymphatic system is utilized for the direct absorption of long-chain fatty acids via chylomicrons formation, thus avoiding entry in portal circulation. Several colloidal drug carriers like microemulsions and self-microemulsifying drug delivery systems (SMEDDS) have been employed to achieve lymphatic targeting [97, 98].

Advancement in the liposome technology covers the approach called self-microemulsifying drug delivery system, which comprises of careful selection of isotropic mixture of oils, surfactant, cosurfactants and solvents. It differs from conventional emulsions in terms of thermodynamic stability and spontaneous formation of emulsion in vivo without any energy input. Phase diagram was found to be a useful tool for the formation of optimal microemulsion with suitable concentration of different ingredients [99].

Hydrophobic drugs are added to the isotropic mixture comprising majorly of oils, surfactant and cosurfactants. Upon oral administration in vivo, SMEDDS gets released into the gut lumen, where it gets dispersed to form a fine emulsion. This allows the active to be presented in a solution form in the gut, thereby avoiding the dissolution step. Generally, this can lead to improved bioavailability. To achieve self-emulsification, ultra-low oil-water interfacial tension and/or substantial interfacial disruption are required. SMEDDS have gained advantage as it does not require bile salts and other enzymes for their absorption so there are less chances of intra and inter subject variability. SMEDDS are advantageous as delivery systems as they provide a large interfacial area for the active to partition between oil and GI fluid (aqueous compartment). SMEDDS are known to enhance the drug absorption by several mechanisms, namely, enhanced solubilization of drug, increment in membrane permeability in GIT and increasing lymphatic uptake of drug [100].

The key features of SMEDDS are:

1. SMEDDS are a novel and simple drug delivery systems which have shown promise in enhancing the bioavailability of the BCS II/IV drugs via solubility enhancement and lymphatic targeting.
2. SMEDDS provide improved lymphatic targeting efficiency hence can lower the drug amount required to have a clinical effect, reducing the systemic side effects, thereby improving patient compliance and cost of therapy.
3. SMEDDS are used for lymphatic targeting. Manipulation of the relative contribution of the two absorption pathways, i.e. lymphatic transport and absorption via portal system, is possible for the pharmaceutical scientist based on the structure of the excipients.
4. Oil included in the SMEDDS can significantly affect the intestinal absorption of drugs via lymphatic transport in a dose-dependent manner.
5. Short-chain fatty acids are transported mainly by the portal pathway and long-chain, saturated fatty acids via the lymph.

New et al. [97] prepared a w/o emulsion (Bridgelock formulation), wherein salmon calcitonin was included in the aqueous phase. The formulation was administered orally via a cannula to the jejunum in surgically manipulated juvenile pigs. The electron microscopy images exhibited that salmon calcitonin was transported via lymphatic transport and entered the blood stream via the thoracic lymph duct. The authors also suggested that the peptide may be transported via hepatic portal system or lymphatic route based on the size of the peptide and the association of peptide with the lipid present in the interstitial fluid.

Sun et al. developed SMEDDS of a model drug Sirolimus using the medium-chain triglyceride, Cremophor RH 40 and propylene glycol as oil, surfactant and cosolvent, respectively. The study was aimed to determine the impact of different amounts of oil and surfactant on the intestinal lymphatic transport using single-pass intestinal perfusion technique and a chylomicron flow blocking approach. The bioavailability studies were performed in Sprague-Dawley rats to determine the pharmacokinetic parameters. Oil-free batches were transported via the portal blood, whereas batches with oil amounts greater than 25% in SMEDDS exhibited lymphatic transport as the major pathway for drug absorption and thereby contributing to the enhanced oral bioavailability of Sirolimus. On the other hand, surfactant had only a small effect on the intestinal transport. The authors also concluded that besides the transcellular route, the route via M cells and GALT especially PP is an important contributor for lymphatic transport of lipophilic drugs like Sirolimus [101].

Bhalekar et al. formulated a self-microemulsifying drug delivery system of an antiretroviral drug, darunavir, with the aim of improving its bioavailability. They employed Imwitor 988 as oil phase along with various surfactant to cosurfactant ratios of Tween 80:Span 80 and Tween 20:Span 20. The lymphatic uptake of developed SMEDDS was studied using everted gut sac intestinal segments of Wistar rats in the presence and absence of lymphatic blocker. The results of the ex vivo studies suggested the lymphatic uptake of Darunavir. The findings were further supported by in vivo pharmacokinetic studies [102].

Paclitaxel, an anticancer agent, possesses poor oral bioavailability (<10%), which can be attributed to poor aqueous solubility and dissolution along with its affinity for intestinal and liver cytochrome P-450 metabolic enzymes (i.e. CYP3A4) and the multidrug efflux transporter P-glycoprotein (P-gp). Cho et al. [103] prepared Paclitaxel-loaded solid self-emulsifying drug delivery systems using oil (ethyl oleate), surfactant mixture (Tween 80:Carbitol) and cosolvent (PEG 400). Results of in vivo studies performed in Sprague-Dawley rats exhibited higher lymphatic targeting efficiencies than reference solution.

Holm et al. formulated SMEDDS of a highly lipophilic antimalarial active, Halofantrine, using structured triglycerides. Two different triglycerides C8:0-C18:2-C8:0 (MLM) and C18:2-C8:0-C18:2 (LML) were employed in the formulation of SMEDDS. The formulations were administered to lymph-cannulated male greyhound dogs. Their findings suggested the utility of these lipid-based formulations for improving the oral bioavailability of poorly soluble drugs. The authors concluded that the lipids used as excipients in formulating SMEDDS are crucial in deciding the extent of lymphatic transport and absorption via the portal system [104].

Kiyasu et al. studied the transport of C14-labelled palmitic acid (short-chain fatty acid) and C14-labelled decanoic acid (long-chain fatty acid) in Long-Evans strain male rats. Ratio of plasma fatty acid of the portal vein to that of the inferior vena cava upon administration of C14-labelled palmitic acid was about unity, whereas in similar experiments with C14-labelled decanoic acid, the ratio exceeded unity [105].

Chen et al. prepared the solid dispersion and SMEDDS formulations of a poorly water-soluble antiepileptic drug Vinpocetine. Solid dispersions employed Poloxamer F68, whereas SMEDDS was based on oleic acid/Labrafac combination. The two formulations were compared in terms of solubility, dissolution, lymphatic absorption, intestinal permeability and bioavailability. SMEDDS approach exhibited a 17.3-fold enhancement of solubility of active as compared to solid dispersion approach. The SMEDDS also exhibited a better dissolution and bioavailability in comparison to solid dispersions and pure drug. Higher uptake of Vinpocetine in PPs was analysed when administered in SMEDDS as compared to solid dispersions. The higher uptake in PP indicates higher lymphatic absorption, which may be attributed to excipients like oleic acid and Labrafac. Oleic acid and Labrafac had been proved to accelerate lymphatic absorption in many other lipid-based formulations, and SMEDDS could increase membrane permeability and the amount of drugs partitioning into lymph chylomicron or lipoprotein [98].

Prasad et al. used Labrasol and D-α-tocopheryl-PEG 1000 succinate to develop SMEDDS formulation of Vancomycin and, intraperitoneally administered once, exhibited significant plasma levels of Vancomycin in comparison to the saline solution due to lymphatic transport via PP [106].

Li et al. prepared SMEDDS of an alkaloidal drug, Huperzine A, obtained from the traditional Chinese herb. The excipients employed included castor oil, propylene glycol and Cremophor RH40. Several in vivo studies were performed in Male Sprague-Dawley rats wherein SMEDDS containing Huperzine A was administered and compared with Huperzine A suspension, which acted as control. The results revealed that a significantly ($P < 0.05$) higher concentration of Huperzine A was released into the mesenteric lymph nodes from the SMEDDS in comparison to control formulation. The chylomicron flow blocking studies confirmed the absorption of Huperzine A SMEDDS through the lymphatic route. Further, the authors opined that the route via GALT (PP) and M cells could be one of the crucial routes out of the three routes responsible for lymphatic uptake of SMEDDS [100].

Wilkhu et al. used newly developed nonionic surfactant technology with lower temperature for the production of niosomes and bilosomes to reduce antigen exposure against potentially damaging conditions and higher stability against enzymatic degradation. Incorporation of antigen in niosomes and bilosomes showed increased delivery and targeting of the antigen to the PP. Delivery to both the PPs and mesentery lymphatics was dose dependent at lower concentrations, whereas at higher concentrations, it was found to achieve saturation kinetics [107].

5.5.5 Liposomes

The artificial membranes of bilayer phospholipids, vesicles are being useful carrier for the targeted delivery of several actives to gut-associated lymphoid tissue. They are composed of phospholipids and cholesterol which make them stable in acidic solution of physiological fluids, diluted bile and pancreatin solution. Following an oral administration, liposomes were preferentially taken up by the PPs in the lower ileum via lymphatic drug delivery. Liposomes are a delivery system of choice for the formulator, and much research related to this dosage form has been envisaged because of (a) its ability to enhance drug permeation across the enterocyte, (b) stabilization of drugs and (c) opportunity of controlling the release [3].

A key advantage of liposomes for delivery systems is due to their versatility and plasticity. Several macromolecules like nucleic acids, carbohydrates, peptides, proteins, haptens, etc. (hydrophilic moieties) can be intercalated within the aqueous core (inner space of liposomes), whereas hydrophobic actives (linker molecules/lipopeptides) are associated into the lipid bilayer [108].

Liposomes are nanosized vesicular structures composed of lipids possessing the ability to ameliorate the efficacy and oral bioavailability of actives by selectively using intestinal lymphatic absorption, thus bypassing hepatic first pass effect.

Cefotaxime is a third-generation cephalosporin antibiotic with poor oral bioavailability and short biological half-life. Ling et al. prepared phosphatidylcholine-based liposomes of cefotaxime and studied the in vivo performance in rats. Liposomal formulation and aqueous solutions were administered, and concentration of cefotaxime in the lymph and plasma was determined. They reported a 2.3–2.7 times increment in bioavailability of the liposomal formulation as compared to the aqueous solution. The authors concluded that the liposomal system could promote the lymphatic transport in the intestinal lymph. Further, the increased bioavailability was partly due to the encapsulation of drug into liposomes as it protects the drug from low pH effects and partly due to increased localization of the drug at the intestinal lymphatics [109].

Tiantian et al. prepared docetaxel liposomes by sonication and thin-film hydration techniques. The liposomes were further coated with hyaluronic acid by electrostatic attraction. Uncoated and coated liposomes were evaluated for lymphatic targeting and lymph node uptake. The impact of pharmaceutical factors on lymphatic targeting was also examined. In vitro studies suggested greater release of high and low molecular weight hyaluronic acid-coated liposomes in comparison to uncoated liposomes. Various in vivo studies were performed after subcutaneous administration of uncoated and coated liposomes in Kunming mice. In vivo imaging studies suggested better lymph node uptake and lymphatic drainage of low molecular weight hyaluronic acid-coated liposomes when compared with high molecular weight hyaluronic acid-coated liposomes and hyaluronic acid-uncoated liposomes. The findings revealed that molecular weight of hyaluronic acid had an inverse relationship on lymphatic drainage and lymph node uptake. The authors suggested the employment of coated liposomal carrier for delivering diagnostic and therapeutic agents to lymphatic system [110].

Kaur et al. employed stearylamine and dicetyl phosphate to formulate zidovudine (ZDV)-loaded surface-engineered liposomes (SE liposomes) for lymphatic targeting. The organ distribution studies of SE liposomes suggested significant reduction in serum concentration of free ZDV, whereas significantly ($p < 0.05$) increased ZDV quantity was detected in the spleen and lymph nodes. The uptake and localization of the SE liposomes was improved in the lymph nodes and spleen which was confirmed by the results of fluorescent microscopy. Thus, the SE liposomes seem to be attractive novel vesicular system for improved targeting of ZDV to lymphatics, in AIDS chemotherapy [111].

Hirano et al. studied the lymphatic transport of a model compound (14C-sucrose) in liposomes following intraperitoneal administration in rats. Liposomes having a mean diameter of approximately 200 nm were administered to thoracic duct-cannulated rats. The authors concluded that changing liposome composition altered the relative ability of liposomes to be retained by lymph nodes [112].

Parker et al. administered fluorescent dye carboxyfluorescein (CF), entrapped in liposomes and administered by intraduodenal injection to thoracic duct-cannulated rats. These findings indicate that liposomal entrapment effectively limits passage of CF into the splanchnic blood vessels while enhancing the lymphatic uptake of the dye from the peritoneal cavity [113].

Parker et al. prepared liposomes entrapped with [^{14}C]cytosine beta-D-arabinofuranoside. The authors compared the metabolism, excretion, uptake by lymphatic system and biodistribution of liposomal delivery system containing antitumour agent with control. A threefold reduction in metabolic activity of liposomal-entrapped drug was recorded in comparison to free drug. The liposomal formulation recorded a tenfold higher lymphatic uptake and 300–1000-fold higher localization in lymph nodes when compared with control. The authors suggested the beneficial role of liposomes in tumour management across lymph [114].

Parker et al. reported an enhanced uptake of liposome-entrapped Adriamycin relative to free drug in lymph nodes in rats treated by the intraperitoneal route [115].

Jackson formulated inulin-loaded liposomes and studied the impact of the factors, namely, size, amount of injected lipid and surface area on the intramuscular absorption and lymphatic uptake of drug upon administration in mice. Liposomes with a lower particle size exhibited an enhanced uptake of drug via the lymphatic system as compared to larger size liposomes. In the case of larger liposomes, when the quantity of injected lipid was reduced, a slower intramuscular absorption and a higher uptake via the lymphatic system resulted [116].

Kaledin et al. prepared liposomes of two metastatic drugs namely, cis-diamminedichloroplatinum(II) (DDP) and hydrocortisone, and studied their effect into metastasized A/He mice. Liposomal and control (free drug) formulations were administered via the intra-lymphatic route. The control formulations were ineffective, whereas the liposomal formulations could significantly reduce the growth rate and frequency of tumour metastases in the lymph nodes, suggesting the ability of its vesicular delivery system in prophylaxis [117].

Kaledin et al. formulated liposomes using phosphatidylcholine to entrap [3,5,3′-125I] triiodothyronine. Male A/He mice were administered the radiolabelled

liposomes and free drug following which the biodistribution was studied in various organs. 5–50-folds higher radioactivity was visualized in lymph nodes upon liposomal administration in comparison to control formulation. The findings exhibited that liposomes injected via subcutaneous route could enter the lymphatic pathways and reach the lymph nodes and may serve as a useful armour in prevention of postoperative metastases to lymph nodes [118].

Khato et al. prepared two types of liposomes of anticancer drug—melphalan—by varying the sonication times and studied their distribution in tissues upon subcutaneous administration in rats. Small-sized liposomes with a narrow particle size distribution were obtained when liposomes were prepared using longer sonication times, whereas the bigger sized and nonuniformly distributed liposomes were produced on brief sonication times. A substantially high concentration of the drug was located within the lymph nodes upon injection of smaller liposomes, whereas larger liposomes exhibited a poor localization with the lymph nodes [119].

Doxorubicin and other anthracyclines are commonly used in the treatment of B-cell non-Hodgkin's lymphoma, but their clinical use is hindered due to their cardiovascular toxicity like cardiomyopathy and congestive heart failure. Liposomal conjugation of doxorubicin preferentially distributed into tumour tissue and reduced the tumour toxicity. Visani and Isidori in their study reported that the non-pegylated liposomal doxorubicin efflux due to P-glycoprotein which is overexpressed in non-Hodgkin's lymphoma is decreased. This causes increased circulation times in the blood and further internalization into tumour tissue by enhanced permeation and retention effect [120].

Pukanud et al. developed mannosylated liposomes of antiviral drug, Acyclovir, for oral drug delivery using thin-film hydration technique. Mannosylation of the liposomes was done using mannosamine HCl (ManN) and p-aminophenyl-α-D-mannopyranoside (PAM), whereas non-mannosylated liposomes and acyclovir suspension were treated as control. In vitro studies were performed using ileal sac of male Swiss albino mice. Both types of mannosylated liposomes exhibited a higher percentage of drug absorption and apparent permeation across ileal segments when compared with plain drug suspension and conventional bioadhesive carrier. Upon oral administration, mannosylated liposomes exhibited a strong adherence to gut mucosal cells including PP. These bioadhesive carriers could be potential delivery systems for improvement in bioavailability [121].

5.6 Conclusion

After oral administration, macromolecules are transported by the M cells in PPs and distributed via the mesenteric lymph towards the lymph nodes. Particle uptake by PPs offers the possibility of tailoring macromolecules including vaccines that can be delivered orally. However, several important factors including physicochemical properties of the particles, the physiopathological state of the animal, the analytical method and the experimental model used to evaluate the uptake are crucial in determining the efficacy of drug/macromolecule/vaccine delivery through the PPs.

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Colonic Drug Delivery Systems as Multiunit Potential: Therapeutic Strategies and Opportunities

6

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Contents

Abstract

Multiparticulates are formulations in which the active substance is present as small independent subunits. Small size enables the multiparticulates to reach the colon quickly, and they are retained in the ascending colon for a relatively longer period of time. Prevention of the drug release in the stomach and subsequent release of the drug in the colon, is the requirement of colon-specific delivery. This

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_6

can be achieved better by the development of the multiparticulate systems instead of single-unit systems. Other advantages of multiparticulate systems over single-unit systems include increased bioavailability, reduced risk of systemic toxicity and local irritation, predictable gastric emptying and hence better/reproducible pharmacokinetic behaviour. Present chapter reviews research efforts for development of multiparticulate for colon targeting utilizing different strategies like prodrug, bioadhesion, pH sensitivity, etc.

Keywords
Multiparticulates · Nanoparticles · Colon targeting · Prodrugs · pH sensitivity

6.1 Introduction

Colonic drug delivery systems have been used not only for treatment of local colonic pathologies like Crohn's disease (CD), ulcerative colitis (UC), irritable bowel syndrome (IBD), spastic colon and colorectal cancer, but they also hold potential for systemic delivery of proteins and therapeutic peptides, e.g. analgesic peptides, contraceptive peptides, oral vaccines, growth hormone, insulin, interferons, erythropoietin and interleukins [1, 2]. Moreover, colonic drug delivery is also preferred when a delay in absorption is desired, in the treatment of diseases that have peak symptoms in the early morning, such as nocturnal asthma, angina or arthritis.

Several strategies have been employed to attain drug delivery to the colon like using pH-sensitive systems and microbially triggered systems, linking drug to a carrier, using polymers that specifically degrade in the colon, etc. Most of these delivery systems have been formulated as single-unit systems, i.e. tablets or capsules. Single-unit colon-targeted drug delivery systems suffer from the disadvantage of untimely disintegration, due to manufacturing defect or unusual gastric physiology, which may lead to unexpected systemic drug bioavailability and failure to achieve local therapeutic action in the colon [3]. Hence, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single-unit systems. Multiparticulate drug delivery systems (MDDS) consist of number of subunits, typically thousands of spherical particles having diameter of about 0.05–2.00 mm [4, 5], leading to potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [3]. For ease of administration, these subunits are compressed into a tablet or filled into a capsule or sachet [4].

As early as 1985, Hardy et al. studied MDDS, for colon targeting, to overcome the disadvantages of single-unit dosage forms [6]. They reported that multiparticulate systems, because of their smaller particle size as compared to single-unit dosage forms, enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively longer period of time. Also, these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject

variability. Similar results, reported by other researchers, confirm more uniform drug absorption, when drug is delivered as microparticles [7–9]. Pellets, beads, granules, matrices, microspheres and nanoparticles are the most commonly studied multiparticulate systems for colon-specific drug delivery [5, 10–14].

Release patterns can be tailored by preparing multiparticulates with different strengths of drugs or using different coatings with single strength, or two incompatible drugs can be administered in a single dosage by incorporating them separately in different microparticles. Further, compared with other delivery systems, multiparticulate formulations offer design flexibility and the ability to administer high potency products.

6.2 Factors Influencing Colonic Delivery

Colonic drug delivery system and colonic bioavailability of the drugs depend largely on the anatomy of the colon, physiological conditions prevailing in the colon as well as the formulation factors [15–19].

6.2.1 Anatomical/Physiological Factors

The anatomy and physiology of the colon differ significantly from other parts of the gastrointestinal tract. Colon is divided into four parts—ascending, transverse, descending and sigmoidal colon—and all these parts differ in physiology and physical properties of colonic contents [20]. The major factors that influence colonic delivery of drugs are colonic transit time, pH, volume and viscosity of colonic fluids and enzymatic metabolism in the colon. There is a variation in transit times of healthy colon and diseased colon. Patients with UC are known to have shorter colonic times (~24 h) compared to healthy subjects (~52 h) [21], and in patients with IBD, the orocaecal transit time has been shown to be delayed [22]. Also, the time of administration, presence/absence of food, sleep/wake cycle and the type of dosage form affect the transit time. Larger dosage forms, e.g. capsules, transit faster than smaller dosage forms like microparticles/dispersed particles [23].

pH is another factor that varies significantly in different regions of gastrointestinal tract, ranging from 1 to 2 in the stomach to 7.5 in the distal small intestine. The pH drops to *5.7* in the caecum but again gradually increases, reaching pH *6.7*, in the rectum. Significant intra- and inter-subject variability in the pH has been observed between disease states, fasted/fed states, sexes and ages in humans [14, 24–27]. The pH of the colon may be influenced by a carbohydrate-rich diet because of the fermentation of polysaccharides by colonic bacteria and formation of short-chain fatty acids [28]. Polysaccharide-based drugs may also alter colonic pH. Laxative drugs like lactulose are known to be fermented by colonic bacteria to produce lactic acid and reduce colonic pH [29]. The pH in turn affects the pharmacokinetic and pharmacodynamic behaviour of drug delivery systems, by influencing the solubility of drugs in the colonic fluid. Furthermore, if one or more components of the delivery

system are pH-sensitive, the effect of colonic pH on the drug release is even more pronounced. The low volume of colonic fluid (1–44 ml, averaging approximately 13 ml) limits the dissolution of drugs from the dosage forms and hence local bioavailability of drugs [30]. Another factor which limits the dissolution of drugs is viscosity of colonic contents. Due to a higher water-absorbing capacity of the colon, the viscosity of the colonic luminal contents is higher than upper gastrointestinal tract contents. The viscosity of contents progressively increases as it transits from the ascending colon towards the descending colon, resulting in a reduced drug dissolution and mucosal absorption [31]. Viscosity also influences the penetration of the drug into the disease-causing bacteria in the colon. The mobility of bacteria in the colon has been shown to be dependent on the viscosity of colonic contents [32].

The colon contains a complex and dynamic microbial ecosystem with high densities of living bacteria, which achieve concentrations of up to 10^{11} or 10^{12} cells/g of luminal contents. It consists of over 400 different species of aerobic and anaerobic microorganisms [33]. These bacteria are known to produce several hydrolytic and reductive metabolizing enzymes [34], which in turn catalyse a range of reactions, including the metabolism of drugs and biomolecules, deactivation of harmful metabolites as well as carbohydrate and protein fermentation [35]. When colon-targeted dosage forms are prepared using polysaccharides such as chitosan, guar gum, pectin, etc., as release rate-controlling polymers, these remain intact in the stomach and the small intestine, but, on reaching the colon, they are metabolized by anaerobic bacteria in the colon resulting in drug release [36–38]. Drugs are also known to undergo biotransformation by colonic enzymes. The metabolism of drugs by colonic enzymes may result in the formation of metabolites that are pharmacologically active, inactive or sometimes even harmful [39, 40].

6.2.2 Formulation Factors

The formulation factors that influence colonic drug delivery and bioavailability include physicochemical properties of the drugs, the dose and the dosage form factors. Due to the lower amount (1–44 ml) of colonic fluid available for dissolution, the solubility and the dose of a drug become important factors for its colonic bioavailability. Although the highly potent drug budesonide (dose, 9 mg) has a lower aqueous solubility, it is absorbed well in the colon and is used successfully in the treatment of ulcerative colitis [41]. Mesalamine has a significantly higher solubility (3.64 mg/ml) compared to budesonide (0.24 mg/ml); however, it also has a significantly higher dose (4.8 g daily) which becomes a rate-limiting factor for its colonic absorption [42]. The technology used in the dosage form development can also influence the colonic bioavailability of drugs. Uceris® and Entocort EC® are currently approved budesonide products for the treatment of ulcerative colitis and Crohn's disease [43]. Uceris® is a Multi Matrix (MMX)-based delayed-release tablet, which ensures the drug release in the colon, while Entocort EC® is a capsule which releases the drug in the ileum to treat Crohn's disease.

Table 6.1 Ideal drug candidates and target diseases

Criteria	Examples of drugs	Diseased condition
Drugs used for topical/ local effect	Hydrocortisone, budesonide, prednisolone, sulfasalazine, mesalamine	Inflammatory bowel disease, irritable bowel syndrome, Crohn's disease
Drugs poorly absorbed from upper GIT	Nitroglycerine	Hypertension, angina
Drugs for colon cancer	5-Fluorouracil and capecitabine	Colorectal cancer
Drugs that degrade in stomach and small intestine	Proteins, peptides	Insulin, vaccines
Drugs that undergo first-pass metabolism	Nitroglycerine, corticosteroids	Angina, inflammatory bowel disease
Drugs used for chronotherapy	Prednisolone, salbutamol	Arthritis, asthma

6.3 Ideal Drug Candidates and Target Diseases

Selection of drugs for colon-targeted delivery should be based on certain criteria; the drugs which exert local effects in the colon, drugs that undergo substantial first-pass metabolism, drugs that degrade in the stomach and small intestine, drugs used for colon cancer, drugs poorly absorbed in the upper GIT (gastrointestinal tract) and drugs used for chronotherapy are all candidates for colon-targeted drug delivery system. Examples of drugs are mentioned in Table 6.1 [17, 44].

6.4 Strategies for Repositioning as Multiparticulate Systems for Colonic Drug Delivery

6.4.1 pH-Sensitive Systems

One of the easiest ways to formulate the multiparticulate systems for colonic drug delivery is the use of pH-sensitive polymers. These polymers are not soluble in stomach but soluble at colonic pH. In humans, pH of the GIT increases form acidic to basic. In stomach pH is around 1–2 (which increases to 4 at digestion), in small intestine pH is around 6–7.5 and the pH of the colon is 6–8 (ascending colon pH 5.7, transverse colon pH is 6.6 and descending colon pH is 7.0). The pH of the colon is higher than any part of the GIT.

The most commonly used pH-sensitive polymers for colonic drug delivery are methacrylic acid copolymers such as Eudragit L100 and Eudragit S100. Eudragit L100 is soluble at pH greater than 6, while Eudragit S100 is soluble at pH greater than 7. Depending upon the type of formulation, these pH-sensitive multiparticulates may be classified into various categories such as:

(a) pH-sensitive microspheres for colonic drug delivery
(b) pH-sensitive microparticles for colonic drug delivery

(c) pH-sensitive pellets for colonic drug delivery
(d) pH-sensitive nanoparticulate drug delivery system for colon

(a) pH sensitive microspheres for colonic drug delivery

Budesonide microspheres have been formulated for colonic drug delivery using Eudragit S100 as a pH-sensitive polymer using emulsion solvent evaporation technique. The system was able to prevent the drug release below 7 pH [9]. Alf Lamprecht and co-workers formulated pH-sensitive tacrolimus microspheres using a Eudragit P-4135F as a pH-dependent polymer. Eudragit P-4135F was able to prevent the drug release from the dosage form (less than 10% in 6 h). At pH 7.4 almost all the drug was released within 30 min [45]. Meissner et al. also formulated pH-sensitive microspheres of enoxaparin by using Eudragit P-4125F. They studied the effect of various formulation parameters to optimize the pH-sensitive microspheres such as concentration of drug, different surfactant concentrations and different formulation techniques such solvent extraction/solvent evaporation to optimize the pH-sensitive microspheres [46].

pH-sensitive lipid polymer composite microspheres have been prepared for colonic drug delivery by ultrasonic freeze-drying technique. Eudragit S100 along with lipid polymer Compritol 888 ATO was used to prepare microspheres. In vitro drug release studies showed less than 15% drug release below pH 6.8, while instant/immediate drug release occurred at pH 7.4 [47].

(b) pH-Sensitive Microparticles for Colonic Drug Delivery

Apart from the microspheres, some authors have also formulated colon-targeted pH-sensitive microparticles, using Eudragit FS 30 D, for the treatment of Crohn's disease [48]. Microparticles composed of acrylic acid and butyl methacrylate, in different ratios, were found to release more than 90% of drug at colonic pH [49].

(c) pH sensitive pellets for colonic drug delivery

Sustained release pH-sensitive pellets of capecitabine were formulated by Li Gan for the treatment of colon cancer. Pellets were first coated with ethyl cellulose and then with outer pH-sensitive coating layer, composed of Eudragit S100/Eudragit L100. The pellets were able to release its contents into the colon for a period of 24 h [50].

In another study, vancomycin hydrochloride pH-sensitive pellets for colonic drug delivery were prepared using Eudragit FS 30 D, as a pH-sensitive polymer. Eudragit FS 30 D is a copolymer of methyl acrylate, methacrylic acid and methyl methacrylate (7:1:3). This polymer dissolves at pH above 7. Authors concluded that thickness of the coating layer was responsible for altering the drug release from the pellets. Pellets coated with Eudragit FS 30 D (more than 15%) gave the pH-dependent release profile in the colon [51].

Table 6.2 pH-sensitive nanoparticulate drug delivery systems used for colon targeting

Drug	Formulation	pH-sensitive polymer used	Disease	References
5-Fluorouracil	Nanogels	Methacrylic acid-ethyl hexyl acrylate (MAEHA) copolymer	Colon cancer	[53]
Paclitaxel	Nanomicelles	Triblock copolymers of polyethylene glycol poly(N-(N′,N′-diisopropylaminoethyl) aspartamide) and poly (lysine-cholic acid)	Colorectal carcinoma	[54]
Curcumin	Polymeric nanoparticles	PLGA/Eudragit S100	Inflammatory bowel disease	[55]
Cyclosporine A	Polymeric nanoparticles	Eudragit FS 30 D/PLGA	Immunosuppressive agent	[56]
Doxorubicin	Inorganic nanoparticles	Mesoporous silica gated with PEG and hydrolysed starch	Colorectal cancer	[57]

Akhgari and co-workers studied the effect of ratio of pH-sensitive polymers (Eudragit S100 and Eudragit L100) on indomethacin release for colonic delivery. They concluded that ratio of 4:1 (Eudragit S100 and Eudragit L100) at 20% coating level was able to release the indomethacin pellets at colonic pH [52].

(d) pH sensitive nanoparticulate drug delivery system for colon

Since over a decade, nanocarriers are gaining popularity in drug delivery. Among these nanocarriers, pH-sensitive nanoparticulate drug delivery systems are widely used for colon targeting. Table 6.2 lists out some of the examples of nanocarriers used for colonic drug delivery.

6.4.2 Polysaccharide-Based Systems

Polysaccharides are widely used in the formulation of colon-specific drug delivery systems. Obtained from plant, animal, bacterial and fungal sources, they are hydrophilic in nature, less toxic, biodegradable, nonimmunogenic and biocompatible. Guar gum, chitosan, pectin, amylose, chondroitin sulphate, and hyaluronic acid are commonly used polysaccharides for colonic drug delivery as they are insoluble in the GIT tract but are degraded by colonic bacteria, resulting in release of the contents of the dosage form in the colon. Table 6.3 shows the list of polysaccharides which are used in the formation of colon-targeted drug delivery system.

Polysaccharide polymers are grafted/modified to alter the drug release and to obtain the tailor-made release profile. One of the major advantages associated with grating of natural polymers is that they get converted into ionic copolymers by

Table 6.3 Polysaccharide-based systems used for colon targeting

Polysaccharide used	Active ingredient	Dosage form	Method of preparation	References
Chitosan	Curcumin	Microspheres	Emulsion polymerization	[58]
	Vancomycin	Nanoparticles	Ionic gelation and spray-drying	[59]
	Azathioprine	Beads	Ionic crosslinking	[60]
	Riboflavin	Pellets	Immersion coating	[61]
	Doxorubicin Hcl	Nanogels	Ionic gelation	[62]
Guar gum	Mebeverine Hcl	Microspheres	Emulsification method	[63]
	Tamoxifen citrate	Nanoparticles	O/W emulsion polymer crosslinking	[64]
	Indomethacin	Pellets	Film coating	[65]
	Ibuprofen	Microparticles	W/O emulsion method	[66]
	Dexamethasone	Hydrogels	Emulsion polymerization	[67]
Pectin	Resveratrol	Microspheres	Ionotropic gelation	[68, 69]
	Glipizide	Beads	Ionotropic gelation	
	Insulin	Nanoparticles	Ionotropic gelation	[70]
	Ketoprofen	Microparticles	Ionotropic gelation	[71]
	–	Pellets	Coacervation/ crosslinking	[72]
Amylose	5-Aminosalicylic acid	Pellets	Extrusion and spheronization	[12]

hydrolysing the amide groups which gives them pH sensitivity. For example, upon grafting of carboxymethylcellulose sodium (NaCMC) with polyacrylamide, amide functional groups present in polyacrylamide get transferred to the carboxyl group present on the NaCMC, thus rendering the carboxymethylcellulose sodium copolymer pH-sensitive. Spray-dried microspheres of polyacrylamide-grafted-carboxymethylcellulose sodium copolymer loaded with capecitabine have been studied for colonic delivery for the treatment of colorectal cancer [73]. Similarly karaya gum grafted with polyacrylamide has been explored as a pH-sensitive polymer for colon targeting [74].

6.4.3 Pulsatile Drug Delivery Approach/Chronotherapeutic-Based Approach

Pulsatile drug delivery systems are characterized by time period during which there is no drug release (often described as lag time) followed by rapid release. These pulsatile/chronotherapeutic/time-dependent systems have been studied for colon targeting. Different kinds of pulsatile colon-targeted drug delivery systems are as follows:

(a) Rupturable multiparticulate pulsatile system
(b) Osmotic pressure-activated rupturable pulsatile system
(c) Erodible/soluble multiparticulate pulsatile system
(d) Multiparticulate pulsatile system with altered membrane permeability

(a) Rupturable Multiparticulate Pulsatile System for the Colon

One of the examples of multiparticulate pulsatile system is time-controlled explosion system (TES) [75]. They are also referred to as rupturable systems. The system consists of four layers. The innermost core is made up of nonpareil seeds (first layer). On to the surface of nonpareil seeds, drug layer is adsorbed (second layer). The next layer is swellable polymer layer made up of low substituted hydroxypropyl cellulose (third layer) followed by the outermost rupturable polymer layer, composed of ethyl cellulose. After passing the outermost layer, when GIT water comes in contact with the swelling layer, it swells and exerts its pressure onto the rupturable layer. Once the pressure/stress surpass the outermost membrane strength, the rupturing of the system takes places followed by rapid drug release after a predetermined lag time [76]. The swelling of the inner layer and hence the lag time can be tailored using different swellable polymers. Although swelling force/potential is dependent on pH and ionic concentration of the dissolution medium, increasing the amount of swelling layer decreases the lag time [77].

(b) Osmotic Pressure-Activated Rupturable Pulsatile System for the Colon

Hung et al. formulated a multiparticulate, osmotic pressure-activated rupturable pulsatile drug delivery system for propranolol hydrochloride. Pellets containing propranolol hydrochloride and osmotic agent (sodium chloride) were prepared by extrusion/spheronization technique. The pellets were coated with Eudragit RS which acted as outer rupturable controlled-release layer. The rate of drug release from the system is not due to swelling mechanism, but it is because of the generation of osmotic pressure in the system which exerted its pressure on outer rupturable membrane. The lag time was extended for pellet formulation containing 20% osmogen as compared to formulation containing 4% osmogen at the similar coating level. Results concluded that by altering the outer coating, thickness and the plasticizer content, various lag time can be obtained [78].

Similarly, Peter Schultz et al. formulated an osmotic pressure-activated rupturable pulsatile system for acetaminophen. Pellets containing an osmotic active ingredient were coated with cellulose acetate semipermeable membrane. 2–4 mg/cm coating level of semipermeable membrane was sufficient to cause any leakage from the system. A lag time of about 6 h was obtained thereafter the drug release was obtained in a sustained manner [79].

(c) Erodible/Soluble Multiparticulate Pulsatile System for the Colon

Gazzaniga et al. developed an erodible/soluble multiparticulate pulsatile system for the colon. In comparison to time-controlled explosion system (TES), the swelling and rupturable coatings were replaced by soluble/erodible layer. The system is made up of drug-loaded pellets, coated with soluble/erodible layer, (high viscosity polymer such as Methocel K4M), followed by additional enteric coat of Eudragit L. This soluble/erodible layer solubilizes or erodes after a certain period of time to provide a lag time. In this kind of systems, the lag time prior to drug release can be controlled by the thickness of the coating layer [80].

(d) Multiparticulate Pulsatile System with Altered Membrane Permeability

To achieve a time-controlled/colon-targeted drug delivery system, sigmoidal release system (SRS) was developed [81]. In these systems, the outer coating membrane of multiparticulate pulsatile system is made permeable by the use of organic acids. In SRS the inner core is made up of nonpareil seeds. A powder mixture of theophylline and succinic acid was coated onto the surface of nonpareil seeds, and then loaded beads were coated with the Eudragit RS. The Eudragit RS polymer is insoluble in water and has low permeability. As the water enters into the system, it dissolves the contents of the beads. The solubilized organic acid interacts with the Eudragit RS which causes changes in the membrane permeability and which is responsible for characteristic sigmoidal curve. Desired lag time can be obtained by changing the thickness of the outer Eudragit layer.

6.4.4 Prodrug Approach

Prodrug is an inactive form of a drug, which is activated by the specific conditions at the targeted site. Two classes of prodrugs are generally used (Fig. 6.1a, b). Prodrugs of the first type are broken inside cells to form active substance or substances (Fig. 6.1a). In contrast, the second type of prodrugs usually is the combination of two or more substances. Under specific intracellular conditions, these substances react forming an active drug (Fig. 6.1b). Special types of prodrugs (DDS) have been developed during the last decades. These usually include three components: (1) a drug, (2) a targeting moiety and (3) a carrier (Fig. 6.1c). The carrier binds the prodrug components together and facilitates the solubility of the whole complex. The drug (active component) provides treatment. The targeting moiety/penetration enhancer substantially increases the internalization of active component specifically into targeted cells enhancing specific activity of the whole prodrug and decreasing adverse side effects on healthy tissues [82].

Azo conjugates (drug linked to azo group containing polymers) are one of the most researched groups of compounds that fall into type (A) category. These are susceptible to degradation by enzyme azoreductases present in the colon [84, 85].

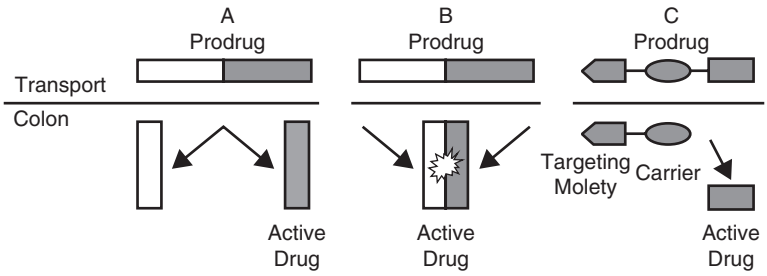

Fig. 6.1 Main types of prodrugs used for targeted drug delivery to the colon. Prodrugs of the first type (**a**) are broken inside cells to form active substance or substances. The second type of prodrugs (**b**) is usually the combination of two or more substances. Under specific intracellular conditions, these substances react forming an active drug. The third type of prodrugs, targeted DDS (**c**), usually includes three components: a targeting moiety, a carrier and a drug. (Reprinted from Tamara Minko 2004 [83], with kind permission from the publisher)

Kim et al. synthesized N-nicotinoyl-2-{2-(2-methyl-5-nitroimidazol-1-yl) ethyloxy}-D,L-glycine (NMG) as a colon-specific prodrug of metronidazole, which rapidly got cleaved to yield the active drug, metronidazole when placed in rats' caecal contents [86]. This prodrug did not metabolize in the small intestine, and the systemic absorption of this prodrug was also found to be much lower as compared to that of oral metronidazole. Similar results were obtained with a prodrug of metronidazole prepared using a sulphate group [87]. Metronidazole has also been conjugated with pectin for colon-targeted delivery [88]. The pectin-metronidazole prodrug showed significantly reduced drug release in the upper GIT compared to pectin microspheres, in which metronidazole was physically entrapped. However, there was a significant higher drug release from the prodrug in the colon.

Succinyl-prednisolone (SP), a prodrug of prednisolone, has been successfully delivered to the colon. Chitosan- SP conjugate was obtained by carbodiimide coupling and was used to obtain its microparticles and subsequently coated with Eudragit L100 or S100. These microparticles achieved a specific delivery of prednisolone to the lower intestine and long retention there as compared to simple chitosan microparticles and simple Eudragit microparticles loaded with prednisolone [89].

6.4.5 Bioadhesive Systems

Local colonic concentration of drugs is very important in treatment of diseases like ulcerative colitis, Crohn's disease, pseudomembranous colitis, etc. But these diseases are often characterized by severe diarrhoeal episodes [90]; hence attainment of higher levels of local drug concentrations, for a long period of time, becomes difficult [30]. The bioadhesive approach can prove to be an effective strategy to prevent the wash-out of the drug from the colon [91]. Bioadhesive drug delivery system adheres to the colonic mucosa, delivering drug over a long period of time, assisting absorption of poorly absorbable drugs. Examples of the polymers which

have been explored as bioadhesive components for these systems include chitosan, polycarbophils, polyurethanes and polyethylene oxide [92].

Microparticles containing metronidazole benzoate (prodrug of metronidazole) and coated with chitosan have been prepared for local drug delivery to the colon [93].

Another polymer known to have mucoadhesive properties is sodium alginate. Microspheres prepared using sodium alginate as a core and subsequently coated with Eudragit S100 could be used for the colon targeting of drugs. The presence of sodium alginate in the core imparts mucoadhesion in the colon after the removal of Eudragit coat by the mildly alkaline pH of colonic contents, which leads to increased residence time of the drug in the affected area [94].

Assam Bora rice starch also has proven to be a natural ingredient to develop a bioadhesive microsphere for targeting the delivery of metronidazole to the colon [95]. The microparticles were found to have higher retention time in the colon and helped increase absorption of the drug in the colon.

Curcumin-containing nanoparticles with mucoadhesive properties have been successfully formulated. Encapsulated curcumin exerted an influence on the adsorption of mucin due to H-bonding as well as π-π interactions between the phenolic moieties of curcumin and mucin [96].

Tamarind seed polysaccharides may be suitable for the formulation of mucoadhesive nanoparticles for better efficacy and sustained delivery of anticancer drug, irinotecan, with reduced toxicity [97].

Another approach for imparting mucoadhesive property to the drug delivery systems, including microparticles, is to attach them with ligands, such as lectins, which can specifically interact with the receptors uniformly present in specialized areas in the gastrointestinal tract. Wheat germ agglutinin (WGA) is a glycoprotein which has affinity for N-acetylglucosamine and sialic acid residues on the cell membrane. Several studies have shown that sialic acid is over-expressed in colon cancer tissues, so if surface of microparticles is coupled with WGA, it may improve the specificity of the delivery system for the colon cancer cells. Also, under physiological conditions, sialic acid is known to have negative charge; hence positively charged particles may provide adherence [98]. This approach has been explored, in the laboratory, to effectively deliver 5-fluorouracil in the treatment of the colon [99].

As compared to microparticles, nanoparticles have a large specific area, which can interact with biological surfaces. Binding nanoparticles with different molecules can impart bioadhesive properties to them [100]. A prerequisite for covalent attachment is the presence of free functional groups, such as carboxylic or amine residues on the surface of nanoparticle. Laila et al. prepared nanoparticles from gliadin protein isolated from wheat gluten, and these gliadin nanoparticles were conjugated with lectins, for making them bioadhesive. It was shown that the binding of lectin provided greater specificity for colonic [101].

6.4.6 Miscellaneous Approaches

A few studies have indicated the involvement of macrophages and dendritic cells in active IBD [102, 103]. Biodegradable microspheres are known to be efficiently taken up by macrophages. Hence, microparticles loaded with anti-inflammatory agents are proven to be efficient in the treatment of patients with IBD. Poly(DL-lactic acid) microspheres containing dexamethasone were administered orally to mice in which colitis was induced [104]. Mucosal repair was reported without increase in the serum levels of dexamethasone proving that this could be an ideal strategy for the treatment of inflammatory bowel disease where local action in the colon is needed without systemic drug absorption.

Microparticles [105] as well as nanoparticles [106] using biodegradable polymer, poly[DL-lactide-co-glycolide] 50/50(PLGA), have been prepared for targeted oral drug delivery to the inflamed gut tissue in inflammatory bowel disease. These multiparticulates enabled the drug to accumulate in the inflamed tissue with higher efficiency than when given as solution.

Drug-loaded nanofibrous microspheres, injected locally to specific anatomic sites, providing for a slow, long-term release of a chemotherapeutic while minimizing systemic exposure, is another approach being explored to increase antitumour activity of chemotherapeutics. Docetaxel (DOC)- and curcumin (CUR)-loaded nanofibrous microspheres (DOC + CUR/nanofibrous microspheres), self-assembled from biodegradable PLA-PEO-PPO-PEO-PLA polymers, were developed as an injectable drug carrier without adding surfactant during the emulsification process. These microspheres could release curcumin and docetaxel slowly in vitro maintaining local concentrations of active drug [107].

Owing to lower proteolytic enzyme activity, the colon has been explored as a site to deliver protein and peptide drugs. It has been attempted to deliver insulin using a terpolymer of styrene and hydroxyethyl methacrylate cross-linked with a difunctional azo compound [108], as insulin containing polyanhydride microspheres [109] and poly(methacrylic-*g*-ethylene glycol) hydrogels of insulin. These systems ensured protection of insulin from degradation in the upper portion of the gastrointestinal tract and release into distal portion of the small intestine and proximal colon for systemic absorption following degradation of the polymeric carrier [110].

6.5 In Vitro and In Vivo Behaviour of Multiparticulate Systems

In vitro and in vivo behaviour of the colon drug delivery system reveals the performance of the delivery system. Ideally, drug delivery system must remain integrated and intact till it reaches to the colon. Several tools and techniques are available for in vitro and in vivo assessment of colon-targeted drug delivery system. In vitro assessment tools are compendial dissolution tests, in vitro fermentation studies (using rat caecal contents, human faecal contents and isolated bacterial cultures) and cell culture techniques such as in vitro permeability studies using Caco2 cell

line as a model and cytotoxicity studies, i.e. MTT assay, etc. In vivo assessment techniques cover animal models and some imaging techniques.

For the in vitro assessment of the colon-targeted drug delivery systems, no standardized technique exists for the evaluation of the drug delivery systems since ideal in vitro assessment tool should possess the in vivo conditions of the gastrointestinal tract such as the pH of the GI fluid, volume of the fluid, presence of microbial flora, presence of enzymes and presence of food components. Commonly, these conditions are affected by the diet and physical stress which make it difficult to design a standard in vitro assessment model.

Generally, it is recommended that first, compendial apparatus and methods should be used for novel dosage forms. Drug release from the colon-targeted drug delivery systems has been assessed by USP dissolution apparatuses I, II and III with minor modifications. Different fluids are used as media to mimic the in vivo conditions of GI tract like simulated gastric fluid, intestinal fluid and colonic fluid.

Bacterial culture from the colonic region can be used to evaluate the drug release of the controlled drug delivery system. Drug delivery formulation is incubated with suitable media for culture microorganisms in a fermenter. Drug released at different time intervals is estimated, which is directly proportional to degradation rate of polymer, e.g. Wakerly et al. have evaluated pectin-based drug delivery systems by enzymes and bacterial culture. Owing to its pectinolytic activity, *Bacteroides ovatus* was chosen. Results suggested that timing and release profile of dye from the enzyme were similar, and bacterial studies showed similarity in mode of pectin breakdown [111].

Since the last few years, utilization of intestinal cell line has increased to study the intestinal permeability and for toxicity assessments. Caco-2, human epithelial cell line, is largely used as a model of the intestinal epithelial barrier. Caco-2 cell line creates morphologic characters of normal enterocytes when grown on plastic dishes or nitrocellulose filters. Caco-2 cell monolayers mimic the intestinal absorptive epithelium and signify a very helpful tool for studying transepithelial transport.

In vivo evaluation of the drug delivery system is generally performed to access the site specificity of drug release and to gain information about the pharmacokinetic behaviour of the systems. Nevertheless, animal models have evident advantages to assess the colon drug delivery systems, and some imaging techniques, e.g. γ-scintigraphy imaging, are also utilized using human subjects. Various animal models have been widely used to access the performance of colonic drug delivery such as rats, pigs and dogs. The choice of suitable animal model to evaluate colon-targeted drug delivery depends on its design and its triggering mechanism, which can nearly simulate the human physiological environment of the colon. For example, guinea pigs have comparable digestive anatomy - physiology and, glycosidase and glucuronidase activities in the colon, to the humans. In vivo evaluation of the colon-targeted drug delivery systems by different animal models demonstrates the variability of the response as compared to human subjects because of considerable diferences in physiology, gastric transit time, enzyme activity, the presence of the

microflora, etc., and therefore finding attained by animal studies should be elucidated carefully.

Furthermore, γ-scintigraphy imaging technique is a non-invasive modality through which the in vivo assessment of drug delivery systems can be visualized under normal physiological conditions. With rising complications in the design and development of novel colon-specific drug delivery systems, conventional pharmacokinetic performance may not produce sufficient data to justify the intended rationale of system design, in most of cases. γ-Scintigraphy has been utilized to study the functionality of solid dosages, tablets and capsules in vivo since long time and became a well-recognized technique and is widely used to monitor the performance of novel drug delivery systems within human GI tract [112, 113].

With rising complexity in the design and development of the novel multiparticulate-based delivery systems, in addition to the current assessment tools for in vitro and in vivo evaluation, demands more specific, sophisticated in vitro and in vivo assessment tools to understand the performance of the systems, precisely.

6.6 Patented/Marketed Technologies

Several patented technologies have been studied extensively based on the different working mechanisms and their unique characteristics. Some of the technologies such as CODES™, Pulsincap systems, Phloral™, MMX™ (Multi Matrix technology), etc. have been described in Table 6.4. Furthermore, some of the patents on the multiparticulate-based colon drug delivery systems and clinical trials are mentioned in Tables 6.5 and 6.6.

6.7 Future Opportunities and Challenges

Recently colon-targeted drug delivery systems have gained a lot of attention for the delivery of therapeutics. Certain challenges to colon drug delivery, such as abruption and degradation in the upper GI tract etc., limit the applications of the drug delivery systems. Nevertheless, design and development of drug delivery systems such as multiparticulates, overcomes the challenges by specific targeting to the colon in treatment of various local and systemic disorders. Currently, several technologies are available in the market with added advantages to conventional systems. Bearing in the mind the complexity of the colon-targeted drug delivery systems and the uncertainty of the current in vitro dissolution techniques in ascertaining possible IVIVC, obstacles remain for the pharmaceutical researchers to design, develop and validate a dissolution technique that integrates the physiological characteristics of the colon and yet can be utilized regularly in an industry setting for the assessment of the colonic drug delivery systems.

Development of the technologies to achieve the optimum therapeutic outcomes for colon-specific drug delivery is a challenging area for future research and holds great potential for developing efficient drug delivery systems. Advancements of the

Table 6.4 Some of the patented/marketed technologies for colon-targeted drug delivery

Sr. no	Technology	Formulation details	Mechanism and applications
1	COLAL-PRED™ system	Combination of colonic drug delivery system (COLAL®) and prednisolone sodium metasulfobenzoate (PMSBS)	Possibly the effective treatment of ulcerative colitis without the usual debilitating side effects of steroids
		Contains small pellets containing PMSBS, with an ethyl cellulose (EC coating) and a specific form of amylose (derived from starch) that is broken down in the colon only by enzymes from locally occurring bacteria	Phase III clinical trial showed significantly improved risk-benefit profile to that of conventional oral prednisolone
2	CODES™ technologies	This system is joint approach of pH-dependent and microbially triggered CDDS	Utilizes a unique mechanism involving lactulose, which acts as a trigger for target-specific drug release in the colonic region
		It consists of tablet core containing lactulose, coated with Eudragit E which is an acid-soluble material and then consequently overcoated with Eudragit L, an enteric material	
3	EUDRACOL™	System contains pellets layered with Eudragit RL/RS and Eudragit FS 30 D	Reduction of dose frequency
		Multiple unit system with pH- and time-controlled mechanism	Owing to its specific coating structure, the technology offers a new aspect for colon drug targeting through oral delivery
4	Pulsincap™ system	System consists of a water-insoluble capsule enclosing the drug reservoir	When the capsule body comes in contact with the dissolution fluid, system swells, and after a lag time, the plug pushed itself outside the capsule body and quickly releases the drug
		Swellable hydrogel plug is used to seal the drug contents into the capsule body	Technology can provide increased therapeutic benefits to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc.

5	Port® system	System comprises semipermeable membrane-coated capsule	Such system utilizes to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system
		Inside the capsule there is an insoluble plug consisting of osmotic agent and the drug formulation	System avoids second time dosing, which may be beneficial for school children during daytime
		When this capsule comes in contact with the dissolution fluid, the semipermeable membrane permits the water to enter, which causes the pressure to develop and the insoluble plug expelled after a lag time period	
6	OROS-CT delivery	System can be a single osmotic unit or may be multiple (5–6 push-pull) units, encapsulated within a hard gelatin capsule	System can be used for treatment of ulcerative colitis
		Each bilayer push-pull unit comprises an osmotic push layer and a drug layering, both enclosed by a semipermeable membrane	System is intended with a 3–4 h post-gastric delay to prevent drug release in the small intestine region
			Drug release initiates when the unit reaches the colon
			System can maintain a constant release rate for up to 24 h in the colon or as short as 4 h as well
7	Microbially triggered colon-targeted osmotic pump (MTCT-OP)	The combination of osmotic technology and microbial-triggered mechanism had a high potential to deliver to drug load in colonic region	Technology developed for controlled drug delivery system based on chitosan for a model drug, budesonide
		In this technology the core tablet consisting active therapeutics was prepared with chitosan, which is used to produce osmotic pressure and to form the in situ delivery pores for colon-specific drug release	
		Tablet was coated by semipermeable membrane made by cellulose acetate in acetone with chitosan and lastly coated with enteric polymer Eudragit L 100-55 in ethanol that could inhibit semipermeable membrane from forming pore or rupture before it reaches to the colon	

(continued)

Table 6.4 (continued)

Sr. no	Technology	Formulation details	Mechanism and applications
8.	Phloral™	Novel technology represents a significant enhancement in colonic delivery providing 'fail-safe' delivery of drug to the target site by employing two complimentary mechanisms to trigger the release of drug	pH-dependent coating also incorporates a resistant starch component which is broken down particularly by the microbiota in the colon
			Dosage units with the combination coating all disintegrated in the colonic area as desired
9	MMX™ (Multi Matrix technology)	System consists of tablets coated with pH-resistant acrylic copolymers which delay the release until the tablet reaches the indicated intestinal location where the programmed dissolution begins	Technology allows for protection of the drug from adverse pH conditions and enzymates in the upper GI tracts
			Technology allows the delivery of active therapeutics into the lumen of the colon through tablets in a delayed and controlled extent with the effect that the active pharmaceuticals can be applied to the full length of the colon
			Used for other diseases affecting the colon and can be used as a platform technology for applications outside the colonic region where a delayed release is essential
10	Diffucaps	Granulated or layered drug core is created onto a neutral surface following the application of rate-controlling, functional polymer membranes	Systems can incorporate functional, release-controlling polymers or protective coatings onto drug-layered cores. These multiparticulate systems offer sophisticated control of drug delivery and optimize release profiles for single drugs and drug combinations
		Layering of drug can be done from either aqueous or organic solvent-based drug solutions/suspensions and consequences in a small, spherical, multilayered bead	
11	IPDAS (intestinal protective drug absorption system)	System comprises high-density controlled-release beads, compressed into a tablet. Polymer coating can be used to make controlled release. On the other hand, the drug can also be coated into on an inert carrier such as nonpareil seeds to create instant release of multiparticulate units	Improve the gastric tolerability of NSAIDs and other irritant drugs

12	PRODAS (Programmable Oral Drug Absorption System)	System contains number of minitablets enclosed in hard gelatin capsule	Can be possible to include different numbers of minitablets, each one formulated separately and programmed to release drug at different sites within the gastrointestinal tract
13	PDS (Pelletized Delivery System)	It consists of pellets layered by powders or solutions	Diffusion-based drug release with erosion or by osmosis
		Release modified polymers are sprayed on the pellets by various coating methods and filled into the capsules	Pellets can be prepared to produce first-order or zero-order release pattern
14	Peltab® (pelletized tablet)	System makes use of polymer-coated drug pellets or drug crystals, which are compressed into tablets	Systems can be used as controlled drug delivery
15	Flashtab	Multiparticulate active drugs with the excipients such as swelling agent and disintegrant, compressed into tablets	Oro-dispersible tablet dosage forms which disperse quickly before the patient swallow them
		It is a fast dissolving/disintegrating oral tablet formulation	
16	Minitabs	Tiny tablets with the gel-forming excipients for the controlled release and can be filled into capsules	Offers the benefits of a tablet in combination with those of multiparticulate drug units

Table 6.5 Some of the patents on the colon-specific delivery systems

Sr. no	Title	Formulation details	Patent no.
1	Pharmaceutical Compositions For Colon-Specific Delivery	Pharmaceutical composition contains the core consisting an active pharmaceutical agent or salt thereof, an inner coating surrounded by the core and an outer coating which surrounds the inner coating. In different configurations, a particulate of the present systems can be a pellet, a bead or a minitablet	WO2017/156214 A1
2	Osmotically Controlled Drug Delivery Systems	The invention relates to osmotically controlled drug delivery systems containing fenugreek osmopolymer	WO 2013/168177 A2
		Inventions also present the processes for preparing such compositions and methodologies of using such pharmaceutical compositions	
3	Colon-specific drug delivery using interpolymer complexations	Invention narrates to the pharmaceutical compositions for drug delivery in the colon using an interpolymer complexation of a cationic polymeric glucosamine or its derivative and an anionic, cross-linked, polyacrylic acid or its derivatives	WO 2005/030173 A1
4	Pharmaceutical compositions for colon-specific delivery	A particulate comprises a core containing an active moiety, an inner coating surrounded by the core, wherein the inner coating contains a pharmaceutically suitable polysaccharide that is vulnerable to enzymatic digestion by one or more enzymes present in the colonic microflora, and an outer coating surrounding the inner coating, wherein the outer coating consists a polymer which is stable at upper GI pH but can dissolve at colon luminal pH in less than about 60 min	US 2017/0258869 A1
5	Optimal Colon Targeting Technology	Invention relates to a formulation for the controlled-release formulations comprising one or more active moieties or one or more active moiety containing cores, covered by one or more envelopments, which are dissoluble or permeable above an individual defined pH value, again covered by an envelopment, which is dissoluble or permeable above still another individual defined pH value	US 2014/032231.6 A1
6	Indigestible polymer: starch acetate-based film coatings for colon targeting	A colon-targeted delivery system for controlled release of the drug consists an active moiety coated in a polymeric mixture of a water-insoluble polymer composition containing at least a starch acetate and an indigestible polysaccharide	US 2013/0078289 A1

(continued)

Table 6.5 (continued)

Sr. no	Title	Formulation details	Patent no.
7	Multiparticulate pharmaceutical formulation for colon absorption	Multiparticulate systems contain the particles having a particle size of between 2.2 and 4 mm, preferably 2.5–3.1 mm and most preferably about 2.8 mm, each particle comprising a core containing or carrying at least one active therapeutics and at least one layer showing adhesion and/or being crushable in the colon consisting (i) one or more poly(meth)acrylates and (ii) nonporous inert lubricant, selected from the stearates, kaolin, pharma glass, talcum and mixtures thereof	US 2012/0328707 A1
8	Multiparticulate osmotic delivery system	The invention relates to a multiparticulate osmotic delivery system for an oral route. The composition contains a core that includes at least one drug in combination with at least one excipient. The composition further includes an osmotic subcoat surrounding the core and a modified release overcoat surrounding the osmotic subcoated core	

colon-targeted drug delivery systems can be achieved by the ways like combining the two working mechanism-based systems and overcoming the challenges of the single-unit systems, and drug delivery systems with biodegradable characteristics in vivo. Additionally, development of nanotechnology-based drug delivery seems promising for future research and technological advancements, e.g. pH-sensitive nanoparticles [55], montmorillonite nanodevices [131] and solid lipid nanoparticles [132]. In the current time, specifically in the cancer research, there is a concern in the direction of site-specific delivery of the oncology drugs, particularly to the affected site of the colonic region in an expectable and reproducible manner. Nevertheless, the biggest concern for the efficacious drug targeting for the colon is the absorbance avoidance in the colon and enzymatic degradation in the GI tract before it reaches to the target site. Nanotechnology-based drug delivery systems circumvent these challenges. Some of the novel nanotechnology-based drug delivery systems are being explored in the cancer research covering the immunoliposomes, metal oxide nanoparticles, dendrimers, carbon nanotubes and smart nanocomposite hydrogels [133].

Furthermore, the nanotechnology highlights new dimensions on the cancer imaging and diagnostic applications. Nanoparticulate systems have plentiful characteristics that are significant in the development of imaging device, detecting certain changes at the cellular levels, e.g. gold nanoparticles. Multiparticulate systems with nanotechnology-based approach demonstrate remarkable characteristics including the controlled release of the therapeutics, targeting efficiency of the drugs and improvement in the safety profile in vivo.

Table 6.6 Some of the clinical trials in the colon-specific drug delivery systems

Clinical trial no.	Clinical trial title	Drug/formulations	Clinical trial details	References
NCT03774680	Targeted Polymeric Nanoparticles Loaded With Cetuximab and Decorated With Somatostatin Analogue to Colon Cancer	Oral polymeric particles loaded with cetuximab and decorated with somatostatin	Objective of the study is to deliver polymeric nanoparticles loaded with anticancer drug cetuximab and decorated with somatostatin analogue in the form of polymeric nanoparticles, which can release at only above pH 6.8 by ethyl cellulose	[114]
NCT02716285	Peppermint Oil for the Treatment of Irritable Bowel Syndrome: Optimizing Therapeutic Strategies Using Targeted Delivery (PERSUADE)	Peppermint oil containing colon-targeted delivery capsule	Multicentre randomized, placebo-controlled trial Aim of the study is to examine the effects of an 8-week peppermint oil treatment in irritable bowel syndrome patients	[115]
NCT00744016	Mesalamine Pellet Formulation to Maintain Remission of Mild to Moderate Ulcerative Colitis	Mesalamine pellet formulation	Phase 3, multicentre, double-blind, randomized, placebo-controlled study Objective is to compare the maintenance of mild to moderate ulcerative colitis remission with 6 months of treatment with mesalamine pellets each day with placebo	[116]
NCT01033305	Oral Ciclosporin for Colonic Release in Ulcerative Colitis (CyCol™)	Controlled-release minicapsule formulation of cyclosporine (CyCol™)	Phase 2, randomized, double-blind, placebo-controlled study To evaluate the safety, efficacy and tolerability of a minicapsule formulation of cyclosporine in improving mild to moderate ulcerative colitis	[117]
NCT00867438	Efficacy and Tolerability of a New Oral Extended-Release Formulation Containing Parnaparin Sodium, Administered Add-on Therapy	Oral extended-release formulation containing parnaparin sodium	A multicentre randomized, double-blind, comparative study versus placebo To assess the effectiveness and the tolerability of oral parnaparin sodium as extended-release tablets (CB-01-05-MMX™)	[118]

NCT03378388	A Study to Assess the Effectiveness and Safety of Treatment With Vedolizumab in Adult Participants With Ulcerative Colitis (UC) or Crohn's Disease (CD) in Real Life (GEVOL)	Vedolizumab	Prospective, noninterventional and pharmacoepidemiological study of participants with inflammatory bowel diseases	[119]
NCT03452501	Safety and Effectiveness Study of Remsima® in the Treatment of Inflammatory Bowel Diseases Among Saudi Arabia Patients	Infliximab	A multicentre, observational, prospective, cohort study To evaluate the safety and efficacy of infliximab biosimilar in inflammatory bowel disease patients in Saudi Arabia	[120]
NCT02745678	Localized Therapeutics for the Treatment of Gastrointestinal Disorders II	Thermosensitive topical gel	Purpose of study is to evaluate novel thermosensitive topical gel for the treatment of inflammatory bowel disease, particularly ulcerative colitis	[121]
NCT02291445	Comparing a 182 mg Colon-targeted-delivery Peppermint Oil Capsule (Tempocol-ColoPulse®) and a 182 mg Enteric-coated Peppermint Oil Capsule (Tempocol®), a Pharmacokinetic Study	Colon-targeted delivery capsule (Tempocol-ColoPulse®) and enteric-coated capsule (Tempocol®)	A randomized, double-blind, two-period, two-treatment crossover study Pilot study to evaluate the relative bioavailability between two peppermint oil-based formulations	[122]
NCT01130272	Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Irritable Bowel Syndrome With Diarrhea	JNJ-27018966 oral tablets	Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicentre study To assess the effectiveness, safety and tolerability of JNJ-27018966 in the treatment therapy of patients with irritable bowel syndrome with diarrhoea	[123]
NCT03484195	Neoadjuvant FOLFOXIRI Chemotherapy in Patients With Locally Advanced Colon Cancer	FOLFOXIRI chemotherapy (irinotecan, oxaliplatin/L-leucovorin and 5-fluorouracil IV 48 h continuous infusion)	Open-label, single-arm, multicentre phase II study To assess the safety and efficacy of neoadjuvant FOLFOXIRI chemotherapy in the locally advanced colon carcinoma patients	[124]

(continued)

Table 6.6 (continued)

Clinical trial no.	Clinical trial title	Drug/formulations	Clinical trial details	References
NCT02727751	A Long-Term Safety Study of Tenapanor for the Treatment of IBS-C (T3MPO-3)	Tenapanor	Phase 3, open-label long-term safety study To evaluate the safety of tenapanor 50 mg BID in subjects with constipation predominant irritable bowel syndrome	[125]
NCT02504060	Clinical Trials of N-acetyl Glucosamine Capsule for IBS-D Treatment	N-acetylglucosamine capsule	Multicentre randomized double-blind placebo-controlled clinical studies To evaluate the safety and effectiveness of N-acetylglucosamine capsule for irritable bowel syndrome with diarrhoea	[126]
NCT00180050	Budesonide Treatment for Lymphocytic Colitis	Budesonide	Study to evaluate the efficacy of oral budesonide in the treatment of lymphocytic colitis	[127]
NCT01779765	The Efficacy of Hydrolyzed Guar Gum (PHGG) in the Treatment of Patients With Irritable Bowel Syndrome (IBS)	Hydrolysed guar gum (PHGG)	Double-blind, placebo-controlled, randomized study To study the efficacy of hydrolysed guar gum in the patients with irritable bowel syndrome	[128]
NCT00679432	(CB-01-02/01) Randomized Placebo Controlled Trial of Budesonide-multi-matrix System (MMX™) 6 mg and 9 mg in Patients With Ulcerative Colitis	Budesonide Multi Matrix system (MMX™)	A multicentre, randomized, double-blind, double-dummy comparative study versus placebo To study the efficacy and safety of new oral budesonide MMX™ (CB-01-02) extended-release tablet formulations with mild or moderate ulcerative colitis	[129]
NCT00545389	Phase II Dose-Ranging Study in Subjects With Mild to Moderate Ulcerative Colitis Treated With SPD476	Extended-released polymeric matrix formulation of mesalamine	A phase 2, randomized, multicentre, double-blind, parallel-group, dose-ranging, exploratory study To study the percentage of subjects in remission at the end of treatment	[130]

Among the recent advancements in the nanotechnology-based multiparticulate drug delivery systems, one system, bio-nanocomposite beads, showed potential as a colon-specific delivery. System consists of pectin-coated chitosan/pectin-layered double hydroxide beads for the controlled-release delivery in the therapy of colon diseases. Ribeiro et al. selected 5-aminosalicylic acid as a model drug. Developed pectin-coated beads were stable to swelling by water and were capable of controlled release of the drug in in vitro studies, demonstrating promising candidates for the colon-targeted drug delivery [134]. Furthermore, lectins and glycoconjugates can be used as molecular targets for the colon drug delivery. Lectin-mediated drug delivery may turn into a promising approach to improve the efficacy of weakly permeable therapeutics by epithelial tissue transport [83].

In nutshell, development of the novel multiparticulate-based drug delivery systems for the colon targeting has gained promising potential for the treatment of colon diseases. Nevertheless, physiochemical characteristics of the therapeutic and physiological factors of the gastrointestinal tract influence and may present the challenges to the successful colon-targeted delivery, and further lots of research is necessary to advance the in vitro and in vivo assessment techniques for multiparticulate-based drug delivery systems.

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7 Parenteral Controlled and Prolonged Drug Delivery Systems: Therapeutic Needs and Formulation Strategies

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_7

Abstract

Parenteral delivery is the second leading drug delivery approach after oral delivery. With the current surge of targeted therapeutic (proteins and peptides) and novel formulation approaches, two major sectors of parenteral controlled drug delivery, prolonged release injectables and stimuli-controlled injectables, are projected to grow extensively in the coming two decades as indicated by the current regulatory product approval and industrial pipeline. This chapter discusses these two sectors with details on the impacted therapeutic disease area, potential drug candidates, advancements in manufacturing technologies, and formulation technologies. Moreover, a comprehensive account is also given on the current and next-generation injection devices. Detailed discussions will provide a thorough guide for the development of the parenteral-prolonged and controlled drug delivery systems.

Keywords

Injectable · Liposome · Microspheres · Long acting · Prolonged release · Stimuli responsive · Implants

7.1 Introduction

Approaches in any pharmaceutical industry that explores the development of a new drug product can be subdivided into three basic categories. First is the development of new molecular entities (NMEs) or new biological entities (NBEs) and the development of formulation thereof so as to get high returns through long-term market exclusivity granted by the patent. This in turn is associated with high investment and high risks during the thorough development phase. Second is the therapeutic repurposing of the already approved NMEs/NBEs. Though this removes a few risk factors, the drug or biologic still must go through a thorough investigation requiring a long time to reach the market. Due to this, much less time is spent on therapeutic repurposing of drugs. The third and considerably most pursued strategy, given the much lesser associated risk, is the application of the development of dose-modified versions of products. Applying a next-generation formulation technology to a new drug or even an existing drug has its own perks. As these products allow 505(b)2

pathway for registration, development time reduces considerably. In recent times, this could benefit both innovator companies working on NMEs/BLEs and other pharmaceutical companies working on new drug products.

For innovator pharmaceutical companies, it is not uncommon after patent expiry for a drug's sales to decrease as much as 90% due to generic competition [1]. With regulatory guidelines becoming stringent, increasing costs of drug development, and threats from generic surge after patent expiry, it is challenging for pharmaceutical companies to maintain their growth [2]. Hence, in the current scenario, it makes much sense for an innovator company to start working on novel approaches of drug delivery, which even after patent expiry gives them less competition from generics. Moreover, once validated, other NMEs/BLEs can be benefited from the same technology.

In case of other pharma industries working on product development, application of a new technology to approved drugs becomes a very rationalized approach giving next-generation benefit to their drug after its patent expiry. Apart from addressing the patients' needs from the point of view of drug delivery, it also gives the developer an exclusive market through patenting the technology. With a lot of reduction in development cost, the company can have the innovator privileges in the market. In terms of product development, companies get benefits from the availability of the existing literature knowledge of drug and excipients available. Reformulating drugs with novel strategies apply to delivery via oral, nasal, parenteral, or pulmonary routes.

In the past two decades, the pharmaceutical industry has witnessed immense growth with new industries taking on the market through their innovative novel delivery technologies. Started with oral and transdermal specialty formulations, technology now is moving toward growth in parenteral drug delivery. Oral delivery is now in its maturity phase, and it is routinely used in a large industry segment for product life cycle management. Other routes of delivery, except parenteral, have a very low market segment. Parenteral delivery, on the other hand, is showing immense upward growth trend as it is becoming more and more patient friendly (self-administration, wearable-technology, long-term patient adherence). With 2018 global market valued at $390 Bn, sterile injectable portfolio is going to register 5.9% CAGR through 2018–2028 [3]. According to the market research report from The Freedonia Group, the fastest and major growth will be seen in prefilled syringes, and growth will be underlined by safety features (retractable needles), improved response time, and enhanced bioavailability with reduced toxicity advantages.

Current approvals and product pipeline give a pretty good idea of what we will be seeing in healthcare in the near 10–15 years (Fig. 7.1a and b). Approval and product pipeline data of 2017 show that pipeline for injectable shows a lot of development work going on in injectables. Of 134 USFDA approvals and 60 EMA approvals, 44 and 21 formulations belonged to injectables. Among the injectables, solutions lead the strategies; however, suspension, lyophilized powder for solution/suspension, emulsions, and implants constitute more than 25% of the formulations in the industrial pipeline. Among 6400 drug delivery and formulation technologies (prescription and OTC) identified by PharmaCircle in 2017, ~4800 were active (2819 associated with one/more identified products and 2010 mainly released in

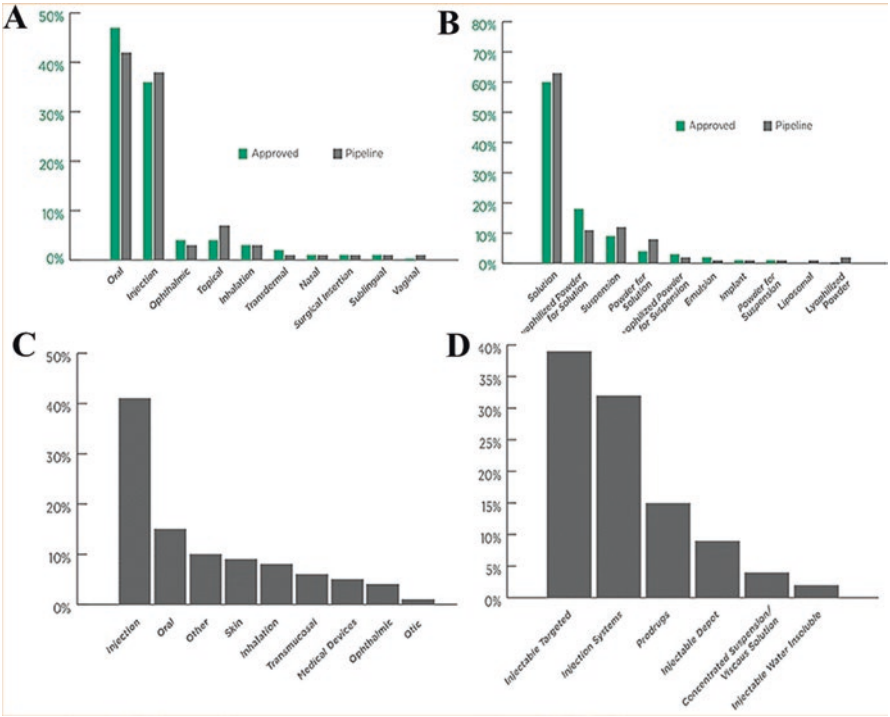

Fig. 7.1 (**a** and **b**) Drug product approval and industrial pipeline 2017 by administration route and by top 10 injectable types. (**c**) Drug delivery and formulation technologies in active development. (**d**) Injectable drug delivery and formulation technologies segmented in major groups. Injectables targeted represent the therapeutic antibody-based drug delivery systems. Injection systems represent a wide range of device-based injectables (prefilled syringes, autoinjectors, needle-free injectors, large-volume injectors, or infusion pumps). Data source: PharmaCircle, 2017. Figures reproduced with permission from Drug Development Delivery Magazine and PharmaCircle Inc

patents, publications, posters, or press releases). Analyses of these 4800 technologies (Fig. 7.1c) identified two major groups, that is, injectable formulations (41% of total) and oral formulations (16% of total). Among the injectables (Fig. 7.1d), more than 70% were targeted injectables and injection systems, while prodrugs and injectable depots represented ~25%. With this premise, the injectable-controlled and prolonged-release formulations hold a very interesting future.

This chapter details the controlled parenteral drug delivery systems in two segments:

(i) Rate-controlled drug delivery systems (termed prolonged-release (PR) injectables herein)
(ii) Stimuli-controlled drug delivery systems

While detailed focus is given on PR injectables, an important account is given to stimuli-controlled formulation as well.

7.2 Prolonged-Release Parenterals

Rate-controlled drug delivery holds a very important place in the current healthcare system for prolonged and chronic management of diseases. Interchangeably identified as PR injectables, sustained release injectables, or long-/ultra-long-acting injectables, these systems comprise a diverse group of formulation technologies and are continuously evolving.

7.2.1 Disease Areas and Drug Candidates

The market impact of prolonged-release injectables by therapeutic indication and their prediction through 2024 is shown in Fig. 7.2 and is projected to grow extensively. This also gives an indication of the industrial R&D path of coming years. Table 7.1 details the therapeutic indications and potential drug candidates for PR injectable.

Addiction Addiction is the market going through competitive transition with 29 million people suffering from one or other forms of drug use disorder. With adherence being particularly problematic with this kind of patients, making prolonged-release products for these patients would provide a solution. Two major disease groups in this area are opioid addiction (morphine and heroin mainly) and alcohol addiction, and demographics include North America as a major market. Opioid addiction is a chronic disease with 33 million opioid users worldwide with nonprescription use of prescription opioids and opiates (opium and heroin, which make up the 17.4 million users of the total) [4]. While only a few medications are available for opioid dependence including one for naltrexone, a systematic analysis

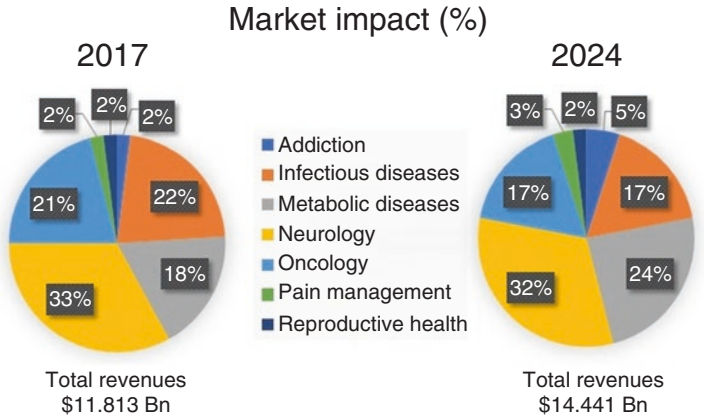

Fig. 7.2 Market impact of prolonged-release products by indication. The addiction area covers alcohol dependence and opioid addiction. Neurology includes chronic CNS disorders such as schizophrenia, depression, Parkinson's disease, etc. (Source: Greystone Estimates, Aug 2018)

Table 7.1 Disease areas and drug candidate analyses for suitability in development of PR injectables

Disease area		Drugs for treatment/ management of the disease[a]	Prolonged-release injectables available in market
Addiction	Opioid addiction	Narcotic antagonists: naloxone, naltrexone# Drugs for withdrawal symptoms: methadone#, buprenorphine	Naltrexone (Vivitrex®/ Vivitrol®, Naltrel® and Depotrex®) Buprenorphine (Sublocade™)
	Alcohol addiction/ alcohol use disorder	Drugs to reduce alcohol intake: naltrexone, acamprosate, disulfiram, varenicline, gabapentin, topiramate Drugs for withdrawal symptoms: benzodiazepines, risperidone, topiramate	Naltrexone (Vivitrex®/ Vivitrol®, Naltrel® and Depotrex®) Risperidone (Risperdal Consta®)- off-label use
	Cannabis addiction	Buspirone, dronabinol, entacapone, lithium	None
	Smoking or smokeless tobacco	Nicotine, varenicline, bupropion, nortriptyline, clonidine	None
Infectious diseases	Hepatitis C infection (HCV 1)	Interferon α2b Direct acting antivirals: NS3/4A protease inhibitors (glecaprevir, paritaprevir, etc.), Nucleoside and nucleotide NS5B polymerase inhibit or (sofosbuvir), NS5A inhibitors (ombitasvir, daclatasvir, etc.), Non-nucleoside NS5B inhibitor (dasabuvir)	Interferon α2b (PegIntron®, Pegasys®)
	HIV	NRTIs (Stavudine, zidovudine, tenofovir disoproxil, lamivudine, didanosine) NNRTIs (rilpivirine, etravirine, doravirine, delavirdine, efavirenz, nevirapine) Protease inhibitors (ritonavir, indinavir, tipranavir, atazanavir, saquinavir, fosamprenavir, darunavir, nelfinavir) Entry inhibitors (enfuvirtide, maraviroc) Integrase inhibitors (raltegravir, cabotegravir) Antibody (ibalizumab)	Ibalizumab (Trogarzo®) Several small molecules in clinical trials

(continued)

Table 7.1 (continued)

Disease area		Drugs for treatment/ management of the disease[a]	Prolonged-release injectables available in market
Endocrinology/ metabolic diseases	Diabetes (type 1 and 2)	Insulin# Biguanides (metformin) Sulfonylureas (glyburide, glipizide, glimepiride) Meglitinides (repaglinide, nateglinide) Thiazolidinediones (rosiglitazone, pioglitazone) DDP-4 inhibitors (sitagliptin, alogliptin, saxagliptin, linagliptin) GLP-1 agonists (exenatide#, liraglutide#, dulaglutide#, albiglutide#, semaglutide#, lixisenatide#) Amylin analogs: pramlintide#, SGLT2 inhibitors (canagliflozin, dapagliflozin, ertugliflozin, empagliflozin)	Insulin (insulin glargine, insulin detemir, insulin degludec, NPH) Exenatide (Bydureon®, Bydureon® Bcise™) Semaglutide (Ozempic®) Albiglutide (Tanzeum®) Dulaglutide (Trulicity®)
	Central precocious puberty, endometriosis and fibroids	GnRH agonists (buserelin#, goserelin#, leuprorelin#, naferelin, triptorelin#, histrelin#) Progestins (dienogest, didrogesterone, medroxyprogesterone#, norethisterone, levonorgestrel, etonogestrel#)	Goserelin (Zoladex®) Leuprorelin (Lupron® depot, Prostap SR®, Enantone®, Lucrin depot®, Trenantone Gyn®)
			Triptorelin (Decapeptyl SR®, Gonapeptyl®) Histrelin (Vantas™, Supprelin® LA) Medroxyprogesterone (Depo-Provera®, Depo-Ralovera®, Depo-Subq provera®, Lunelle®) Etonogestrel (Nexplanon®)
	Acromegaly	Somatostatin analogues: Octreotide#, lanreotide# Growth hormone antagonist: Pegvisomant# Dopamine agonists: cabergoline, bromocriptine	Octreotide (Sandostatin LAR Depot®) Lanriotide (Somatuline LA®, Somatuline depot®)

(continued)

Table 7.1 (continued)

Disease area		Drugs for treatment/ management of the disease[a]	Prolonged-release injectables available in market
	Contraception	Progestins (dienogest, didrogesterone, medroxyprogesterone#, norethisterone, levonorgestrel, etonogestrel#, desogestrel, norgestrimate, norelgestromin) Estrogens (ethinyl estradiol, estradiol#, esterified and conjugated estrogens, estropipate)	Progestins (Listed above) Estradiol (Delestrogen, Progynon Depot, Progynova, Depo-Estradiol)
	Infertility	GnRH antagonists: Cetrorelix#, ganirelix acetate# Gonadotropins: follitropin#, urofollitropin#, menotropin#, chorionic gonadotropin#, lutropin alfa# clomifene	
	Miscellaneous hormone deficiency or hormone supplements	Estradiol#, somatropin#, testosterone#, calcitonin#, parathyroid hormones#, mecasermin#, glucagon#	Estradiol (listed above) Somatotropin (Declage™, Nutropin depot™) Testosterone (Depo®-testosterone, Testoviron®-depot)
Neurology	Schizophrenia and related psychoses disease	Haloperidol, flupenthixol, fluphenazine, zuclopenthixol, pipothiazine, paliperidone, olanzapine, risperidone, quetiapine, olanzapine, aripiprazole	Risperidone (Risperdal Consta®, Perseris™) Haloperidol (Haldol Decanoate®) Flupenthixol (Flunxol Depot®) Fluphenazine (Fluphenazine Decanoate®, Modecate®) Zuclopenthixol (Clopixol Depot®) Pipothiazine (Piportil Depot®) Paliperidone (Invega Sustenna®) Olanzapine (Zyprexa relprevv®) Aripiprazole (Aristada®, Abilify maintena®)

(continued)

Table 7.1 (continued)

Disease area		Drugs for treatment/ management of the disease[a]	Prolonged-release injectables available in market
	Depression and related disorders	Tricyclic antidepressants (imipramine, chlomipramine, desipramine, trimipramine, dibenzepine, dimetacrine, dosulepin, doxepine, nitroxazepine, noxiptiline, opipramole, lofepramine, melitracen, amitriptyline, nortriptyline, protriptyline) Tetracyclic antidepressants: amoxapine, maprotiline, mianserine, mirtazapine, setiptiline	Risperidone (Risperdal Consta®, Perseris™)
		Selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, paroxetine, fluvoxamine, sertraline Selective norepinephrine reuptake inhibitors: venlafaxine, desvenlafaxine, duloxetine, milnacipram, levomilnacipram Serotonin modulators/ stimulators: vilazodone, vortioxetine Monoamine oxidase inhibitors: isocarboxazid, phenelzine, tranylcypromine, selegiline, metralindole, moclobemide, pirlindole, toloxatone	
	Bipolar disorder	Risperidone, aripiprazole, olanzapine, quetiapine, clozapine, ziprasidone	Risperidone Aripiprazole (Aristada®, Abilify maintena®) Olanzapine (Zyprexa relprevv®)
	Multiple sclerosis	Interferon β1a#	Interferon βla (Plegridy®)

(continued)

Table 7.1 (continued)

Disease area		Drugs for treatment/ management of the disease[a]	Prolonged-release injectables available in market
Oncology	Prostate cancer	GnRH agonists	Leuprorelin (Lupron® depot, Prostap SR®, Enantone®, Lucrin depot®, Trenantone Gyn®) Triptorelin (Decapeptyl SR®, Gonapeptyl®) Medroxyprogesterone (Depo-provera®, Depo- ralovera®)
	Melanoma	Immune therapies#: Interferon α2b, interleukin-2, talimogene laherparepvec "T-Vec," nivolumab, pembrolizumab, ipilimumab Targeted therapies: encorafenib, dabrafenib, vemurafenib, binimetinib, cobimetinib, trametinib Chemotherapy: dacarbazine	Interferon α2b (Pegintron®, Sylatron®)
	Chemotherapy associated nausea and vomiting	Granisetron#, tropisetron, ondansetron#, dolasetron#, palonosetron# Aprepitant, rolapitant, fosaprepitant#, dexamethasone, prochlorperazine	Granisatron (Sustol®)
Pain & inflammation	Surgical pain, chronic pain associated nonsurgical ailments	Local anesthetics#: bupivacaine, ropivacaine, lignocaine, etc. Opioids#: oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, meperidine, codeine, fentanyl, sufentanil, methadone, tramadol NSAIDS#	Morphine (DepoDur®), Bupivacaine (Exparel®)
	Osteoarthritis	Corticosteroids (cortisone#, triamcinolone#, etc.) NSAIDS#	Triamcinolone (Zilretta®)

[a]List is not comprehensive, however, includes recent and newer agents. #drugs for which injectable formulation is available in the market. Abbreviations: Nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), nonsteroidal anti-inflammatory drugs (NSAIDs), gonadotropin-releasing hormone (GnRH)

has shown that PR injectable has shown benefits in terms of cost and less hospital utilization [5]. Alcohol addiction is another chronic disease that makes the major proportion of drug abuse disorders. According to WHO, with per capita consumption of 6.2 l per year for people aged 15 years or older, alcoholism accounts for 3.3 million deaths each year [6]. Table 7.1 lists the drugs used in alcohol addiction. Two PR injectables available for alcohol addiction include naltrexone and risperidone.

Cannabis was till now the most illegally utilized psychoactive agent [7]. Based on UN data, the Americas (the USA and Canada top most other countries in the world) followed by Africa remain the highest cannabis consumption regions [4]. As of 2014, 182.5 million people worldwide are affected by cannabis addiction [4]. Now many countries are in the phase of shifting policies to legalize/decriminalize cannabis for medical as well as recreational use with most important and recent addition of 6 states in the USA (total of 9 states and the District of Columbia for recreational use and 30 states for medicinal use) and Canada for recreational use [8]. While also giving benefit to the medicinal development, the population being affected by cannabis addiction is going to increase. With this said, drop-dead clinical trial industry for the development of drugs for cannabis addiction would be revived with drugs reaching the market opening up the possibility for development of PR formulations. Buspirone is the only drug till now showing clinical benefit in dependence due to cannabis smoking, while other clinically evaluated drugs are entacapone, dronabinol, lithium, and nabiximols, which require further studies [7, 9]. A few preclinical studies have suggested the possible utility of URB597 (a fatty acid amide hydrolase inhibitor), endocannabinoid-metabolizing enzymes, and methyllycaconitine (a nicotinic α7 receptor antagonists) [7]. Development of PR injectables for cannabis addiction would be a promising area of research in the current scenario. Finally, tobacco addiction (smoking and smokeless tobacco) is a chronic disease for which the symptoms are rather not solely related to nicotine itself but with the smoke in case of smoking and tobacco-specific nitrosamines (TSNAs) in case of smokeless tobacco, which are implicated in a variety of cancers [10, 11]. Eighty percent of lung cancer deaths are thought to be due to smoking, while smokeless tobacco is linked with mouth, lung, cheek, gum, esophageal, and pancreatic cancers. The pharmacological therapies for tobacco addiction are either in the form of nicotine (nicotine replacement therapy (NRT), with wide range of nicotine dosage forms such as oral gum or lozenge, transdermal patches, nasal spray, or inhalers) [12] or with drugs like nicotine receptor partial agonists (cytisine, dianicline, and varenicline), antidepressants (bupropion, nortriptyline), and codeine [13, 14]. Other addiction categories include cocaine, emphetamine, and other illicit drugs with rising concerns for polydrug use as well. While oral extended release formulations are available for a few drugs, the development of effective and rationally designed injectable formulations would provide more patient-compliant options.

Infectious Diseases Infectious diseases of interest for PR injectables are hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections. The infections, apart from other means, have a major connection with addiction (12 million people worldwide inject addictive drugs, of these 1.6 million have HIV and 6 million have HCV infection; data as of 2014) [4]. Globally, around 170 million persons show chronic HCV infection with 3–4 million get infected every year. PR injectables can provide solutions to the issues associated with infectious disease pharmacotherapy such as (1) simplified dosage regimen (better adherence), (2) reduced side effects, (3) superior control on plasma concentration, (4) improved patient quality of life (QoL), and (5) a suitable option for preexposure prophylaxis (PeP). A very recent clinical trial on long-acting antiretroviral therapy (ART) with long-acting injectable of cabotegravir+rilpivirine (termed LAART) enabled monthly or bimonthly injection compared to daily oral regimen [15]. Patients were satisfied with the convenience of dosing while allowing for better privacy. Moreover, this was considered as a significant advantage because of not having to take pills daily as a reminder of their HIV status thereby offering mental peace to patients while improving adherence. There are three nanosuspension LAART injectables for every 8 weeks of administration [16–18]. Research is headed in the direction to provide ultra-long-acting ART injectable, which can be removed in medical emergency [19]. Other infectious diseases that can be benefited from PR injectables are hepatitis B infection. Though PR injectables could be of benefit in these areas, they need to be rationally designed and developed to surpass the issues of resistance, drug interactions (as in coinfections), and discontinuation or change of therapy.

Endocrinology Endocrine diseases mostly require long-term hormonal/drug treatment making these diseases ideal targets for PR injectable development. Precocious puberty (PP) (sexual precosity/prepuberty), endometriosis, and fibroids are the major groups for which the majority of treatments are developed as PR injectables (Table 7.1). PP is a rare chronic condition in children with an incidence rate of 1 in 5000 to 1 in 10,000 with male to female ratio of around 1:10 [20]. PP-affected children show earlier puberty than normal, that is, before 8 years age in girls and before 9 years age in boys. Without any treatment, PP-affected children show shorter height due to premature fusion of growth plates. This also leads to secondary anxiety, irritability, and social withdrawal. Treatment usually include gonadotropin-releasing hormone (GnRH) agonists [21]. Endometriosis is a chronic inflammatory condition in female with 5% of the females suffering from it and is implicated in chronic pelvic pain and infertility [22]. Apart from GnRH agonists, other class of drugs used in endometriosis is progestins. GnRH agonists share their therapeutic use in males with prostate cancer as well chronic treatment. Hence, this makes the development of GnRH PR injectables much more justified and rationalized having multiple therapeutic indications. While there are a lot of PR injectables already available in these categories, there is still room for development with other classes of agents or newer agents due to inherent resistance to some of the agents (i.e., 1/4th to 1/3rd endometriosis patients do not respond to progestins [22]).

Diabetes (types I and II) is another chronic endocrine disease with global estimated burden of 422 million adults in 2014 with major population affected by diabetes type II (90% of all cases) [23]. Insulin still remains the mainstay therapy for diabetes of both types, while there are other agents available. Although insulin formulations are available in intermediate-, long-, and ultra-long-acting versions and each work differently, they still require daily administration [24]. Even though self-administration devices save the patient trouble, the cost is a major factor. Hence, formulations/devices that make it possible to control drug administration and release externally for longer period while addressing cost factor would attract a large market. While improvement on insulin front is required, there is still a need to adopt other newer classes of agents as well for PR injectables. Only one PR formulation in the market till date is Bydureon® (exenatide). Hence, there is a need for cost-effective PR formulations for diabetes.

Neurology Neurology market encapsulates all major chronic mental health disorders including schizophrenia, depression, anxiety, bipolar disorder, and dementia [25]. This vast area still requires development of PR injectables to (i) solve patient-compliance issues, (ii) reduce adverse events associated with drugs, and (iii) provide better control of their disease improving QoL. Worldwide, 300 million people are affected by depression (accounting 4.3% of global burden of the disease), 60 million people by bipolar disorder, and ~21 million by schizophrenia [26]. 76–85% of those with mental disorders in low- and middle-income countries and 35–50% in high-income countries receive no treatment for their disorders. Schizophrenia and depression can also have a toll on the lives of patients with increased incidence of morbidity and mortality [25]. Moreover, these diseases affect and are affected by other major diseases such as cancer, diabetes, and HIV infection. The PR injectable formulations available in the market with neurological indications are shown in Table 7.1.

Oncology Cancer is a leading cause of deaths worldwide with 18.1 million new cancer cases and 9.6 million cancer related deaths in 2018 [27]. In both sexes combined, lung cancer is the most frequently occurring cancer (11.6% of all cancer cases) and the leading cause of cancer related deaths (18.4% of all deaths related to cancer). Breast cancer, prostate cancer, and colorectal cancer follow it with 11.6%, 7.1%, and 6.1% incidence rates.

Hormone-dependent cancers are of main interest areas for the development of PR injectables where therapeutic outcome can be suitably controlled by suitable drugs (hormone agonists or antagonists or receptor modulators) and drug delivery systems. Breast cancer (~2.088 million cases in 2018), prostate cancer (~1.276 million cases), ovarian cancer (~0.295 million), uterine cancers (~0.864 million), and testicular cancer (~71.1 thousand) are the most common cancers that can develop as hormone-dependent cancers. Among these, breast and prostate cancers are the most common cancers. While there are a number of GnRH agonists available as PR

injectables, there is none available for other hormone-dependent cancers with limited research at the same time.

With the advent of new technologies and formulation strategies, PR injectables can be developed for solid tumors as well by utilizing intratumoral injection/implantation with formulations of chemotherapeutic drugs [28]. While providing plenty of advantages, these strategies can benefit by improving the delivery of drug to cancer cells by better penetration in the necrotic tumor while reducing the systemic side effects [28]. As there is only modest amount of research going on in this direction, there is a plenty of room for improvement and advancement. To date, only one formulation strategy (ReGel® technology, paclitaxel-loaded OncoGel®) has reached the clinical trial. Moreover, biologic evolution has peaked recently with a wide range of therapeutic antibodies available for the treatment of almost all major cancers. Formulation and delivery strategies augmenting these drug potentials would also be of interest in the coming era of medication.

Pain Management Pain after surgery or injury is the area that has attracted a good attention of pharmaceutical companies since the past two decades. Prescription opioids have been used most frequently for surgical pain management. With this said, there has been growing nonprescription use of prescription opioids with its increasing burden on society [29]. In line with this view, Exparel® (liposomal bupivacaine phosphate) has made it to the market with growing acceptance. Chronic postsurgical pain (CPSP) or chronic posttraumatic pain persists for months after surgery/injury [30]. CPSP affects 1 or 2 in 10 patients undergone surgery and is of intolerable level in 1 of 100 patients undergone surgery [31]. Pain management could be the a potential market for PR injectables with limited competition.

Other potential therapeutic areas are chemotherapy-related emesis, allograft rejection medications for prophylaxis, inflammatory conditions such as ocular inflammation and osteoarthritis, and chemotherapy-related pain.

7.2.2 Administration Modalities

Parenteral administration, especially IM and IV, requires healthcare professional's assistance creating implications for delivery settings and cost and benefit aspects. In contrast, in the current paradigm, the pharmaceutical industry is moving toward specialty drugs (except for oncology, largely), which have self-administration possibility, while the products are still covered under prescription drug insurance benefits in all major countries. In the current scenario, many injectables will be replaced by orals, while those not replaced demand for improvement in terms of formulation strategy and delivery devices. With this background, drug development ecosystem now has become very complex with multilayered interdependence and collaboration between the formulation technology inventor and device designers with physicochemical testing intervened between these two.

While intravenous infusions are conceptually the traditional form of externally prolonged administration, they do not fit under the umbrella of long-acting injectables (LAIs) or PR injectables that are administered as single or multiple slow bolus administration subcutaneously (SC), intramuscularly (IM), and intradermally (ID). The selection of the administration route mainly depends on the physicochemical properties of the product (particle nature, solution, implant system). Usually, simple aqueous solutions and the nanosized particulates below 200 nm size are the only systems that enable IV administration (along with SC and IM administration), while oily solutions/suspensions, microparticulate systems, and gelling systems are administered through SC or IM route.

The major difference between the SC and IM routes is the adaptability of larger volumes and ease and suitability for administration. IM space can accommodate larger volumes (2–5 mL in large skeletal muscles such as triceps, deltoid, gluteus maximus, and rectus femoris), while the SC route put constraint on volume (1–2 mL) due to irritation, pain, and injection site reaction issues. Moreover, IM administration is more adaptable due to rich vascularity and less sensory nerves. With this said, the majority of the PR injectables are either given by IM administration to accommodate mainly two characteristics of PR formulations, that is, i) larger than usual dose of the drug incorporated in formulations for long-term availability of the drug and ii) specific physicochemical properties of PR injectable (oily solution, particle/gelling nature, rigid implant nature, etc.) specifically built in to the product for prolonged release characteristic, which otherwise is not possible for SC administration. Therefore, many long-acting IM injections are available in the market (oil-based injections, injectable drug suspensions, and injectable microspheres), while only a few PR injectables for SC administration can be found in the market (i.e., Depo-SubQ Provera, Pfizer; Nutropin Depot, Genentech; and Atrigel® formulations).

Moreover, the SC route is routinely used for self-administration, however, majorly with traditional injection devices (27–32 g needle). This puts constraint on the formulation characteristics in terms of syringeability, rheology, concentration of drug, etc. Hence, the formulation development needs to be done with the knowledge of these device variables beforehand. While the new devices available for SC administration have different components and different mechanisms, compatibility with device components, stability, and sterilization are important factors to consider.

While several PR injectables are developed for systemic drug delivery, some are for local or regional prolonged release. These products require product-specific routes of administration depending on their metabolism and disposition after administration, for example, intrathecal administration was used for DepoCyt for the treatment of lymphomatous meningitis and glioma. This route for PR formulation offers advantages as well as challenges; that is, it can accommodate aqueous-based formulations ranging from solutions to PR microparticulate systems and can be employed for several CNS ailments, while requires thorough safety evaluation. Other routes being explored for local PR parenterals include intraarticular (for

InGell®), intratumoral (for OncoGel™), intracranial (for Gliadel®), subgingival (for Atridox®), or intraocular (for Retisert®). However, this calls for detailed toxicity analysis of excipients that can be employed for formulation development and thorough safety evaluation post development.

7.2.3 Development Considerations for PR Injectables

A large lot of drugs and drug products have come or are coming off-patent and off-exclusivity soon. Table 7.1 describes the available approved drug candidates based on their therapeutic indication, which are prevalently preferred for PR parenteral formulations. The list is not compiled based on their suitability for parenteral PR formulations, rather it is a list of available candidate drugs in the therapeutic class and provides an idea of the ratio of marketed PR formulations vs available drug candidates. Moreover, their physicochemical and pharmacokinetic parameters need to be considered along with the desired strategy. For simplicity, drugs can be divided into two categories (small molecules and biologics) to assist in the selection of formulation technology, though there might be some overlaps of technology that are suitable for both kinds of drugs. While rationalized development of PR parenteral can be employed for any drug, drugs for which injectables are already available in the market (identified by # in Table 7.1) would be more apt for development. The following are the general considerations for any PR injectables:

1. Pharmacokinetic considerations (dose and duration of therapy)
2. Drug physicochemical properties

7.2.3.1 Pharmacokinetic Considerations

General formulation consideration that applies to intravenous infusion formulations also applies to PR injectables, that is, rate in (Ri) = rate out (Ro). Ro is governed by first-order elimination process, which is the case for most of the drugs following one compartment open model and can be calculated using

$$\text{Rate out Ro} = \text{Ke} \cdot \text{Xp}$$

(Ke is first-order elimination rate constant and Xp is plasma drug level = Cp x Vd and Cp for PR injectable is desired steady-state concentration of drug (Css))

$$= \text{Ke} \cdot \text{Vd} \cdot \text{Css} \qquad \left(\text{Ke} \cdot \text{Vd} = \text{total clearance } \text{Cl}_\text{T}\right)$$
$$= \text{Css} \cdot \text{Cl}_\text{T}$$

Ro provides an estimate of the drug release rate from the formulation that ultimately governs Ri. Usually PR products are designed to provide zero-/near zero-order release characteristics to match the Ro. For systemic delivery using PR injectable of a drug following first compartment open model, assuming 100% bioavailability and no presystemic metabolism, no drug loss,

$$\mathrm{Ri} = \mathrm{Ro} = \mathrm{Css} \cdot \mathrm{Cl}_{\mathrm{T}}$$

Based on this, the minimum dose for PR injectable (D_M) to maintain Css for τ period can be calculated using the following expression.

$$\mathrm{D}_{\mathrm{M}} = \mathrm{Css} \cdot \mathrm{Cl}_{T} \cdot \tau$$

The abovementioned is the case when the loading dose (D_L) is not included in the formulation to achieve desired Css instantly. The product releases the drug, which slowly achieves the Css and Css is then maintained throughout the period formulation for which it is designed for. For some products, loading dose is present in the formulation to achieve the desired Css instantly, which can be maintained by the maintenance dose, that is, products containing free drug in the PR injectable formulation or has initial faster release that helps to reach the Css instantly or in a short period of time. In such a case, the total dose can be expressed as follows.

$$\mathrm{Dtotal}\left(\mathrm{mg}/\mathrm{day}\right) = \mathrm{D}_{\mathrm{L}} + \mathrm{D}_{\mathrm{M}}$$

where

D_L = loading dose (dose to achieve desired Css by immediate release.
D_M = maintenance dose (minimum dose to be included in formulation).

$$\mathrm{Dtotal} = \mathrm{D}_{\mathrm{L}} + \mathrm{Css} \cdot \mathrm{Cl}_{\mathrm{T}} \cdot \tau$$

Based on this, the total dose is dependent on the Css, Vd, $t_{1/2}$, and τ.

As Css is correlated to the potency of the drug, higher potency drugs are best suited PR injectables, that is, drugs with Css in pg/mL range are more suitable than those with ng/mL range, which in turn are more suitable than those with Css in μg/mL range. The higher the potency of a drug, the longer the duration of release that can be designed into a PR product. Nexplanon 68 mg etonogestrel implant for subdermal use provides therapeutic (contraceptive) activity for 3 years once injected, while Probuphine 74.2 mg buprenorphine implant for subdermal use provides therapeutic activity for 6 months. Thus, low dose is the key requirement for the long-acting injectables, that is, <5 mg/day for suspension and <1 mg/day for implants. This applies to most PR injectables (Table 7.2) with fewer exceptions such as where the delivery is required only for a few days to a week, large-dose drugs can be considered feasible.

For a given Vd, the dose is inversely proportional to $t_{1/2}$ and directly proportional to τ. Hence, PR formulation of drugs with shorter half-lives (1–2 h) for longer duration of activity requires quite large doses sometimes making it impossible for administration considering the bulk of the formulation, which is quite larger than the dose of the drug due to the presence of excipients. This consideration does not apply to PR products for local-controlled release where the local tissue compartment kinetics should be considered. In such a case, drug kinetic parameters in local tissue and accounting for loss of drug to systemic circulation are required as it might affect systemic toxicity and reduce local activity.

Table 7.2 Generalized guide for development of PR injectable formulations

Strategy	Target dosage regimen	API characteristics	Formulation complexity
Oily solution (drug dissolved in oil)	Dose: >5 mg/day Regimen: ≤ 1 M	Low aqueous solubility and high lipophilicity Solubility in selected vehicle Prodrug approaches can be utilized to modify API characteristics	Low complexity Simple formulation strategy Dissolution controlled by diffusion out of oil
Aqueous suspension (microsuspension/ nanosuspension)	Dose: <5 mg/day (NMT 300 mg total) Regimen: 1–4 M	Low aqueous solubility High stability of API in water Particle size control can be utilized to modify release	Low complexity Ensuring physical stability is easy but dissolution controlled by particle characteristics Burst release and PK tails are the major challenges E.g., carbotegravir LA 200 mg/mL
In situ implants/gels (API and polymer dissolved in suitable solvent)	Dose: <2 mg/day (NMT 200 mg/day) Regimen: 1–6M	Can be adapted to accommodate diverse physicochemical properties of API through formulation characteristics Selection of organic solvent for solubilizing drug and API both required	Medium complexity Viscosity control required for easy administration Selection of organic solvent critical to provide adequate solubility without tolerability/toxicity issues E.g., Sublocade
Polymeric microspheres (API in polymer matrix)	Dose: <2 mg/day, (NMT 200 mg total) Regimen: 1–6M	Can be adapted to accommodate diverse physicochemical properties of API through process optimization Properties of protein/peptide API might get affected by process or formulation	High complexity Interplay of process, formulation, and drug characteristics Bust release may need control Dissolution controlled by particle and polymer properties E.g., Risperdal Consta

Polymeric implants (reservoir systems)	Dose: <1 mg/day (50–400 mg total) Regimen: 6M–3Y	Can be adapted to accommodate diverse physicochemical properties of API Only very high potency APIs	High complexity Implant size increases with increasing dose Surgical removal to stop therapy or after duration Nondegrading polymers are used Diffusion-controlled release from coating (zero and 1st order) E.g., Implanon
Polymeric implants (matrix systems)	Dose: <1 mg/day (50–400 mg total) Regimen: 6M–1Y	Can be adapted to accommodate diverse physicochemical properties of API Only very high potency APIs	High complexity Implant size increases with increasing dose Surgical removal to stop therapy Degradable polymers are used Polymer erosion and drug diffusion-controlled release (zero order) E.g., Lupron Depot
Pumps	Dose: < 0.5 mg/day Regimen: 6M–1Y	Can be adapted to accommodate diverse physicochemical properties of API Very high potency APIs Requires solubility in selected solvent	High complexity Device parameters controls drug release Highly controlled release possible Must be removed and refilled May come as wearable devices in future

For a given drug candidate, the longer the duration of therapeutic activity (τ) required from single PR injection, the larger the dose of injection. For example, Zoladex 3.6 mg goserelin acetate implant is for 28-day cycle, while Zoladex 10.8 mg implant is for 3 months cycle of administration. This indicates that a single instance of administration needs to be designed for a specific time period only depending on the dose of the drug, which can be accommodated in the drug delivery system and then the frequency of administration can be manipulated.

From the view point of formulation,

$$D_{total} = D_L + D_M$$

where $D_M = k_r^0 \cdot t_d$ (where k_r^0 is zero-order drug release rate constant and t_d is target duration of drug release)

Ideally, the maintenance dose should release the drug after Css is achieved by the loading dose; however, it is not possible in reality and maintenance dose starts releasing the drug instantly after administration [32]. Hence, the loading dose should be corrected by the amount of drug released by the maintenance dose during time till Css is achieved (t_{Css}) $k_r^0 \cdot t_{Css}$.

$$D_{total} = D_L - k_r^0 \cdot t_{Css} + k_r^0 \cdot t_d$$

If the loading dose is not included in the formulation, $D_{total} = D_M = k_r^0 \cdot t_d$. Note that t_d and τ may be and may not be the same. The duration of drug release cannot be designed to exactly match the duration of therapeutic activity due to formulation design limitations. In such a case, the subsequent dosing needs to be done after the formulation is exhausted of the drug after the release period. Hence, it is important to establish an IVIVC, which can help determine the robust in vivo performance through in vitro drug release testing.

Certain characteristics of the drug suitable for PR injectable from the pharmacokinetics perspective are as follows:

1. *Chronic therapeutic need (frequent administration)*: The higher the frequency of administration, the more noncompliance is seen among patients. Hence, such drug candidates requiring chronic frequent administration are suitable for parenteral PR formulations to improve patient adherence, which also allows for better control over therapy.
2. *Potent drugs*: Potent drugs make good candidates, while large-dose drugs are poor candidates.
3. *Poor/variable oral absorption*: When better therapeutic control over drug bioavailability is required.
4. *Longer half-life drugs*: Drugs with longer half-life are suited for PR injectables. The longer the duration of activity required, the longer the half-life of the drug should be.
5. *Narrow therapeutic index*: Drugs with narrow therapeutic index require critical control of drug level in the blood, which is not possible or is troublesome with multiple dosing of drug.

7.2.3.2 Physicochemical Properties of Drugs

Apart from PK characteristics, physicochemical properties of the drug are important as they directly affect the formulation design. The suitability of a drug candidate for PR parenteral from the physicochemical properties perspective can be based on one or more of following criteria:

6. *Solubility*: Suitable aqueous and organic solubility characteristics are required for each formulation design, that is, water solubility of drug is required for DepoFoam technology, while lipophilicity is necessary for oily solutions or aqueous suspensions. Also, it has a hold on the drug's release from formulation. Manipulation of drug solubility by salt modification, polymorph selection, prodrug preparation, etc., might help in designing of a specific dosage form.
7. *Drug stability in delivery system*: Storage stability and in-use stability (particularly in case of biologics, conformational changes in molecules can occur in matrix-type systems). The longer the duration of therapeutic activity desired, the more robust the drug molecule should be. Or the formulation should be designed in such a way to improve the stability of the drug, that is, lyophilized product against liquid dispersion.
8. *Compatibility with excipients*: Nonspecific interaction of the drug with excipients or excipient degradation products needs to be carefully evaluated as the drug excipient is supposed to be in contact for longer periods.

Two important factors to consider are the solubility of the drug (solubility in biological milieu) and dose of the drug. Solubility plays a major role in formulation development and drug release. Aqueous solubility dictates intrinsic release rate. Based on dose of drug and solubility in biological milieu, basic formulation selection chart could be devised (Fig. 7.3). As described earlier, because the drug product is cumulative of drug dose plus the excipients, which are mostly even higher in amount than the drug; implant size/injection volume also puts a major constraint during formulation development. Hence, for large-dose drugs, formulation strategy with lower excipient content and shorter duration of therapy should be considered, while for potent drugs, the formulation strategy is not forced by excipient content and duration of therapy. However, precise control of drug release becomes a major issue as the potent drugs have narrow therapeutic index. For large-dose drugs, drug properties play a more a central role, while for potent drugs, formulation technology plays a more central role. Stability of the product also needs to be considered. The longer the in-use period, the higher the stability of the molecule should be. Table 7.2 describes basic conceptual differences in available technologies, which can be used as a guide for screening of formulation strategies:

In the following text, the available technologies that have been used as PR injectables are described. The details cover the following four major components that play a major role in each of the formulation technology.

1. Drug properties
2. Excipient properties

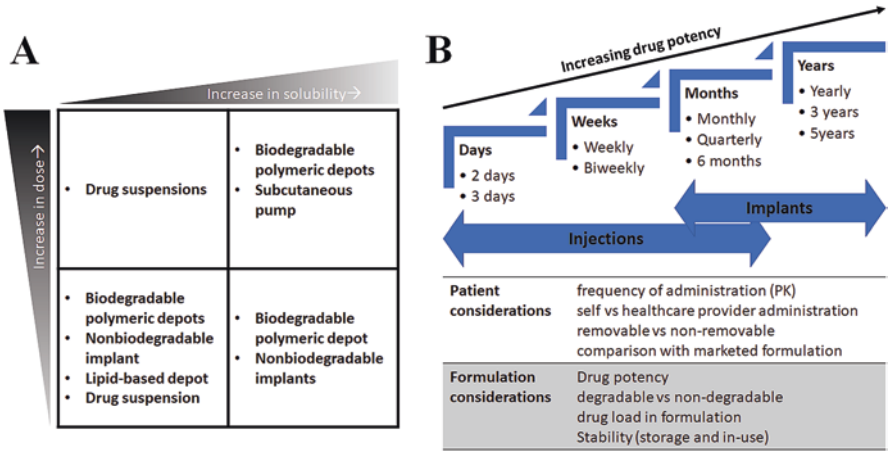

Fig. 7.3 (**a**) Suitable PR injectable strategies based on dose and aqueous solubility of drug candidates. (**b**) Formulation and patient considerations for the development of PR injectables

3. Manufacturing process
4. Physicochemical characteristics of formulation

7.2.3.3 Traditional Approaches with Advanced Technologies

Traditional approaches such as aqueous suspension of a lipophilic drug or oily solution/suspension of a drug have been the most widely used approaches in the industry due to straightforward approach and extensive process know-how available in the literature to address anticipated challenges during development. These formulations usually propose API modifications that can alter the solubility/dissolution behavior of the drug subsequently providing the desired prolonged release. API modifications that have been explored so far have been detailed in the following text and enumerated in Table 7.3.

The basic differences between different prodrugs of a same drug are in onset of action, peak concentration, and duration of action. Increasing chain length/size of ester group can increase the onset of action and prolong the duration of action, that is, benzoate, valerate (C5), and cypionate (C7) prodrug of estradiol showed peak plasma concentration after 2 days, 2 days, and 4 days, respectively, with elevated estrogen levels for duration of 4–5 days, 7–8 days, and ~11 days, respectively [33]. The selection of a salt form or prodrug can be based on the initial physicochemical properties of a drug. First of all, any drug requiring prodrug/salt modification must have required functional groups that can be modified with salt/ester forming organic acid without affecting its pharmacological activity, that is, OH or COOH group for ester modification with fatty acids/fatty alcohol or amino groups for salt formation. The technology developed by LinkeRx by Alkermes introduces the rapidly cleavable hydroxyl group containing moiety to the amine functionality of the drugs for suitable modification with fatty acids. Examples include paliperidone palmitate, which is developed from paliperidone and which

Table 7.3 API modification approaches for PR injectables

Formulation	Drug (prodrug/salt)	Marketed formulation, administration, duration	Remarks
Aqueous suspension	Olanzapine (pamoate salt)	Zyprexa Relprevv, IM, every 2–4 weeks	Powder for suspension
	Aripiprazole (monohydrate crystal form)	Abilify Maintena, IM, once a month	Powder for suspension
	Aripiprazole (lauroxyl prodrug)	Aristada, IM, once a month to once every two months	C12 ester prodrug Aqueous suspension
	Paliperidone (palmitate prodrug)	Invega Sustenna, IM, once a month	C16 (tail length) ester prodrug Nanocrystals in aqueous suspension
	Medroxyprogesterone (acetate prodrug)	Depo-Provera, IM, every 3M Depo-Subq provera, SC, every 3M	C2 ester prodrug Aqueous suspension
	Methylprednisolone (acetate prodrug)	Depo-Medrol, IM, variable depending on requirement	C2 ester prodrug Aqueous suspension
Oil-based injection	Haloperidol (haloperidole decanoate)	Haldol Decanoate, IM, once a month	C10 ester prodrug Solution in sesame oil
	Flupenthixol (decanoate prodrug)	Fluanxol Depot, IM, every 2–4 weeks	C10 ester prodrug Solution in fractionated coconut oil
	Fluphenazine (decanoate prodrug)	Fluphenazine Decanoate, IM, every 2–4 weeks Moderate, IM, every 2–5 weeks	C10 ester prodrug Solution in sesame oil
	Zuclopenthixol (decanoate prodrug)	Clopixol Depot, IM, every 2–4 weeks	C10 ester prodrug Solution in thin vegetable oil (undisclosed)
	Pipotiazine (palmitate prodrug)	Piportil Depot, IM, every 4 weeks	C14 ester prodrug Solution in sesame oil
	Testosterone (enanthate prodrug)	Delatestryl, IM, every 24 weeks	C7 ester prodrug Solution in sesame oil
	Testosterone (cypionate prodrug)	Depo-Testosterone, IM, every 2–4 months	C8 ester prodrug Solution in benzyl benzoate and cottonseed oil
	Estradiol (valerate prodrug)	Delestrogen, IM, every 4 weeks	C5 ester prodrug Solution in sesame oil or in benzyle benzoate+castor oil
	Hydroxyprogesterone (caproate prodrug)	Makena, IM, once a week	C6 ester prodrug Solution in benzyl benzoate and castor oil
	Estradiol (cypionate prodrug)	Depo-Estradiol, IM every 3–4 weeks	C8 ester prodrug Solution in cottonseed oil

Source: Data from accessdata.fda.gov, medicines.org.uk, medsafe.govt.nz and product inserts

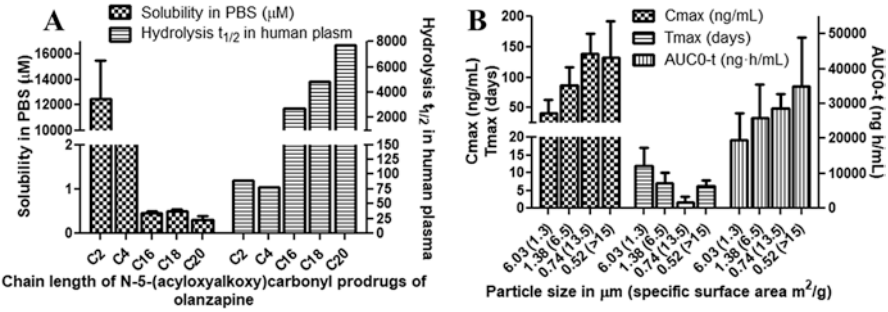

Fig. 7.4 (**a**) Impact of lipid chain length of N-5-(acyloxyalkoxy)carbonyl prodrugs of olanzapine developed by Alkermes (*Plotted data adapted from a table with permission from [37], Copyright© RSC Publishing*). (**b**) PK parameters of 7.02% paliperidone-C16 prodrug aqueous suspension after IM dosing in dogs at 2.5 mg/kg using a 21 g needle. Particle size represents the median particle size in μm. *Data plotted from US patent US6555544B2 [36]*

does not have hydroxyl functionality. Another example is pioglitazone prodrugs [34]. Second, the chain length of fatty acid or size of salt forming acid could be selected to give appropriate aqueous/lipid solubility characteristics to cater the desired release profile (Fig. 7.4a). Modified APIs can be used as either aqueous suspensions or oily solutions.

For aqueous suspensions, particle properties govern the drug release, and hence, formulation strategy can be used as an additional tool to achieve the desired particle size of the crystals. Majority of approaches follow top-down approach to produce the desired size for aqueous nano-/microsuspensions of desired size. Moreover, based on stability (physical and chemical), the formulation could be presented as ready-to-use suspension or powder for suspension. Figure 7.4a shows the impact of dissolution profile of a low solubility API (5 μg/mL solubility limit) with different particle sizes. A patent protecting aripiprazole suspension reports freeze-dried formulation with 1–10 μ particle size range [35]. Examples described in the patent report one method using wet milling technique with zirconium oxide beads (DYNO-MILL) to size reduce aripiprazole monohydrate/excipient suspension to produce suspension with 10% solid content ready for lyophilization. Another method uses jet milling of ethanol solution of aripiprazole impinged with fine stream of water. The resulting crystals can be filtered, dried, and suspended in aqueous vehicle with excipients for freeze-drying. Both methods produced particles of 2.5 μ median size. The milling technology to produce micron to submicron particles has been in trend since then and advanced by pharmaceutical companies such as Alkermes and Janssen Pharmaceutica. Patent dealing with ready-to-use suspension of paliperidone-C16 prodrug using wet milling assigned to Janssen Pharmaceutica evaluated the impact of particle size on PK parameters in dog PK study (Fig. 7.4b) [36]. The data show that there is an increase in Cmax and AUC and a decrease in Tmax with

increasing surface area. that is, lowering particle size. Smallest particle sizes did not show extensive differences in relation to drug's fast clearing in dogs compared to humans, and much larger effects of particle size were seen in humans with no data provided in the patent [36].

Areas of improvement in these formulation strategies include minimizing the lag phase before the therapeutic concentrations of the drug reach desired levels in plasma after administration [38]. For several formulations (paliperidone palmitate and aripiprazole monohydrate), patients have to continue oral medications after initial injection [38]. On subsequent doses, the drug release from prior injections covers the lag period and eliminates the requirement of oral dose. However, 1–3 weeks lag period upon first injection cannot be easily explained, and, hence, research is needed to uncover this by looking into the physiological component of this as well. Once report describes local tissue response to long-acting antipsychotics, however, without backing PK studies [39].

With oily solutions, the major factors to consider are the total dose and solubility in the selected oil vehicle. Though selection can be made from a lot of approved oils (arachis oil, sesame oil, soybean oil, cottonseed oil, castor oil, etc.), solubility plays a prime role. For example, it is impossible to make an oily solution of aripiprazole suitable for> 5 mg/day dose due to its < 1 mg/ml solubility in majority of oils. Approaches involving suspension of antipsychotic prodrugs (paliperidone decanoate, paliperidone palmitate) and salts (risperidone pamoate) suspended in sesame oil have been evaluated and, however, have resulted in burst effects (reviewed by Remenar, 2014 [38]). Till date, no marketed oil-based long-acting antipsychotic suspension is available. Though several vegetable and synthetic oils have been evaluated, sesame oil has become the choice due to its solubility advantage (> 100 mg/mL for haloperidol decanoate, fluphenazine decanoate) and safety advantage. Moreover, for other molecules, other solvents have also been used with the use of solubilizers such as benzyl benzoate.

7.2.4 Liposome Technology

Prolonged-release liposomal delivery systems to reach the market can be divided into two categories, namely, liposomes that sustain the release of encapsulated drug (true prolonged release) and long-circulating liposomes (increase the residence of drug in blood, which otherwise is not possible with simple intravenous injection of drug). A major difference in these two is the drugs chosen for these technologies, that is, the former requires the drugs that have longer half-life, while the latter are ideal for shorter half-life drugs.

The most widely studied and utilized technologies belong to the first category with DepoFoam technology as its front-runner. Originally developed and marketed by Pacira Pharmaceuticals (formerly Skye Pharma/DepoTech), the

technology is being partnered with several other companies currently with three products already in the market till date (Table 7.4). Unlike classical multilamellar liposomes (MLVs), which have concentric bilayers, DepoFoam produces particles (termed multivesicular liposomes—MVLs) with numerous nonconcentric vesicles forming honeycomb-/foam-like structure. The applicability of DepoFoam technology extends from small molecules to large molecules that require continuous infusion/frequent dosing and have narrow therapeutic index. Flexibility of the DepoFoam process allows the encapsulation of traditional drugs, proteins, peptides, and nucleic acid–based drugs (oligonucleotides/DNA). Though clinical applicability is still limited to small molecules (marketed formulations of bupivacaine, morphine and cytarabine, and meloxicam and tranexamic acid in pipeline), a great preclinical account is available exploring the applicability for large molecules and biologics along with small molecules for antineoplastic, antibacterial, and antiviral use (see review by Angst and Drover [40]). This leaves the field to be explored by the scientists to develop DepoFoam formulations for protein/peptides and nucleic acid drugs as well as drugs for CNS disorders, which hold promising markets in the future.

The major advantage of this technology for macromolecules is that it does not alter the structure of macromolecules (as in case of PEGylated macromolecules) or does not affect its conformation unlike the matrix-type formulations such as PLGA microparticles. In contrast, the product is developed as ready-to-use suspension, which can be administered easily using 25–31 g needles. The market advantage is that the major product and process patents held by Pacira on DepoFoam technology are due to expire soon or have expired recently, opening up the opportunity for other pharmaceutical industries to test it on other drugs and also to improve or modify the processes or formulation parameters.

The manufacturing process includes the patented double emulsification technique. The basic workflow is solubilizing the water-soluble drug in aqueous phase, which is emulsifying in organic phase containing lipids to obtain w/o emulsion. The resultant emulsion is further emulsified in aqueous phase containing osmolarity-adjusting agents (glucose and lysine typically) to form w/o/w emulsion. The organic solvent is removed from the emulsion through nitrogen flushing over double emulsion resulting in the DepoFoam particles of 1–100 μm size. Pacira also has filed patent applications for remote loading of MVLs with therapeutic agents using gradient technique and by using cyclodextrins as well [41] and a spray process that would allow continuous processing rather than batch processing [42]. The particle consists of microscopic, polyhedral, lipid-based honeycomb structure with numerous, nonconcentric internal aqueous compartments loaded with drugs. Typical freeze-fracture transmission electron microscopy (FFEM) of intact and fractured cytarabine MVL particle is shown in Fig. 7.5a and b. [43]. FFEM of particles and analysis of internal structure during release studies revealed that the release occurs by internal restructuring of particles by coalescence of internal compartments leading to an increase in their size and a decrease in their number [44].

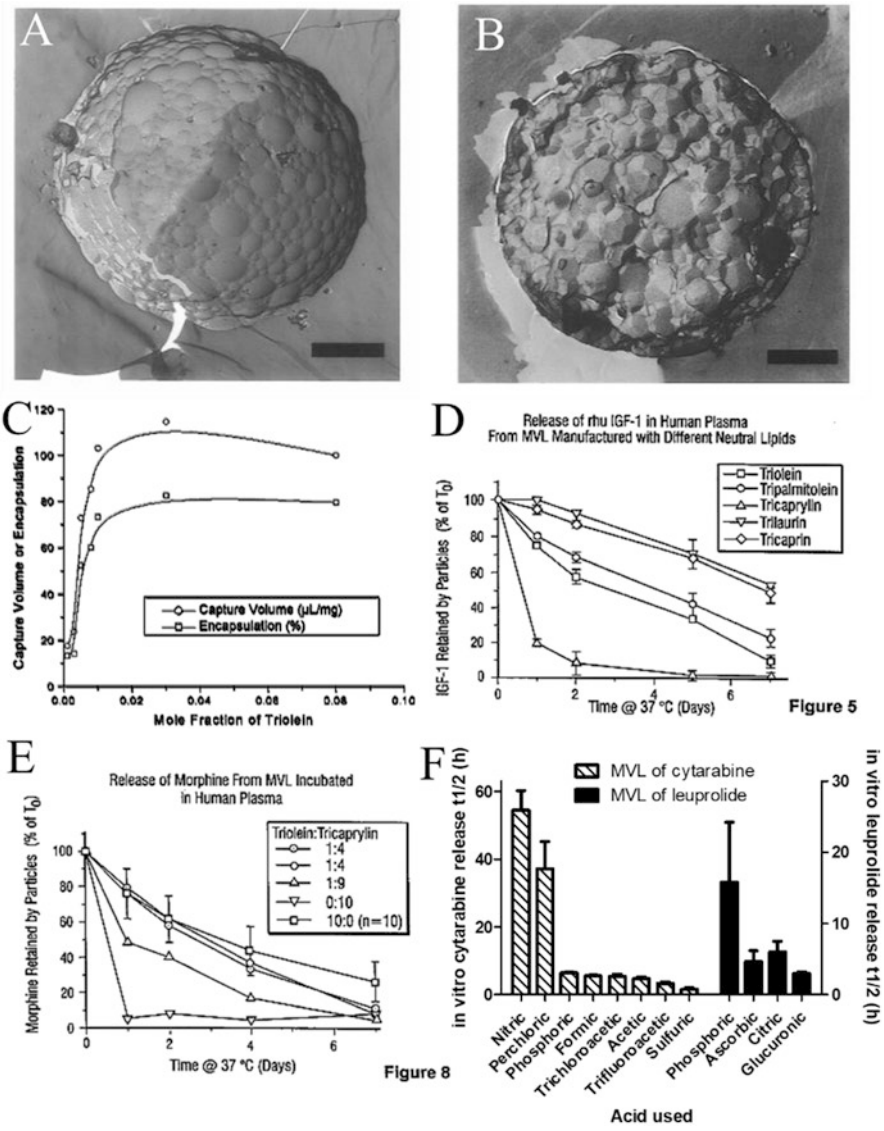

Fig. 7.5 (**a**) TEM micrograph of freeze-fracture replica showing an intact MVL showing pebbled exterior surface and (**b**) a fractured MVL with polyhedral compartments of 100 nm to several µm in size. MVLs are on average 10 µm size. Bars represent 2 µm size. (**c**) Effect of molar fraction of triolein on capture volume (µL/mg of lipid) and encapsulation of drug in MVLs made of phosphatidyl choline, cardiolipin, and cholesterol. (**d**) Release of recombinant human insulin-like growth factor-1 (rhuIGF-1) in human plasma from MVLs manufactured with different triglycerides. (**e**) Morphine release in human plasma from MVL made with different ratio of trioleinto tricaprylin**.** (**f**) Effect of different acids on drug release t1/2 from MVLs. *A & B adapted with permission from [43]. Copyright© 1996 American Chemical Society; C reprinted with permission from [44], Copyright © 2002 Elsevier Science Ltd., D & E reprinted from aUS patent 5,891,467 [45], F represents the plotted data from a table of a US patent US 6132766 [46]*

The formulation composition of three approved DepoFoam formulations is given in Table 7.4. The drug release rates can be adjusted to cater to the needs of drug and therapeutic indication to prolong the release from days to months by tuning the following components:

- *Lipid composition (lipid type and amount)*: Total lipid content of the DepoFoam particles is less than 3% by weight comprising essentially of phospholipids (an unsaturated phosphatidylcholine (Dieurocoyl phosphocholine-DEPC or DOPC)), a negatively charged phosphatidyl glycerol (DPPG), cholesterol, and a triglyceride (triaprylin or triolein). Lipid composition plays a major role in the drug release characteristics of the MVLs. Selection of an appropriate unsaturated phospholipid and a triglyceride and fine-tuning of their composition are required for different molecules to achieve the desired release characteristics, for example, DepoCyt has DOPC and triolein, and DepoDur has DOPC, tricaprylin, and triolein, while Exparel uses DEPC and tricaprylin. Triglyceride is required for the formation of the MVLs as well as for modifying release characteristics. Type of triglyceride and mole ratio to other lipids play role in the total encapsulation volume in liposomes as well as release characteristics (Fig. 7.5c, d and e) [44] [45]. Moreover, the selection of phosphatidyl choline of different chain lengths affects the release characteristics. Generally, the longer the chain length of TG and PC, the slower the release is, and use of combination of TG with longer and shorter chain lengths could be used for modifying the release from days to weeks.
- *Acid (counter ion) for drug*: Over a wide range of publications and patents, the effect of acid on the release is characterized (see example in Fig. 7.5f). In case of bupivacaine, instead of bupivacaine HCl, bupivacaine phosphate was used initially; however, in 2011 the manufacturing process was modified to use free base for the preparation of lipid solution, and phosphoric acid is used in internal aqueous phase in the manufacturing process [47]. For cytarabine and leuprolide MVLs, the effect of various acids led to wide changes in the release characteristics [44]. Hence, selection of appropriate acid is required for suitable drug release.
- Another important factor to consider during the development is to evaluate the effect of coadministered drugs and diluents, as changes in osmolarity can affect the drug release drastically. The use of hypotonic solution for dilution is not recommended. Detailed pharmacological account of DepoFoam formulations is given in Table 7.5

DepoCyt(e) was the first product to reach the market in the USA and EU countries of this platform for intrathecal administration for lymphomatous meningitis and received orphan drug approval for glioma. It improved effective half-life of cytarabine by a factor of 41.7 (142 h for DepoCyt(e) vs 3.4 h of free drug), which enabling biweekly dosing on outpatient basis compared to every other day cumbersome in-patient infusion with the free cytarabine. However, as of July 2017, Pacira permanently halted production of DepoCyt(e) due to product-specific supply issues and is no longer being marketed.

Table 7.4 Formulation characteristics of marketed DepoFoam formulations

Formulation	Drug/mL	Acid	Lipids (lipid content in mg/mL)	Size (μm)	Activity for
Exparel	13.3 mg bupivacaine base anhydrous	Phosphoric	DEPC:DPPG:Chol:Tricaprylin (8.2:0.9:4.7:2.0)	24–31	72 h
DepoCyt(e)	10 mg cytarabine	–	DOPC:DPPG:Chol:Triolein (5.7:1.0:4.4:1.2)	10–30	2 w
DepoDur	10 mg morphine sulfate pentahydrate	Hydrochloric	DOPC :DPPG:Chol:T ricaprylin:Triolein (4.2:0.9:3.3:0.3:0.1)	17–23	48 h

Table 7.5 Detailed pharmacological analyses of clinically evaluated liposome-based PR injectable formulations

Formulation (drug)	Administration route	Development phase and indication	Comparison with simple solution for injection/marketed formulation
DepoFoam™ technology			
Exparel® (bupivacaine phosphate)	Soft-tissue administration Surgical infiltration and nerve block anesthesia[a]	Marketed (postsurgical pain management in adults) Phase II (postsurgical pain in pediatrics)	Median diameter 24–31 μm Long-lasting local anesthetic effect (up to 72 h vs. 7 h) [51] High mean cumulative pain score through 72 h (283 vs. 329, $p = 0.039$) [54] Longer median time to first use of opioid (10 h vs. 3 h, $p < 0.0001$) [54] Reduced use of opioids (12 mg vs. 19 mg; $p < 0.0001$) [54] Reduced incidence of opioid-related adverse events (20% vs. 36%; $p < 0.0001$) [54]
DepoDur (morphine sulfate-MoSul)	Epidural administration	Discontinued (major surgery including cesarean section)	Lower pain visual analog scale score at rest (VAS-R) 554±334 (@10 mg) and (484±425 @15 mg) vs MoSul (1186±939 @5 mg) ($p < 0.001$) Lower VAS-with activity (VAS-A) 1235±775 @10 mg and 1036±726 @15 mg vs. MoSul (2086±875 @ 5 mg) ($p < 0.001$) Reduced use of opiate (fentanyl available as patient controlled analgesia) through 48 h (19 mg @10 mg DepoDur and 18 mg @15 mg DepoDur) vs. 38.2 mg @5mg MoSul) ($p < 0.05$)
DepoCyt(e) (cytarabine)	Intrathecal and ventricular	Discontinued (lymphomatous meningitis and glioma (orphan status) in adults)	t1/2 142 h vs. 4.3 h for cytarabine free drug 27 to 71 times increased t1/2 based on administration route and sampling compartment Biweekly administration vs. everyday administration
DepoTXA (tranexamic acid)	Intracapsular in total knee arthroplasty	Phase II (postsurgical bleeding)	Single administration vs. oral administration or IV injection (anticipated) No results from clinical trials yet
DepoMLX (meloxicam)	Infiltration	IND (postsurgical analgesia)	Single administration vs. every day dosing with tablet (anticipated) No results from clinical trials yet

DepoVax™ technology			
DPX-Survivac (survivin HLA class I peptide antigens)	Subcutaneous	PhaseI/Ib Orphan status (Ovarian cancer)	Alone and in combination with cyclophosphamide (CPA) Manageable injection site reactions High and sustained immunocellular response (CD4 and CD8 T (central memory and differentiated) lymphocytes) were seen with DPX-Survivac Combination of DPX-Survivac with cyclophosphamide had best response Dose response showed better activity at 0.5 mL DPX-Survivac dose than at 0.1 mL dose ($p = 0.013$) Dosing: q3W
	Subcutaneous	Phase Ib (recurrent ovarian cancer)	Combination therapy with epacadostat (IDO-1 inhibitor) and CPA Trial ongoing Preliminary results showed combination was well tolerated and evidence of surviving specific T-cells in blood and tumor ([55]
	Subcutaneous	Phase II (recurrent ovarian cancer)	Combination therapy with pembrolizumab (anti-PD-1) and CPA Trial ongoing
	Subcutaneous	Phase II (diffuse large B-cell lymphoma)	Safety and efficacy study in combination with pembrolizumab (anti-PD-1) and CPA
DPX-E7 (E7 viral protein from HPV)	Subcutaneous	Phase Ib/II (oropharyngeal, cervical, and anal cancers related to HPV)	Safety and efficacy study in combination with CPA
DPX-RSV(A) (small hydrophobic ectodomain-SHe antigen from RSV subgroup A)	Intramuscular	Phase I (respiratory syncytial virus infection)	Acceptable safety profile with no serious adverse events 75% patient at 10 μg dose and 100% patient at 25 μg dose showed antigen specific immune response Sustained antibody response after booster dose lasting up to 180 days for lower dose group and 421 days in higher dose group [56]

[a]Only interscalene brachial plexus nerve block. Efficacy and safety in other nerve block are not established clinically

DepoDur and Exparel have been developed for postsurgical pain management using this technology with the potential for providing prolonged analgesia eliminating the need for epidural catheters or epidural pumps or patient-controlled analgesia (PCA) pumps, which are usually cumbersome, time consuming, and prone to medication and pump programming errors. DepoDur significantly reduces pain scores while reducing the requirement of supplemental analgesics compared to morphine sulfate injection [48]. DepoDur was discontinued, and Exparel is the leading product currently for surgical pain management. The process of MVL preparation was modified for Exparel in 2011 by Pacira to improve the encapsulation efficiency by using free anhydrous bupivacaine base. Bupivacaine base is dissolved in oil phase of first emulsion with phosphoric acid included in the internal aqueous phase [47].

Most of the bupivacaine is encapsulated in MVLs with 3% present as free drug, which become available immediately upon administration. MVLs then provide extended release over a period of time. Several clinical studies have demonstrated its efficacy and superiority over conventional measures and placebo. It reduces the overall opioid consumption in terms of increase in the percentage of opioid-free patients ($P < 0.01$) and time to first opioid rescue ($P = 0.0230$) in comparison to bupivacaine HCl [49], while prolonging the median time to first opioid use in comparison to placebo (14.3 h compared to 1.2 h with placebo) [50]. This also reduces the overall cost to patients using bupivacaine HCl (Marcaine®) by reducing the requirement of opioids [51]. A recent study has shown similar early analgesia with periarticular injection (PAI) of Exparel and intrathecal morphine sulfate for total knee arthroplasty and improved pain management compared to PAI of ropivacaine, which also caused much higher incidences of pruritus, and thus favored the treatment with Exparel [52]. Thus, Exparel can reduce/eliminate the need for opioids; however, its use in opioid-dependent patients is still questionable [53]. While the clinical benefit of this is not established, the technology might reduce the opioid use in clinic, thereby reducing the number of opioid users.

Another technology to reach clinical trials is DepoVax® formulation by ImmunoVaccine Technologies Inc. (Table 7.5). It uses liposomes of antigen and adjuvant (lipopeptide/polynucleotide), which are lyophilized and then resuspended in oil that forms a depot at the site of injection, and liposomes act as suspending components for antigen and adjuvant in oil. Dosing of antigen for infection is in μg dosage (10 and 25 μg), while that required for cancer is in mg dosage. It is developed for vaccination to provide sustained antigen delivery for immunization against infectious diseases such as RSV (respiratory syncytial virus) infection for which no vaccine is available till date and cancer.

The process of manufacture of DepoVax formulations is essentially a two-step process: preparation of liposomes and lyophilization to a cake and resuspension in oil. Lyophilized liposomes are supplied as separate vials for mixing with mineral oil to form clear suspension. Lyophilized liposomes provide better shelf stability of incorporated antigens against w/o emulsion or other aqueous representations of vaccines available in the market. ImmunoVaccine holds the patent covering "any antigen, any adjuvant, any liposome and any oil" (US6793923B2) [57]. However, no application has been furthered to small molecules and therapeutic proteins of interest.

Phospholipids (phosphatidyl choline) and cholesterol (10:1 w/w ratio) are hydrated using antigen suspended in suitable solvent system (buffer/butanol solution/buffer) and then extruded through 200 nm polycarbonate membrane to form liposomes followed by the addition of proprietary lipopeptide or RNA-based Polyl:C polynucleotide adjuvant. A range of publications report different preparation methods differing in the preparation of liposomes with different phospholipids, that is, DOPE is used for DPX-Survivac [58] but not in DPX-E7, selection of buffer components, that is, phosphate buffer (for DPX-E7) [59] or acetate buffer (for DPX-Survivac and DPX-SRV(A)) [58], etc. The liposomes have been prepared using different techniques, that is, by thin film hydration method using rotary evaporated films on glass beads using chloroform:methanol as lipid solvent or by directly hydrating lipid mixture with buffer and antigen solution followed by extrusion for size reduction or by lyophilizing the lipid dissolved in butanol (30–40%) aqueous solution mixed with antigen to produce.

Lyophilized cake is supplied in separate vials for reconstitution at the time of vaccination using a mineral oil (Montanide™ ISA51 VG – mixture of mannide monooleate surfactant and mineral oil) supplied in a separate vial [58, 60]. The patent also presented examples showing effect of oil (vegetable-canola oil vs mineral oil) that was evaluated on the antibody titer, and it was shown that antibody titers were higher with mineral oil [57].

Sustained availability mechanism of the antigen was demonstrated by evaluating in vitro release by dialysis and in vivo longitudinal disposition of the supramagnetic iron oxide (SPIO) tagged antigen or oil by MRI. In vitro studies showed that oil did not provide passive release of antigen due to reverse micelles formed in oil holding the antigen, while in vivo studies demonstrated that antigen is actively cleared by immune infiltration of injection site. Figure 7.6 shows in vitro release of all antigens from DPX-Survivac did not exceed 12% over 1-month period [58]. Figure 7.6 also shows in vivo sustained clearance (half-life 2 months) of SPIO-antigen from the site in the draining inguinal lymph nodes with MRI contrast retained at the site several weeks after vaccination, while results with SPIO-oil showed that MRI contrast almost remained unchanged indicating active clearance of antigen from the depot [61]. Moreover, comparison to w/o emulsion also showed that release was more sustained with DepoVax formulation [58]. With three clinical programs (DPX-Survivac and DPX-E7 for cancers and DPX-RSV for infection), IMV has the pipeline of malaria and Zika virus vaccines under preclinical evaluation and two late-stage animal trials for veterinary use.

7.2.5 Polymeric Technologies

Through the last few decades, polymeric strategies that started from in situ gelling systems, which can form implant upon SC/IM administration, have advanced in both formulation strategies (implant systems and micro-/nanoparticulate systems) and manufacturing processes (to prepare and obtain uniform formulation characteristics. Table 7.6 details all marketed formulations (including discontinued).

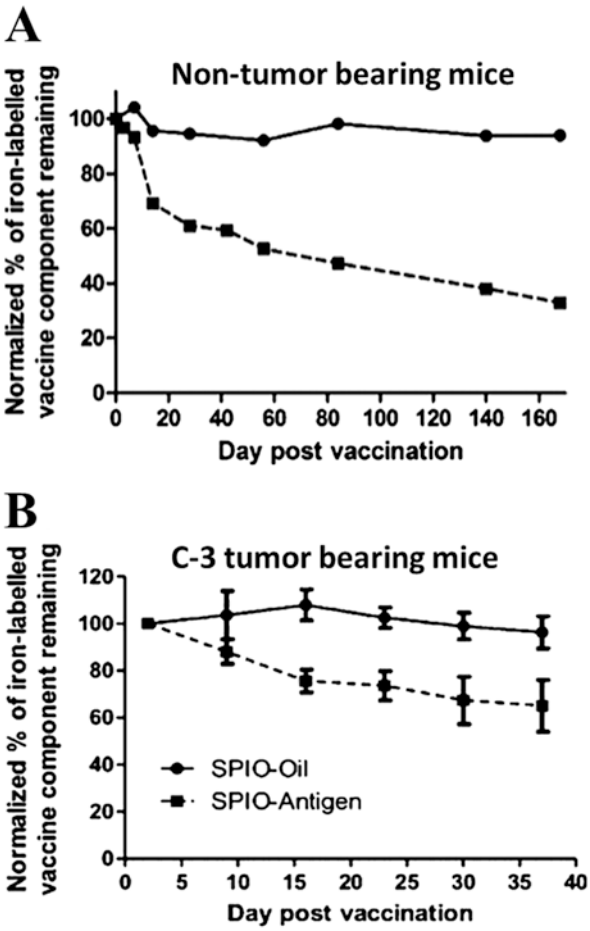

Fig. 7.6 Semiquantitative analyses of clearance of SPIO-tagged antigen or oil from the site of injection in (**a**) non-tumor-bearing mice (n = 2/group) and (**b**) tumor-bearing mice (n = 5/group). The most significant clearance of antigen occurs within 3 weeks of administration. Image adopted with permission from [61] *Copyright © 2014 Elsevier Science Ltd*

7.2.5.1 Solid Implants

Solid implantable systems use either active mechanism of drug release (external force) such as propellant infusion, osmotic gradient pumping, and electromechanical force or passive mechanism through formulation design and release drug through diffusion, matrix degradation or erosion, and controlled swelling. Passive systems such as biodegradable/swellable polymer-based systems have been the main focus so far due to their more commercially viability [74].

Passive systems, as earlier mentioned, are relatively simple and comprise of drug contained in a biocompatible reservoir or matrix whose release kinetics are controlled by the properties of drug, matrix, their concentrations, and surface and morphological properties. These implants can be further classified into biodegradable and nonbiodegradable implants.

Table 7.6 Polymeric PR injectables and their formulation characteristics

Drug	Marketed product, route, duration	Remarks
In situ implants		
Risperidone	Perseris, SC, once a month	Available as powder for reconstitution with PLGH+N-methyl-pyrrolidine (NMP) system (Atrigel® delivery system) Polymer: PLGH 80:20 molar ratio Drug is solubilized as well as suspended in polymeric solution [62]
Leuprolide acetate	Eligard, SC, every 1–6 months	Available as powder for reconstitution with Atrigel® delivery system (polymer+NMP) With increasing doses of 7.5, 22.5, 30, and 45 mg, PLGH with carboxyl end-group used for 7.5 mg dose while PLG copolymer with hexanediol (for all other higher doses) and molar ratios of LA:GA 50/50, 75/25, 75/25, and 85/15, respectively
Buprenorphine	Sublocade, SC, every month	Available as ready to use 18%w/w solution in Atrigel® delivery system Polymer: PLGH 50:50 molar ratio
Doxycycline hyclate	Atridox, subgingival, 4 months	Available as powder for reconstitution with Atrigel® delivery system Polymer: Polylactic acid (PLA)
Microspheres		
Naltrexone	Vivitrol®, IM, once monthly	Method: Double emulsion technique Polymer: 75:25 polylactide-co-glycolide (PLG) Loading of 337 mg of naltrexone per gram of microspheres
Risperidone	RISPERDAL® Consta (by Janssen/ Alkermes), IM Dose of 25/37.5/50 mg every two weeks	Method: Double emulsion (oil in water) Polymer: 75:25 molar ratio polylactide-co-glycolide (PLG) Microencapsulated Risperidone 381mg in diluent: Polysorbate 20, sodium carboxymethyl cellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection
Bromocriptine	Parlodel LAR™/ Novartis	Method of preparation: Spray drying

(continued)

Table 7.6 (continued)

Drug	Marketed product, route, duration	Remarks
Somatropin	Nutropin® Depot, SC doses of 1.5 mg/kg, once monthly 0.75 mg/kg, twice monthly	Available as injectable suspension Method: Cryogenic spray-drying Each 13.5 mg 3 cc single-use vial of Nutropin Depot contains 13.5 mg somatropin, 1.2 mg zinc acetate, 0.8 mg zinc carbonate, and 68.9 mg PLG. Diluent for Nutropin Depot contains 30 mg/mL carboxymethyl cellulose sodium salt, 1 mg/mL polysorbate 20, 9 mg/mL sodium chloride, and sterile water for injection; pH 5.8–7.2.
Triptorelin pamoate	TRELSTAR®, IM Dose of 3.75 mg every 4 weeks, 11.25 mg every 12 weeks, 22.5 mg every 24 weeks	Available as injectable suspension Method: Phase separation Polymer: PLGA TRELSTAR 3.75 mg has loading of 3.75 mg/138 mg polymer
Octeriotide acetate	Sandostatin® LAR (by Novartis), IM, every 4 weeks	Available as powder for injectable suspension Method: Phase separation Polymer: PLGA Loading of 11.2 mg drug/188.8 mg polymer
Lanreotide	Somatuline LA 30 mg, IM, every 14 days	Available as powder for suspension Method: Phase separation Polymer: PLGA
Leuprolide	Lupron Depot®/TAP, IM, depots of 7.5 mg, every 4 weeks 22.5 mg, every 12 weeks 30 mg, every 16 weeks 45 mg, every 24 weeks	Available as powder for suspension Method of preparation: Double emulsion (water in oil in water) Polymer: PLA Loading of 11.25 mg drug/99.3 mg polymer Generic versions Enantone Depot® /Takeda, Trenantone® /Takeda, Enantone Gyn/ Takeda
Buserelin	Suprecur® MP/ Sanofi- Aventis	PLGA microspheres Marketed in Japan
Solid nonbiodegradable passive implants		
Levonorgestrel	Norplant® (by Population Council), SC, up to 5 years	Discontinued from market Reservoir-type silicon capsule [63]
	Jadelle (by Bayer), SC, up to 5 years	Reservoir type silicon capsule [64]

Etonogestrel	Implanon™ (by Organon), Subdermal, 3 years	Discontinued from market 4 cm long and 2 mm diameter rod consisting of ethylene vinyl acetate (EVA) copolymer core containing etonogestrel coated with EVA copolymer [65] Release rate 60–70 μg/day in week 5–6 and decreases to ~35–45μg/day, ~30–40 μg/day, and 25–30 μg/day at the end of the first, second, and third year, respectively Preloaded in a sterile needle of a disposable applicator
	Nexplanon® (by Merck), subdermal, 3 years [66]	Dimensions and composition same as Implanon but the core contain barium sulfate (opaquent) and magnesium stearate Radiopaque along with drug in core reduces the insertion errors Release rates same as Implanon Preloaded in a sterile needle of a disposable applicator
Ganciclovir	Vitrasert® (by Bousch & Lomb), intravitreal, 3 months	Discontinued from market Tablet coated with polyvinyl alcohol (PVA) and EVA polymers Surgically implanted intravitreously [67]
Fluocinolone acetonide	Retisert® (by Bousch & Lomb), intravitreal, 30 months	Tablet of 3 mm × 2 mm × 5 mm with PVA membrane in silicon elastomer cup with drug release orifice and cup is attached with silicon elastomer suture tab with silicon adhesive Surgically implanted intravitreously Initial drug release rate of 0.6 μg/day which decreases over a month to reach a steady rate of 0.3–0.4 μg/day over 30 months
Histrelin acetate	Vantas™, SC, 12 months	3 cm × 3.5 mm cylindrically shaped nonbiodegradable hydrogel reservoir (made of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100) with 50 mg drug formulation core Surgically implanted subcutaneously Drug release rate of 50–60 μg/day for12 months [68]

(continued)

Table 7.6 (continued)

Drug	Marketed product, route, duration	Remarks
Solid biodegradable implants		
Goserelin acetate	Zoladex® (by Astrazeneca), SC, Dose of 3.6 mg, for 28 days 10.8 mg, for 12 weeks	Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (12.82–14.76 mg/dose) containing less than 2% acetic acid and up to 10% goserelin-related substances and presented as a sterile, white to cream colored 1.5 mm diameter cylinder, preloaded in a special single-use syringe with a 14-gauge x 36±0.5 mm siliconized needle with protective needle sleeve
		(SafeSystem™ Syringe) in a sealed, light, and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule Surgically implanted subcutaneously [69]
Carmustine	Gliadel® (by Arbor Pharmaceuticals), intracranial	Each wafer contains 7.7 mg of carmustine and 192.3 mg of a biodegradable polyanhydride copolymer [70] The copolymer, polifeprosan 20, consists of poly [bis (p- carboxyphenoxy)] propane and sebacic acid in a 20:80 molar ratio Surgically implanted
Buserelin acetate	^{Pr}Suprefact® (by Sanofi aventis), SC, 2 and 3 months	Loading of 6.6 mg buserelin acetate/26.4 mg PLGA in 2 month depot and 9.9 mg/39.4 mg in 3 month depot PLGA with 75:25 molar ratio [71]
Active implants		
Sirolimus	Cypher stent (by Johnson & Johnson/ Cordis)	Electropolished stainless steel (316L), laser-cut from seamless tubing in a sinusoidal pattern coated with a polymer and sirolimus mixture
Paclitaxel	Taxus stent (by Boston Scientific)	Stainless steel tubing stent coated with a polymer and paclitaxel mixture
Everolimus	Xience V (by Abbott Vascular)	Cobalt chromium (CoCr) alloy stent coated with a formulation containing everolimus, the active ingredient, embedded in a nonerodible polymer mounted on a delivery system
	PROMUS Element + Everolimus (by Boston Scientific)	Eluting platinum chromium coronary stent system
Exenatide	ITCA 650 (by Intarcia Therapeutics)	Currently in pipeline, matchstick-sized osmotic pump based implant [72]
Zotarolimus	Endeavor (by Medtronic)	A cobalt-based alloy stent, with a phosphorylcholine polymer and zotarolimus dose concentration of 10 μg/mm stent length
Ziconotide	Synchromed (by Medtronic)	Peristaltic pump implant, featuring external microelectronic control of the delivery rate [73]

Sources: Data from accessdata.fda.gov, medicines.org.uk and medsafe.govt.nz, product inserts and product information sheets available on industry websites

Nonbiodegradable Implants These implants have a good mechanical strength but require a clinical procedure for insertion and removal. They could be further divided into matrix type (having a homogenous dispersion of drug into the polymer) and reservoir type (having a drug core contained in a permeable nonbiodegradable polymer membrane). Polymers such as acrylates, elastomers (urethane, silicone), polyethylene vinyl acetate (PEVA), and other copolymers have been used widely in these implants whose biocompatibility has already proven by researchers [75]. This type of implants was first used for the treatment of glaucoma, where pilocarpine is sandwiched between two insoluble ocular inserts with a rate-controlling membrane on the retinal side. Such implants then were widely available for commercial use mostly for contraception in females delivering drugs like levonorgestrel, etonogestrel, estradiol, etc.

Biodegradable Implants The need of implants, which did not require the post drug release surgery, leads to the exploration use of biodegradable polymers such as poly(caprolactone) (PCL), polyanhydrides, polyorthoesters, polyphosphoesters, poly (lactic acid) (PLA), and poly (lactic-co-glycolic acid) (PLGA) in implants. These had a major advantage over the latter implants by complete degradation into easily excretable metabolites in the body. The release of the drug is mainly governed by the degradation kinetics, which is highly variable and is influenced by numerous physiological properties. These implants can deliver various drugs, peptides, and hormones and antibiotics because of their good compatibility with most of the polymers [76]. These systems are usually manufactured using extrusion (hot-melt) and may require stable drug molecules. These systems have been developed for small molecules as well as macromolecules (Table 7.6).

Active systems work through a positive displacement force, which enables and controls the drug release more precisely compared to passive implants. These are again subdivided with respective to the driving force that enables the drug release into implantable pumps and electrochemical systems. The implantable pumps either work by osmotic gradient or the propellant infusion technique by which the drug is constantly released in a controlled manner. Some implants that work on the osmotic gradient principle are Alzet® and DUROS®. InfusAID is a propellant infusion pump using fluorocarbons separated from the drug chamber by a disk-shaped titanium housing. Electromechanical systems are used when there is a need of larger doses at precise control on the drug release for a prolonged period. SynchroMed® developed by Medtronic Inc. is such a device in which a peristaltic implant is used in pain management and treatment of spasticity. These systems are now becoming less attractive due to their more complex nature, requirement for surgical removal, or nonbiocompatibility. Yet, they have evolved into advanced wearable devices with more attractive market for easy infusions.

7.2.5.2 In Situ Forming Implants

In situ gelling systems are polymeric formulations that undergo transformation from sol form to gel/solid depot form through various mechanisms, that is, under certain environment conditions such as pH, temperature, ionic media, etc., or diffusion of drug/polymer solvent out of system leading to solid depot formation. In PR injectables, these systems hold a specific place due to their less complexity and easy manufacturing processes as compared to complex systems such as microspheres or liposomes. In situ implant systems are usually formulated by matrixing the drug with the polymer in suitable solvent that upon administration forms a depot inside the body such that it releases the drug in a controlled manner for a prolonged duration. The in situ gels have been an area of interest for several researchers with applications spread throughout all areas of administration like ophthalmic, oral, parenteral, rectal, and vaginal. While polymers used for such systems are essentially biodegradable, based on the source of polymers, in situ gelling systems can be either natural polymer–based gels or synthetic polymer–based systems.

Synthetic Polymer–Based In Situ Implant Systems The majority of marketed formulations fall in this category (Table 7.6). In situ implants are the systems that are usually devised with biodegradable polymers (such as PLGA) and have flowable consistency for administration with the aid of an organic nonirritant solvent (NMP), which upon administration form implant by rapid diffusion of organic solvent leading to depot formation. The system has been marketed as Atrigel® technology by Atrix Laboratories and has been developed for several drugs of varied physicochemical properties. The final formulation is usually a solution of polymer and drug or a mixture of solution and suspension of drug in polymer solution. For example, Perseris™, when reconstituted, has drug as solubilized as well as suspended in polymer solution [62]. Table 7.6 describes the marketed in situ implants and their formulation characteristics. The polymer composition, that is, lactic acid/glycolic acid ratio, is the prime factor governing the release rate and hence the frequency of administration. Moreover, some systems are available as ready-to-use systems, while others as powder for reconstitution, which typically is based on the stability of the drug or system. A family of patents by Atrix Laboratories, which are past their expiry, cover these systems under thermoplastic and thermosetting polymers and methods of using it [77]. Thermoplastic polymers (usually high molecular weight copolymers based on DL-lactic acid and glycolic acid) are used with a suitable water-soluble organic solvent to cure to form solid implant upon administration. The Atrigel systems are based on this mechanism. Thermosetting polymers are of low molecular weight copolymers of DL-lactide or L-lactide with ε-caprolactone, which are liquid and gel at body temperature upon administration.

While there are several publications reporting in situ gelling systems made of synthetic triblock copolymers such as PLGA-PEG-PLGA [78] poly(PEG-PPG-PHB urethane) [79], PCL-PEG-PCL polymers [80], methoxyPEG-polysebacic acid-DL-lactic acid-methoxy PEG (mPEG-poly(SA-LA)-mPEG) [81], and PCLA-PEG-PCLA [82], only a few have been conceptualized in veterinary trials and

clinical trials. The examples are InGell® by InnoCore Pharmaceuticals, which has been evaluated for pet canine back pain and ReGel® by MacroMed, Inc./BTG international and SABER®, which have been evaluated in clinical trials.

OncoGel™ is paclitaxel-loaded ReGel® made of thermally reversible PLGA-PEG-PLGA-based in situ gelling system without organic solvents for direct intratumoral injection in solid tumors. OncoGel has been evaluated in various preclinical safety and efficacy studies that showed local release of paclitaxel and reduced tumor burden with only little systemic exposure providing acceptable safety profile [84]. It has been evaluated in clinical trials for intratumoral delivery in solid tumors such as breast tumor, pancreatic tumor, and esophageal tumor [85–87]. The gel is injected in 0.5–1 mL aliquots throughout the tumor and degraded over a 6-week period providing sustained local tumoral release of paclitaxel (Fig. 7.7a and b). Phase I and II clinical trials showed that the formulations were safe however and did not improve the overall tumor response in combination with the standard of care treatment resulting in the termination of phase IIa study (NCT00573131) [86], while it showed improvement in tumor burden in another trial as an adjunct to radiation therapy [86]. Another trial in horses of celecoxib-loaded gels showed sustained intraarticular release (Fig. 7.7c) with no adverse effects. Currently, ReGel® is being developed for protein molecules.

To overcome challenges with the current technology, that is, use of organic solvents and hydrophobic environment within the implant that affect protein stability, InnoCore Pharmaceuticals is developing new PCLA-PEG-PCLA triblock copolymer under the name InGell®. The systems have similar mechanisms as described earlier for in situ implant formation; however, the implant has hydrophilic moieties to protect the intact structure of protein. The triblock polymer is developed with varying PCLA and PEG block lengths to create two sets of polymers, that is, i) gamma polymer that dissolves in water at below body temperature and forms hydrogels at body temperature forming a soft macroscopic depot physically entrapping the drug inside and ii) liquid polymer (LQP), which is liquid at room

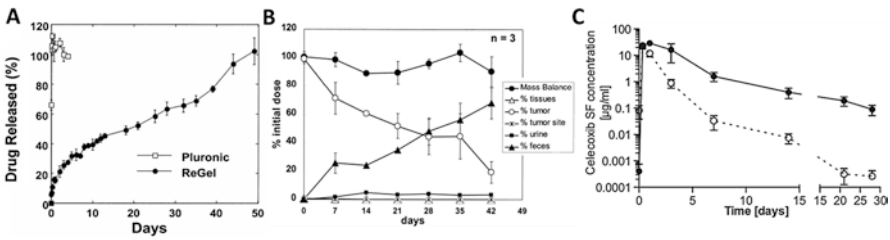

Fig. 7.7 (**a**) In vitro paclitaxel release from ReGel (23%w/w, in water) and Pluronic F-127 thermogel. (**b**) Tissue distribution profile of intratumoral OncoGel™ loaded with ^{14}C-paclitaxel in MDA231 human xenograft model in nude mice. (**c**) Synovial fluid concentration of celecoxib after intraarticular administration of low celecoxib (50 mg/g) gel (open circles) and high celecoxib (260 mg/g) gel (filled circles) in five healthy horses. *A & B adapted with permission from [83], Copyright © 2001 Elsevier B.V. and C adapted with permission from [82], Copyright© 2015 Elsevier Ltd*

temperature and hence does not require solvent and forms the depot at body temperature similar to gamma polymer. Hence, both systems avoid organic solvents. Moreover, both polymers can solubilize hydrophobic small molecules providing high drug loading (up to 25%). Intraarticular injection study in gelding with a celecoxib-loaded PCLA-PEG1500-PCLA in situ implant system is shown in Fig. 7.7c, which shows sustained release for up to 30 days [82]. The study also evaluated systemic exposure of celecoxib and observed minute systemic absorption of celecoxib. Further studies with celecoxib in situ implant showed safety after SC administration in mice and after intradiscal administration in canines and showed improvement in back pain in canines for extended period with no adverse events [88]. Currently, InGell® systems are being developed for the delivery of protein drugs.

Other formulation approaches are directed to get low-viscosity alternatives. Two such nonpolymeric systems under development are SABER® and CLOUD® platforms by Durect and FluidCrystal® platform by Camurus. SABER (sucrose acetate isobutyrate (SAIB) extended release) is based on SAIB, an acceptable solvent (benzyl alcohol) and additives forming low-viscosity liquid that upon SC or IM administration increases in viscosity substantially as the solvent diffuses away (63). SABER®-bupivacaine (POSIMIR®) is designed to deliver drug for 72 h to treat local postsurgical pain and was evaluated in phase I-II-III clinical trials (NCT01052012, NCT01139866, NCT00993798, NCT00993226). While phase III (NCT02574520) trial failed to meet efficacy trial [89], it has led to one FDA-approved veterinary product SucroMate™ Equine for sustained release of deslorelin acetate and phase I trial of risperidone-SABER depot using needle-free injector DosePro (NCT01592110, NCT02411526) with positive outcomes. Currently, it is being explored for protein/peptide hormone delivery and for ophthalmic sustained release injectable. CLOUD® (currently under preclinical evaluation) is based on a noncovalent complexation process to form low-viscosity aqueous/organic vehicle for administration by fine needle and to reduce solubility and modify dissolution characteristics while enhancing the stability of the drug. FluidCrystal is based on lipid-based liquid comprising of a mix of endogenous polar lipids that is low-viscosity liquid for easy administration and forms in situ liquid crystal gel matrix with minute quantities of aqueous fluid present at the injection site (SC/IM). The lipid/solvent mix allows for higher drug payload (up to 30%), compatibility with protein/peptide drugs such as leuprolide, octreotide, somatostatin, buprenorphine, etc., and tunable release from daily to up to 3 months. Preclinical success has led to phase II clinical trial of leuprolide acetate FluidCrystal injection depot – CAM2032 (NCT02212197) – which showed well-tolerable formulation with higher AUC compared to Eligard and octreotide FluidCrystal injection depot, CAM2029 for 4 week delivery (NCT02299089), which showed formulations were well tolerated and SC injection provided higher AUC compared to IM injection [90].

Natural Polymer–Based In Situ Implant Systems Natural polymers are said to be advantageous over the synthetic polymers due to their ability to show cell adhesion, biological signaling, and remodeling, but they lack adequate mechanical prop-

erties. Synthetic polymers, on the other hand, usually present controllable degradation rates, mechanical strengths, and microstructures. Hence, naturally occurring polymers are generally used in a combination with synthetic polymers or modified to form semisynthetic versions. These polymers can form thermosetting- and thermoplastic-type implants as well as work by pH/ion induced gelling. A few examples of in situ implants of natural polymers are described in the following text.

Chitosan-Based Hydrogels Chitosan is a linear polysaccharide composed of randomly distributed β-(1,4)-linked D-glucosamine and N-acetyl-D-glucosamine units. Chitosan is identical to glycosaminoglycans in terms of structure0 and has good biocompatibility, less toxicity, and immunostimulatory activities. Chitosan can be used in a minimally invasive manner because it can undergo thermal and pH-triggered gelation and be enzymatically degraded in vivo by lysozyme and chitosanase enzymes [91].Chitosan-β-glycerol phosphate disodium salt combination (BST-Gel) developed by BioSyntech Inc. has been used in cartilage repair. It shows sol-gel transition at physiological pH and temperature as a result of electrostatic interactions and hydrogen bonding [92]. Grafting of chitosan with Pluronic® or poly (N-isopropylacrylamide) also shows thermosensitive properties with better mechanical strength [93].

Hyaluronic Acid–Based Implants Hyaluronic acid consists of alternate disaccharide units of [β (1,4)-D-glucuronic acid-β(1,3)-N-acetyl-D-glucosamine] linkages. It is the only nonsulfated glycosaminoglycan that is widely distributed in connective, epithelial, and neural tissues, such as skin, cartilage, and the vitreous humor. It has been used to deliver drugs like dexamethasone to treat rheumatoid arthritis [94] and peptides/proteins like recombinant human bone morphogenetic protein-2 to promote bone augmentation [95].

Alginate Hydrogels Alginates are linear unbranched polysaccharides consisting of homopolymeric blocks of 1,4-linked β D-mannuronic acid and of a-L-guluronic acid. Alginates being approved by USFDA and generally regarded as safe (GRAS) excipients have found its way in wide application domains from delivery of drugs like dexamethasone and doxorubicin, some peptides, proteins, and genes [96]. It forms supramolecular assembly at lower pH and forms gel in media with bivalent cations such as barium, strontium, and calcium. It has a limitation of having burst release due to poor mechanical strength, which is caused by diffusion of ions at physiological media [97]. Sulfated alginate gels were found to be more biointerfacial with growth factors like vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor [98].

Miscellaneous Systems *Heparin* is a highly sulfated negatively charged glycosaminoglycan abundant in the liver. Heparin has characteristic N- and O- sulfated

residues that are known to interact with the arginine and lysine residues in protein-like growth factors [99, 100]. *Gelatin*-based hydrogels have also been researched upon for delivery of growth factors and tissue regeneration. The disadvantage is that these hydrogels are highly unstable and must be grafted with any other copolymer to change the gel temperature [101]. *Fibrin and fibrinogen* are active components in the blood clotting and wound healing mechanisms and also serve as a vehicle for delivery of some proteins, drugs, and genes. These components possess low gelation times like 5–10 s so difficult to handle; therefore, sodium chloride is used, which binds on thrombin increasing the gel transition time [102]. Chemically induced or enzyme-catalyzed transition of these natural polymers is also being experimented. Cross-linking of horseradish peroxidase and H_2O_2 to these polymers has a capacity to form supramolecular hydrogels within 10 min and is degradable in 15–30 days [103–106]. Schiff's base, Michael addition, and disulfide linking of the chitosan have proven to show gel transition properties and could be improved in the presence of oxidizing agents [107–112].

7.2.5.3 Microspheres

Next-generation polymeric PR injectables were developed as microspheres. PR injectable microspheres are small sphere-shaped particles in micrometer range (1–1000 μm) loaded with small molecule, macromolecule (proteins/peptides) drugs or nucleic acid drugs as either matrix systems or as reservoir systems for administration with a syringe needle [113]. The reservoir systems are usually similar to the nonbiodegradable/biocompatible implant systems with particle properties so as to cater desired drug release, while matrix systems are similar to biodegradable/biocompatible depot formed by in situ biodegradable implant systems, but both of these have particle nature. Both types of systems differ in their drug release mechanisms, that is, reservoir microspheres work by diffusion-based release of drug from microsphere core, while matrix microspheres initially show diffusion-based release from the outer surface of microsphere and then erode as the biodegradable polymer degrades from surface to core releasing the embedded drug. While there are several reservoir type microspheres in the market, the majority of PR injectable microspheres that are under development and marketed are biodegradable matrix systems.

Manufacturing Processes For both formulation types, the manufacturing techniques usually overlap and are usually based on single/double emulsion-solvent removal by diffusion/evaporation, phase separation, spray drying, or freeze-drying that are commercially used (see Table 7.6), that is, Medisorb® technology by Alkermes is based on emulsion phase separation for Risperdal Consta and Vivitrol and double emulsification process for Bydureon manufacturing [114, 115]. Each technique has a specific mechanism of drug encapsulation within microsphere; however, the major challenge so far is to attain uniform particle size distribution, which ultimately governs the release characteristics as well as syringeability and to overcome the initial lag and burst release issue. Newer techniques being developed by the industry are usually based on similar principles as conventional techniques (emulsification) but have sophisticated equipment and highly controllable processes parameters to continuously

produce homogeneous microspheres with minimum batch-to-batch variability. Few of such systems are enlisted and described in the following text:

1. Stratμm™ technology (precision particle fabrication – PPF – technology) by Orbis Biosciences (microfluidic approach)
2. 3D flow focusing droplet chip by Dolomite (microfluidic approach)
3. Plexis™ technology by Auritec Pharmaceuticals
4. Kureha microsphere technology by Kureha
5. FormEZ™ technology by Evonik
6. Q-Sphera™ by MidaTech Pharma (micro-piezo technology)

Stratum™ Platform This platform is based on precision particle fabrication (PPF) technology that can produce matrix as well as core-shell microspheres of ~4 μm–1 mm size with very precise control of particle size (± 5% of mean particle size) (WO2017189645A1, [116]). PPF platform was developed by Berkland et al., which was later patent protected by Orbis Biosciences, and it uses coaxial fluid-fluid or fluid-gas flow to create a jet with desired diameter and vibration from ultrasonic transducer to break the jet creating narrow distribution droplets [117]. The process has advantages of scalability of the vibratory process to provide batch-to-batch reproducibility; coaxial fluid-fluid or fluid-gas approaches can create microparticles or microcapsules with desired porosity, coating thickness, and surface characteristics. Moreover, precise control of the process parameters can create particle size spanning that was obtained with all existing technologies (Fig. 7.8a–g). Stratum platform, which is a specific variant of PPF technology, is used for PR injectable manufacturing, for example, exenatide microspheres (Fig. 7.8h) and etonogestrel microspheres (Fig. 7.8i). Moreover, this single-step continuous process can adopt wide range of polymers including PLG, polyanhydrides, ethyl cellulose, chitosan, gelatin, and hetastarch [117, 118]. This technology is excellent for providing release accuracy for narrow therapeutic index drugs and increased safety by minimizing burst release (rat PK study in Fig. 7.8j). The core-shell microparticles can be formed by this technology with a polymer shell filled with either a polymer, oil, or even water [119]; however, the application of core-shell microparticles with biodegradable shell made of PLGA is being evaluated for oral formulations only at this time by Orbis.

3D Flow Focusing Droplet Chip Platform The system uses microfluidic system with x-junction to manufacture emulsion of polymer in organic solvent (DCM) in aqueous surfactant containing carrier fluid through flow rate manipulations to generate continuous production of emulsion droplets of precisely controlled size. Dolomite has a range of microfluidic systems to create custom-made single or double emulsions and to produce lipid/polymeric microparticles. The technology is being developed under the name of Telos® high-throughput production systems to

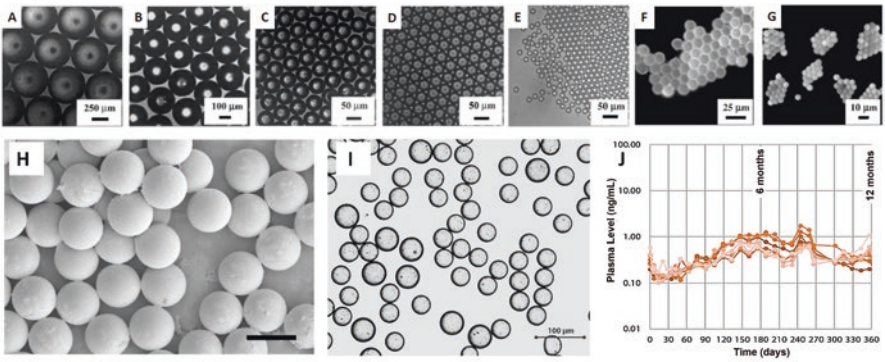

Fig. 7.8 (**a**–**g**) Light microscopy (**a**–**e**) and fluorescence microscopy (**f**–**g**) images of PLG microspheres produced using PPF technology using acoustic excitation. Particle sizes from A to E are 540 µ, 215 µ, 60 µ, 45 µ, 24 µ, 11 µ, and 6 µ. The figures demonstrate the particle size range that can be achieved with this technology. Figures adapted with permission from [117], Copyright © 2001 by Elsevier B.V. (**h**) SEM image of exenatide PLGA (50,50 lactic acid, glycolic acid content) microspheres produced using PPF technology with 5% exenatide loading, scale bar represent 50 µm size. Figure adapted with permission from [120], Copyright © 2018 Springer Nature. (**i**–**j**) Light microscopy of etonogestrel PLGA microspheres produced using this technology with 1-year rat PK data of plasma etonogestrel level. Figures reproduced with permission from Orbis Biosciences, Inc

easily scale up the process. The technology can provide 100% encapsulation of API generating 50 nm–50 µm particles with narrow distribution (CV <5%) depending on the system version used. The technology is currently under development and is not yet associated with any formulation in the market or under clinical trials.

FormEZE*™ *Technology Evonik has this patented platform that uses closed equipment (a packed-bed column) to aseptically carry out a continuous emulsion-based extraction process for producing defined narrow size distribution PLGA microparticles of up to 100 µ size. The process reduces the operation time, reduces unit operations ultimately reducing the waste, and provides an easily scalable alternative compared to batch process. Uniform particle size allows easy administration with a small diameter needle. BioDelivery Sciences International/Evonik has IND approval from US FDA for buprenorphine depot based on this technology and are planning phase I studies.

Q-Sphera*™ *Technology This is a novel platform by MidaTech employing micropiezo technology to individually print narrow size distribution particles of 30 µm size to give predictable PK with low variability in plasma drug concentrations. Two leading programs under this technology are Q-Octreotide for once-monthly administration and OpsiSporin for a 3-monthly intravitreal injection for uveitis.

PEPTIDOTS™ Platform This platform by Carlina Technologies is specifically designed for protein macromolecules and deals with controlled nanoprecipitation of protein suspension by adding a hydrophilic nonsolvent forming nondenaturing aggregates (50–100 nm) of protein [121]. In the second stage, nanoprecipitates are encapsulated in microspheres or gels or implants without being denatured. The technology is being evaluated for microencapsulated insulin formulation for type I diabetes.

Plexis™ Platform Auritec Pharmaceuticals applied their nonbiodegradable membrane-based implant systems (Versa™ platform) concept used in Retisert® and Vitrasert®, however, to utilize the benefit of linearization of drug release with those of injectability by forming biodegradable microparticles [122]. Conceptually, the injectable depot is made of thousands of biodegradable microcapsules. The polymer used for the microparticle membrane is stable over the projected time of drug release, however, ultimately biodegrade. In this patented platform, solid hydrophobic drug (crystalline or amorphous) particles with appropriate dimensions, which act as hydrophobic sustained release core, are produced and coated with appropriate technique to produce semipermeable membrane that allows higher drug loading compared to matrix systems and the diffusion-based release of the drug out of the membrane [123]. Auritec has developed sustained release tacrolimus microparticles (SR-TAC) that are currently being evaluated for 60 days SC injection in clinical trial (NCT03626714) for prophylaxis of organ transplant rejection. Another formulation evaluated in clinical trials (NCT02609126) by Auritec Pharmaceuticals along with Eupraxia Pharmaceuticals is EP-104IAR for delivery of fluticasone for osteoarthritis patients using ultrasound-guided delivery to the knees. The results of the study will provide proof of concept of the Plexis™ platform.

Polymer Properties Formulation development of microspheres is very complex in terms of its formulation composition as well, and selection of an appropriate polymer is very important. The most widely used biodegradable polymers are based on polylactic acid and polylactic acid coglycolic acid (PLGA) due to its regulatory approval and biocompatibility. Still each marketed product differs in LA:GA ratio, molecular weight, and loading ratio. Factors that need to be assessed include drug-polymer compatibility, storage stability, in vivo biodegradability profile, and loading efficiency. Apart from PLGA, there are several other polyesters evaluated thoroughly in research reports including polycaprolactone (PCL), polyanhydrides, polyorthoesters (POE), and poly(phospho esters) (PPE). However, applicability of these polymers is mostly limited to preclinical research except for PCL.

Other technologies for microspheres are directed to modify polymers or modified drug-polymer complexation so as to improve the drug/protein stability and provide tunable release. Notable names include the following:

1. SynBiosys® by InnoCore Pharma – based on multiblock copolymers composed of lactide, glycolide, ε-caprolactone, and PEG with tunable molecular weight.
2. ProLynx by ProLynx LLC – ProLynx β-eliminative cleavable linker tethering drug and tetra-PEG-hydrogel microparticle [124, 125] is the base of three lead programs, (i) PEGylated SN-38 (PEG~SN-38) (in phase I), (ii) PLX039 30 μm once-monthly microparticles of exenatide, and (iii) PLX040 once-weekly 30 μm microparticles of octreotide.
3. PolyActive™ by OctoPlus – biodegradable poly(ether ester) multiblock copolymers approved as implantables by USFDA and EMA is based on PEG and poly(butylene terephthalate) (PBT) and degrades by ester hydrolysis and ether bond oxidation. Tunable polymer blocks can provide different release rates and are currently under evaluation for insulin microspheres made using w/o/w emulsion technique.

7.3 Stimuli-Controlled Parenterals

The emergence of material science along with nanotechnology revolutionized drug delivery systems for a variety of diseases. Development of intelligence in drug delivery systems that can release the therapeutics on demand has changed the central paradigm of disease therapy. Stimuli-controlled drug delivery systems always work in a manner alike: After successful injection of nanocarriers, it would evade reticuloendothelial systems (RES) and accumulate in target tissue via active or passive targeting. Then, intrinsic (tissue environment) or extrinsic (externally applied) triggers, depending upon site of action and type of carriers, lead to release of drug. Receptor targeted delivery systems (targeted nanocarriers, antibody-drug conjugate, protein-drug conjugates) are also considered as stimuli responsive as they target specific receptors/proteins for localizing drug in tissues; however, they will not be discussed here, and readers can refer vast available literature [126–128]. Figure 7.9 depicts various stimuli-controlled injectables with their mechanism of drug release. Stimuli-controlled drug delivery systems are generally proved to be advantageous for following cases [129–131]:

1. Highly labile drug that may require protection during distribution to targeted tissues. For example, proteins are degraded by protease enzymes present in the blood.
2. Highly toxic drugs that should have minimal concentration in target organ or tissues but not affect healthy organs or cells.
3. Targeting to specific tissues, cellular structures, and cell components that are very hardly accessible from direct administration to bloodstream.

7.3.1 Disease Areas, Drug Candidates, and Administration

Stimuli-responsive drug delivery systems are still in their infancy in respect to their clinical availability and are usually formulated with specialized excipients

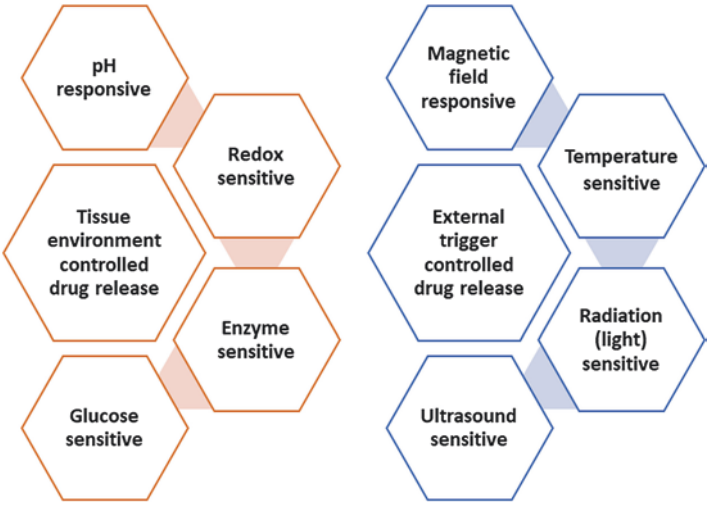

Fig. 7.9 Various stimuli-controlled drug delivery systems and their mechanisms of drug release

ultimately leading to their patent protections and higher costs. Hence, the delivery systems are most often targeted to critical diseases where these delivery systems can make a difference. The most extensive research and clinical development have been done so far in cancer, which lends itself in a group of diseases that can arise in several organs of the body. Moreover, other diseases (including cancer) where neovasculature development is responsible for disease progression can also be primary aims of stimuli-controlled drug delivery systems.

Stimuli-responsive formulations are usually designed to get pulsed or sometimes prolonged release at a site that is remotely located and where local delivery is usually not possible or recommended. Examples include the tumors, bone marrow, liver, etc. Hence, the most appropriate route for administration is intravenous injection, which can take advantage of blood circulation to access remote tissues. Moreover, in case of cancer, local administration (SC/IM/ID) of cytotoxic agents, except for intratumoral administration, is not possible due to local toxicity concerns [132]. Among all the parenteral routes, IV administration has the advantage for rapid delivery of drug to the bloodstream and efficient pharmacological effect, which has a direct interrelationship with the dose [133].

Stimuli (or triggers) can be divided into two categories: i) intrinsic stimuli, which are tissue microenvironment-specific changes induced in response to different pathological conditions, for example, change in pH, temperature changes at inflammation site, and change in redox potentials of specific cells, and ii) extrinsic stimuli such as temperature, ultrasonic waves, and light and electric field that are applied externally to trigger drug release from the therapeutic systems [134]. Stimuli-controlled parenteral formulation strategies are described in the following text.

7.3.2 Tissue Microenvironment–Controlled Injectables

Tissue microenvironment–controlled delivery systems have wider application compared to external stimuli controlled delivery because of their ease of product scale up, cost-effectiveness, patient compliance, and therapeutic application [135]. Once these types of systems are administered, release majorly depends on physiological state of systems and bio-milieu of the tissues and not modified externally [136].

7.3.2.1 pH-Controlled Drug Delivery Systems

pH-responsive systems take advantage of locoregional changes in pH in the body, that is, tumor microenvironment and pH of endosomal and lysosomal compartments [137]. Major disease areas where these systems are applicable are cardiovascular disease, asthma, hypertension, and cancer [138]. Tumors milieu and inflammatory tissue environment flaunt lower pH (pH 6.8–7.2) than blood (pH 7.3–7.4) due to Warburg effect. Similarly, intracellular endosomal (pH 5–6) and lysosomal environment (pH 4.5–5.0) show different pH than extracellular pH [139]. Ideal systems prevent drug release in the blood, while they exhibit predetermined drug release at inflammatory site interstitium, lysosomes (pH 4.5–5.5), endosomes (pH 5–6) [140]. Hence, polymers/lipids can be designed with ionizable character using weak bases or acids that enables protonation or release of protons to affect drug release at specific pH through phase transition [141, 142]. Alternatively, such polymers/lipids can be designed with degradable linkers that degrade at specific pH to achieve the desired release. Some pH-responsive injectables in research are described in Table 7.7 and are extensively studied for delivery of diverse drug cargo including small molecules, proteins, peptides, and therapeutic nucleic acids.

The use of acetylated amino acids like N-palmitoyl-L-homocysteine (PHC) was found in initial pH-sensitive liposomes. PHC acts as an acid-sensitive component and formulates pH-sensitive liposomes with dipalmitoyl phosphatidylcholine (DPPC) and diheptadecanoyl phosphatidylcholine (DHPC) [154]. These liposomes are specifically designed to release drug under destabilization with effect of weakly acidic environment surrounding tumors and inflammatory sites. PHC acts as free fatty acid at neutral pH 7.0 and at lower pH below 6.8; PHC destabilizes by the separation of protonated molecules [155].

Next-generation pH-sensitive nanosystems evolved to mimic viral particle behavior. Phosphatidylethanolamine has an inverted hexagonal phase, which may be responsible for membrane fusion of nanosystems at cell membrane surface [156]. At weak acidic pH (pH 5–6.6) in endosomes, fusogenic actions of lipids help release cargo in cytoplasm before fusion with lysosomes [157]. Doxorubicin-loaded mixed micelles behave as an ideal system at physiological pH and give burst release medicament at pH 6.6 with histidine protonation present at the surface of micelles [158].

7.3.2.2 Enzyme-Controlled Drug Delivery Systems

Physiological enzymes uphold various functions in the body, and deficiency of an enzyme exhibits disease state. Exploiting enzyme dysregulation pathway in various diseases is useful for targeting, therapeutic, and diagnostic purposes to trigger drug

release from carriers. One can imagine a system that acts as a stable formulation in the absence of a particular enzyme or a group of enzymes (i.e., in nontargeted tissues such as blood/normal tissues) and releases medicament after only degradation by the target enzyme [159]. Cancer is an excellent target for such systems. Excessive growth of cancerous cells leads to excessive expression of a specific set of enzymes that can be used as triggers for drug release to considerably lower off-target toxicity and enhance therapeutic effectiveness [160]. Enzyme-sensitive formulations comprise two major classes. First, drug-carrier conjugates where release of active moiety occurs after the enzymatic degradation of linkage between the drug and the carrier [161]. Another approach is to encapsulate the drug within the carrier, which is degraded by specific enzymes affecting the release of the drug [162].

Matrix metalloproteinases (MMPs) (especially MMP-2 and MMP-9) are catalytic enzymes present in abundance in tumor microenvironment during tumor progression [163]. MMPs are a family of approximately 24 human zinc-containing endopeptidases that degrade extracellular matrix and other proteins. Incorporation of peptides that are sensitive to these MMPs is used to develop MMP-responsive nanoparticle systems. These types of nanoparticles are inert in the blood and normal tissues and are cleaved in the presence of MMPs [164]. MMP-responsive liposomes with DOPE-PEG(3400) with linker peptide are cleaved by MMP2 in tumor, while longer PEG chains provide long circulation and low off-target release [165].

Cathepsin B is another enzyme overexpressed in tumors and cleaves tetrapeptide sequence glu-phe-leu-gly (GFIG). This tetrapeptide was inserted as a cleavable linker in PEGylated dendrimers, which showed enzymatic triggered release in tumor cell while giving twofold reduction in side effects compared to doxorubicin solution [166]. Another lipid, TATp-PEG(2000)-DSPE, has a TAT peptide to enhance endocytosis and a cleavable linker to release PEG cover in tumor to remove its shielding effects [165].

Formulations that are under active development by industries include Opaxio® and LiPlaCis®. Opaxio® (earlier Xyotax®) is paclitaxel poly-L-glutamic acid nanoparticle developed to get higher therapeutic index of paclitaxel. Proteolytic enzymes, mainly Cathepsin B, are responsible for the cleavage of poly-L-glutamic acid linkage from paclitaxel and enhance targeting with prolonged antitumor activity as suggested by recent studies [167, 168]. Opaxio has passed the phase III clinical trials, and it is only polymer conjugate drug delivery system that reaches successfully to the market [169]. LiPlaCis®, a target-controlled liposomes of cisplatin, enables a more selective uptake of cisplatin at the tumor site. Once it has accumulated in the cancer tissue, the drug is broken down by secretory phospholipase A2 (sPLA2), an enzyme present in tumors. The lipid composition of LiPlaCis is tailored to be specifically sensitive to degradation by the sPLA2 enzyme and thereby for release of the encapsulated cisplatin. The most advanced drug is LiPlaCis® (cisplatin in a new liposomal reformulation), which has shown proof of concept in preclinical studies and which is in a phase I dose escalating trial by LiPlasome [170].

Though the last few years have witnessed tremendous growth in enzyme-controlled drug delivery systems for cancer and other diseases, there are many more

Table 7.7 pH responsive systems under development

Functional bond	Functional ingredient	Delivery system	Remarks	Ref.
pH responsive systems using polymers				
Hydrazone	PCL-hydrazone-PEG-hydrazone-PCL macrodiol (soft segment), L-lysine ethyl ester diisocyanate (hard segment) and hydrazone-linked mPEG (end-capper)	Nanoparticles	pH-dependent detachment of shell at low pH improves biodistribution upon administration but leads to exposure of nanoparticle core to acidic pH of tumor cells releasing paclitaxel	[144]
	6-maleimidocaproyl (EMCH) hydrazone derivative	Prodrug forming drug-polymer conjugates	DOXO-EMCH is first albumin-binding prodrug of doxorubicin with acid-sensitive properties to reach clinical trials that demonstrates superior antitumor efficacy	[145]
Acetal	Poly(ethylene glycol)-block-poly (propylene glycol)-poly(ethylene glycol)	Hydrogel	Prolongation of survival time in comparison with free drug therapy. The release rate can be accelerated by decreasing the environmental pH from acidic to alkaline	[146]
	4-Methoxybenzaldehyde bisacrylate acetal crosslinker 1,1-bis-(2-acryloyloxy ethoxy)-[4-methoxy-phenyl] methane)	Polyplexes	Polyplexes showed improved toxicity profile and in vivo biocompatibility compared to stable control polymers	[147]
	PEGylated aliphatic dendritic polyester Boltorn® H40 (H40)	Polymeric micelles	Polymer self-assembles to stable micelles with hydrophobic H40 core and many hydrophilic mPEG arms and releases drug in acidic microenvironment	[148]
Acrylate	Poly(n-isopropylacrylamide-copropylacrylic acid-co-butylacrylate) (*p*[NIPAAm-co-PAA-co-BA])	Hydrogel	By responding to local changes in pH in an animal model of ischemia, this hydrogel system provided sustained, local delivery of bFGF, improved angiogenesis, and improved regional blood flow and cardiac function	[149]
Orthoester	PEGylated poly(γ-benzyl L-glutamate) (PBLG)	Polymeric micelles	Micelles improved cytotoxicity of doxorubicin in comparison to control polymer without orthoester linker	[150]
pH responsive systems using lipids				
Ionizable lipids	Lipid (N-palmitoyl-L-homocysteine (PHC)	Liposome	PHC is designed to release drug in slightly acidic environment of tumor/inflammatory site	[141]
	DOPE-dirhamnolipid	Liposomes	Modified DOPE gives pH-responsive lipid mixing below pH 6 releasing drug while maintaining fusogenicity	[151]
	Histidine-octadecylamine	Liposomes/ lipoplexes	Improved fusogenicity and transfection due to pH-dependent ionization	[152, 153]
Succinic acid	Egg yolk PC-succinylated poly(glycidol)	Liposomes	Improved fusogenicity of liposomes below pH 6 compared with unmodified liposomes	[154]

challenges that must be overcome. Isomeric forms of enzymes are associated with the same disease; therefore, therapeutic systems that can differentiate isomers should be developed for precise targeting. Enzymatic reaction pathways are very broad and distinct in nature, and before developing any systems that utilize enzymes as triggers, all the pathways should be clearly related to enzyme production and degradation in vivo [162].

7.3.2.3 Redox-Controlled Systems

Concentration of GSH (glutathione) has been reported 4 times higher in tumor tissues than normal tissues. GSH is a tripeptide, which is major reducing agent,and is responsible for thiol-disulfide reaction [171]. Huge differences in intracellular GSH concentration between cytosol, nucleolus (2–10 mm), and blood (2–20 μm) are facilitating targeted delivery. Two distinct properties are possessed by redox-controlled systems. First, high stability in normal tissue and blood shows less off-target toxicity. Second, redox systems are very specific to GSH concentration and release medicament only in tumor micromilieu [172].

Disulfide bond–based redox-controlled systems tend to reduce by reducing glutathione moiety and converting into sulfhydryl groups. This conversation leads to the degradation of carriers and the delivery of drug. Delivery systems made for redox-responsive delivery mostly use disulfide bonds as linkers with conjugates or cross-linking agents in polymeric carriers. Polymeric carriers have repeating monomers or grafts connected with disulfide bonds. Polymers of amino acids like cystamine [173], N-succinidyl-3-(2-pyridyldithiol) propionate [174], dimethacrylate with disulfide bonding [175], and cystine [176] contain disulfide bonding in their structures. For example, reducible poly(amino acid) when compared to poly (amino acid) in cell line studies rPAA (reducible poly(amino acid) shows less cytotoxicity of polymer and higher release rate compared to nonreducible poly(amino acid) [177]. One study on hyaluronic conjugated emtansine through disulfide linkage (HA-SS-DM1) exhibited a superior targetability to MCF-7 cancer cells with an exceptionally low IC50 of 0.13 μg DM1/mL [178]. Though disulfide bond containing systems have good selectivity, stability of these structures is major concern, and it is very difficult to modify rigid structure of amino acids. Therefore, these types of systems are not studied extensively [179].

Diselenide bond–based redox-controlled systems have higher sensitivity than disulfide bonds as these bonds possess lower energy than disulfide bonds [180]. Therefore, diselenide bonds in therapy proved to be more sensitive systems for tumor targeting. Cheng et al. developed diselenide containing esters to branched oligoehtyleneimine and synthesized polycationic carriers. From the results of cytotoxicity study, diselenide bond containing monomers have lower cytotoxicity compared to polymers of ethylenemine. However, transfection studies suggest higher selectivity of diselenide bond containing systems compared to disulfide bond containing systems [181].

There are some other redox systems in investigation, such as succinimide-thioether linkage. These linkages are also found to be sensitive to reducing microenvironments of tumors and degrade in the presence of glutathione [182].

Succinimide-thioether linkage is found to have higher stability and sustained release of pharmaceutical ingredients compared to disulfide bonds. However, these types of systems are in their infancy stage of development due to problems associated with solubility and stability.

7.3.2.4 Glucose-Controlled Drug Delivery Systems

Endogenous secretion of insulin triggers drug release from glucose-controlled drug delivery systems. Glucose-controlled systems are mainly applied to manage diabetes complications in patients. Despite greater application with response to glucose, short responsive time and nonbiocompability are major issues faced during development and clinical trials [183]. Glucose-controlled systems are based on two phenomena, that is, i) oxidation of glucose in the presence of glucose oxidase and ii) specific binding of glucose with lectin [184]. Glucose oxidase causes oxidation of glucose into gluconic acid and H_2O_2, which leads to glucose sensitivity. Conjugation of poly(acrylic acid) (PAA) with glucose oxidase responds to increasing blood glucose level and releases gluconic acid, which leads to reduction of pH and protonation of carvoxylate group of PAA. All these events collectively result in the release of loaded insulin in a mimicking manner like endogenous insulin release [185].

The second approach utilizes the unique carbohydrate-binding properties of lectin, a multivalent protein used for the fabrication of a glucose-sensitive system. Lectin has a very specific response to only two sugars, glucose and mannose. Concanavalin A (Con A) is a lectin with four binding sites, which used to modify insulin and attach to a specific carrier that can only release insulin in response to blood glucose level [186]. The glycosylated insulin-Con A complex exploits the competitive binding behavior of Con A with glucose and glycosylated insulin. The free glucose molecule causes the displacement of glycosylated Con A-insulin conjugates within the surrounding tissues.

7.3.3 External Trigger-Controlled Injectables

External trigger-controlled systems are more reliable and much controllable to target drug release due to easily manageable external artificial parameters that control drug release. Light, temperature, magnetic field, and electric field are exogenous triggers that control drug release externally.

7.3.3.1 Magnetic-Controlled Drug Delivery Systems

Magnetic-controlled drug delivery systems target specific tissues or organs and release their cargo by means of external magnetic field. Among all exogenous-responsive drug delivery systems, magnetic nanoparticles (MNPs) draw attention due to their intrinsic magnetic properties, which can tracked with help of radiology and magnetic resonance devices for imaging [187]. Moreover, magnetic frequencies below 400 Hz are not absorbed by the tissues; hence, targeting to the remote location in the body is possible rather than light-sensitive delivery systems, which can

be absorbed by all tissues limiting its use to body surfaces only [188]. Magnetic-controlled drug deliveries are divided in two categories:

Magnetic Field-Assistant Drug Delivery Magnetic nanoparticles containing Fe_3SO_4 were used to target tumor tissues under external magnetic field guidance. On alternative magnetic field application, it will generate local hyperthermia, and this heat transfer to magnetic nanoparticles will trigger the drug release to a specific area of target. Precision in process parameters plays a pivotal role in the synthesis and functional properties of MNPs such as physicochemical properties, colloidal stability, and biological behavior [189]. A large variety of MNPs are available in different literature, but maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) containing superparamagnetic nanoparticles have august prospective in pharmaceutical drug delivery [190]. Upon exposure to an external magnetic field, a superparamagnetic nanoparticle tends to reach saturation magnetization, which is demagnetized once external magnetic field is removed and particles become inert. For the purpose of pharmaceutical delivery, superparamagnetic nanoparticles should be modified by surface-active molecules, which can target specific area or tumors. The large surface area of nanomaterials and their activated functional surface groups are proved very opportune to anchor a targeting agent to the MNP surface [191]. Advantageously, the number of targeting molecules can be readily controlled. Polyethylene glycol can be surfaced to nanoparticles to provide a stealth property that can avoid reticuloendothelial systems [192].

A number of research studies were carried out on drug-loaded magnetic nanoparticles, but there is a poor performance of magnetic nanoparticles when release of high doses of drug is required to specific target area. To solve this problem, four separate oleic acid–surfaced iron oxide nanotubes and oleic acid–modified PEG molecules are used to form magnetic nanoclusters by Xiong et al. [193]. These magnetic nanoclusters maintained high paclitaxel (PTX) drug loading, high magnetism, and rapid and extended release behavior. Compared with the same dose of free PTX, the PTX magnetic nanoassemblies had greater antitumor activity in vivo [194].

FeRx Inc.'s delivery strategy has focused on the use of external permanent magnets and particle transport through tissue [195]. FeRx's strategy has been to use milled 1 μm iron-activated carbon, which has a much higher magnetic moment when compared to magnetite. Iron is injected into the blood vessels near the target organ, and then a single external permanent magnet pulls the particles out of the bloodstream and into the epithelium layers of the organ. The field is removed from the target organ after approximately 15 min, and an angiogram is performed to ensure blockage of the main arteries has not occurred. Various drugs are attached to the iron-activated carbon depending on the application. This method for drug delivery has been performed for both the liver and the bladder [195].

Magnetic hyperthermia: Magnetic field-assisted therapy has also application to induce local hyperthermia in cancer cells to further induce apoptosis. To induce cell apoptosis, temperature should be above 43 °C, but the removal of heat after external heat application is faster than energy provided by external magnetic radiation [196]. As suggested by Gordon, cellular membrane may act as an insulator for the thermal

conduction process; hence, it is necessary to develop magnetic nanoparticles that are easily taken up by specific cells and then apply external magnetic environment to induce apoptosis [197]. While there are formulations available in the market for such applications, it does not deal with actual drug delivery; hence, more details on magnetic hyperthermia are not discussed here.

7.3.3.2 Thermally Controlled Delivery

Though local hyperthermia is characteristic of cancer-affected and inflamed tissues, temperature difference between the normal and pathological tissues are not significantly high that it can be used to control drug delivery. However, external heat source can be applied to locally trigger drug release very precisely. For external heat stimuli, different techniques are used: microwave irradiation, ohmic heating technique by high frequency electrode application, fiber optics alimented with optical laser, ultrasound technology, laser photocoagulation, and water bath heating (for large area) is applied [198, 199].

As the tumor site or pathologic area is heated as a result of this, endothelial pore size increase and blood flow to the distal area take place, which leads to extravasation of developed delivery systems [200]. Moreover, hyperthermia leads to reduction of DNA synthesis, increase production of heat shock proteins that accounts for altered protein synthesis chains, and changes in a microtubule centers and growth factors. All these events collectively result in changes of cellular morphology [201].

A class of phospholipids called lysolipids has one or both acyl group derivatives removed. Due to its noncylindrical structure of lysolipids, it is easily incorporated into a lipid bilayer and alters chemical and physical properties of bilayer, such as membrane permeability, morphology, and stability [202]. Incorporation of lysolipids in lipid mixture also associated with reduction in the phase transition temperature of lipid mixture Moreover, their accumulation at the grain boundaries and the formation of stabilized defects may result in an increased release rate of drugs [203]. The decrease of *T*m is necessary and clinical trials recommend temperature below 43 °C because higher temperature can cause hemorrhage or damage to the surrounding healthy tissue.

A newly developed liposomal product of doxorubin (ThermoDox®), which is composed of combination of lipids (DPPC:MSPC:PEG2000-DSPE/90:10:4), shows release of doxorubicin to the target tumors at temperature of 41–42 °C [204]. Drug release from ThermoDox® formulation was faster than that obtained from the convectional thermosensitive formulation at 42 °C, as required by an ideal thermosensitive system [205]. Thermal release of drug from ThermoDox is achieved through different methods such as magnetic hyperthermia, radiofrequency ablation, or external heat application. It has been evaluated in several clinical trials for liver cancer (NCT00441376, NCT02181075) and breast cancer (NCT00826085). Currently, ThermoDox® is being evaluated for hepatocellular carcinoma in phase III trials (NCT00617981) and phase I trial in relapsed/refractory solid tumors in children, adolescents, and young adults (NCT02536183) and phase I study in breast cancer (NCT03749850).

Photothermal irradiation responsive nanoparticles developed by Naomi Halas and group comprised of Au(core) nanoshellscoated with PEGylated silica have entered in clinical trials in 2008 [206]. Metal nanoshells consist of spherical dielectric core nanoparticles and possess a highly tunable plasmon resonance whereby light induces collective oscillations of conductive metal electrons at the surface of nanoshells [207]. The particle's plasmon resonance, in turn, determines the absorbing and scattering properties of the particle. From the results of preclinical studies, it is concluded that nanoshells do not accumulate in healthy tissue due to AuroLase therapy, which applied thermal ablation of tumor and allows to cover its irregular boundaries while safeguarding surrounding healthy tissues [208].

Another study done by Tagami and group developed HaT (heat-activated cytotoxic) liposome containing DPPC and Brij78, which shows increased drug release for a number of drugs at temperature of 40–41 °C. Moreover, when compared with free DOX, HaT enhanced drug uptake in the heated tumor by 5.2-fold and reduced drug delivery to the heart by 15-fold. A single intravenous treatment with HaT-DOX at 3 mg DOX/kg in combination with localized hyperthermia demonstrated enhanced tumor regression compared to lysolecithin-containing thermosensitive liposome of doxorubicin and free doxorubicin, and exhibited little toxicity [209]. A thermo-responsive poly(γ-2-(2-(2-methoxyethoxy)-ethoxy) ethoxy-ε-caprolactone)-b-poly(γ-octyloxy-ε-caprolactone) (PMEEECL-b-POCTCL) diblock copolymer was synthesized by ring-opening polymerization using tin octanoate (Sn(Oct)2) catalyst and a fluorescent dansyl initiator [210]. The PMEEECL-b-POCTCL had a lower critical solution temperature (LCST) of 38 °C, and it was employed to prepare thermally responsive micelles [211]. The blank micelles showed a low cytotoxicity. In comparison, the micelles loaded with DOX showed a much higher in vitro cytotoxicity against MCF-7 human breast cancer cell line when the incubation temperature was elevated above the LCST.

7.3.3.3 Ultrasound-Controlled Drug Delivery Systems

Due to noninvasiveness and high tissue penetration, ultrasound-controlled delivery systems have greater advantage of in-depth targeting of developed delivery systems where light and external heat systems fail. Ultrasound can induce drug release from carrier by cavitation and mechanical effects [212]. Release of drugs depends on time period, frequency, density and type of ultrasound whether (pulsed or continuous) along with lipophilicity of drugs [213]. Deeper penetrations are achieved with low frequency 20–100 kHz ultrasound, which can target and release drug to deeper areas but lacks in sharp focusing beam than high frequency ultrasound 1–3 MHz [214].

Ultrasound-responsive microbubbles can be used for a variety of pharmaceutical agents, as they have shown dual functions (cavitation and hyperthermia) of ultrasound responses and intracellular delivery in response to external ultrasounds. First-generation air-filled bubbles have mean diameters of 1–8 μm capable of passing through pulmonary capillaries. Air-filled microbubbles rapidly disappear from the bloodstream so high molecular weight gases (sulfur hexafluoride or perfluorocarbons) filled microbubbles are developed as second-generation microbubbles [210].

There are several ultrasound contrast agent formulations in market worldwide based on this strategy including Sonazoid® (a perfluorobutane microbubble formulation containing hydrogenated egg phosphatidyl serine by GE Healthcare), Lumason® (sulfur hexafluoride lipid type-A microspheres by Bracco Imaging), SonoVue® (a sulfur hexafluoride microsphere formulation of macrogol 4000 DSPC, DPPG and palmitic acid by Bracco Imaging) and Definity® (perflutren lipid microsphere containing DPPA, DPPC, mPEG5000-DPPE by Lantheus Medical Imaging) for contrast-imaging of liver and heart tissues. However, there are none which are used for drug delivery using the same principle. Such microbubbles have been shown to target tumor tissue in the liver [215] enhancing contrast in the liver parenchyma within about 10 min of injection.

Instead of microbubbles, nanobubbles along with liposomes are used to deliver the drug because micron-sized bubbles have short circulation time [216]. Liposomal doxorubicin (Caelyx®) has shown increased antitumor activity in response to external ultrasonic application [217]. Doxorubicin-loaded liposomal carriers (Caelyx®) when conjugated to microbubbles' surface through a biotin-avidin linkage provide faster cellular uptake, increased doxorubicin nuclear accumulation with reduction in drug efflux from the resistant cells under the action of ultrasound, compared to just doxorubicin-loaded liposomes with and without addition of P-gp inhibitors or liposomes complexes with bubbles without applied ultrasound [218, 219].

7.3.3.4 Radiation-Controlled Drug Delivery Systems

Radiation provides a very broad range of adjustable parameters (i.e., wavelength, duration, and intensity), which can be controlled both spatially and timely for drug release [220]. For radiation-specific delivery systems, photo-responsive groups are conjugated with drug or encapsulated in therapeutic delivery systems. A number of mechanisms are involved that include photoisomerization, light-triggered reversible switch in polarity or irreversible switch in polarity, photo-cross-linking, photo-decross-linking, polymeric backbone photo-degradation, and photosensitization-induced oxidation [221].

Azobenzene and spiropyran molecules are well known of their photoisomerization properties, namely, cis-trans transformation, under ultraviolet (UV) light radiations (340–380 nm) [222]. Therefore, azobenzene molecules were encapsulated into mesoporous silica nanoparticles loaded with camptothecin (CPT), forming a light-activated nanoimpeller. Such cellular-endocytosed nanoimpeller could impel the capsulated drugs out of the carrier and in the meantime into the cancer cytoplasm once under illumination at the specific wavelengths through the transformation from binding to unbinding states between azobenzene and CPT [223].

Visudyne (liposomal verteporfin for injection) is a light-activated drug used in photodynamic therapy for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis [224]. A low-energy laser (689 nm) wavelength is directed into the back of the eye at the abnormal vessels, activating the drug. The activated drug closes these abnormal vessels, most of which are thereby destroyed or sealed in such a way that they no longer leak. Photoactivation of visudyne is controlled by the total light dose delivered [225]. In the treatment of

choroidal neovascularization, the recommended light dose is 50 J/cm2 of neovascular lesion administered at an intensity of 600 mW/cm2. This dose is administered over 83 s. *Visudyne* offers an anatomical treatment that also occludes mature vessels that may be expressing less or no VEGF. It works to effect vaso-occlusion of the arteriolarized neovessels that may be the cause of persistent activity.

Despite a lot of development in the field of stimuli-controlled drug delivery systems, the strategies reaching the clinical trials are only few. Table 7.8 details the stimuli-controlled release formulations in market/clinical trials. This indicates that strategies that could translate from in vivo animal experimentation to human trials are lacking. More advanced screening studies such as in vitro 3D cultures of cancer cells and 3D cocultures with tumor-associated fibroblasts and stem cells would bridge the gap for screening these strategies for which there is a low correlation between in vitro 2D cultures and in vivo experiments. Moreover, availability of advanced technologies, that is, RNAi and Crisper/Cas9 strategies would help develop more relevant both in vitro and in vivo animal models for successful preclinical development, which can provide more probability of success. Moreover, there are novel modalities that also play major role in next-generation stimuli-controlled delivery, that is, gene delivery systems [226–229], novel gene encapsulation technologies [230–232], novel drug loading techniques [233, 234], which could provide added benefit to stimuli-responsive systems.

7.4 Advancements in Administration Modalities: Self-Administration and Large-Volume Injectors

The era of outpatient injectables, which started with simple vial/syringe presentations and newer advancements to prefilled syringes (PFS), is now moving toward more advanced devices. This is evident from the management of diabetes in the current time, which is becoming very convenient for patients with more and more pronounced use of injection pen devices. Moreover, the formulation technologies have moved dosing from several times daily to once daily to even once or twice a week. Considering the example of human insulin (MW 5.8 kDa), which itself is a very large molecule compared to small molecule drugs, its delivery has been accomplished using syringes for self-administration. Now moving to even larger biologics such as monoclonal antibodies (MW ~145–150 kDa) [127, 128]. The higher mg/mL concentrations of these macromolecules can result in high viscosities, which are extremely difficult, if not impossible, to deliver using simple syringes or with regular devices (Fig. 7.10a and b). This is evident from major injection devices in the market that are available for peptides or small molecules. As described earlier, the targeted injectables (biologicals) will hold a large market share in near future, and as oral delivery is hardly possible with these molecules, the second-generation devices are needed for delivery of these molecules. Moreover, second-generation devices, which are aimed to be viscosity independent and less painful, can also handle complex injectables with variable viscosities. Discussion of these developments along with formulation characteristics is important, as prior understanding and selection of a suitable drug delivery device assists in formulation development to keep in mind the factors

Table 7.8 Stimuli-controlled drug delivery systems in market/in clinical trials

Marketed product	Stimulus, stimuli responsive components	Formulation	Remarks
Visudyne® By Bausch & Lomb for choroidal neovascularization in AMD patients	Light (external), Verteporfm	Liposomes composed of ascorbyl palmitate, butylated hydroxytoluene, egg phosphatidyl glycerol, DMPC, and lactose	Powder for reconstitution to form liposomes Possible release of drug by verteporfin which acts as a photosensitizer producing reactive oxygen species which oxidize the components of liposomes-inducing release
Thermodox™ By Celcion liver for cancer, lung cancer, breast cancer	Thermal (external), lysolipids	Liposomes composed of DPPC:MSPC:PEG2000-DSPE/90:10:4	Temperature-triggered doxorubicin release at 40–42 °C temperature Has been/being evaluated in several phase I, II, and III trials in different cancers with different hyperthermia techniques i.e., 1. Microwave hyperthermia in breast cancer recurrence (NCT00826085) 2. Magnetic resonance-guided high intensity-focused ultrasound – MR-HIFU for refractory solid tumors (NCT02536183) 3. Radiofrequency ablation for hepatocellular carcinoma (NCT02112656) 4. Focused ultrasound for liver tumors (NCT02181075)
LiPlaCis® By LiPlasome Pharma For advanced or refractory solid tumors, breast and skin cancer	Phospholipase A2 (internal), DMPC	Liposome formulation of cisplatin	In phase I (NCT01861496) trial with advanced or refractory solid tumors and phase II study with metastatic breast and skin cancer
Opaxio® By CTI Life Sciences for advanced NSCLC, ovarian, esophageal cancers, glioblastoma	Cathepsin B (internal), biodegradable glutamic acid polymer	Paclitaxel poliglumex (paclitaxel-polyglutamic acid conjugate nanoparticles)	Proteolytic enzymes mainly Cathepsin B cleaved biodegradable glutamic acid polymer under clinical evaluation for NSCCL (phase III), ovarian cancer (phase II), glioblastoma, and esophageal cancers (phase II)

AuroLase™ By Nanospectra Biosciences for solid primary and/or metastatic lung tumors	Thermal (external), gold nanoshells	PEG-coated silica-gold nanoshells	Thermal ablation of solid primary and/or metastatic lung tumors using near infrared light
RadProtect® by original BioMedicals for acute radiation syndrome	Magnetic (external), iron	PEG, iron, and amifostine micelle	Transferrin-mediated chelation for amifostine releases In phase I (NCT02587442) dose escalation and safety study for acute radiation syndrome
NBTXR3 (PEP503) By Nanobiotix for carcinomas and soft tissue sarcoma	Radiation (external), halfnium oxide	Hafnium oxide nanoparticles	External radiation to enhance tumor cell death via electron production Evaluated in phase I (NCT01946867) and phase II/III (NCT02379845) trials Results showed well-tolerability and positive results with complete response in combination with radiotherapy in soft tissue sarcoma in Phase II/III
Magnablate by University College London for prostate cancer	Magnetism (external), iron	Iron nanoparticles	Magnetic hyperthermia using external magnetic force Under phase 0 trial (NCT02033447)

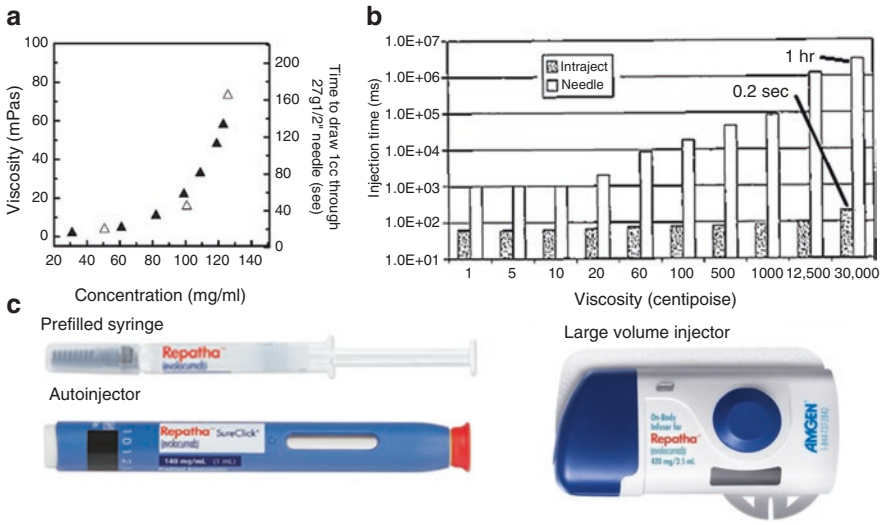

Fig. 7.10 (**a**) Effects of protein concentration on viscosity (filled triangles) and syringeability (open triangles) of mAb at increasing concentrations. Syringeability is depicted by time to draw the mAb solution into a syringe by drawing the plunger to the end of a 1 cc syringe. Figure reproduced with permission from [236], Copyright © 2005 Elsevier B.V. (**b**) Effect of viscosity on injection time for a needle-syringe system (23 g needle, at force of ~20 N) and a needle-free injector (Intraject, Zogenix Inc.) for delivery of 0.5 mL nonthixotropic liquids of various viscosities. Figure adapted from patent US8066661B2 [237]. (**c**) Comparison of Repatha prefilled syringe injection (140 mg evolocumab/mL), Repatha SureClick autoinjector (single use 15 s injection, 140 mg/mL evolocumab), Repatha Pushtronex™ on-body 9 min infusor with prefilled cartridge 420 mg/3.5 mL evolocumab). (Image courtesy: Amgen Inc)

such as concentration of drug, concentration of excipients, types of excipients, etc., that affect the rheological properties of formulation in mind. Advanced devices offer some leverage on the volume and rheological properties that are simply not an option for conventional syringes. Figure 7.10c shows comparison of a PFS, an autoinjector, and a large-volume injector developed for same drug by Amgen.

Simple needle-syringe injection is still widely used, and syringeability is an important factor to consider. It affects the time to draw a fluid into a syringe as well as time to inject. It relates to the force required to flow a liquid formulation at a specific flow rate with a needle of specific length and diameter. Hagen-Poiseuille equation can be rearranged to describe the flow of a Newtonian fluid through a hollow needle:

$$F = 128Q\mu LA / \pi D^4$$

F = plunger force
Q = flow rate (volumetric)
μ = dynamic viscosity
L = needle length
D = needle internal diameter
A = plunger surface area

This equation does not consider the plunger's friction and resistance posed by tissue at the needle tip; however, the formulation viscosity within the needle plays an important role. Smaller bore needles offer easy and less painful insertion; however, plunger force is inversely proportional to fourth power of bore diameter. Hence, a change from 25 g needle (inner diameter-ID 0.26 mm) to a 30 g needle (ID 0.16 mm), for the same flow rate and same length of needle, the force needs to be increased by ~700%. Or to deliver the same volume requires considerable time. The equation applies to ideal liquids, that is, Newtonian fluids (shear stress is proportional to shear rate). However, pharmaceutical products might exhibit non-Newtonian character, that is, dilatant (shear thickening) and plastic/pseudoplastic (shear-thinning behavior systems, which further adds to the complexity of injection [235].

First-generation injection devices are usually prefilled syringes (PFS) (ready-to-use and prefilled dual chamber devices for reconstitution prior to administration) and spring autoinjectors that have their own advantages and applications; yet, the principles of syringe-needle injection apply all the same, that is, viscosity of formulation plays a major role. The patients usually prefer injection handling times to be <15 s (time to insert and inject the formulation); hence, these devices are built to deliver it. These devices are driven by convenience, safety, and cost factors. These devices offer nonclinical administration (at pharmacies and self-administration at home) while offering safety options such as retractable needle. One major leap in this area is reusable devices, which can be reloaded with new drug cartridges when needed resulting significant cost reduction for patients. Xyosted (testosterone enanthate) subcutaneous injection (available in 50 mg/0.5 mL, 75 mg/0.5 mL and 100 mg/0.5 mL strengths) is the first once-weekly 27 g autoinjector for self-administration for testosterone replacement therapy.

Second-generation needle-free injections (NFIs) work to reduce time of delivery (usually <50 ms) and provide more patient compliance by not having to insert a needle. NFI resorts a fine, high velocity jet of liquid formulation through an orifice/orifii using high pressure generated by various mechanisms (Lorentz force and spring or compressed gas) to pierce the skin and underlying tissue. Unlike injection devices where the flow is governed by Poiseuille's equation, the force in needle-free delivery is usually governed by Bernoulli's equation:

$$F = 2\rho A\left(4Q / C_f \pi D^2\right)^2$$

where F = plunger force
Q = flow rate (volumetric)
ρ = fluid density
C_f = orifice flow coefficient
D = orifice diameter
A = plunger area

Table 7.9 Self-injectable devices in the market

Device name	Formulation type	Volume	Administration
Gas-propelled devices (gas)			
Powderject (He)	Solid (powder)	–	ID
Sumavel® DosePro™ (N_2)	Liquid	0.5 mL	SC
Biojector® 2000 (CO_2)	Liquid	Up to 1 mL	IM/SC/ID
Penjet® (N_2)	Liquid	0.1–0.5 mL	IM/SC/ID
Jupiter Jet™ (CO_2)	Liquid	0.03–0.2 mL	IM/SC/ID
Spring-propelled devices			
Vitajet™ 3	Liquid	0.5 mL	SC
Medi-Jector Vision®	Liquid		SC
Injex®30	Liquid	0.05–0.3 mL	SC
Injex®150	Liquid	0.8–1.5	SC
Crossject Zeneo®	Liquid	0.2–1 mL	IM/SC/ID
Tev-Tropin®	Liquid	Variable	SC
PharmaJet®Tropis	Liquid	0.1 mL	ID
Glide SDI®	Solid (extruded rod-shaped pointed implant)	–	SC
PharmaJet®Stratis®	Liquid	0.5 mL	IM/SC
Miniject	Liquid	0.1–0.3 mL	IM/SC/ID
Bioject®ZetaJet™	Liquid	0.05–0.5 mL	IM/SC/ID
Electromagnetic actuation device			
Portal PRIME system	Liquid	Up to 1 mL	SC

Sources: http://www.zogenix.com/, http://www.penjet.com, product websites

Compared to Hagen-Poiseuille's equation, liquid property in abovementioned equation is density, meaning the NFIs can ideally deliver the same volume, at the same rate, using the same energy irrespective of the viscosity of different liquids. This is only true for zero thickness orifii plates, however, though minute, orifii have a finite length, and exhibit some viscous loss. Nevertheless, this is of least importance as viscosity ranges of practical range of pharmaceutical interest are usually unaffected by this viscous loss. Figure 7.10b shows that over viscosity range of 1-~12,500 cP, the delivery time is <0.1 s for Intraject NFI. NFIs available in the market and approved in drug-device combination products are given in Table 7.9. It is worth noting that the upper limit of administration for the majority of these injectors is ≤1 mL.

Large-volume injectors (LVIs) are the latest innovative devices, which take the time of injection as an advantage that allows injection of large and ultra-large volumes. 1 mL has been regarded historically as upper limit for self-administration; however, large doses up to 50 mL can be administered with LVIs that come as wearable devices to offer for adherence monitoring and dosage control with app-based connectivity. With each device with its own mechanism and formulation approach can handle delivery of different therapeutics, for example, Herceptin SC® pump has Herceptin formulation based on Enhanze™ technology that uses rHuPH20

(recombinant human hyaluronidase), which reversibly breaks down hyaluronan in SC tissue for increasing absorption surface. Currently, three LVI based drug-device combinations are available in the market (Pushtronex™ – 9 min evolocumab patch pump by Amgen/West Pharmaceuticals, Neulasta® OnPro™ kit – 45 min pegfilgrastim patch pump by Amgen/Insulet and Single-use injection device (SID) for Herceptin SC® (patch pump by Roche) and several under development include ND0612 (levodopa-carbidopa dual pump 24 h belt-pump and patch pump infusion systems by NeuroDerm), ND0701 (apomorphine base 12 h belt-infusion pump by NeuroDerm), sc2Wear™ furosemide infusor (5 h infusion system by scPharmaceuticals), and The Imperium® wearable injector (for insulin multiday wearable patch pump by UniLife), other wearable injectors by UniLife, MiniMed™ 670G insulin delivery system (real-time insulin delivery control with glucose and insulin level monitor by Medtronics) and enFuse™ by Enable injections. Several devices come into single-use or reusable formats. Major advantages with LVIs are as follows:

1. Minimizes stability studies requirement as
   (a) Primary containers remain the same (standard vials/syringes/cartridges)
   (b) Use of materials used in standard IV set – minimal short-term material compatibility studies
2. Formulation flexibility
   (a) Provision to automatically reconstitute the lyophilized drugs (no patient handling so no variability)
   (b) SC injection of up to 50 mL
   (c) Can handle wide viscosity range
3. Patient friendly
   (a) Cost-effective (reusable, no hospitalization-related costs)
   (b) Small needle size for least pain
   (c) Small size so easily concealed under clothing without hindering patient mobility
   (d) Provision to automatically warm the drug (refrigerated drugs require 30 min wait for standard room temperature acclimatization)
   (e) Mobile app-based connectivity

For a detailed account and current development status of injectable devices including LVIs/wearable injectors, readers are referred to online free ONdrugDelivery Magazine and individual industry websites. Readers should refer to the references for detailed guide [238]. For any devices and the design, the formulation challenges that need prior evaluation are as follows:

- Container-closure integrity of the device to ensure the sterility and particulate matters during storage and transportation
- Compatibility/stability of the drug in contact with the container and closure (usually glass/plastic units and rubber stopper)
- Drug integrity after its administration (the impact of jet-force on drug) particularly for protein drugs (For NFIs)

7.5 Conclusion

Prolonged injectable delivery systems have evolved extensively with numerous newer technologies in the field of in situ gelling systems, microspheres, and liposome strategies in the pipeline, thereby broadening the scope for different applications. Moreover, adoption of advanced manufacturing processes provides solutions to challenges associated with stability and release characteristics with more precise control of release characteristics. In case of stimuli-controlled delivery systems, the technologies are still in their growth phase, and it will take time to reach maturity. However, with rapidly advancing knowledge space due to increasing research inclination by academia and small and medium pharmaceutical industries in nanotechnology-based medicine, the time is not so far where personalized medicine will be a common concept.

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Transdermal Drug Therapy: Emerging Techniques and Improved Patient Compliance

8

Avinash Kumar Seth

Contents

Abstract

Transdermal drug therapy has made a breakthrough over the past few years amid emerging technologies and strategies for repositioning of drugs to deliver through the skin: a strong barrier. In spite of various benefits of transdermal routes of drug delivery such as avoidance of first-pass metabolism, easy mode of

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_8

application, high patient compliance, and controlled release of medication, researchers today are facing numerous challenges in order for patients and clinicians to embrace transdermal drug delivery system (TDDS). One of the key impediments facing TDDS is the narrow range of drug positioning as a result of the skin being a strong barrier for drugs with molecular weight > 500 Da and its hydrophilic nature. To overcome these challenges, immense research work was carried out to extend the scope of TDDS to incorporate wide range of drug molecules which may include high molecular weight drugs, especially biotechnologically developed macromolecules and vaccines. Moreover, extensive research was undertaken by scientists in developing new transdermal technologies to deliver wide range of drugs to treat various chronic diseases. The quantum of research work is demonstrated by many patents filed and granted to industries and academic institutions. This chapter discusses about the basics of transdermal permeation mechanisms considering physiochemical characteristics of drug molecules and drug delivery systems. Furthermore, it focuses on emerging technologies for skin permeation enhancement that has led to high patient compliance. Besides, it also illustrates on the current available TDDS in the market with narrow range of drugs; however, ongoing clinical trials and new technologies suggest that there is a great future of TDDS in repositioning wider range of drugs bypassing the existing patents.

Keywords
TDDS · Stratum corneum · Transcellular route · Transdermal patch · Electroporation · Inontophoresis · Thermal ablation · Microneedle array

8.1 Introduction

Transdermal drug delivery system (TDDS) has gained the popularity because of its easy administration, painless and convenient mode of application, and high patient compliance for noninvasive skin route especially in elderly and young people, those who have difficulties in swallowing and suffering from nausea and vomiting. This approach of drug delivery is beneficial over other medication delivery systems such as oral, topical, and parenteral. TDDS provides a controlled release of the medication. Such a patient-friendly medication delivery system has attracted researchers to exploit it for the delivery of medication avoiding hepatic first-pass metabolism and certain side effects which are the common disadvantages in conventional medication drug delivery systems [1].

TDDS provides the opportunity to the researchers to deliver the medication in a slow and controlled rate without varying the plasma drug concentration significantly. These attributes of TDDS make it one of the important delivery systems to deliver drug molecule in the predetermined release rate to the patients' systemic system.

However, all the drug molecules do not fit to be incorporated in TDDS because they may not penetrate the skin which is a very effective barrier. Few selective drug molecules having molecular weight less than 500 Dalton are the good candidates to be delivered by this method. This limitation of size of drug molecules has posed a challenge before the researchers to develop appropriate technologies to incorporate even large drug molecules in TDDS without affecting the penetration of drug through skin barrier. A large number of TDDS containing low molecular weight drug molecules are available in the market in the form of patches. A huge scope is expected in near future in the discovery of transdermal patches adopting novel application systems and technologies to deliver any drug molecule including macromolecules and vaccines. The researchers are focused to develop TDDS to be placed at a particular region of the body to deliver the drugs to the targeted site for maximizing drug availability and reducing the drug-dependent side effects. This may be advantageous to treat various chronic diseases such as rheumatoid arthritis, asthma, and cancers.

Recent development in polymer science technology has made polymers a significant contributor in formulating TDDS [2]. The world of polymers has opened a new era for the researchers to select and/or design appropriate polymers on application of impressive polymer technology. Polymers are designed to bear required physicochemical and mechanical properties of various components of TDDS like matrix former, rate-limiting membrane, backing layers, release liner, and pressure-sensitive adhesive. Furthermore, polymers must be biocompatible and chemically compatible with the drugs incorporated and other components of the system such as penetration enhancers.

The first TDDS of scopolamine was marketed for motion sickness in late seventies. Later on, many other transdermal patches like nicotine for smoking cessation, nitroglycerin for angina, clonidine for hypertension, and estradiol for estrogen deficiency had revolutionized in transdermal drug delivery system and opened up a new opportunity for the pharmaceutical industries to exploit the advantages of TDDS to provide systemic effect of all the drugs through skin route. But there are limitations for the drugs to penetrate intact in the stratum corneum, a skin barrier, if they do not have the following ideal properties:

- Molecular weight < 500 Da.
- Adequate solubility in both lipid (oil) and aqueous (water) phase to obtain required membrane concentration gradient acting as a driving force for passive diffusion of drug through the skin barrier; stratum corneum.
- Adequate partition coefficient (1–4) for better partition between a vehicle and the skin barrier; stratum corneum.
- Adequate melting point (< 200 °C), an important criterion correlating solubility.

Biopharmaceuticals do not meet these criteria which are nowadays drugs of choice to control a wide range of illness. Such drugs may have poor bioavailability and susceptibility to first-pass metabolism. Thus, they are often ideal candidates for

transdermal delivery but fail to meet the abovementioned ideal condition for TDDS. For example, macromolecules like vaccines, proteins, and peptides; due to their large molecular size and vulnerability to acid destruction in the stomach, cannot be given orally and hence administered parenterally. These classes of drugs are precluded from the successful transdermal administration not only by their large molecular size but also by their high hydrophilicity. These limitations of drug molecules provided an opportunity to the formulators to make use of several chemical or physical approaches to enhance the transport of drugs through the stratum corneum.

Researchers were interested to the repositioning of any drug irrespective to their abovementioned physicochemical and pharmacokinetic characteristics in TDDS. The drug must passively cross the stratum corneum, the outermost layer of the skin. If drugs do not comply with the required parameters for TDDS, the phenomenon of crossing the skin barrier, i.e., the stratum corneum, does not take place. Extensive research work has been done to solve this problem in order to position large number of drug molecules in TDDS. Physical methods providing external driving force like iontophoresis, sonophoresis, electrophoresis, magnetophoresis, and microneedle were employed to force the drug molecules through the stratum corneum, a strong skin barrier.

Besides these physical techniques, some distinctive methods have been suggested to disrupt the skin barrier and allow all the drug molecules irrespective of the criteria given for TDDS [3, 4].

This chapter is focused on the transdermal permeation mechanisms, drug and polymer desirable attributes, and emerging techniques developed to reposition all the drug molecules in TDDS for all types of diseases by allowing them to cross the skin barrier (stratum corneum) in order to provide improved patient compliance.

8.2 Challenges in Developing Transdermal Drug Delivery Systems

The major challenge in designing transdermal drug delivery system is to perform an intensive research on the skin providing the second largest surface area ranges from 1.5 to 2.0 m^2 as an interface between the human body and the external environment. This consists of a remarkable barrier having thin outer most layer called the stratum corneum. It is made up of corneocytes (aggregated keratin filaments encased in a cornified envelop) surrounded by lipids organized as multiple lamellar bilayers (Fig. 8.1) [5].

These structured lipids between the corneocytes restrict unnecessary loss of water from body and due to the similar reason restrict entry of many topically applied drug molecules except those that are lipid soluble and possessing molecular weight less than 500 Da.

A significant challenge was on the shoulder of researchers to administer drug molecules transdermally either for local dermal effects or for systemic therapy because the drug molecules can reach to the system through superficial capillaries

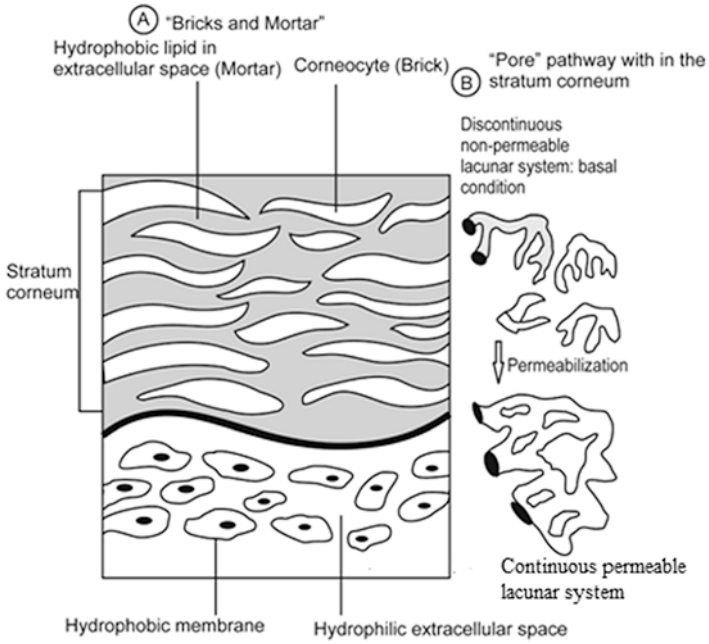

Fig. 8.1 Two compartments (**a**) brick and mortar system and (**b**) pore pathway. (Reprinted from Dermatology, 4th, Prausnitz, M. R. Elias P. M, Franz T. J., Schmuth M., Tsai Jui-Chen, Menon, G. K. et al., Skin Barrier and Transdermal Drug Delivery, 2065–2073, Copyright (2012), with permission from Elsevier)

of the dermis. Another important obstacle or challenge that the TDDS suffers is slow penetration of drug through the skin because of its extremely low permeability. Researchers must know the input rate of the drug from the TDDS which is expected to be equal to its output rate. This is a great challenge for the researchers and the formulation developers. Three important pharmacokinetic parameters such as (a) volume distribution (Vd), (b) total body clearance (CL_T), and (c) steady-state or therapeutic concentration (CPss) under steady-state condition are accounted significantly to find out the output rate of the drugs from TDDS which can be considered as the input rate as per the law of mass balance.

TDDS was becoming very popular because of its exceptional quality of avoiding hepatic first-pass metabolism, drug-related side effects and the capability to deliver drug in a slow and controlled rate. However, they were not found clinically suitable for drugs possessing high molecular weight. A great task was handed over to the scientists and researchers to invent some suitable technologies to permeate any drug which possesses more than 500 Dalton molecular weight and 20 mg daily dose, through intact skin at therapeutic rate. In order to exploit the advantages of TDDS for all types of drugs which may even have more than 500 Dalton molecular weight, the only way was to develop novel formulations or technologies to ablate or to modify the nature of the skin barrier, i.e., the stratum corneum, in order to enhance

the permeability for drugs having molecular weight more than 500 Da. The formulation and development departments of pharmaceutical companies and academic research centers have been dealing with such formulations to resolve obstacles related to skin permeability in order to deliver all drugs irrespective of any size (molecular weight) and dose. Many technologies have been developed to improve the permeability of drugs through the skin's barrier, which have been dealt in the coming sections of this chapter.

8.3 Transdermal Permeation Mechanisms

To understand the permeation mechanisms of transdermal drug delivery systems, it is necessary to be acquainted with the various routes of drug absorption into the skin for transdermal drug delivery system. Primarily three types of routes by which drugs can be transported through the skin are depicted in Fig. 8.2 and are described as follows [6]:

1. Appendageal route (shunt route)
2. Transcellular route
3. Intercellular route

Appendageal Route This route is considered as the shunt route which allows the drug to permeate through the sweat gland and across the hair follicle and associated sebaceous glands. This is a straightforward route in the form of channels allowing the drug molecules across the stratum corneum barrier. However, this route is considered insignificant because of its relatively small area equivalent to approximately 0.1% of the total skin area.

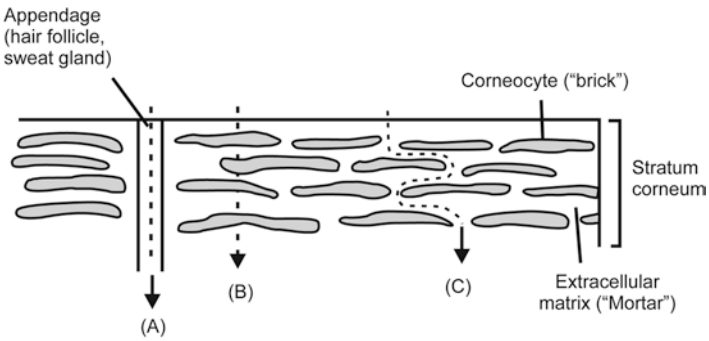

Fig. 8.2 Possible micro routes of drug permeation through human skin. (**a**) Appendageal route or shunt route, (**b**) transcellular route, (**c**) intracellular route. (Reprinted/adapted by permission from Springer Nature: Springer, Berlin, Heidelberg (Skin Deep: The Basics of Human Skin Structure and Drug Penetration), Ng, K.W. and Lau, W.M., Copyright (2015))

Transcellular Route The stratum corneum is the main skin barrier which is made up of keratinocytes or sometimes called corneocytes. When drug delivery is applied on the skin to administer the drug transdermally, it passes through the corneocytes consisting of hydrated keratin and thus generates the hydrophilic pathway. The lipids in the stratum corneum surround the corneocytes. Therefore, a process of partitioning and diffusion steps takes place while passing of drug through the cell matrix. It is the most common route for drugs to cross the skin barrier. The highly hydrated keratin is suitable pathway for the hydrophilic drugs.

Intercellular Route The corneocytes cells are surrounded by the lipid bilayers. The drugs diffuse through the lipid bilayers and find the path surrounding corneocytes reaching to the dermis. This is the most widely used pathway for the lipid-soluble drugs.

The permeation pathways of drug through skin suggest directions for the development of new approaches enhancing permeation of drug molecules through the skin.

The drug which is to cross the skin must have certain physicochemical characteristics required to facilitate the permeation through the skin and reach systemic circulation. The rate of permeation of drug through the skin is given by

$$\mathrm{d}q/\mathrm{d}t = P\mathrm{s}\left(x_{\mathrm{d}} - x_{\mathrm{r}}\right) \tag{8.1}$$

where

x_{d} = concentration of a skin penetrant (drug molecule) in the donor phase (stratum corneum)
x_{r} = concentration of penetrant in the receptor phase (systemic circulation)
$P\mathrm{s}$ = overall permeability coefficient of the skin

The overall permeability coefficient is defined as

$$P\mathrm{s} = K_{\mathrm{s}}.D_{\mathrm{ss}} / h_{\mathrm{s}} \tag{8.2}$$

where

K_{s} = the partition coefficient of the penetrant
D_{ss} = the apparent diffusivity of penetrant
h_{s} = the thickness of the skin

Thus, permeability coefficient ($P\mathrm{s}$) may be constant, if K_{s}, D_{ss}, and h_{s} are constant under a specific set of circumstances. A constant rate of drug permeation is achieved if $x_{\mathrm{d}} >> x_{\mathrm{r}}$; then Eq. 8.1 may be reduced to

$$\mathrm{d}q/\mathrm{d}t = P\mathrm{s}.x_{\mathrm{d}} \tag{8.3}$$

The skin restricts the diffusion of penetrant to penetrate transdermally. Let us consider the total diffusional resistance is (R_{skin}) which is given by Chien as

$$R_{\mathrm{skin}} = R_{\mathrm{sc}} + R_{\mathrm{e}} + R_{\mathrm{pd}} \tag{8.4}$$

where

R_{skin} = the total diffusional resistance
R_{sc} = the diffusional resistance by stratum corneum
R_{e} = the diffusional resistance by epidermis
R_{pd} = the diffusional resistance by papillary layer of the dermis

In percutaneous absorption, the significant rate-limiting factor is the resistance due to the skin barrier; the stratum corneum [7]. Total flux of matter across the membrane is the sum of the fluxes of each route configured in parallel to one another and is expressed by

$$J = A\left(f_1 \;\; P_1 + f_2 \;\; P_2 + \ldots f_n \;\; P_n \right)\Delta_{\mathrm{c}} \tag{8.5}$$

where

J = the diffusional flux
A = cross-sectional area
$f_1 \;\; P_1 + f_2 \;\; P_2 + \cdots f_n \;\; P_n$ = the overall permeability coefficient
Δ_{c} = the concentration drop

The permeation of the drug molecules through the skin must possess certain characteristics to initiate passive diffusion mode of transport through transepidermal pathway at steady state or through transappendageal pathway at initial non-steady state. Researchers must consider various physicochemical desirable attributes of the drug molecules as well as drug delivery systems for the better clinically required percutaneous absorption [8]. Such attributes are briefly discussed as under.

8.3.1 Physicochemical Characteristics of the Drug Molecule

The selection of drug candidate for TDDS is based on three important physicochemical parameters such as partition coefficient, pH, and the drug concentration apart from molecular weight and melting point [9–11] and is dealt herewith as follows:

(i) *Partition coefficient*: This attribute is the measure of how hydrophilic or lipophilic a drug or penetrant is. It is useful to estimate distribution of drug or penetrant within the body. Lipophilic drugs with high octanol/water partition coefficient are preferentially distributed to lipophilic compartments such as

lipid bilayers cells, while hydrophilic drugs preferentially are found in hydrophilic compartments such as blood serum. Even though drugs which are soluble in oil and water are absorbed through the skin, but eventually their transdermal permeability is dependent on the value of the partition coefficient. Generally, the required partition coefficient for better transdermal permeability is between 1 and 4.

(ii) *pH conditions*: pH of the drug solution is an important criterion to be considered since high variation either toward higher or lower side can be destructive to the skin. Secondly, the ratio of changed and unchanged drug species can be altered due to the influence of change in pH which ultimately affects their transdermal permeability.

(iii) *Drug concentration*: It is an important factor affecting the percutaneous absorption. The amount of drug percutaneous absorption per unit of surface area per unit time interval increases with the increase in the concentration of the drug in TDDS (Eq. 8.3). When the drug concentration is higher than its solubility, the excess drug turns to act as a reservoir to maintain a constant drug concentration for a prolonged period of time.

8.3.2 Physicochemical Characteristics of Drug Delivery System

Drug delivery system contains variety of ingredients which are important to transform the dosage form to a true delivery system providing blood plasma level of drug in a required therapeutic window (i.e., above the minimum effective concentration but below the level at which side effects become apparent) for the prolonged period of time.

Thus, along with the physicochemical characteristics of drug, physicochemical characteristics of components of drug delivery system are significantly important to develop a good formulation with desired physical, chemical, and biological compatibility in order to provide better patient compliance.

Formulation scientists must consider the following physicochemical characteristics which may contribute to alter the release rate mechanism of drug from the delivery system:

(i) *Drug solubility in vehicle*: Solubility of drug plays an important role in deciding the release rate from the delivery system. Greater attraction of drug toward the skin will leave the vehicle in favor of the skin. The effective percutaneous absorption is initiated by drugs having solubility in both lipid and water. Such drugs are supposed to be the desirable candidate for transdermal drug delivery systems. Other important factors associated to this attribute are whether drug molecule is in dissolved or suspended form, interfacial partition coefficient of drug, and the pH of the vehicle. Drugs in the unionized form have higher lipid solubility; as a result, they penetrate easily through the skin barrier. Nonpolar drugs having high lipid solubility tend to cross the cell barrier through lipid-rich

Table 8.1 Polymers utilized for TDDS

Natural polymers	Synthetic elastomers	Synthetic polymers
Cellulose derivative, zein, gelatin, waxes. Protein and their derivatives, natural rubber, starch, chitosan, etc.	Polybutadiene, hydrin rubber, polysiloxane, silicon rubber, nitrile, acrylonitrile, butyl rubber, styrene butadiene rubber, neoprene, etc.	Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyurea, polyvinylpyrrolidone, polymehtyl methacrylate, epoxy, ethyl cellulose, hydroxypropyl cellulose, polyamide, etc.

Reprinted from Journal of Controlled Release, 29, Sugibayashi, K. and Morimoto, Y., Polymers for transdermal drug delivery systems, 177–85, Copyright (1994), with permission from Elsevier

area (intercellular route), whereas the polar drugs tend to cross between cells (transcellular route).

(ii) *Components and their composition*: Various components and their ratio present in the system affects the rate of release of the drug from the delivery system. The formulators must take advantage of the capability of composition of the components incorporated in delivery system which can increase the permeability of the stratum corneum by means of hydration and affinity toward skin lipids.

Polymers used must have compromised ratio of molecular weight, glass transition temperature, and chemical functionality to control the release rate of the drug from the delivery systems [2]. In addition to these, polymers should also be stable, nonreactive, and nontoxic. An important criterion in the formulation of TDDS is the drug/polymer ratio which can affect the mechanical properties of the polymers. Polymers utilized for TDDS may be natural, synthetic elastomers, or synthetic polymers which are shown in Table 8.1 [2].

Even after having complete knowledge of mechanisms of drug permeation through the skin, formulators or product development scientists must realize that transdermal route of drug absorption is not suitable for all drugs. Few drugs (Table 8.2) having certain desirable attributes listed below are complying to deliver drug by passive diffusion mechanism through the skin by one or combined transdermal permeation mechanisms.

Thus, in order to exploit transdermal route of drug administration to the blood system with enormous advantages over limitations of conventional dosage forms such as ups and downs (peaks and troughs) in blood plasma level of drug, first-pass metabolism, etc., scientists must do significant efforts suggesting novel techniques in order to find possible ways to enhance transdermal penetration of large number of drugs.

8.4 Desirable Drug Attributes for Transdermal Permeation

The selection of the drug attributes for TDDS is one of the key challenges to obtain a product which can provide slow and controlled rate without varying the plasma drug concentration significantly. The first sustained release transdermal patch was

Table 8.2 FDA-approved drugs delivered by passive diffusion for transdermal patch [12]

Year	Drug	Indication
1979	Scopolamine	Motion sickness
1984	Clonidine	Hypertension
1986	Estradiol	Menopausal symptoms
1990	Fentanyl	Chronic pain
1991	Nicotine	Smoking cessation
1993	Testosterone	Testosterone deficiency
1996	Nitroglycerin	Angina pectoris
1998	Estradiol/norethindrone	Menopausal symptoms
1999	Lidocaine	Postherpetic neuralgia pain
2001	Ethinyl estradiol/norelgestromin	Contraception
2003	Estradiol/levonorgestrel	Menopausal symptoms
2003	Oxybutynin	Overactive bladder
2006	Methylphenidate	(ADHD) and narcolepsy
2006	Selegiline	Depression
2007	Diclofenac epolamine	Acute pain
2007	Rivastigmine	Dementia
2008	Granisetron	Chemo-induced emesis
2009	Capsaicin	Neuropathy pain
2010	Buprenorphine	Chronic pain
2012	Rotigotine	Parkinson's disease

Some more transdermal patches were approved by FDA which deliver the drugs by external iontophoresis pressure or heat assistant system instead of passive diffusion. Such products will be dealt in further section of this chapter

approved for delivering scopolamine for 3 days in 1979 for the treatment of motion sickness [13]. Few drugs delivered transdermally to systemic circulation by passive diffusion mechanism have been approved by US Food and Drug Administration (Table 8.2). Indeed, a very small number of drugs for the transdermal drug delivery system are available for the dual facts of achieving the desired pharmacological activity and the appropriate physicochemical characteristics of the drug molecules to enable transdermal permeation to the level of their therapeutic index [14, 15].

The drug molecules capable of penetrating the stratum corneum through the passive diffusion require low molecular weight (< 500 Da) and the partition coefficient (log P) equal to between 1 and 4 which provides balanced lipophilicity. Very high partition coefficient may inhibit drug clearance from the skin and increase drug retention. The solubility of drugs in oil and water should be balanced to achieve the high concentration gradient increasing the diffusion force across the skin because drug has to cross both the phases: the lipophilic stratum corneum and the aqueous phase of central compartment of systemic circulation [15, 16]. Another important characteristic which is very important to predict the approximate solubility of the drug is the melting point. Melting point of the drug selected for the TDDS should be low (<200 °C) which provides the approximate solubility of the drug candidate selected for TDDS [17–19]. However, all drug molecules do not possess such desired attributes which are required for the passive penetration through the skin

and make the TDDS limited for few drug molecules. This situation gave a great opportunity to the researchers to work on the various transdermal techniques to modify the nature of barrier stratum corneum which may enhance the penetration of drug molecules across the skin [14, 16, 20].

Extensive research work was initiated in research institutes and industries to allow the drug molecules to permeate easily across the "dead layer of tissues," i.e., the stratum corneum which has the ability to prevent the drug molecules and other foreign compound [10, 21]. As a result, many chemical and physical approaches have been designed and invented to enhance the drug permeability through the skin. As a result many drugs have been administered transdermally with significant drug plasma concentration thereby considering TDDS a well-accepted delivery system with improved patient compliance [22, 23].

8.5 Emerging Technologies Augmenting Transdermal Permeation of Drugs with Undesirable Attributes

Transdermal drug delivery systems are most convenient to deliver drug across the skin provided it manages all the hurdles which play roles in restricting the drug to transfer through the stratum corneum. Drugs which do not fit in the criteria of TDDS may require certain additional approaches for augmenting drug transport through the skin. Some contemporary approaches like passive/chemical or active/physical have been devised to modify the nature of the stratum corneum for enhancing the drug transport.

8.5.1 Passive Methodologies

Passive methodologies which can influence the penetration behavior of drug and vehicle through the skin may be summarized [24, 25] as follows.

8.5.1.1 Formulation Optimization

Drugs incorporated in vesicle-type formulation like liposomes, niosomes, or micro/nano emulsions can easily be penetrated through the skin. Drugs which do not have the desirable attributes of TDDS can be transported through the skin by loading them into such modified vesicles or micro/nano emulsions dispersed in suitable gel vehicles which promote the skin penetration by virtue of the advantages which can cross the skin barrier by various possible mechanisms [26].

8.5.1.2 Chemical Penetration Enhancers

Certain chemicals like alcohols, sulfoxides, azones, pyrrolidones, essential oils, terpenes and terpenoids, fatty acids, and urea [27] are reported to enhance drug penetration across the skin by increasing drug partitioning significantly so as to breach the barrier domain of the stratum corneum without adversely affecting the skin [3]. Such chemical enhancers are capable to enhance the skin permeability of drug by

several mechanisms of action like decrease in the viscosity of stratum corneum lipid bilayers, protein-protein intercellular interaction, intercellular lipid disruption, significant increase in the drug's thermodynamic activity, and hydration of the stratum corneum [3, 27]. The limitations of penetration enhancers are poor efficacy and safety. The selection of penetration enhancers should be done considering all other parameters like interaction with the drug and other ingredients, skin compatibility, and efficacy to increase the transport across the skin. Penetration enhancers must possess such characteristics in order to avoid skin disorders including local inflammation, erythema, swelling, and dermatitis [28]. Passive methods of increasing skin penetration are advantageous, but the only disadvantage is the delayed onset of action because of the excessive time required between the application and the drug reaching to the systemic circulation [29].

8.5.2 Active Methodologies

To overcome limitations of passive methods, TDDS developers introduced active methods to use the external energy to push the drug across the skin by the driving force generated or damaging the stratum corneum for the rapid skin penetration. Such active methods include ultrasound, electrically assisted methods (may be electroporation and iontophoresis), some devices based on injection velocity, methods based on thermal application (may be lasers and radiofrequency heating), and most innovative technologies such as microneedle (MN) arrays and tape stripping [29–33].

Based on these active methodologies, devices were developed for the rapid transport of drugs through the skin. Such technologies have been exploited for the development of TDDS. They are described in detail below.

8.5.2.1 Ultrasound Devices

Fellinger and Schmidt in 1950 utilized sonophoresis in combination with hydrocortisone ointment for the successful treatment of polyarthritis [34]. This concept of transporting drugs through the skin with the assistance of sound waves picked up and worked out to develop such ultrasound devices. Ultrasound waves at frequencies of 20 kHz–16 MHz sufficiently reduce the resistance of the skin and hence improve the transdermal movement of drug molecules [22, 31]. Thus, ultrasound has turned to be the effective way of delivering different categories of drugs which do not have the normal characteristics of drugs suitable for TDDS. Although, the reason for increasing the skin penetration using ultrasound waves is not well known [30]; it is believed that ultrasound waves due to perturbation at frequencies of 20 kHz–16 MHz increase the skin permeability supported by the thermal and cavitation effects caused by collapse and acoustic streaming [22]. The thermal effect on the skin under the effect of ultrasound waves is brought by the absorption of the sound waves with a frequency greater than the upper limit of the human hearing range. Extensive research work has been carried out, and it is believed that

cavitation is the main mechanism in the enhancement of penetration of drug molecules through the skin due to the ultrasound treatment along with the drug delivery [30].

However, number of challenges is yet to overcome before reaching with ultrasound devices to the community. After a thorough assessment of the device, it has been identified that no user-friendly devices are available. The use of devices is little cumbersome. Patients do not find it easy and comfortable to use. There is no indication for the duration of treatment required which is an important criterion for the patients. The significant problem with such devices is the adverse effects of ultrasound approaches. Minor skin reaction in dogs has been observed with low-intensity ultrasound. Similarly, second-degree burns have been reported with high-intensity ultrasound waves [35, 36]. Thus, researchers must work upon these challenges and shortcomings of ultrasound devices to gain the patient acceptance.

8.5.2.2 Electrical Techniques

There are two important methodologies based on electrically facilitated systems which promote the drug transfer through the skin. Such technologies are electroporation and iontophoresis [31, 37].

8.5.2.2.1 Electroporation

This method is developed for improving the drug penetration through the skin [38]. The skin permeability is enhanced due to the aqueous pores developed into the lipid bilayers of the stratum corneum by temporarily exposure of cells to high intensities of electric pulses. This has resulted in improving the rate of diffusion of drugs across the skin [22, 38, 39]. *In this method*, electric pulse of high voltage (50–500 V) for short period of time (only for one second) showed increase in diffusion rate of drugs with small molecular weights ranging from, e.g., fentanyl, timolol [40, 41], or calcein [42] to high molecular weight (up to 40 kDa) drug molecules such as luteinizing hormone-releasing hormone (LHRH), calcitonin, heparin, or fluorescein isothiocyanate-dextran (FITC-dextran) [43–47].

This methodology has limitations of delivering precise drug dose, cell damage or death with high fields, and possible damage to heat labile drugs, e.g., proteins [39, 48].

8.5.2.2.2 Iontophoresis

This method transports ions (drug) into the skin by the development of potential gradient through electrostatic effects by using physiologically acceptable electric current (0.1–1.0 mA/cm^2) [22, 45, 49, 50]. It is a painless, sterile, and noninvasive technique. The basic principle of iontophoretic drug delivery is that "like charges" repel "like charge" so the drug ions are repelled or pushed into the underlying tissues. When direct current (DC) is applied to an ionized drug solution, the ions that have the same charge as the electrode are repelled by the electrode and are delivered through the skin. Iontophoresis is the technique by which medication is delivered at a constant rate. The advantage of this method is to obtain effective plasma concentration within a therapeutic index for an extended period of time. USFDA

Table 8.3 FDA-approved drugs delivered by iontophoresis and heat assistance system for transdermal patch [51]

Year	Drug	Indication	Mechanism/technology
1995	Lidocaine/epinephrine	Local dermal analgesia	Iontophoresis
2004	Lidocaine	Local dermal anesthesia	Sonophoresis
2005	Lidocaine/tetracaine	Local dermal analgesia	Heat assistant system
2006	Fentanyl	Acute postoperative pain	Iontophoresis
2013	Sumatriptan	Migraine	Iontophoresis

approved few TDDS drugs delivered by iontophoresis and heat assistance systems are depicted in Table 8.3.

Iontophoresis is the method by which charged drug molecules can be administered through the skin which is not possible in normal course. This technique modifies the properties of the skin and allows administering charged ions. It increases the absorption rate when compared with passive skin application. Many factors affecting the rate at which an ion may be delivered are (a) ions concentration, (b) pH of solution, (c) molecular weight of solute (molecular size), (d) current density, and (e) treatment time [50, 52–54].

Iontophoresis is supposed to be a good technique of delivering medication transdermally because it has several advantages relative to oral medication: (a) drug can be concentrated at a specific area which may be utilized for targeting the drug at a particular site, (b) drug avoids the absorption through the GI tract, and (c) drug has safe administration than the parenteral dosage forms.

In iontophoresis methodology, there are two electrodes: (a) cathode and (b) anode. Cathode bears highest concentration of electron with negative charge. It repels negatively charged ions and attracts the positive ions. On the other hand, anode bears low concentration of electrons with positive change. The anode repels positively charged ions and attracts negatively charged ions. Thus, the movement of positively charged ions into tissues takes place from anode and negatively charged ions from the cathode. The force required for moving ions through the tissues depends on strength of the electrical field and the electrical impedance of tissues to current flow. The strength of electrical field is determined by the current density. The difference in current density between active electrode (the one being used to drive the ion into the tissue) and inactive electrode establishes a potential gradient difference which triggers ion migration within the electrical field. The quantum of the current density can be optimized by manipulating current intensity and electrode size (increased size of electrode will decrease current density under that electrode). Ion movement in the areas of thick skin and fat layer requires high current intensities which may produce the burn around the electrode. The main route of ion movement is via sweat ducts penetrating the ions across the skin and decreasing the electrical impedance which significantly facilitates the flow of direct current as well as ions.

Thus, in order to optimize the iontophoresis method for transferring drug ions through the skin, formulators must understand few important factors: (a) quantity of ions transferred into tissues is directly proportional to the current density at the

active electrode, (b) duration of current flow, and (c) the concentration of ions in solution. Hence, current intensity is one of the important criterions for this methodology. It has been reported that effective driving force is obtained by low amperage than the currents with higher intensities which reduce the effective penetration into the tissues. The iontophoretic current must be adequately high to provide a sufficient flux to propel the ions through the skin without giving irritation. It has been reported that the maximum physiological acceptable iontophoretic current is 5 mA/cm^2 which can safely be used in enhancing skin penetration of drug ions by iontophoresis technique [55, 56].

The polarization effect on the skin is initiated due to continuous direct current (DC) and hence can decrease the drug flux [54]. In order to overcome this problem, pulsed current has been used [57].

Most common electrodes that are used in iontophoresis technique are made up of aluminum foil, platinum, and silver/silver chloride electrodes [53]. Out of these three electrodes, Ag/Agcl is the most preferred one since it does not allow the changes in pH. Other desirable characteristics of the electrode materials used for iontophoretic delivery should be safe to the body and flexible to have an intensive contact with the body surface [53].

The iontophoretic delivery has limitation to deliver the drug molecules successfully those having molecular weight less than 12.0 kDa [55]. In order to deliver molecules more than 12.0 kDa, an alternate method is to be developed to cross the barrier of the stratum corneum in order to speed the passage of drug through the skin.

The literature reported that a small protein cytochrome c (mol. Wt. 1204 kDa) was delivered noninvasively across intact skin [50, 58]. Ribonuclease A with isoelectric point of 8.64 (mol. Wt. 13.6 kDa) was successfully delivered across porcine and human skin [59]. Recently, it has been found that the biologically active human basic fibroblast growth factor (hbFGF having mol. Wt. 17.4 kDa) was transdermally delivered by iontophoresis technique [60, 61].

Recently iontophoresis technique has been utilized for diagnostic purpose, e. g., diagnosing cystic fibrosis [62] and monitoring blood glucose level [63]. The main advantage of iontophoresis technique in diagnostic application is to boost the manufacturing of diagnostic medical devices because it does not require mechanical penetration or disruption of the skin [17, 64].

8.5.2.3 Velocity Base Devices

These devices deliver the drugs either in powder form or liquid form through the skin with a high-speed velocity jet with velocities ranging from 100 to 200 m/s using a power of compressed gas or a spring [65]. This mode of administering drug is 50 years old when drugs like anesthetics, antibiotics, and vaccines were administered parenterally [3]. The innovative needle-free device called jet injector is capable of delivering controlled dose of medication electronically resulting in administering dose precisely with minimum pain [29, 66]. There are two types of injectors available: (a) liquid jet injectors and (b) powder jet injectors.

Liquid jet injector is a device having orifice ranging from 50 to 360 μm. This orifice is smaller than the outer diameter of standard hypodermic needle which is measured to 810 μm [50, 67, 68]. The injector propels the drug through the skin consisting of various layers like (a) intradermal (id), (b) subcutaneous (sc), or (c) intramuscular (im), by changing the jet velocity and orifice diameter [50]. Thus, according to the target delivery of drug, a formulator must optimize the jet velocity and the orifice diameter. The additional advantages of such devices are the avoidance of needle disposal and needle stick injuries. However, there are fair chances of cross contamination due to splash back of interstitial liquid from the skin. This is the reason why multi-use nozzle jet injectors have been terminated, and such devices are used to deliver the drug to the same individual, e.g., Tjet® device, which delivers somatropin (human growth hormones (hGH, mol. Wt. 22.124 kDa).

Solid jet injectors consist of a power source of compressed gas, a compartment for loading the drug, and nozzle to administer solid particles piercing through the skin [69]. Since the drug is delivered in solid form, it improves the stability of the formulation and avoidance of cold storage resulting in easy transportation and hence makes the product more economic. The powder may be formulated in the form of nano- or microparticles that contain active drug or lyophilized drug with excellent stability and bioavailability. The important parameters for the development of the solid jet injectors are particle size, its density, and impact velocity of compressed gas [3]. Although the popularity of such devices is very less due to intermittent pain and bruising caused to patient during injection [65], still their benefits cannot be ignored because they have advantage of fast transdermal delivery of drug molecules although having more than 20 kDa molecular weight. Secondly, it overcomes the challenges of disease transmission through reuse of the needles in the developing world. Thus, researchers have tremendous scope of developing the needle-free injector to deliver drugs more efficiently, safely, and conveniently with minimum associated cost.

8.5.2.4 Thermal Methods (Laser and Radiofrequency Heating)

These methods are used to remove the main skin barrier, i.e., the stratum corneum, by heating and delivering the drugs systemically through the skin without affecting the deeper tissues [32, 70]. Thermal ablation is carried out using either laser [71], radiofrequency, or electrical heating elements [32, 72]. The high temperature is needed to ablate the skin barrier, i.e., the stratum corneum. The precaution must be taken to check any damage to underlined epidermis with high temperature. This can be done by short thermal exposure resulting in high-temperature gradient across the stratum corneum with extremely hot skin surface with nonsignificant increase in epidermis temperature [70]. This technique of thermal ablation is currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone, and influenza vaccine [73].

8.5.2.4.1 Thermal Ablation by Laser

Laser technology is the method by which selective removal of the stratum corneum is possible without giving any harmful effect to the deeper tissues resulting in

enhancing the delivery of lipophilic and hydrophilic drugs through the skin layer [45, 74, 75]. Laser ablates the stratum corneum due to deposition of optical energy, which evaporates the intact water and forms the microchannels in the skin [76]. The whole mechanism of ablation of the stratum corneum depends on the various factors like (a) wavelength, (b) pulse length, (c) tissue thickness, (d) pulse energy, (e) time absorption coefficient, (f) pulse number, (g) duration of laser exposure, and (h) pulse repetition rate [29, 45, 75]. Formulation developers have the scope of optimizing the quantum of these factors to control the degree of barrier disruption with respect to optimum transfer of different macromolecules and vaccines through the skin.

8.5.2.4.2 Thermal Ablation by Radiofrequency (RF)

This technique is the thermal ablation of the skin due to the application of high-frequency alternating current (~100–500 kHz) to penetrate macromolecules through the skin which create microscopic pathways in the stratum corneum allowing the high molecular weight drug molecules (> 500 Da) to permeate through the skin barrier [32, 70]. The ablation in cells occurs due to ionic vibrations generated by the high-frequency alternating current resulting in drug transport across the skin [77].

8.5.2.5 Mechanical Methods to Mediate Skin Permeation

The penetration of macromolecules through the skin can be enhanced by the application of mechanical devices or approaches such as the use of tape stripping and microneedle array [78, 79]. These novel technologies will be described further below.

8.5.2.5.1 Tape Stripping

This is the method of removing the stratum corneum layer by repeated application of adhesive tape [80]. Some key factors responsible for the removal of amount of the stratum corneum are (a) thickness of the stratum corneum, (b) patient's age, (c) composition and amount of lipid on the site, (e) transepidermal water loss, and (f) pH of the skin. Other physical factors also considered to augment the removal of the stratum corneum are (a) force of removal of the tape from the skin and (b) duration of pressure on the skin. This technique is used to quantify drug penetration through the skin [81].

8.5.2.5.2 Microneedle (MN) Arrays

Hypodermic and subcutaneous needles have been used since long to deliver the drugs through the skin with invasive technology which has the disadvantage of pain and issues of a medical person requirement for injection of drug molecules. This has resulted in the patients' non-compliance [15, 78, 79, 82]. Microneedle arrays have come up as a minimally invasive drug delivery, a novel technology to deliver drugs either of low molecular weight (<500 Da) or high molecular weight (>500 Da). Intensive research has been conducted by researchers and other academic institutions to develop devices of minimally invasive microneedles [79, 83] capable of delivering drug systemically through the skin with additional advantages of microneedle technologies which make them popular as far as patient compliance is

concerned. They do not cause bleeding [84], eliminate the problem of transdermal dosing variability of drugs [27, 85], have minimum introduction of pathogens [51, 71], have potential for self-administration [13], and protect against accidental needlestick injuries [79, 82].

The design of microneedle devices have been successfully developed in which multiple microscopic projections are assembled on one side of the base or patch ranging from 25 to 2000 μm in height [82], 50 to 250 μm in base width, and 1 to 25 μm in tip diameter [86, 87]. The schematic diagram of microneedle device is shown in Fig. 8.3.

The microneedle array should be so designed in order to enhance the penetration of therapeutic molecules into the skin to avoid nerve contact when inserted into skin layers [21]. The microneedle array penetrates the drug molecules through the skin by the formation of aqueous channels across the skin which resulted in enhancing the flux and thereby skin permeability of drug molecules ranging from small hydrophilic molecules such as alendronate [88] to macromolecules like heparin [89], insulin [90], and vaccines [91]. First two MN-based devices which have been commercially launched are Intanzi® and MicronJet [92] based on metal and silicon MN, respectively. Intanzi® was developed and licensed by Sanofi Pasteur MSD Ltd, for the delivery of influenza vaccine through the skin, while MicronJet is a single use MN-based device developed and licensed by NanoPass, for intradermal delivery of vaccine and drugs.

Recently, microneedle array is considered to be the best choice for transdermal drug delivery systems which provides the opportunity for the researchers and the

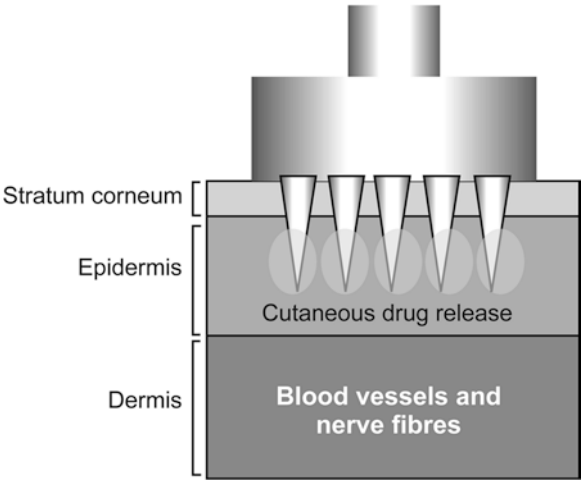

Fig. 8.3 Schematic diagram of microneedle array showing penetration of stratum corneum delivering drugs to the underlying viable epidermis, without reaching the blood vessels and nerve endings located in the dermis. (Reprinted from European Journal of Pharmaceutical Sciences, 50, Tuan-Mahmood TM et al., Microneedles for intradermal and transdermal drug delivery, 623–37, Copyright (2013), with permission from Elsevier)

formulators to deliver macromolecules transdermally with high molecular weight and hydrophilicity which prototype transdermal patches fail because they can deliver drugs only with specific physicochemical properties (Mol. Wt. <500 Da), adequate lipophilicity, and low melting point.

An extensive research work has been done to design various categories of microneedles like hollow, solid, dissolving, coated, and hydrogel forming made up of silicon, metal, or polymers depending on the application [16]. Although with various challenges coming across with microneedles including irritation, microbial contamination, and delivery of therapeutically relevant concentration of drugs and the type of biomaterials used to manufacture microneedles which do not require mechanical strength and capacity to load the required dose [93], microneedles have the potential to overcome all the physical, biological, and manufacturing problems in the near future to deliver all drug molecules transdermally providing immense patient compliance because a number of research institutes, pharmaceutical industries, and academic institutes are actively involved in their fabrication and evaluation. Scientist and formulators are looking forward to exploit the favorable features of MNs in cosmetology to treat acne, pigmentation, and scar and wrinkle as well as for skin tone improvement [94].

8.6 Patents

TDDS has a long history of its development as one of the important noninvasive delivery systems providing controlled release of drug through the skin into systemic circulation. Extensive research work has been performed in academic and pharmaceutical research institutes which developed many products to deliver all types of drugs whether with low molecular or high molecular weight or for the drugs which are not suitable for oral drug delivery. Many patents have been granted by the US Patent and Trademark Office. A list of some patents with their title is given in the Table 8.4, which would be a good resource for the researchers to work further for the better product development and patient compliance in this advance area of novel drug delivery systems.

8.7 Current Scenario of Transdermal Delivery Systems

Transdermal drug delivery system (TDDS) is one of the most acceptable novel dosage forms as far as patient compliance is concerned. In 1981, Transderm Scop® was approved and marketed as the most acceptable transdermal patch based on passive delivery methodology providing sustained blood levels with minimal drug blood plasma variation via non-oral, non-parenteral route of delivery. Catapres-TTS® is the first transdermal patch launched in 1984, which delivers clonidine for 7 days to hypertensive patients who otherwise were taking one tablet twice a day [115]. Such delivery systems become the boon for the chronic hypertensive patients. With a continuous development in this direction, formulators developed a postsurgical pain

Table 8.4 List of some patents

Patent No.	Assignee	Title	References
US4201211A	Alza Corp.	Therapeutic system for administering clonidine transdermally	Chandrasekaran et al. [95]
US4559222A	Alza Corp.	Matrix composition for transdermal therapeutic system	Enscore and Gale [96]
US4814168A	Noven Pharmaceuticals Inc.	Transdermal multi-polymer drug delivery system	Sablotsky, Questel [97]
US4994267A	Noven Pharmaceuticals Inc.	Transdermal acrylic multi-polymer drug delivery system	Sablotsky [98]
US5164416A	LINTEC corp.	Transdermal therapeutic formulation containing a limonene	Nagai, Takayama [99]
US5300291A	Noven Pharmaceuticals Inc.	Method and device for the release of drugs to the skin	Sablotsky and Gentile [100]
DK0474647T3	Noven Pharma	A method and device for the release of drugs to the skin	Sablotsky and Gentile [101]
US 09/965,610	3M Innovative Properties	Composition for the transdermal delivery of fentanyl	Cantor, Ocheltree [102]
US6531149B1	Lts Lohmann Therapie-Systeme Ag	Estradiol-containing patch for transdermal application of hormones	Kirstgen and Meconi [103]
US 7,029,694	Watson Pharmaceuticals, Inc.	Compositions and methods for transdermal oxybutynin therapy	Kirstgen and Meconi [103]
US11/128,636	Alza Corp	Transdermal administration of fentanyl and analogs thereof	Venkatraman, Li [104]
US8524272B2	Mylan Technologies, Inc.	Transdermal patch incorporating active agent migration barrier layer	Miller [105]
US8668925	Thomas Langguth	Transdermal delivery of hormones without the need of penetration enhancers	Langguth, Bracht [106]
US 11/361198	Cormier Michel J	Transdermal electrotransport drug delivery systems with reduced abuse potential	Cormier and Padmanabhan [107]
US 5096885	Genentech Inc.	Human growth hormone patch formulations	Pearlman and Oeswein [108]
US 11/987480	Akinori Hanatani	Stabilized donepezil-containing patch preparation	Hanatani, Sekiya [109]
US 15/389,599	Johnson & Johnson	Once-a-day replacement transdermal administration of fentanyl	Hwang and Gale [110]
US 12/354,422	Akorn, Inc.	Method of inducing topical anesthesia and transdermal patch	Alam, Reichel [111]

(continued)

Table 8.4 (continued)

Patent No.	Assignee	Title	References
US 5,843,472	Cygnus Inc.	Transdermal administration of tamsulosin	Ma, Audett [112]
US6953589B1	Alza Corp	Transdermal delivery of large agents	Trautman and Kim [113]
US10016451B2	Leland Stanford Junior University	Introduction of nucleic acid into skin cells by topical application	Khavari and Fan [114]

care transdermal patch in 1990, which is capable to provide sustained release opioid pain management for 3 days per application. Soon after this product, fentanyl transdermal patch was launched in 2004, which was the first generic transdermal patch [116]. Lidocaine transdermal patch, Lidoderm®, for topical pain treatment was launched in 1999 and gained maximum patient compliance reflected by its annual sales of over $1.1 billion by the end of 2010. Further, a transdermal patch of rivastigmine named Exelon® patch was launched in 2007 for the patients and their caregivers suffering from the dementia. This has a dual advantage of visible reminder to both patients and their caregivers and reduced dose frequency of once a day with minimum side effects of nausea and vomiting [117]. In addition to these, other transdermal patches include LidoSite™, an iontophoretic patch for dermal analgesia on intact skin; Synera®, a topical anesthetic patch that delivers transdermally lidocaine and tetracaine to numb intact skin in 20 minutes prior to minor needle procedure for pediatric patients; and Ionsys®, a transdermal patch of fentanyl launched in 2006, for better pain management. These patches were found to have potential lethal overdosing risk and henceforth suspended from the market by the European Medicine Agency [115].

Currently, many pharmaceutical companies launched various TDDS with variety of drugs including clonidine, estradiol, combination of estradiol and levonorgestrel, combination of estradiol and norethindrone, combination of ethinyl estradiol and norelgestromin, fentanyl, granisetron, methylphenidate, nicotine, nitroglycerin, oxybutynin, rivastigmine, scopolamine, selegiline, and testosterone [73].

Many drugs under the classification of TDDS had undergone required clinical trials (phase I to IV) and were permitted for various indications by US FDA. These drugs that were allowed to market by many pharmaceutical companies include scopolamine, nitroglycerine, clonidine, estradiol, fentanyl, nicotine, testosterone, lidocaine, epinephrine, norethindrone, ethinyl estradiol, norelgestromin, levonorgestrel, oxybutynin, lidocaine, tetracaine, methylphenidate, selegiline, rotigotine, and rivastigmine [73]. The success of these transdermal delivery systems of such drugs inclined many researchers and pharmaceutical industries to concentrate on intensive research to exploit the possible techniques of enhancement of skin penetration of macromolecules whether through the use of chemical enhancers, applying external driving force, or disrupting the stratum corneum in order to enhance penetration of large molecules to pass into the systemic circulation. All the three techniques have been studied and tried to develop TDDS for many macromolecules. According to

the literature [73], some important drugs are in the process of different clinical trial phases which include acyclovir (phase II), enterotoxin of *E. coli* (phase II), human growth hormone (phase I), insulin (phase I), ketoprofen (phase III), and parathyroid hormone (phase II).

Scientists have further worked on the type of the TDDS and evolved with transdermal metered sprays, for example; Evamist®, which deliver estradiol or the gel formulation such as AndroGel® delivering testosterone. These new development in the type of TDDS may become the counterpart of the patches because of the fact that they are highly effective, cost-efficient and found to be a good alternative to patch manufacturing for very potent drug molecules.

Pharmaceutical industries are engaged in developing TDDS of many generic drugs with enhanced safety, efficacy, and cost-effectiveness. However, development of TDDS with full clinical and safety programs according to the guidelines has increased the cost which may be the challenging factor for introducing and competing TDDS with other conventional dosage forms [118]. Considering the present scenario of TDDS, formulators should concentrate on transdermal active technologies using electrical, thermal, and mechanical approaches for administering drugs with high molecular weight involving iontophoresis, laser thermal ablation, radiofrequency thermal ablation, microneedle arrays, and tape stripping for achieving immediate release of drug in a less invasive manner through the intradermal route. These technologies have significant opportunities to administer all drug molecules especially vaccine delivery to the intradermal region of the skin; naturally rich in immune-responsive cells [119].

8.8 Conclusion and Future Directions

Transdermal drug delivery systems have become the most successful innovative research area providing opportunity to design most acceptable and noninvasive drug delivery system which will have high patient compliance.

Looking to the future scope, formulators are constantly working to design TDDS utilizing various promising passive and active strategies. Iontophoresis has significant scope in future to deliver the drug in a controlled manner because rate of drug delivery is proportional to the electric current. Electroporation and sonophoresis techniques can also be used with precaution for certain drugs. However, these techniques did not get much popularity as far as patient compliance is concerned because both techniques cause pain, local skin reaction and may cause structural modification of therapeutic entity. Henceforth, these techniques will have less potential and uncertain future to deliver drugs through the skin.

The most encouraging and seems to have better future as a transdermal drug delivery system are microneedle (MN) arrays, minimally invasive device bypassing the stratum corneum barrier and thus achieving drug plasma level through transdermal delivery. With new techniques of micro-fabrication, microneedle arrays are prepared by using silicon, metal, and polymers. The MN arrays are very popular among the patients because MN arrays are applied to the skin surface and pierce the

epidermis without feeling any pain, creating thin channels through which drugs diffuse to dermal microcirculation. MN arrays are long enough to penetrate to the dermis but are short and narrow enough to avoid stimulation of dermal nerves. Many macromolecules like oligonucleotides, desmopressin and human growth hormone, insulin DNA, and protein antigens have been successfully delivered by this mechanical approach bypassing the skin barrier and administering drug directly to dermis and finally to blood circulation. The literature and many patents filed reflect the promising future of MN arrays to administer the macromolecules possessing undesired attribute for transdermal drug delivery system.

To sum up, TDDS is not only an emerging field for the pharmaceutical companies but also for young researchers to focus their attention in its development. The comprehensive use of passive and active methodologies could be leveraged to deliver macromolecules, immunobiologicals, and any other drugs not suitable for oral use. The formulation developers should stay vigilant that the end products adhere to recent regulatory guidelines to assure safe and effective drug delivery system to improve patient compliance.

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Inhalation Drug Therapy: Emerging Trends in Nasal and Pulmonary Drug Delivery

9

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_9

Abstract

The success of drug therapy is highly dependent on route of administration, and oral route of administration is the most successful, popular, and patient friendly. However, the bioavailability of many drugs is less due to first-pass metabolism which paved a way for development of innovative drug formulations and routes of administration. Biologics and antineoplastic therapeutics are restricted to parenteral route only due to bioavailability issues in other routes of administration which often leads to off-target toxicities; therefore inhalational route for therapeutic delivery has been gaining attention recently to enhance bioavailability by taking advantage of rich blood supply of lungs. This route is used for delivering agents locally to the lungs during diseased states such as chronic obstructive pulmonary disease, asthma, or cystic fibrosis. It also acts as a portal to access blood and lymphatic systems. Nasal route has been explored since the beginning of human civilization, and Indian Ayurvedic system of medicine uses this route since long. Rapid onset of action of systemically acting products is an important advantage. The present chapter covers factors affecting absorption, drug repositioning strategies, characterization tests, and clinical trials of nasal as well as pulmonary therapeutics.

Keywords

Inhalation drug therapy · Dry powder inhaler · Intranasal drug delivery devices · Metered dose inhaler · Nasal and pulmonary drug delivery

9.1 Introduction

The advances in the molecular basis of diseases have opened enormous vistas for new medicines. However, de novo synthesis of new therapeutic molecules is not only an expensive but also a multifaceted, complex, and time-consuming process. New drug discovery profits are weighed down due to high attrition rates

encountered. Drug repositioning – as repurposing or reformulation – is fast becoming the new normal in the scenario. The advents in nanotechnology, genomics, proteomics, and excipients have driven the drug repositioning. Statistics reveal that around 30% of new drug approvals are either drugs repositioned for new indications or reformulated or new combinations. The lifecycle business of drugs gets a boost with the repositioning. The drug repositioning arena had deterred the manufacturers due to reasons like intellectual property rights issues and possibility of unravelling some serious adverse effects. Drug repositioning business offers very simple yet potent benefits of defense against generic and pipeline expansion.

The drugs which were originally demonstrated as safe but failed to show sufficient therapeutic activity for a particular indication may be harnessed for other indications where it competes with NCEs for drug efficacy rather than safety. When evaluated in economic terms, the cost of repositioning of drugs is starkly low as compared to new drug discovery. Some of the repositioned drugs have pleasantly surprised the markets with their newfound blockbuster status. Not only do repositioned drugs fetch huge investment returns but can be outlicensed also to ultimately improve the R&D productivity. Hence, drug repositioning may be hailed as one big milestone in lifecycle management strategies [1].

Drug repurposing is a broad field of drug redevelopment which encompasses four major strategies. It includes drug repositioning to find a new indication for a drug. Another strategy is reformulation wherein new formulations with better efficacy and/or fewer drawbacks are designed for the existing drugs. Exploring combination therapies is another good way of using old drug candidates to better use. Repositioning aided by reformulation is another realm where a new formulation is designed for a new indication of a candidate [2].

Reformulation is an attractive option in comparison to search for NME or new indications for an old drug. Change in pharmaceutical form or delivery route is often explored by drug repurposing companies. The advances in the formulation technology can also be harnessed for reformulating the existing drugs. Novel drug delivery systems help to optimize the delivery vectors' performance. Innovative excipient changes can also bring out a better formulation for existing drug. Sometimes drug release patterns are modified using formulation design to optimize the therapeutics.

9.2 Fate of Conventional Therapeutics and Search for Alternative Routes of Administration

The success of drug administration is highly dependent on route of administration. Oral drug delivery is by far the most successful, popular, and patient friendly. However, often the therapeutic goals are not achieved as desired due to several limitations already known. This propelled the innovation in drug formulations and routes of administration. Further, our increased knowledge of the intricacies of drug transport across tissues has driven the exploration of alternative modes of drug delivery to cater to our therapeutic goals. Point to consider here, these advances are attractive relative to the costs of new drug development. The advent of the twenty-first century saw numerous proteomic and genomic therapeutics entering the market

or in the final stages of clinical studies. These biologics or biologicals have been restricted to, more or less, the parenteral route of administration. The innovations in drug delivery have improved patient compliance to the therapeutic regimen, pharmacologic response, and addressed stability and safety issues of both conventional drugs and biologicals alike. With the growing need for optimization of therapy, a number of reports describing the "off-label" routes of administration are clearly a reflection of the clinicians' attempts for better, more reliable, and less painful methods of drug administration [3, 4].

9.3 Trends in Pulmonary Drug Delivery Systems:

9.3.1 Pulmonary Route: Forming Parts of Inhalational Drug Therapy

Pulmonary delivery refers to the delivery of therapeutic agents to the lungs. As evident from the site, this route is used for delivering agents locally to the lungs during diseased states such as chronic obstructive pulmonary disease, asthma, or cystic fibrosis. Further, delivery of agents via pulmonary route outweighs the risk to benefit ratio for therapeutic effect vs adverse effects. The need for local delivery is preferable and also arises from the fact that this approach is noninvasive. As systemically administered therapeutic agents need to be administered in higher amount for achieving therapeutic benefits in pulmonary ailments, local delivery may be advantageous, and it may lower the chances of adverse effects. Local delivery also leads to reduction in the dosing requirement [5]. However, there has been a shift in focus for delivery of systemic agents as well via pulmonary route for achieving therapeutic benefits for agents such as peptides, protein, genes, and certain other molecules that are labile to GIT, are poorly absorbed, have incomplete oral bioavailability, or show adverse effects. It also acts as a portal to access blood and lymphatic systems [6, 7].

An overview of the pulmonary system is presented over here for giving a quick outline of the delivery system requirement based on the morphological aspects. The two critical parameters that control the pattern of inhaled particle deposition in the pulmonary tract are particle size and inspiratory flow rate. The entrainment of the aerosolized particles in the lung is dependent on the breathing activity and should be carefully maneuvered to maximize alveolar deposition and subsequent absorption systemically. The size, shape, and density of the particles determine the aerodynamic diameter of the particles. The respiratory track can be divided into three principal regions, namely, nasopharyngeal region (NPR), trachea-bronchial region (TBR), and alveolar region (AR), and as shown in Fig. 9.1, it gets increasingly branched as one moves toward deep lung region. The size of particles is a key parameter that determines the deposition of particles in these three regions, and thus a careful consideration is to be given when designing a formulation intended for systemic delivery. Particles greater than 5μ penetrate till peripheral regions, while those in size range of 1–5 μ will bypass the bronchioles and enter the alveolar

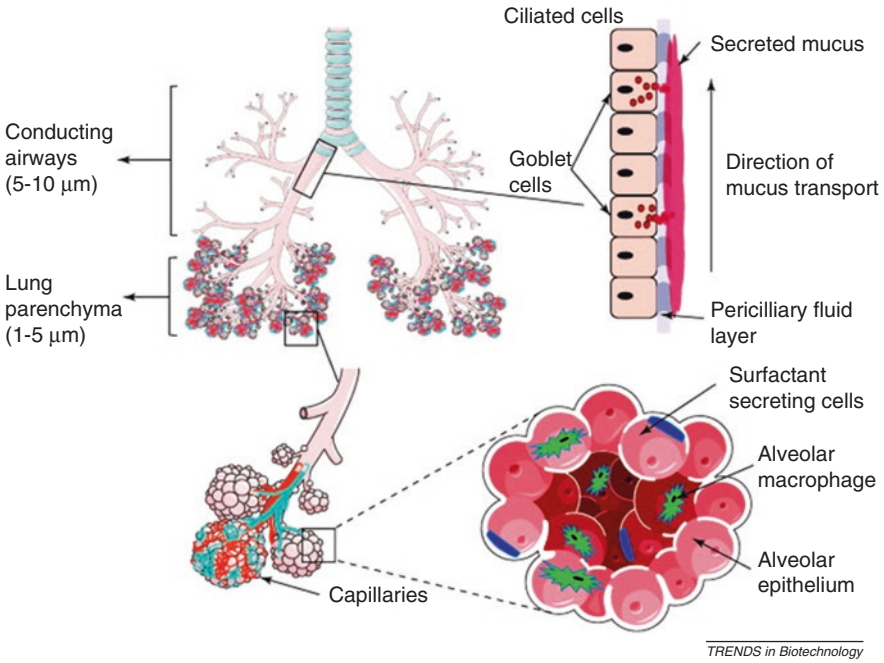

Fig. 9.1 Diagram of the lung and particle-size requirements based on intended deposition region in the respiratory tract. Images on the right are magnified, cartoon views of tissue structures of the conducting airways (i.e., trachea, bronchi, and bronchioles) and alveoli in the parenchyma region. The mucosal tissue of the conducting airways consists of ciliated epithelium and mucus-producing goblet cells which remove inhaled antigens through upward mucociliary clearance, with the help of secretory IgA produced by local plasma cells. Blind-ended alveolar sacs are lined by a specialized, thin-walled epithelium to aid gas exchange with the underlying capillaries, interspersed with surfactant-producing epithelial cells. Immunosuppressive alveolar macrophages and serum-derived antibodies provide a final line of protection against invading pathogens. A cellular and humoral immune response can be generated after interaction with innate immune receptors present on epithelial cells and tissue-resident dendritic cells. (Reproduced with permission from reference [9])

region. The particle size also determines the deposition mechanisms in the airways. A larger particle will be unable to change directions rapidly with the changing paths or bifurcations in tracheal region and will subsequently impact at upper airways due to inertial moment. The particle in this region also encounters higher air velocities than at bronchioles and alveolar region which may contribute to the higher impaction of deposited particles. The particle deposition resulting from the influence of gravity is sedimentation and becomes more and more important at bronchiolar and alveolar regions wherein the airstream velocity is relatively low. Brownian motion is displayed by particles with size less than 1μ, and such particles collide with airways after they get displaced randomly by bombardment with gas molecules. Such deposition behavior is directly proportional to particle size [8]. Additionally, mechanisms such as interception and electrostatic interactions also take part in deposition of particles in the lung.

9.3.2 Properties of Drug Suitable for Pulmonary Delivery

Only a few decades before, pulmonary drug delivery was not a big market. But times have changed, and this route of drug delivery has stormed the market in a big way. Pulmonary delivery of drugs is very attractive if the intention is to achieve local action within the respiratory tract. Not only local action, this route has been exploited for the systemic delivery as well. Drugs delivered through pulmonary route are absorbed mainly through passive diffusion and active endocytosis. Hence, molecules favoring these routes of passage like small nonionic ones with relatively high hydrophobicity are good candidate molecules. It has been observed that the absorption of lipophilic compounds increases as the partition coefficient increases (–3 to 2), while the absorption rate of hydrophilic compounds is inversely related to the molecular weight (range 60–75000 Da). The drugs delivered through airways are required to exhibit chemical and enzymatic stability as tracheolar pathways are potential sites for degradation. Presence of transporters like PEPT2 and efflux transporters like MDR1 and MRP1 modifies the uptake profiles of substrate drugs. If the intention is local action, then molecules which defy the Lipinski's rule of five are more appropriate. The categories of drug molecules traditionally delivered include beta-agonists, anticholinergic drugs, mucolytics, anti-infectives, and corticosteroids. The list has got expanded with the introduction of anticancer agents, peptides, antibodies, vaccines, hormones, opioids, and genetic molecules (e.g., SiRNA, shRNA, and miRNA) through this route of delivery [10, 11].

9.3.3 Barriers and Factors Affecting Particle Deposition in the Airways

9.3.3.1 Physicochemical and Patient-Related Factors

9.3.3.1.1 Mucus Barrier and Mucociliary Clearance

The mucus is the first barrier that is encountered by drug/formulation at the TBR and limits the direct penetration of the molecules across the epithelial lining before being absorbed. Mucus is a viscoelastic layer consisting of approx. 95% of water and inherently lines the epithelial cells. However, the release of mucus may increase in case of external stimuli such as dust, gases, irritants, smoke, or invasion by microorganisms or airway diseases (asthma, bronchitis). The thickness of this is usually around 0.5–5 μm and varies based on the diseased state (up to 50μm). The barrier presents a rate-limiting step for hydrophobic molecules such as corticosteroids which are formulated as dry powders for inhalation. Further, there is ambiguity among the researchers whether this route is superior to oral or parenteral route as this barrier is a prominent one and prevents drug reaching to the target site in case of infection which may be in the deep lung too [12, 13]. Mucolytic agents such as N-acetylcysteine, Nacystelyn, Thymosinβ4, etc. [14] are used in formulation of aerosols and inhalers to decrease viscosity of mucus layer. The mucus

produced does not remain stagnant at the epithelial linings but gets constantly propelled along the airways by an organized rhythmic moment (1000 beats/min) that occurs toward the throat. As shown in Fig. 9.1, this propulsion is facilitated by beating of cilia present on the cells, and their presence is maximum at TBR and absent at AR. Such movement is of significance in clearing TBR from particles and also includes deposited formulations. The removal time may range from minutes to hours and depends on the thickness of mucus layer present during that stage which may be at normal levels during normal circumstances or be overloaded due to hypersecretion of mucus during disease condition. This mucus distribution also determines the deposition pattern of the aerosol formulation. A localized deposition will occur in patients with severe diseases such as cystic fibrosis, e.g., in cystic fibrosis patients, high levels of gentamicin, which was a significant share of the deposited dose, were found in the sputum, when the aerosolized drug was delivered to the central airways [15].

9.3.3.1.2 Alveolar Clearance

For those particles that escape the upper respiratory tract and reach/deposit at the deep lung or the AR, clearance occurs aided by alveolar macrophages. The clearance mechanisms include transport across the mucociliary escalator, phagocytosis by macrophages, transcytosis, or paracellular diffusion across epithelial layer by macrophages and intra-alveolar degradation [16]. The mucociliary escalator route is also a highly pursued one and involves transport via interstitium and lymphatic tissues to lymph nodes and finally to bloodstream [16].

9.3.3.1.3 Lung Morphology

The highly branched morphology of the airways which gets increasingly smaller in diameter and length results in increasing impaction chances for the particles and also decreases displacement needed for its surface contact. To reach the AR, the particles must remain airborne and change directions across the successively decreasing branching tubes. Thus, the highest deposition of the particles will occur at the points that have the shortest average path length.

9.3.3.1.4 Breath Holding, Inspiratory Flow Rate (IFR), and Tidal Volume

These three parameters are related to the proper training and technique of handling inhalation devices for maximizing therapeutic outcome and may vary from patient to patient. The holding of breath at the end of inhalation capitalizes on the sedimentation propensity of the airborne particles in the airways, and the recommended time is approx. 10 s. An IFR increase will increase the particle momentum and resulting turbulence at the proximal TBR and thus enhance the deposition of particles due to impaction at TBR and further lead to generation of aerosol with smaller particle size. The quantification of volume of air inhaled in one breath is done by determining the tidal volume, and an increase in that will thus result in better penetration/deposition of the aerosolized particles to the TBR and AR.

9.3.3.1.5 Diseased States

The diseased state in the airways will directly impact the smooth flow of air across the different regions, and its obstruction in diseased states will result in turbulence in flow of particles and higher deposition at the TBR.

9.3.3.2 Pharmaceutical Factors Influencing Aerosol Deposition

9.3.3.2.1 Aerosol Velocity

The inspiratory process and physiology of the lungs determine the velocity of entrainment of inspired particles from the inhalers and nebulizers and their transport-cum-deposition behavior across the regions of the respiratory tract. The particle kinetics is different in case of metered-dose inhalers as the particles are aerosolized with velocities higher than the inspiratory flow rate and consequently exhibit higher deposition in the oropharyngeal region.

9.3.3.2.2 Size and Shape

The most critical characteristic determining the distribution of particles in the respiratory tract is the size distribution. It is practically difficult to obtain particles with monodisperse characteristics, and hence size distribution needs to be defined for a particular dosage form and needs to corroborate closely to the target site requirement. The diameter of particle having spherical shape and unit density that sediments at the same rate as that of particle being investigated is termed as aerodynamic diameter. Half value of aerosol mass size distribution is termed as mass median aerodynamic diameter (MMAD). Assuming a lognormal distribution of particles, geometric standard deviation (GSD) is taken as the size ratio at 84.2% on the cumulative frequency curve to the median diameter. Critical aspects that determine the deposition of particles in the lung are monitored through MMAD and GSD. As a generalization, higher deposition of particles in the respiratory tract is observed in aerosol with larger MMAD. The shape of the particles will also determine their relative deposition in the respiratory tract as their physical dimension will vary based on shape, and in such cases one of their dimensions would be greater than the aerodynamic diameter.

9.3.3.2.3 Density

Aerodynamic diameter will be greater than the mean physical diameter for particles with densities less than 1 gram per cubic cm. The densities of particles prepared by spray- or freeze-drying will be significantly less, and hence density will be less than 1. Particle densities of $0.4 g/cm^{-3}$ and physical diameter of 20 μm are the cut-off limits for efficient lung deposition.

9.3.3.2.4 Physical Stability

Due to high concentration of particles in therapeutic aerosols, they are often inherently physically unstable, and such interactions are governed by inter-particulate forces of attraction and repulsion. Most of the time the exposure of aerosol particle to the humid environment of airways may also lead to hygroscopicity leading to

increase in size due to aggregation and subsequent deposition prematurely. However, this may not be the case with particles delivered by aerosol or nebulizers as the solvent evaporation from the carrier system will lead to reduction in size. Thus there is a complex interplay between the particle size and actual stability of particles than that predicted at ambient study conditions.

9.3.4 Strategies of Drug Repositioning Through Pulmonary Route

The drugs may be delivered through respiratory route utilizing one of the two techniques of aerosol inhalation and intratracheal instillation. For aerosol inhalation, three major types of devices have been used, namely, dry powder inhalers, pressurized metered-dose inhalers, and nebulizers. Dry powder inhalers, as suggested by the name, work on the principle of instilling dry powders as aerosols. Pressurized metered-dose inhaler systems were designed to provide a fine mist of medicament using a propellant, and nebulizers are used for aerosolizing drug solutions and suspensions effectively.

9.3.4.1 Prodrugs

Drugs delivered through inhalation need to dissolve prior to absorption. Lipophilic drugs show a lack of aqueous solubility which can be overcome by using hydrophilic prodrugs. Prostacyclin analogs prodrug hexadecyl-treprostinil (C16TR) inhibited bleomycin-induced pulmonary fibrosis in rat model [17]. Similarly testosterone derivatives have been synthesized to permit their delivery by inhalation spray. A single inhaled dose of laninamivir octanoate, a long-acting neuraminidase inhibitor, exhibits efficacy in treating both adult and pediatric patients with influenza virus infection [18].

9.3.4.2 Microparticles

Particles with geometric sizes between 1 and 3 μm and density close to 1 g/cm^3 suffer from disadvantages of particle aggregation in the dry powder inhaler and are prone to clearance by macrophages. Larger microparticles with size >5 μm, lower density (<0.4 g/cm^3), and thus lower aerodynamic diameter escape impaction in upper airways and are able to reach the deeper lung [19]. Polymeric and lipidic materials have been utilized in preparation of such particles like PLGA, chitosan, alginate, polycaprolactone, and lipids as dipalmitoylphosphatidylcholine, tristearin, Compritol, and glyceryl behenate. The inherent properties of the matrix material contribute to the drug release characteristics from the system and, hence, can be tailored as well [20]. Certain polymers have been exploited for their targeting abilities like sodium hyaluronate. Popular techniques for preparation include spray-drying, freeze-drying, emulsification, and high-pressure homogenization. To address the solubility issues of the drug, researchers have even explored complexation of the drug with cyclodextrin followed by spray-drying to achieve porous morphology [21]. Various classes of drugs have been reformulated as microspheres

for investigation in inhalation therapy like anti-TB drugs like rifampicin and isoniazid; anticancer drugs like paclitaxel, doxorubicin, cisplatin, etc.; peptides like insulin and calcitonin; and corticosteroids like budesonide [22].

9.3.4.3 Bioresponsive Systems

Smart bioresponsive systems utilize physiological changes to bring alteration in some property of the delivery system. These triggered changes are responsible for site-specific drug disposition. Lung airways are a host to multitude of enzymes which could be used for design of bioresponsive drug delivery systems [23]. In one of the studies, alginate microparticles coformulated with elastin make it susceptible to degradation by enzyme elastase. The microparticles were prepared by spray-drying and showed release in the presence of elastase which is elevated in inflammation. In another study, high-molecular-weight poly(ethylene glycol) diacrylate-based precursors were used to synthesize polymer that incorporated peptides. They degraded in the presence of matrix metalloproteinases that are overexpressed in pulmonary diseases [24].

9.3.4.4 Liposomes

Liposomes have been the subject of a huge number of research projects in inhalation drug delivery. The interest in liposomes for pulmonary delivery can be attributed to their potential to load therapeutic moieties and, following inhalation, localize the drug effect to airways for longer duration. Liposomes are known to exhibit enhanced permeability and retention effect attributed to their small size (100 nm) [25]. Further, the respiratory system offers distinctive targeting options (both active and passive) due to the enormous surface area presented by the lungs, avoidance of first-pass metabolism, and higher permeability of the pulmonary epithelium They modulate the drug release suitably so that drug release is sufficient to induce a therapeutic response, but not adverse reaction. Their composition includes phospholipids with or without cholesterol, which are having similarity to pulmonary surfactants in mammals making them biocompatible. Thus properties of controlled release and safety are very promising in the context of pulmonary delivery [26]. To be functionally useful, liposome formulations should be capable of being aerosolized with a high fine particle fraction (FPF), and they must encapsulate a therapeutically effective drug concentration which can then display prolonged release from the liposome at the defined target areas within the lung [27]. A multitude of therapeutic agents like cytotoxic anticancer drugs, immunosuppressants, antibiotics, corticosteroids, biologics, hormones, and genetic material have been explored for delivery. It is one of those platform technologies which has made its way to clinics. Success stories include AmBisome®, which is a freeze-dried liposomal formulation of amphotericin B in the market for the management of systemic fungal infections via intravenous infusion. Another good example is Arikayce®, which is a liposomal amikacin for pulmonary delivery via nebulization [28].

Liposomes can be used for pulmonary delivery to the lungs by nebulization of a liposome suspension or as a dry powder. Reports have stated that structural disruption may be observed with nebulization, while dry powders offer better stability as

formulations. Well-known techniques like spray-drying, spray-freeze-drying, or freeze-drying may be employed [22, 29].

9.3.4.5 Lipid Nanoparticles (SLNs and NLCs)

SLNs and NLCs are stable colloidal lipid carriers which have been explored as alternatives to liposomes in pulmonary delivery because of higher stability of the lipid nanoparticles. A lot of research studies have investigated their utility; still, they are developmental studies and the field is in its infancy. They are made up of lipid cores and suspended in an aqueous media. The lipid composition, rigidity, and particle size are key parameters governing their drug release characteristics. A wide array of materials has been used in the formulations and found to be safe and nontoxic for airway applications. They can be tailored suitably for manipulating drug release; their low size (nm range) permits loading on carriers and aerosolization effectively to the deeper lung. They exhibit particle adhesion, accumulation, and retention in alveolar tissues, thus making them suitable for sustained and prolonged drug release. Opportunities exist for active targeting also by coupling to suitable ligands for cell specificity. Reports have indicated better bioavailability, prolonged release translating to less frequent dosing with the use of lipid nanoparticles. Key considerations while designing lipid particles for pulmonary applications are biocompatibility, sterility, isotonicity, and pH range near neutral. They can be aerosolized as suspensions or loaded on carriers to convert them into dry powder. Nebulization again is less preferred than dry powders, but their success depends ultimately on the aerodynamic characteristics. Liquid preparations pose issues like aggregation or leaching over storage time [30].

9.3.4.6 Polymeric Nanoparticles

Inhalable polymeric nanoparticles present an appealing platform for delivery of drugs because of the several advantages associated. They offer high encapsulation efficiencies of the drug and shield the drug from degradation, prolong the drug delivery, and show long shelf life. The added advantage is the possibile modification of the surface properties [30]. Nanoparticles by virtue of their size and surface properties escape uptake by lung-surface macrophages and premature mucociliary clearance. Inhaled nanoparticles could be exhaled during pulmonary administration due to their extremely low mass. Hence, they are often delivered to the respiratory tract by nebulization of colloidal suspensions. Other alternatives are loading them onto porous carriers which dissociate in vivo to release the nanoparticles intact. One can formulate nanoparticles into inhalable micro-aggregates by employing techniques like spray-drying or spray-freeze-drying with carrier material like mannitol, polyvinyl alcohol, or leucine [31]. As discussed, surface modifications are very popular and well investigated with nanoparticles delivered pulmonary. Coating nanoparticles with inert biocompatible polymers such as polyethylene glycol (PEG) is one of the approaches of surface functionalization. PEG coating on nanoparticles envelops them in a hydrophilic and neutral shell which minimizes adhesive interactions with mucus and phagocytic uptake by macrophages [32]. Nanoparticles delivered through airways are able to show enhanced retention due to the enhanced

permeation and retention effect. Apart from passive targeting, active targeting may be achieved by coupling them to various ligands. Active targeting is more important while delivering highly potent therapeutics such as anticancer agents or genomics [33]. Furthermore, the selection of particle size of delivered aerosol can determine specific targeting to lung regions based on the position of diseased cells within the lungs. While larger aerosol particles with a diameter of 5–10 μm are restricted to the oropharynx and large airways, smaller particles with a diameter of 1–5 μm can reach to small airways and alveoli. Nanoparticle size can also affect its cellular internalization. Therefore, tailoring the nanoparticles size appropriately is required to achieve better lung disposition and cellular penetration [22] (Table 9.1).

9.3.5 Device Considerations for Pulmonary Route

9.3.5.1 Marketed Formulations

The inhalation drug delivery effectiveness is equally dependent on the device as much on the formulation. Traditionally three types of devices have been utilized, namely, nebulizers, pressurized metered-dose inhalers, and dry powder inhalers. Device technology has also witnessed several innovations in the years which make them more worthwhile. A brief summary is given on the noteworthy trends in device technologies.

Nebulizers are available in two configurations, jet and ultrasonic, which vary in the force which is used to aerosolize the liquid. They do not warrant patient's coordinated effort between inhalation and actuation. While jet nebulizers utilize the Venturi's principle, ultrasonic nebulizers work on sound waves generated from piezoelectric crystals. The new nebulizers in the market are breath-enhanced, breath-actuated, and vibrating mesh nebulizers. Pari LC® Jet plus nebulizer has been designed so as to permit air entrainment during inspiration and vents out the expired air. One of the breath-actuated nebulizers AeroEclipse® aerosolized droplets in response to patient inhalation, and this prevented drug wastage during exhalation. Vibrating mesh nebulizers work on the principle of vibrating a mesh plate with ultrasonic waves to disperse the liquid into a fine mist which brings about an increase in the volume of aerosol delivered to alveoli. The latest in the mesh nebulizer is the AKITA2 APIXNEB® which possesses an electronic indicator to detect the proper inspiratory flow, and then only it releases the medication. Soft Mist™ inhalers generate a very fine mist of aerosol but using reduced velocity which is beneficial for novel formulations sensitive to abrasion and high pressure. They are pocket-sized devices (Respimat®) which can give a single-breath, inhalable aerosol from a drug solution using a patient-independent, reproducible manner. It uses an environmentally friendly energy supply and includes a dose indicator and a lockout mechanism [80].

Most of the new pressurized MDIs can be classified as breath-actuated or coordination devices. They are working on the principle of sensing the patient breath to release the medication in response. They help to address the issue of poor coordination in inhaler actuation and patient's breath. Autohaler ™ was the first breath-activated pressurized metered-dose inhaler which eliminated the dependence on

Table 9.1 List of some representative drugs explored for pulmonary delivery with novel formulations

Anti-asthma/anti-inflammatory		
Beclomethasone	Lipid NC	[34]
Budesonide	SLN, liposomes	[35, 36]
Curcumin	Polymeric NP, SLN	[37, 38]
Indomethacin	Lipid NP	[39]
Fluticasone	Dried NP	[40]
Pirfenidone	Polymeric NP	[41]
Roflumilast	Spray-dried microparticles	[42]
Anticancer		
Cisplatin	Dried NP, hyaluronan conjugates	[43, 44]
Methotrexate	Polymeric NP	[45]
Paclitaxel	Micelle, polymeric NP	[46, 47]
Silibinin	SLN	[48]
Antioxidants		
Antioxidants – several types	Liposomes, polymeric NP, SLM	[49, 50]
Antimicrobials		
Amikacin	Liposomes, SLN	[51, 52]
Ciprofloxacin	Liposomes	[53]
Moxifloxacin-ofloxacin	Dried NP, MP	[54]
Tobramycin-clarithromycin-vancomycin	Spray-dried NP, MP	[55, 56]
Voriconazole	Polymeric NP	[57]
Tacrolimus	Lipid NP	[58]
Itraconazole	NLC	[59]
Clofazimine	Microparticles	[60]
Rifampicin	Mannosylated dendrimers	[61]
Isoniazid and rifampicin	Surface-modified liposomes	[62]
Pyrazinamide	Polymeric nanoparticles	[63]
Rifampicin, isoniazid, and pyrazinamide	Poly(DL-lactide-co-glycolide) nanoparticle	[64]
Proteins and other macromolecules		
Calcitonin	Polymeric liposomes	[65]
Heparin	Polymeric NP	[66]
Insulin	SLN	[67, 68]
Exendin-4	Polymeric NP	[69]
Vaso-pulmonary and cardiac disorders		
Iloprost	Liposomes	[70]

(continued)

Table 9.1 (continued)

Sildenafil	Polymeric NP, SLN	[71, 72]
Carvedilol	Polymeric NP	[73]
Surfactant, antibody, and genomic delivery		
siRNA/gene	Polymeric NP	[74, 75]
Surfactant therapy	Liposomes	[76]
DNA vaccine	Polymeric liposomes	[77]
IgG1	Self-assembly NP	[78]
P53	Polylysine/protamine polyplexes	[79]

patients' inspiration for aerosolization. This has reduced the inter- and intra-subject variability in patients. In one of the innovations, dissolved CO_2 is added to HFA-134 and ethanol blend. After actuation of dose, "the effervescent effect" due to the CO_2, within the emitted HFA/ethanol droplets, generates a fine mist. Thus, respirable fraction emitted is enhanced in comparison to a conventional pressurized MDI. A variety of spacers with unique designs have been introduced in the market to maximize the potential of the formulations [81].

Dry powder inhalers are small portable devices which need very minimal patient coordination between breathing and device actuation to deliver therapeutics in dry form. Dry powder inhalers often face particle agglomeration issues and have become more efficient with the use of large porous carriers in the formulation. The common DPI devices like Clickhaler®, Multihaler®, and Diskus® propel the powder into a high-speed airflow that deagglomerates particles and generating respirable particles. Other devices like the Turbuhaler® and the Spinhaler® work on the principle of impaction between particles and device surfaces to deagglomerate the particles.

Inspiromatic™ is a smart dry powder inhaler developed by Inspiro Medical which has an internal microcontroller and flow sensor which disperses the drug to appropriate size. It works at low inhalation flow rates with real-time feedback control and data logger indicating proper inhalation technique and follow-up [82]. The Spiros™ device has a battery-powered motor which disperses the powder into an aerosol by impaction of a rotating impeller. The device is comfortable to use for asthmatic patients as well because the motor is activated even by low breathing rates. Another one named as Twisthaler® is a breath-activated dry powder inhaler but has the advantage of working with same efficiency for a wide range of inspiratory flow. Air classifier technology working on force distribution concept has been explored for formulation integrated dry powder inhaler development (FIDPI) to deagglomerate the inhalation powders [83] (Table 9.2).

9.3.5.2 Patented Devices

Several patents related to device and formulations with additional useful features and benefits have been filed over the past few years, and a few important ones are summarized below:

Table 9.2 Some representative device innovations for inhalation delivery

Name of the device	Type	Company
AeroEclipse® II BAN	Breath-actuated jet nebulizer	Monaghan Medical Corporation
PARI LC® Plus	Breath-enhanced jet nebulizer	PARI International
PARI eFlow® rapid	Perforated oscillating membrane	PARI International
CompAIR™ NE-C801	Jet nebulizer with virtual valve technology	OMRON Healthcare Europe BV
AKITA² APIXNEB	Vibrating mesh nebulizer	Activaero GmbH
Respimat® Soft Mist™	Propellant-free soft mist inhaler	Boehringer Ingelheim
Easibreathe ™	Breath-actuated pMDI	Norton Healthcare
K-Haler®	Breath-actuated pMDI with patented valve technology	Mundipharma
MD Turbo™	Breath-actuated pMDI	Respirics
Easidose	Breath-coordinated pMDI	Bespak
Spacehaler™	Low-velocity-spray pMDI	Celltech Medeva
Clickhaler®	Reservoir dry powder device	Vectura
3M™ Taper	Dry powder inhaler based on reverse flow cyclone design	3M
3M Conix™		
Inspiromatic™	Dry powder inhaler with micropump	OPKO Medical
NEXThaler®	Dry powder inhaler with extra fine particles	Chiesi
Breezhaler®	Dry powder inhaler with dose check facility	Novartis
Aspirair®	Dry powder inhaler for systemic drug delivery	Vectura
Diskus™	Multiunit dose dry powder inhaler	GSK
Ellipta™	Single-step breath-activated, multidose mono- or di-drug dry powder inhaler	GSK
Twisthaler®	Dry powder inhaler with specially designed channel for aerosol conduction	Schering/Merck
Spiros®	Breath-activated dry powder inhaler with battery-powered system	Dura

Nebulizer To overcome the shortcomings of conventional nebulizers for achieving efficient particle delivery, new mechanisms that will efficiently drive the liquid medications in the devices have been explored. *EP2644282* states the use of a platinum mesh having multiple through holes having tapered shape that gradually narrows at external surface side of mesh to atomize and nebulize liquids. The angle of taper for the through holes range from 3° to 30°. The application of this modified mesh is for achieving enhanced delivery of particles at alveolar region.*US8616195* describes a device that is either battery or electricity operated and works on vibrating mechanism having perforations which results in generation of particles in the size range of 1–6 μ. The nebulizer device consists of a slanted baffle that directs aerosol outside. Further, to avoid loss of aerosolized particles between inspirations, a rainout trap is installed.

pMDI *WO2016187156* describes propellant 1,1,1,2-Tetrafluoroethane (HFA)-based MDI that provides a smoother aerosol delivery improving patient compliance. It was investigated that the fine particle fraction of the aerosolized particles increases when the distance between the nozzle and mouthpiece was increased (from 0.5 to 10 cm). Restricting aperture of mouthpiece also led to generation of aerosol having desired particle size to the patient's lung. Several inhalers have been developed by using newer technologies such as thermal ink jet of generating more uniform aerosol [84]. *US20170007786* describes a mechanism for actuation and also avoiding accidental delivery of dose through the device. The actuation is controlled via restricted movement of the actuation counter and responds only when it is depressed to a certain level after which a lockout mechanism comes into effect preventing further movement of the dose counter wheel. After the delivery, the spring assembly disengages and cannot be recompressed, thus preventing accidental delivery. To minimize loss of drug during priming operations, which is due to presence of several moving parts, spring-free valves are being developed and patented.

Soft Mist Inhaler WO2010052323 describes an inhaler that is breath-actuated and consists of a hydrogen-containing fluid reservoir, an activator fluid reservoir, a gas chamber, a pre-catalyst and a catalyst chamber, and a container with active drug. The aerosolization mechanism involves entrainment of active substance in the incoming warm air with water vapor produced by its passage through gas chamber and over the catalyst.

DPI The use of DPI has faced several challenges due to change in the use of propellant and increased preference for other delivery technologies as stated above. However, progress has also been made to achieve superior aerosolization and with higher-dose capacities by use of DPIs. US20160228659 describes a multidose device able to dispense specified medication through a sealed disk. US9027551 describes an effective method of achieving deagglomeration of particles by integrating fins in the delivery device. PowdAir is a patented device (US8677992) that has been used for delivery of lactose-based and particle-engineered drug (antibiotics, analgesics, asthmatic drugs) powders and is a capsule-based device delivering 95% of nominal dose amount at a flow rate of 30 lt/min and above. US9192675 describes use of a patient-friendly DPI that has two inlet airflow ducts with a cartridge and was evaluated for delivering antidiabetic and obesity agents. US8651104 describes a DPI in which drug powder adhered to bead-like actuator that is held in a chamber, wherein the oscillation of bead assisted by flow of air through inlet flow channel leads to dislodging cum entrainment of drug and is delivered to the patient. US20140373839 describes a passive inhaler with oscillation or vibratory motion for deagglomeration of powder for inhalation that is packed in blister strips in multiple blister pockets and also comprises of means for generating swirls in opposite rotational directions. To conveniently deliver high dose of drugs, Orbital® inhaler was developed that is a disposable inhaler with multiple uses by Pharmaxis, Australia. The device has one-

touch operation and capable of delivering payloads from 50 mg to several hundreds of milligrams during series of sequential inhalation. Some devices also employ enhancers that favor deagglomeration to improve fine particle fraction. WO2013169473 describes a device having unidirectional 3D rod array in staggered manner. Similarly, Twincer DPI has been claimed to improve fine particle fraction and lessen the wastage as concluded from the study using aminoglycosides [85].

9.3.6 Characterization for Pulmonary Drug Delivery Systems

In recent years, there has been a considerable advancement in the field of evaluation and characterization of pulmonary drug delivery system. These methods can be classified as in vitro, in vivo, and ex vivo methods. Various in vitro methods like physicochemical characterization of particles, evaluation of aerosol performance, particle dissolution studies, and cell culture study have been evolved. Drug administration system, drug deposition, and pharmacokinetic studies are the in vivo methods which are currently in research studies. Ex vivo methods are also developed to check the efficacy and safety parameters of drugs and their delivery mechanisms. An overview of various evaluation methods for pulmonary drug delivery systems is given in Fig. 9.2 [86].

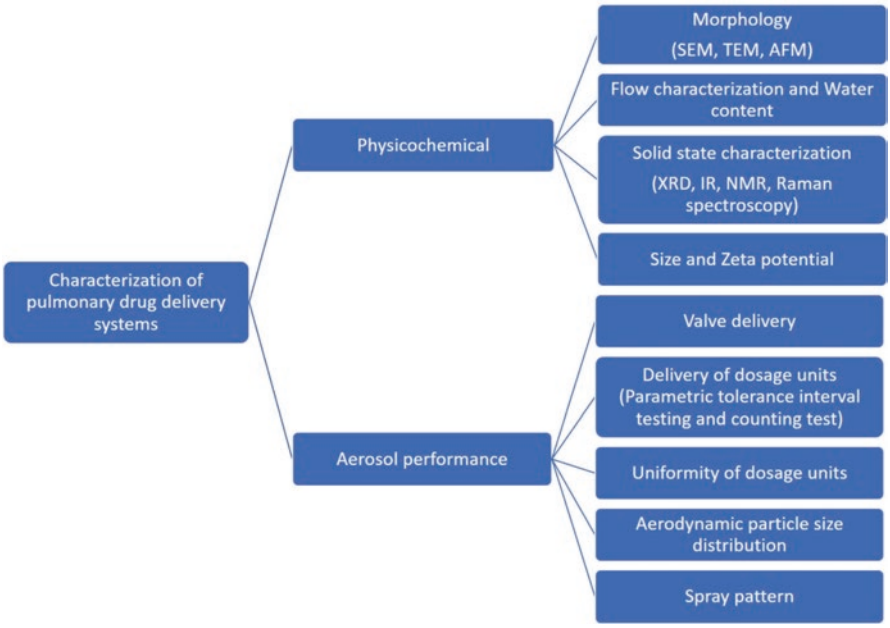

Fig. 9.2 Evaluation for pulmonary drug delivery system

9.3.7 Some Success and Failure Cases of Therapeutics for Pulmonary Route in Clinics

Pulmonary route has shown promise in clinics with novel drug delivery systems. Currently there are few products approved for pulmonary delivery. The first one was Exubera, a dry powder insulin formulation, a product developed by Nektar Therapeutics and marketed by Pfizer. However, it was withdrawn post 1 year of introduction in market [87]. A number of factors have been implicated for its failure like its large device size, higher cost, and dosing-related issues. However, the development of the first noninjectable insulin was a remarkable milestone and paved the way for the second inhalable insulin product "Afrezza" approval by the FDA in 2014. It has been developed and produced by Sanofi and the MannKind Corporation. It is comprised of insulin Technospheres in size range around 2–3 μm made from recombinant insulin and a carrier: fumaryl diketopiperazine [88]. However, the development of few insulin products by pulmonary route was discontinued after discouraging responses in clinical trials like AIR (Eli Lilly) which is a spray-dried dry powder formulation of insulin, dipalmitoylphosphatidylcholine, and sodium citrate. It was discontinued after Phase III studies. Another product, Aerodose (Aerogen) which was a liquid aerosol, was also discontinued midway during clinical trials [89]. Inhaled human growth hormone was explored in a crossover clinical trial on 12 healthy adult volunteers. It was well tolerated, but overall delivery efficiency was less than the business development goal and, hence, was discontinued from further development [90]. A few clinical studies on inhaled GM-CSF (granulocyte-macrophage colony-stimulating factor) displayed utility in developing anti-melanoma cytotoxic T lymphocytes in patients. Further assessments on dose and treatment schedule can ascertain its use [91].

A number of nebulized antibiotics are under clinical trials. The most noteworthy is the very recent FDA approval of liposomal amikacin (Arikayce®, Insmed Inc., USA). It is designed as prolonged release formulation by inhalation by site-specific targeted treatment of serious lung infections. Arikayce™ was categorized as an orphan drug from the FDA in the USA and the European Medicines Agency in Europe for the management of *Pseudomonas aeruginosa* infections in cystic fibrosis patients. Positive trends were obtained from Phase II and III studies, and a clinically significant progress in lung function at the end of treatment session was observed. The approval marks a significant technological advance in the field. Another antibiotic, ciprofloxacin, is being investigated in late-stage clinical trials. Pulmaquin™ (Aradigm Corp., USA) has entered Phase III trials to treat lung infections in non-cystic fibrosis bronchiectasis patients. Lipoquin™ (Aradigm Corp., USA) is another variation of liposomal ciprofloxacin formulation under trials [52]. The difference between Lipoquin and Pulmaquin is the quantity of encapsulated ciprofloxacin. Lipoquin contains all ciprofloxacin encapsulated, while in Pulmaquin a portion of the drug is not encapsulated to provide an initially high peak concentration of drug in the lung. Both liposomal antibiotics demonstrate increased residence time and less systemic uptake [92]. Other inhalable products of antibiotics like tobramycin (TOBI® Podhaler®) and colistin methanesulfonate (Colobreathe®) as

dry powder formulations have been approved [93]. TOBI® Podhaler® utilizes the proprietary porous particle technology of PulmoSpheres produced by spray-drying [94]. Other antivirals and anti-influenza drugs are also under development.

Iloprost solution for nebulisation is used to treat symptoms of pulmonary arterial hypertension (PAH). It was used initially through IV route, and later its solution (Ventavis®, Actelion Pharmaceuticals US, Inc.) was developed and marketed for inhalation [95]. Another similar drug, treprostinil, is used for the management of pulmonary arterial hypertension. The inhaled form of treprostinil was approved by the FDA in July 2009 and is marketed under the trade name Tyvaso [96]. Two clinical trials of adeno-associated virus (AAV) loaded with cystic fibrosis transmembrane conductance regulator (CFTR) cDNA demonstrated safety, but the efficacy reported was limited only. [97]

A few trial reports are there on the inhaled nanocarriers. C. Verschraegen et al. have discussed a dose escalation trial of inhaled liposomal 9-nitro-20-camptothecin in a group of 24 patients. Liposomal 9NC could be delivered successfully to patients with lung carcinoma but efficacy reported was not very encouraging [98]. One of the studies reported the use of liposomal cisplatin. The results showed that inhaled liposomal cisplatin was safe and tolerable to patients and could be of use to patients with metastatic lung disease [99]. Thus, it can be said that success in clinical trials has been a mixed bag for novel carriers or drug repositioning through pulmonary routes. But these early studies are big landmarks for the products which have been approved and the future development studies.

9.3.8 Bridging the Gaps Between In Vitro Activity and In Vivo Efficacy/Therapeutic Potential for Pulmonary Delivery

The majority of products currently in development for systemic administration via the lung contain drugs that are already approved for use by parenteral administration, such as insulin for the treatment of type 1 and type 2 diabetes and morphine or fentanyl for management of pain [100, 101]. The important aspects of this delivery system due to which this route of administration is gaining popularity are safety and noninvasiveness resulting in adherence to the dosage schedule leading to improvement in quality of life of patients. However, in case of drug repositioning, it is of prime importance to establish safe and efficacy of the repositioned drug that produces comparable or similar effects that were obtained by parenteral administration. Proving pharmacodynamic and pharmacokinetic similarity or even improvements in these parameters may prove to be a very difficult task. Such herculean task is being taken care of by developing delivery systems that are improvements of the conventional delivery devices. As discussed in the factors affecting pulmonary deposition, coordinated breathing technique during dosing is a crucial factor for inhaled drugs in maximizing deposition of particles of aerodynamic size in the deep lung [102]). Over and above repositioning for systemic delivery, developing controlled release inhalation formulations for local effect has also taken pace. For local delivery, important consideration needs to be paid on achieving maximal residence

time of the formulation in the respiratory tract as different clearance mechanisms such as macrophages and mucociliary clearance escalator are in place to remove any foreign particles that get deposited on the alveolar region or airway epithelial cell layer. Furthermore, for such formulation, a balance between the rate of deposition and rate of clearance of material is to be attained to achieve therapeutic benefit of the drug delivered locally to the respiratory tract [103]. Similarly, clearance of active ingredients to that of carrier material needs also to be taken into account for preventing unwanted accumulation of inert carriers in the respiratory tract.

9.3.9 Future Perspective

Though there has been a profound increase in the number of inhalation product-based therapies in the last decade, the pace of such therapies leading to a substantial clinical outcome is far from being realized. A large number of innovations in the formulation aspects can definitely increase the number of molecules being repositioned. Special attention needs to be paid to designing devices for geriatric and pediatric populations and in increasing the intuitiveness of the devices and further developing of such devices that can be used by people of all age groups. With the repositioning strategies in place and being adopted for a range of therapeutic agents such as peptides, antibodies, DNA, vaccines, etc., there is a need for tailoring devices according to the specific requirement of the formulation by tuning the mechanical part of delivery devices for ensuring maximum stability of such sensitive molecules. Further, designing devices that are sophisticated yet simple to use by patients and novel yet affordable is the need of the future.

9.4 Introduction to Nasal Drug Delivery System

Nasal drug delivery product market is 2% of the overall drug delivery market. It is growing at tremendous speed. Certain drugs like antibiotics, mucolytics, and decongestants are used to exert local effect in nasal cavity as nasal sprays or nasal drops [104]. Rhinitis and allergic diseases can be targeted locally with efficiency by focusing these drugs. Nasal products may be developed for local or systemic effect. The market value of nasal products is approximately 2 billion US dollars with more than 30 products in the US market for intranasal use [105]. It is an attractive alternative to invasive administration route providing direct access to systemic circulation. Nasal route has been explored since the beginning of human civilization, and Indian Ayurvedic system of medicine uses this route since long. Rapid onset of action of systemically acting products is an important advantage. Sniffing tobacco and psychotropic drugs is used all over the world for CNS stimulation. The use of nasal route for systemic effect began after approval of peptide oxytocin which stimulates uterine contraction and lactation [106]. Nasal delivery offers the following advantages so they are preferred as an alternative to invasive route of administration:

- The nasal cavity has a surface area of 160 cm^2 confirming good absorption of drug.
- It has a tremendous blood supply, thus providing rapid absorption and onset of action and also maintaining sink condition.
- Cavity has less enzymatic degradation activity than the GI tract so peptides and proteins are administered safely through the nasal route.
- It offers readily accessible surface; therefore devices are simpler to fabricate.
- The product can be administered to the patient easily.
- It may emerged as an attractive alternative to oral route of drug administration.

9.4.1 Factors Influencing Nasal Drug Absorption

There are numerous factors affecting systemic bioavailability of drugs which are given through the nasal route. They play a very crucial role for the drugs to achieve therapeutically effective blood concentration. The biological factors and formulation factors affect nasal drug absorption. Figure 9.3 describes various nasal drug delivery pathways.

9.4.1.1 Biological Factors

Biological factors include the anatomy and physiology of nasal cavity.

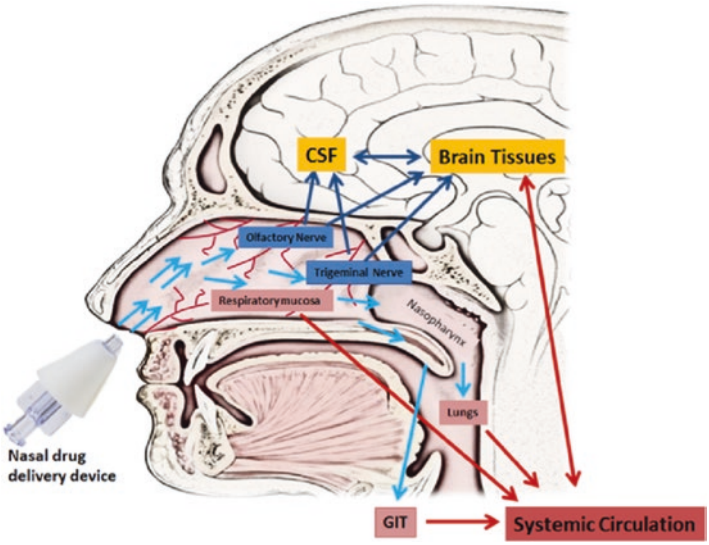

Fig 9.3 *Nasal drug delivery pathways*; Nasally administered drug (light blue) can enter directly into the brain via the olfactory and/trigeminal neuronal pathways (dark blue) or indirectly following absorption into the systemic circulation (red). GIT is the gastrointestinal tract; CSF is cerebrospinal fluid

9.4.1.1.1 Structural Characteristics

Anatomically, the nose is divided into atrium/septum, nasal vestibule, respiratory area, nasopharynx, and olfactory region (Fig. 9.1).The nasal septum is divided into two halves from the center by nasal cavity further each subject by the three turbinates, superior, middle, and inferior turbinate, responsible for the humidification and heating of the inhaled air [107–111].

Airborne particles are removed by the vestibular region, composed of keratinized stratified squamous epithelium along with the nasal hair. The respiratory mucosa comprises of ciliated and nonciliated columnar cells having several microvilli (about 300–400 per cell), goblet cells, and basal cells. The olfactory region is composed of supporting cells, olfactory neural cells, and basal cells. Thus the absorption of drug in intranasal administration depends on cell density, type, and numbers located in the particular nasal region.

9.4.1.1.2 Enzymatic Degradation in Nasal Cavity

A large number of enzymes present in nasal mucus, such as conjugative enzymes, oxidative peptidases, and proteases, together provide an enzymatic barrier to drugs such as peptides on intranasal delivery. These enzymes are responsible for drug degradation, thereby decreasing drug absorption [112, 113].

9.4.1.1.3 Blood Supply and Neuronal Regulation

The sympathetic stimulation and parasympathetic stimulation [114, 115] regulate absorbed drug amount through relaxation [116, 117].

9.4.1.1.4 Nasal Cavity

A longer nasal residence time is observed for the formulation on deposition to the anterior of the nose, and it is also an area with less permeability, while a shorter residence time is experienced on deposition to the posterior portion of the nose and demonstrates a high drug absorption transmucosally. Also, the deposition site is determined by the properties of the formulation and method of administration [118, 119].

9.4.1.1.5 Transporters and Efflux Systems

Hydrophobic and amphiphilic drug transportation across transnasal route is influenced by the presence of multidrug resistance transporters in the human nasal and olfactory mucosa [120]. The entry of drug into the systemic circulation and/or brain may be affected by various transport systems available in the nasal tissue. Several studies have demonstrated that influx of drug into the systemic circulation or brain is prevented by P-glycoprotein inhibitor protein, an ATP-driven efflux transporter expressed in the apical area [121–123].

9.4.1.1.6 Nasal Secretions

Drug entry into bloodstream is also exaggerated by the viscosity and composition of nasal secretion, whereas contact time of drug and nasal mucosa is affected by the viscosity [124].

9.4.1.1.7 Nasal Cycle

Various studies have revealed the effect of circadian rhythm on rate of nasal cycle, clearance rates, and secretion of nasal mucus and hence can affect the nasal drug absorption [125].

9.4.1.1.8 pH of the Nasal Secretions

An ideal nasal formulation should have a buffer capacity with a pH range of 4.5–6.5 identical with nasal pH. Any change in nasal pH affects formulation pH and thereby drug ionization process. Drug ionization can be altered by a change in pH of nasal secretion which further changes the amount of transnasally absorbed drug.

9.4.1.1.9 Mucociliary Clearance

The drug and nasal mucosa contact time influence the drug absorption. Residence time is directly proportional to the mucociliary clearance and inversely related to the administered drug [126].

9.4.1.1.10 Pathological Conditions

The common nasal infections such as rhinitis, colds, and nasal polyposis are common causes of mucociliary dysfunctioning, nasal mucosal irritation, and hyper- or hyposecretions which can affect the absorption of drug transnasally [104]. Numerous drugs have been classified and screened as cilio-inhibitory or cilio-friendly, being a precious tool in the safe nasal drug design [127].

9.4.1.1.11 Environmental Factors

Moderate reduction in the mucociliary clearance rate is seen at 24 °C. However, constant increase in ciliary beat rate is linearly proportional in accordance with increase in temperature [128].

9.4.1.2 Formulation Factors

The following are the main physicochemical characteristics of the drug determining the extent and rate of drug absorption.

9.4.1.2.1 Lipophilic-Hydrophilic Balance

Lipophilic compounds diffuse into the cytoplasm and partition into the lipid layer of the cell membrane readily by crossing the nasal mucosa transcellularly [128–133].

9.4.1.2.2 Chemical Form

Absorption of drugs can be altered by the chemical change of the drug into an ester or a salt form [134].

9.4.1.2.3 Polymorphism

Dissolution and solubility rates of drugs are affected by polymorphism and thus absorption across the biological membranes [135, 136].

9.4.1.2.4 Solubility and Dissolution Rate

The deposited particles on the nasal mucosa must be dissolved before being absorbed transnasally [137–139].

9.4.1.2.5 Molecular Size and the Molecular Weight of the Drug

Drug absorption through nasal route is directly influenced by the molecular size of the drug. In case of lipophilic drugs, molecular weight and drug permeation have a direct relationship, whereas an inverse relationship is seen in water-soluble compounds. The permeation rate is affected by compounds having a molecular weight greater than 300 daltons. However, for the compounds having a molecular weight greater than 1000 daltons, a significant decrease in absorption is observed, except with use of absorption enhancers [140–143].

9.4.1.2.6 Partition Coefficient of the Drug and Pka

Drug is better absorbed in unionized form than ionized form according to pH partition theory which is equally applicable to nasal drug [144, 145, 146].

9.4.1.2.7 Shape

As the cyclic-shaped molecules have better absorption than linear molecule, it can be concluded that shape is also an important factor [147, 148].

9.4.1.2.8 Osmolarity

Tonicity of the formulation affects drug absorption. Ohwaki et al. studied the formulation osmolarity effect on the secretin absorption in rats. In the presence of hypertonic solution, shrinkage of the epithelial cells was seen, resulting in maximal secretin absorption [149–151].

9.4.1.2.9 Viscosity

An increase in the amount of absorbed drug by increasing the viscosity of the formulation, resulting in prolonging the contact time between the nasal mucosa and the drug and the time for drug permeation, as suggested by the study of Jansson et al. [152, 153].

9.4.1.2.10 Drug Distribution

Efficiency of nasal absorption is remarkably affected by drug distribution in the nasal cavity. Also the posture and mode of drug administration affect this distribution, which help in determining the extent of absorption of a drug [154].

9.4.1.2.11 Dosage Form

The choice of dosage form depends upon the proposed indication, drug, patient, and marketing choices. Gels, nasal sprays, drops, and powders are the different dosage forms for nasal administration.

9.4.1.2.12 Formulation Excipients

Excipients such as antioxidants, solubilizers, etc. are used in nasal formulations. Though they are accountable for some nasal irritations, humectants, antioxidants, flavoring or taste masking, and preservatives do not alter nasal drug absorption process [155].

9.4.1.2.13 Delivery Device-Related Factors

For delivery of intranasal formulation, different types of devices are used; site, size, and deposition pattern affect the drug permeation transnasally.

9.4.1.2.14 Size of the Droplet or Powder

The size of device determines the size of the droplets. On the basis of particle size, the particle can either deposited in the upper respiratory tract having a particle size of less than 10 μm or can be retained if the particle or droplet size is 5–7 μm, and if the particle size is less than 0.5 μm, it will be exhaled out [134].

9.4.1.2.15 Site and Pattern of Deposition

Dosage form/type, the formulation composition, the delivery device, the administration technique, and actuators and adapters design affect the site and pattern of drug deposition [156, 157].

9.4.2 Drug Repositioning Strategies

Drug repositioning strategies are implemented to an old drug in a manner that it falls under a classification of a new drug, especially in terms of favorable change in its pharmacokinetic and pharmacodynamic properties. It may be changes in route of administration, dosage form, formulation, dose, etc. Sometimes, nasally administered drugs enter systemic circulation rapidly than oral route due to the rich blood supply in the nasal cavity. For example, nasal spray of propranolol can stop migraine attack even after initiation of symptoms [106, 158]. The local delivery of antibiotics, mucolytics, and decongestants is given through nasal route. Vaccines, antifungals, corticosteroids, antiviral, etc. have been delivered via nasal route, and Table 9.1 describes lists of few intranasally administered drugs for systemic delivery. Moreover, nasal route has been also explored for nose-to-brain delivery and mucosal immunization (Table 9.3).

Table 9.3 Systemic delivery of drugs through nasal route

Class	Drugs
Analgesics	Morphine; oxycodone
Anti-infectives	Gentamicin, cefazolin, acyclovir
CNS stimulants	Cocaine, nicotine
Cardiovascular drugs	Propranolol, timolol, trinitroglycerine, nifedipine, verapamil, hydralazine
Antimigraine drugs	Sumatriptan, dihydroergotamine

9.4.2.1 Designing Formulation and Dosage Form

Formulation scientists have to consider many factors for absorption of compounds through the nasal cavity. Molecular weight, size, and shape are important criteria to be examined [159]. Compounds having molecular weight less than 1000 Da are absorbed easily. Cyclic shapes are more permeable than linear compounds [147]. The inhaled particles of size less than 5 μm may escape the nasal cavity and get deposited into the lungs [160]. Particle size greater than 50 μm imparts favorable distribution pattern in the nose. The pH of the nasal cavity, formulation, and drug are other important aspects to be considered while designing formulation. The ideal pH of nasal formulation should be within 4.5–6.5 to avoid irritation to the nasal mucosa [149]. The osmolarity is another factor of importance. A greater biological effect was observed in adjusting osmolarity of solution with mannitol [155]. A study in rats revealed that 0.462 M mannitol solution could absorb secretin in maximum quantity [161]. Intranasal solution concentration and volume to be administered should be considered. More drug is absorbed in larger delivery volume due to greater nasal passage distribution and coverage [162]. Behl et al. suggested maximum limit of 2 mg/dose and 25–150 μL/nostril for dose and volume, respectively [155]. Aqueous formulations are necessary for local delivery of drug into the nasal cavity only. Mucociliary clearance is a normal physiological process and defense mechanism of the nose which should be least disturbed while administering nasal formulation. Patient acceptability and compliance should be considered while administering nasal products in chronic ailments [163, 164] (Table 9.4).

Powders, sprays, drops, gels, etc. have been formulated till date for delivery into the nasal cavity. The choice of delivery system and dosage form should be aimed toward chemical feasibility and stability. Few important considerations for intranasal dosage forms are described in Table 9.2 [155].

Current nasal drug delivery systems are broadly classified into local and systemic delivery of drugs. They can be also classified as conventional and novel dosage forms as shown in Fig. 9.4.

Table 9.4 Key points in intranasal dosage forms

Dosage forms	Key points
Nasal drops	Suitable for solutions
	Inaccurate dose metering
Solution drops	Useful in metered-dose actuator devices
Suspension drops	Filled in metered-dose actuators
	Frequently used for local affects
Powders	Chances of irritation and gritty sensation
	More expensive
Gels	Filled in metered-dose devices
	Reduction in postnasal dripping and leakage for systemic as well as local delivery
Emulsions and ointments	Used for local action, very less patient compliance

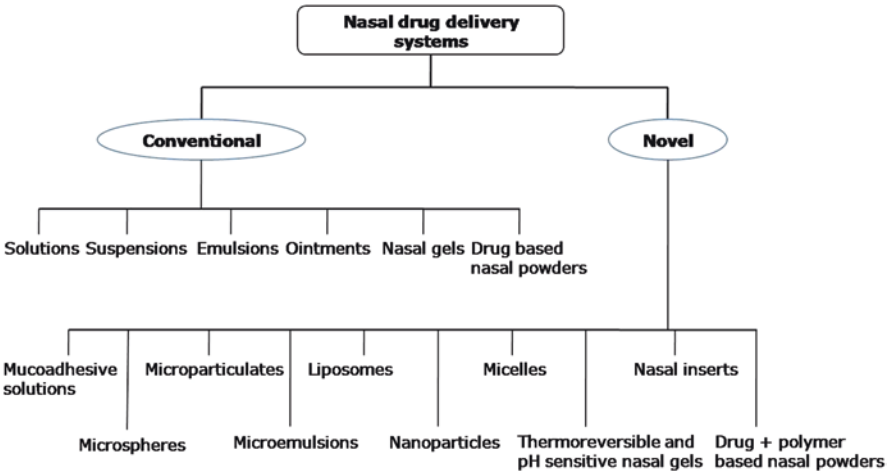

Fig. 9.4 Classification of nasal drug delivery system

9.4.2.2 Examples of Drug Repositioning

Quadir M. et al. developed spray and lyophilized powder of ketorolac tromethamine having analgesic and moderate anti-inflammatory activity. It was given to rabbit nasal cavity and evaluated for pharmacokinetics data [165]. The bioavailability of nasal spray formulations was found to be 91% which was more than powder formulations. The powder formulation showed only 38% bioavailability; therefore it may be inferred that polymer matrix holds drug tightly, and it is not released totally until the nasal epithelium throws it away. *Su et al.* developed intranasal sustained-release formulation of clofilium tosylate and dobutamine hydrochloride [166]. They formulated compounds with short biological half-life into nasal formulation mimicking iv infusion. *Lindsay et al.* developed Tobispray, a dry, metered-dose nasal aerosol having tramazoline, dexamethasone, and neomycin [167]. They checked inhibition of bleeding of patients having nasal surgery and got 94% success rate with this Tobispray formulation. *Borum and Mygind et al.* found a novel method to assess nasal response in healthy subjects and recurrent rhinitis patient by taking ipratropium [168]. It possesses topical activity and bronchodilator property while used in aerosol for the treatment of broncho-obstructive diseases. *Dyke et al.* performed comparison of oral and nasal administrations of cocaine efficacy [169]. They detected cocaine in plasma within 15 min of intranasal administration and reached to peak concentration in 120 min, whereas cocaine could not be traced in plasma until 30 min following oral administration. *Schaffer et al.* measured prospective of intranasal administration of antihistaminic drugs and chlorpheniramine maleate in patients with allergic rhinitis [170]. The combination showed more efficacy than chlorpheniramine maleate, and it was concluded that H1 and H2 receptors are equally important in nasal blood networks, thereby exerting additive effect from H1 and H2 antihistaminic drugs, equal importance of H1 and H2 receptors in nasal blood vessels, and an additive effect of H1 and H2 antihistaminic drugs. Nasal spray

of desmopressin acetate has been approved by FDA to treat nocturnal enuresis. It is marketed by *Rorer Pharmaceuticals*, and it acts by stimulating production of arginine vasopressin, an antidiuretic hormone which controls urine production. Abnormal changes in arginine vasopressin levels are responsible for nighttime enuresis. Drug has a dual-phase half-life comprising of a 7.8-minute rapid phase and 75.5-minute sluggish phase. There was a decline in urinary output and plasma osmolality with increment in urine osmolality. Researchers at the *University of Nottingham, UK, and Novo Nordisk A/S, Gentofte, Denmark*, demonstrated 65% decline in blood sugar level upon administration of an intranasal insulin solution with an absorption enhancer [171]. They concluded that the palmitoyl and stearyl portions of phosphatidylcholine, in 0.5% concentration, created effects comparable to parent compound effect; thus the importance of lysophospholipids as absorption enhancers in nasal delivery had been confirmed.

The nasal drug delivery technologies are targeted mainly to increase the permeability of nasal epithelium and contact time at the absorption site. Alteration in the mucus layer, tight junction, reversed micelle formation, extraction by comicellization, and use of surfactants and enzyme inhibitors are few approaches used to enhance intranasal absorption. Bioadhesives are used widely recently to increase contact time at the absorption site. Bioadhesives stick to biological substances such as mucus or tissue. They work by decreasing clearance from absorption site, increasing drug amount at adhesion site, and protecting drug from degradation by enzymes. Bioadhesive suspensions/solutions, dry powder bioadhesives, and colloidal bioadhesives are few formulations in this category. *Chitosan* tends to increase the viscosity and decrease the rate of mucociliary clearance of insulin from the nasal cavity, thereby enhancing nasal absorption of insulin in rats and sheep. In situ gelling system is also gaining importance under this category. Thermogelling polymers such as Pluronic F127 and cellulosic derivatives are liquid at room temperature, but viscosity increases significantly at physiological temperature. Starch, hyaluronic acid, dextran, etc. can be used to formulate *bioadhesive microspheres* which prolong the retention time of active component in the nasal cavity. The clearance time can be increased to 3–4 h from 15 min for solution. The bioavailability can be improved for gentamicin and insulin-like preparations (Table 9.5).

Table 9.5 Techniques for enhancing intranasal drug absorption

Chemical	Physical	Enzyme inhibitors
Surfactants (a) Synthetic surfactants: Brij, Lauryl-89 (b) Natural surfactants: Phospholipids, bile salts, plant extract like quillaja saponins, polymers like chitosan, poloxamer, cyclodextrins, etc.	(a) Osmotic pressure, pH (b) Drug concentration and viscosity (c) Powder vs solution liposomes thermogelling systems like pluronic, cellulosic derivatives, etc. (d) Microspheres, e.g., starch, dextran, Carbomer, etc.	(a) Peptidase inhibitors Amastatin, boroleucine, aprotinin, camostat mesilate, leupeptin

Drug delivery from the nose to brain is gaining importance which utilizes the unique neural association of the olfactory and trigeminal nerves allowing the nose and CSF to deliver drugs to the brain. This route may be used for delivery of peptides, proteins, low-molecular-weight polar compounds, large proteins, and polysaccharides like vaccines or DNA plasmids [172]. *Nasal gels* are thickened solutions of drug in an extremely viscous polymer. The longer residence time, least drug wastage owing to abridged postnasal dripping and front escape, irritation reduction, and better drug absorption are few main advantages associated with nasal gels [173]. Nasal drug permeation is enhanced by *mucoadhesive solutions* made by mucoadhesive polymers like chitosan, polycarbophil, etc. They exhibit longer residence time due to viscous and mucoadhesive nature. *Illum et al.* have depicted that nasal administration of cationic chitosan solution showed an improvement in insulin uptake across the nasal mucosa of rat [174]. *Liposomes and proliposomes* were formulated and delivered by various routes. *Wattanathorn et al.* formulated intranasal liposomes containing quercetin and studied its effect in rat, and there was reduction in anxiety-like behavior and increased spatial memory [175]. US Patent 6342478 gives description of a nasal micellar or liposomal preparation for the delivery of fibroblast growth factor to the brain [176]. *Vyas et al*. have formulated multilamellar liposomes for intranasal delivery of nifedipine [177, 178, 179].

9.4.3 Device Considerations for Nasal Drug Delivery System

An ideal nasal formulation should explain connections between formulation components, device design, delivery type, and the patient's condition. Various delivery devices are available for intranasal drug administration as shown in Fig. 9.5. Currently, metered-dose systems provide maximum dose accuracy and reproducibility.

9.4.3.1 Patented and Other Devices

Differences also exist in force of delivery, emitted droplet size, and spray patterns. Delivery devices are important for delivering medication, providing an appropriate environment for formulation storage which includes protection from microbial contamination and chemical degradation. The device and formulation should be compatible so as to avoid potential leaching or adsorption. Table 9.1 describes the characteristics of the individual device used to deliver drugs intranasally [172].

Shin Nippon Biomedical Laboratories Limited (SNBL) has invented a proprietary nasal drug delivery technology, µco™ System, comprising of a powder carrier technology (µco™ carrier) designed for improved drug absorption through its mucoadhesive properties and a delivery device technology designed for accurate delivery of intranasal powder formulations. This technology can be applied to a wide range of drugs, peptides, and biological therapeutics. It can be utilized for improved systemic drug absorption, for enhanced muco-immunity for a vaccine, or for enabling drug delivery to the brain through the olfactory area. They are also

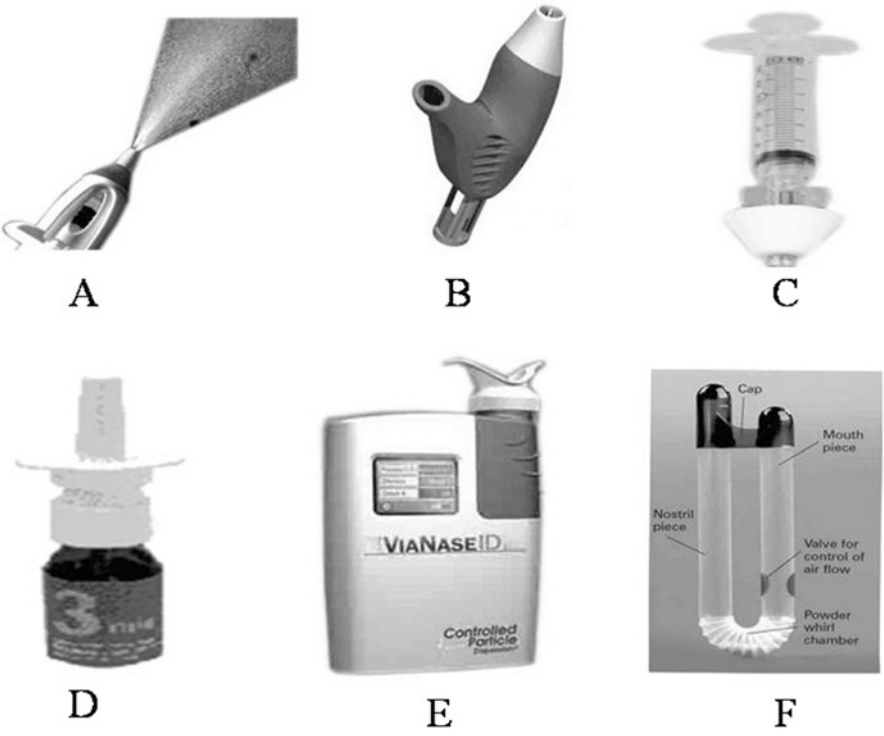

Fig. 9.5 *Various intranasal drug delivery devices*: (**a**) Accuspray Nasal Atomizer, (**b**) OptiNose nasal device, (**c**) MAD (Mucosal Atomization Device), (**d**) Go Medical nasal PCA device, (**e**) ViaNase electronic atomizer, and (**f**) Direct-Haler nasal device

developing a new delivery device technology Fit-lizer™ which is biocompatible and developed according to US regulations of combination product 21 CFR part 4 and 820. Nasal zolmitriptan for migraine is crucial for quick pain relief. A faster pain relief was observed after rapid increase in blood concentration after nasal dosing in a Phase I study conducted in the USA, and it was faster than marketed nasal liquid spray. The bioavailability was also improved 12-fold. Similar results were found in nasal administration of calcitonin for treatment of osteoporosis. It improved bioavailability 16-fold compared to marketed nasal liquid spray using this platform technology. SNBL formulated nasal flu vaccines using the same proprietary technology which confirms mucosal immunity fighting against flu virus infection at entry suite before the virus enters the body. The IgA production was increased fourfold in nonhuman primates after dosing by this technology in comparison with an injection and a nasal liquid spray (Table 9.6).

Table 9.6 Patented nasal drug delivery devices

Nasal drug delivery device	Dosage form	Characteristic	Manufacturer
BD Accuspray	Liquid	Is a single unit needleless device, it creates a spray by forcing the liquid through a pressure-swirl atomizer when the user depresses the plunger on the device	BD Technologies
Direct-Haler	Powder	A bidirectional breath-actuated needleless single-dose device. It consists of a disposable U-shaped polypropylene tube with a corrugated bend and a double cap sealing at the ends of the tube; one arm of the U is slightly longer. To use, the caps are taken off, and the tube is placed between the thumb and the forefinger. Its one end is inserted into one of the nostrils and the other end into the mouth, and the air is blown into the tube to deliver the dose. Results in minimum lung deposition and postnasal dripping. Avoids the use of propellants to deliver the dose by using patient's own breath	Direct-Haler
Go Medical nasal PCA Device	Liquid	Portable, simplest to use, is 0.18mL spray, and incorporates a 3-min fill time (during which another full dose cannot be delivered), minimized postnasal dripping	Go Medical Industries Pty Ltd
MAD (Mucosal Atomization Device)	Liquid	A disposable syringe-based needleless delivery device, atomizes in any position, results in 30–100 m particles, atomized nasal medications absorb directly into the bloodstream avoiding first-pass effect; atomized medications absorb directly into the brain and CSF. Achieves serum medication levels comparable to injections, administration is quick and easy	Wolfe Tory Medical
OptiNose	Powder	A bidirectional breath-actuated needleless single-dose device, the unique bidirectional delivery principle of OptiNose results in improved formulation deposition on nasal parts housing the olfactory region, reduced deposition in the anterior nasal region, and minimized lung deposition. The drug is automatically released when the correct pressure/flow relationship is achieved, more patient compliant	OptiNose
ViaNase ID	Liquid	Pocket-sized needleless single-dose electronic (battery-driven) atomizer, uses the principle of vortical flow to deliver formulations to the entire nasal cavity including the olfactory region and paranasal sinuses, reduced lung deposition	Kurve Technology, Inc.
Vicks	Vapor	Vapor inhaler used in rhinitis and cold	Vicks
Rhinyle catheter	Drops	Desmopressin used in diabetes insipidus, breath powered	Ferring
Mechanical spray pump	Liquid	Hand-actuated mechanical single-dose pump used for influenza vaccine	BD
Multi-dose powder inhaler	Powder	Multi-dose budesonide as nasal inhalation	AZ

Table 9.7 Marketed intranasal products

Drug substance/product name	Indication	Dosage form	Manufacturer
Salmon calcitonin (Karil 200 I.E.)	Osteoporosis	Solution (spray)	Novartis Pharma
Desmopressin (Minirin Nasenspray)	Antidiuretic hormone	Solution (spray)	Ferring Arzneimittel
Protirelin (Antepan nasal) (Relefact TRH nasal)	Thyroid diagnostics	Solution (spray)	Aventis Pharma
Nafarelin (Synarela)	Endometriosis	Solution (spray)	Pharmacia
Buserelin (Profact nasal)	Buserelin	Solution (spray)	Aventis Pharma
Oxytocin (Syntocinon)	Lactation induction	Solution (spray)	Novartis Pharma
Dihyfroergotamin (Migranal∗ Nasal Spray)	Migraine	Solution (spray)	Novartis Pharma
Zolmitriptan (AscoTop∗ Nasal)	Migraine	Solution (spray)	Migraine

9.4.3.2 Marketed Formulations

Intranasal delivery is a rapid and safe method for local and systemic effect. Pharmaceutical industries invested a huge amount of money into this sector after extensive research in nasal drug delivery. A few of the marketed nasal products are listed in Table 9.7.

9.4.4 Characterization of Nasal Formulations

In recent years, like pulmonary drug delivery system, there has been a huge advancement in the field of evaluation and characterization of nasal drug delivery. It can be classified as in vitro, in vivo, and ex vivo methods which are listed in Fig. 9.5. Nasal formulations include nasal spray, nasal drop, and powders in various ways of new drug delivery techniques. In spray generally spray pattern is an additional test to observe formulation characteristic. In case of nasal drop formulations, viscosity of formulation as well as droplet size and shape is an important part to evaluate formulation (Fig. 9.6).

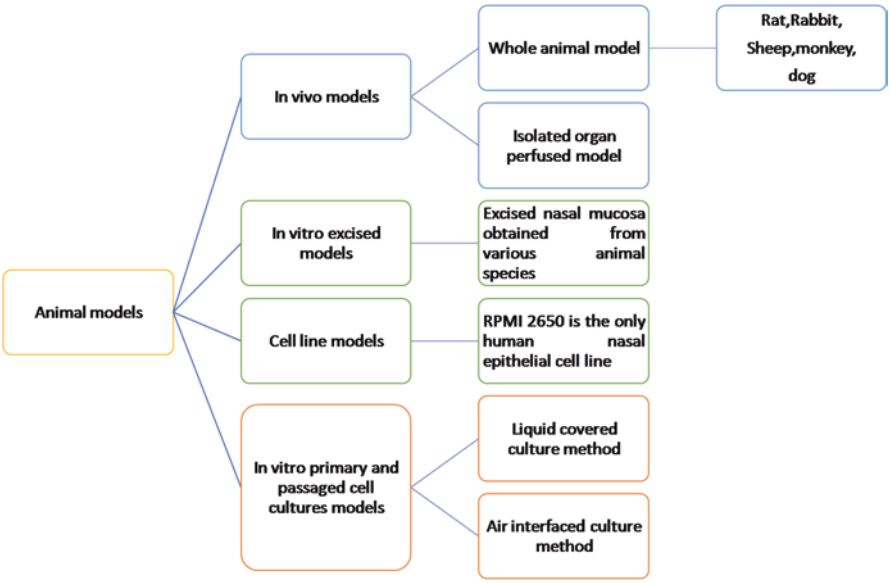

Fig 9.6 Nasal drug absorption and transport study models

9.4.5 Clinical Trials and Patents of Nasal Drug Delivery System (Tables 9.8 and 9.9)

Table 9.8 Clinical trials of nasal formulations

Drugs	Company	Status
Epoprostenol [180]	St. Luke's Medical Center, Chicago, IL 60612	Completed
Sildenafil [181]	Shaare Zedek Medical Center, 91301 Jerusalem, Israel	Completed
Salbutamol [182]	Cipla	Completed
Salmon calcitonin [183]	Novartis	Completed
Desmopressin [183]	Ferring & Partners	Completed
Buserelin [183]	Aventis	Completed

Table 9.9 Nasal formulation patents

Cited patent	Filing date	Issue date	Original assignee	Title
US6610271 [184]	Feb 21, 2001	Dec 15, 2002	Intranasal Tech	The lorazepam nasal spray
US4767416 [184]	Dec 1, 1986	Aug 30, 1988	Johnson & Johnson Patient Care	Spray nozzle for syringe
US5064122 [184]	Aug 10, 1990	Nov 12, 1991	Toko Yakuhin Kogyo Kabushiki Kaisha	Disposable nozzle adapter for intranasal spray containers
US5601077 [184]	Aug 7, 1991	Feb 11, 1997	Becton & Dickinson	Nasal syringe sprayer with removable dose-limiting structure
US8118780 [184]	Aug 23, 2004	Feb 21, 2012	Liebel & Flarsheim	Hydraulic remote for a medical fluid injector

9.4.6 Bridging the Gaps Between In Vitro Activity and In Vivo Efficacy/Therapeutic Potential

The toxicity issues in chronic nasal therapy still remain to be addressed. The next decade will see innovative products on market for therapeutics which are difficult to be absorbed via the nasal mucosa. Furthermore, nose-to-brain delivery of drug is a non-exploited area of research and has a very huge potential. There are number of studies citing nose-to-brain delivery of drugs in animal models for small molecular weight therapeutics as well as biologics. A very less amount of drug (around 1%) goes to CNS compared to drug applied in the nasal cavity. Nose and olfactory membranes are major hurdles of nose-to-brain delivery reaching to the olfactory region; therefore a nasal device is needed that can deposit product to the olfactory region; thus bioavailability can be improved for such drugs in the brain by drug repositioning strategies and absorption enhancers.

9.4.7 Future Perspective and Conclusion

The absorption enhancers have a huge potential and are formulated for peptide and protein drugs, but they failed to reach the market and are still in clinical development. There is only one nasal preparation containing an absorption enhancer that could enter Phase III trial, a nasal chitosan-morphine formulation. A nasal fentanyl spray PecFent contains the absorption modulator PecSys available in the US and Europe market. It could extend drug response by delaying absorption and also keeping the formulation in the nasal cavity for longer time. The future decade will see drug repositioning strategies for those therapeutics that are not speedily absorbed by the nasal route of administration.

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Ophthalmic and Otic Drug Administration: Novel Approaches and Challenges

10

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https://doi.org/10.1007/978-981-13-3642-3_10

Abstract

Disorders of the eye and ear severely influence the life of millions of people worldwide, but management strategies for these disorders present the challenge primarily for the design of formulation and product development. More than 90% of drugs used in various ophthalmic disorders are in the form of conventional formulation that is eye drops; the drugs however applied in the form of topical solution/drops are being washed off by tear drainage/lacrimation, which leads to lower bioavailability in the range of 1–5%. Transport of such topically applied drugs by the use of conventional dosage forms is limited to the ocular tissue, due to unique anatomy and physiology of the eye. To increase the ocular drug bioavailability, effort has been made in the direction of creating the novel drug delivery systems for ophthalmic application. The chapter will basically emphasize on the restrictions with conventional ocular therapy and explore various novel approaches/emerging novel technologies, to improve the ocular bioavailability of drugs to the anterior as well as posterior chamber of the eye. Treatment strategies for inner ear disorders with high safety and efficacy will remain a challenge. The chapter will focus on recent advancement in the field of otic drug delivery along with its potential limitations.

Keywords

Ophthalmic drug delivery · Otic drug delivery · Conventional dosage forms · Novel approaches · Bioavailability

10.1 Ocular Drug Delivery

10.1.1 General Introduction to Ocular Drug Delivery

The eye is an extremely complex organ with a unique structure which restricts the drug entry and makes ocular drug delivery a main obstacle to formulators. Delivery of drug to the eye can be commonly divided into two segments, anterior and posterior. Tissues that cover the anterior portion/segment include the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens, while the posterior segment of the eye is made up of tissues like the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humor. Diseases affecting the anterior part include, but not limited to, glaucoma, allergic conjunctivitis, anterior uveitis, and cataract, while the diseases affecting the posterior segment of the eye include age-related macular degeneration (AMD) and diabetic retinopathy [1].

The most widely preferred noninvasive route is topical instillation using eye drops, which accounts for at least 90% of administered drugs, from which only about 5% of the administered drugs get absorbed due to the washing of drugs through nasolacrimal drainage, reflex blinking, etc. Also, attaining beneficial absorption of drug into the posterior segment of the eye following eye drop instillation is difficult because of the above mentioned obstacles [2, 3].

To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels for the earlier mention ocular diseases. This chapter will provide an overview on various conventional and novel approaches for ophthalmic drug delivery to diseased ocular tissues for the treatment of ocular diseases.

10.1.1.1 Mechanism of Ocular Drug Absorption

The major route by which most ophthalmic drugs enter the eye is traditionally believed to be via the cornea. Recent evidence suggests that a minor route exists involving the conjunctiva and the sclera that are contiguous with the cornea, the so-called non-corneal route [4–6]. The non-corneal route appears to be favored by drugs that are poorly absorbed by the cornea. The bioavailability of ophthalmic drugs is decreased by lacrimal drainage and its systemic absorption through washing from the conjunctiva. Though hydrophilic molecules are absorbed through the sclera and conjunctiva, small-sized hydrophobic molecules get absorbed through the cornea [7]. Negative charge over the corneal surface exerts difficulty in permeability for molecules having negative charge across the pores. Further, tight junction proteins which too are negatively charged prevent permeation of even positively charged molecules [8]. Altogether, the cornea does allow materials through its cells, but various factors influence this flux, like molecular weight, surface charge, lipophilicity, and degree of ionization of the drug [9]. After the transcorneal transport, the molecules diffuse across the aqueous humor to reach the anterior uvea but find difficulty in reaching the posterior segment with therapeutic concentration [10].

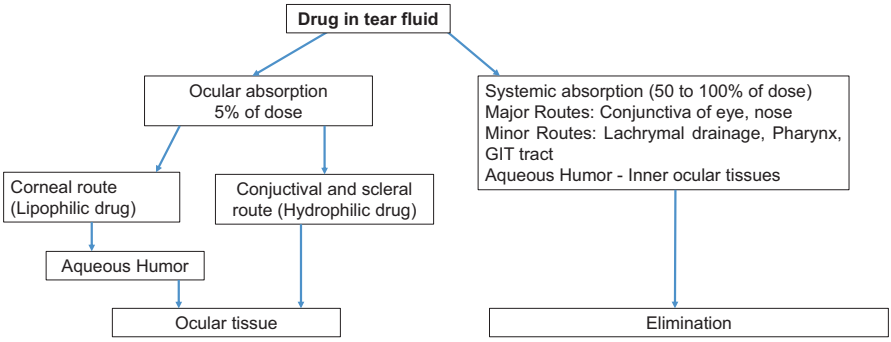

Fig. 10.1 Depiction of drug distribution after topical administration in the human eye

Drug concentration is reduced after the diffusion from the anterior segment to the vitreous humor. Through ion and fluid transfer, the cornea maintains its transparency irrespective of the hindrance posed by the inflammation and endothelium [11]. Major amount of drug loss through the systemic circulation is observed upon administration of drug. Owing to the property of the conjunctiva, drug bioavailability is reduced greatly with its permeation through conjunctival pathway into the anterior segment. The next tissue across the pathway which is the sclera, however, aids diffusion due to its composition which includes polysaccharides and collagen and is poorly vascularized than the conjunctiva. Compared to the cornea, it allows ten times permeation and half that of conjunctiva [12] (Fig. 10.1).

10.1.1.2 Routes of Ocular Drug Delivery-Conventional vs. Novel Routes

Conventional route serves two purposes: (1) treatment to the diseases of the anterior segment of the eye such as conjunctivitis, blepharitis, and keratitis sicca and (2) to deliver medication via intraocular route penetrating the cornea for posterior diseases such as glaucoma or uveitis. Mostly water-soluble drugs formulated as eye drops are used to treat ocular disorders due to benefits like cost-effectiveness, simplicity of formulation development, high patient compliance, stability, little blurring, etc. Problems encountered with topical applications include loss of drug in systemic circulation and related side effects. Only about 20% of the instilled dose is retained into the precorneal sac due to blinking and loss in nasolacrimal drainage [13]. The drug present in the precorneal sac acts like a dynamic force for its passive diffusion into the cornea. However, for effective drug delivery to ocular tissues, high permeation and longer retention in the cornea are required. For improving precorneal residence time and corneal penetration, drug delivery through novel route is requisite.

As the conventional ophthalmic dosage forms offer numerous disadvantages, there is a need of novel drug delivery system. The major problem associated is lower ocular bioavailability, as majority of the drug gets vanished and a small amount essentially reaches the target site. Novel drug delivery systems show an enhanced

retention into the eye and thus offer greater effectiveness and higher bioavailability [14]. To improve ocular bioavailability and to overcome the ocular barriers, various novel drug delivery systems have been developed such as emulsions, suspensions, ointments, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels for the treatments of the ocular diseases [15–18].

10.1.1.3 Challenges for Ophthalmic Drug Delivery Systems

Biopharmaceutical researchers are focused increasingly toward the formulation of a unique approach which can transport the drug in a more bioavailable and safe condition to the active site. As a result, various drug delivery techniques have been developed over the years to target every body part with different molecules ensuring minimum side effects and maximum bioavailability. Therefore, various smart technologies with commendable outcomes have been testified for peptides, proteins, herbal, BCS class IV and class II drugs, etc. Among these techniques, the ones under most exploration are lipid-based system (solid lipid nanoparticles and nanostructured lipid carrier), bioadhesive, vesicular system, nanotubes, emulsion, dendrimers, polymeric nanoparticles, inserts, implants, in situ gel system, etc. [19]. Still, drug delivery to the ocular tissues remains challenging and requires specified characteristics on every development step based on the anatomical and physiological structure of the eye as it hinders the bioactivity and fate of the drug administered. Conventional eye drops are the most desirable ophthalmic dosage forms, due to their compliance and ease in administration to treat local diseases. This makes them highly patient compliance and thus accounts for about 90% of the commercially available ophthalmic products. However, they come with limited therapeutic efficacy and low bioavailability as they are present in the solution form [20]. They do come with some drawbacks: (1) less than 5% of the drug reaches the active site; (2) to get expected effect, frequent instillation is required leading to inconvenience; and (3) blinking leads to drug loss [1]. Based on this consideration, novel delivery systems have been developed for improving corneal residence time, slow drug release, reduced elimination, and improvement of both paracellular and intracellular pathways of epithelial cells. It would be beneficial to reduce dose, dosing frequency which lead to the reduction in side effects by the applied drugs. Thus, ocular drug delivery is a challenging and interesting thing to the scientists working in the field. Previous published data shows many considerable points while developing novel techniques for ocular drug delivery which includes, a constricted size range of more than >200 nm, compatibility, low discomfort, increased habitation time, and little systemic side effect [21]. Thus the most suitable system should be the one which doesn't hinder vision, or produces irritation, and be delivered through eye drops not frequently leading to patient adherence to treatment. Despite hard efforts over the years, desirable ocular drug delivery with efficiency remains a challenge. Therefore, a system designed with improved properties for drug delivery to ocular surface would be a path-breaking step toward ocular disease management. Nanotechnology-based drug delivery can play a key role in ophthalmic drug delivery which may be more than any other administration route [22]. The use of nanocarriers offers

striking substitutions for conventional ocular drug delivery, essentially due to their ability to safeguard the encapsulated drug molecule, beside its assisted passage to the different compartments of the eye [23]. In addition, nanoparticulate devising may provide the possibility of monitoring drug release, making it attractive vehicle for chronic ocular diseases like glaucoma.

10.1.2 Important Factors for Ophthalmic Drug Delivery Systems

10.1.2.1 Barriers to Restrict Intraocular Drug Transport/Factors Affecting Intraocular Bioavailability

Generally ocular preparations are administered topically in the form of eye drops. The drug absorption after ocular application is limited by a variety of barriers which regulate the absorption of drugs into the anterior as well as posterior segments of the eye, hence reducing the bioavailability of ocular medications. These ocular barriers include the conjunctiva, tear film, cornea, blood-ocular barrier, and blood-retina barrier.

- *Tear film*: The film made up of a fluid wrapping the surface of the cornea and restricted between the lid margins. The film thickness is reported to be about 3–10 μm. It is composed of three layers: an external lipid layer; a thick aqueous middle layer having electrolytes, mucins, proteins, and metabolic enzymes; and the inner layer made up of mucin [24]. The secretion and turnover of tears lead to the dilution of drug concentration, and the drainage of drugs through the nasolacrimal duct diminishes the ocular residence time of drugs [25]. The mucins and proteins present in the tears tend to bind to the drug molecules, decreasing the amount of free drug concentration [26].
- *Cornea*: The cornea is another ocular barrier restraining the transport of ocular drugs into the eye. A transparent film present at the forward facing of the eye is the cornea. It comprises of five different layers: the epithelial cells, the Bowman's layer, the stroma, the Descemet's membrane, and the endothelial cells [27]. The epithelial layer comprises of 5–7 cellular layers and has a thickness of about 40–50 μm. The surface of epithelium has tight junctions that limit the transportation of lyophobic as well as ionized molecules owing to its higher lipid content besides the existence of tight intersections. The corneal epithelium pores are charged negatively at the bodily pH. This is because of the presence of carboxylic groups in the proteins of the tight intersection which are negatively charged. As an outcome, repulsive forces of molecules which are negatively charged experience trouble while permeating over the pores. Ionic interaction occurring between the positively charged biomolecules and the negatively charged proteins of the tight junction too poses interference to the penetration of such molecules. The Bowman's layer is approximately 10 μm thick and located after the epithelial basement membrane. The hydrophilic layer, which is having a thickness of about 450–500 μm and accounts for 90% of the thickness of the cornea, is called stroma. Stroma acts as an obstruction for the transport of hydrophobic mole-

cules. Descemet's membrane is nonstructural, flexible, highly drug-resistant layer with a thickness of 10 μm. The layer that remains directly connected with the aqueous humor is endothelial; it is having an approximate 13 μm thickness [28]. Altogether, the cornea difficultly allows the transportation of drugs across the cells, and it is affected by varied factors, like the lipophilicity/hydrophilicity, molecular weight, surface charge, and the degree of ionization of the drug. Additionally, the aqueous humor in addition to the lens placed at the anterior of the vitreous humor limits the drug delivery to the posterior part of the eye [29].

- *Conjunctiva*: The conjunctiva is a layer of mucous membrane which consists of an outer epithelial and goblet cells. The conjunctiva is reflected as the rate-limiting obstacle for the non-corneal route. The epithelium is composed of about two to three cell layers and has a connective tissue which is splendidly perfused by the blood vessels. Due to the highly vascularization of conjunctiva, maximum drugs delivered to the eye enter directly to the systemic circulation. Systemic absorption is viewed as a useless way for controlling ocular disease, causing the drug amount in the anterior as well as posterior segments to be under therapeutic level [27].
- *Sclera*: The sclera comprises of collagen, polysaccharides which is not as vascularized as conjunctiva. This permits many fold permeation than the cornea with almost half of that of the conjunctiva [12].
- *Blood-aqueous barrier (BAB)*: The blood-aqueous barrier is located in the anterior of the eye; it is made up of the epithelium tissue of nonpigmented ciliary and endothelial cells of the iris vascular system, both having tight intersections, inhibiting delivery of drug molecules from the systemic circulation toward the anterior segment [30]. The BAB hinders the permeability of the macromolecules like plasma albumin across the aqueous humor. Smaller lipophilic molecules would easily infiltrate and are generally eradicated through uveal tract [31] (Fig. 10.2).
- *Blood-retinal barrier (BRB)*: The BRB offers constrained penetrability in both, the blood and the retina. The BRB comprises of the retinal capillary endothelium and retinal pigment epithelium, both having tight junctions, limiting the transport of drugs across the systemic circulation toward the posterior segment [32].

10.1.2.2 Physicochemical Property of Drug Candidate

The core physicochemical factors backing the ocular penetration of molecules are partition coefficient, solubility, ionization constant, and molecular weight [9].

- Partition coefficient is an important factor governing the diffusion of the drugs through diverse biological membranes as corneal permeability are subjected mainly on lipophilic characters of drugs. For the hydrophilic drugs with log partition coefficient < 0, the epithelial acts as a resistant/barrier for corneal penetration. While for the lipophilic drugs with log partition coefficient in the range of 1.6–2.5, stroma acts as a barrier for corneal permeation.
- The amount of poorly water-soluble drug in the precorneal tear film might be inadequate which can result in less corneal absorption.

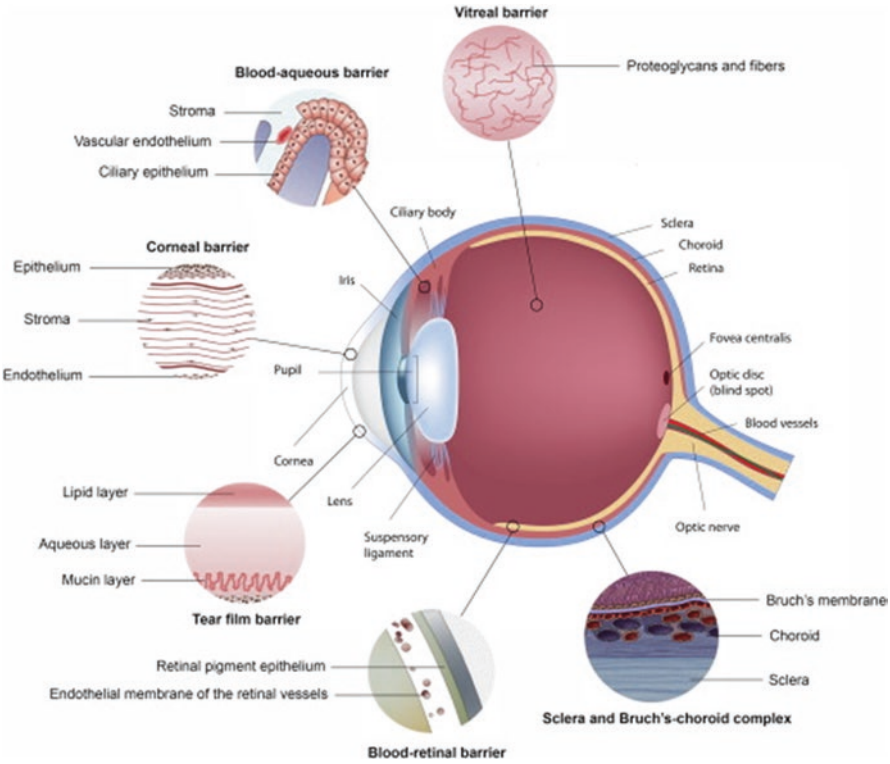

Fig. 10.2 Physiological barriers in ocular drug delivery

- Ionization constant (pKa) of a molecule is an important factor for its corneal permeation. The diffusion of drugs across the membranes is mainly influenced by the ionization constant. Majority of the drugs are either weak bases or weak acids that are ionized partially at biological pH. The ionized form of the drug is poorly soluble in the lipid (limited corneal permeation).
- Generally, transcorneal permeability of hydrophobic drug is primarily governed by lipid solubility, and hydrophilic substances are governed by molecular weight.

Molecular weight is comparatively a less critical factor. Generally, ophthalmic formulations have very low and constricted molecular weight range. Drugs having the molecular weight of more than 500 Da provide poor corneal permeation and vice versa. Exceptions include bacitracin (MW 1411), colistimethate or colistin sulfate (MW 1250), and polymyxin (MW 1200) [29]. These molecules, however, can penetrate the cornea in diseased conditions.

10.1.2.3 Formulation Factors

Various factors like pH, viscosity, optimum lipophilicity/hydrophilicity, irritant drugs, vehicles, tonicity, etc. must be taken into consideration during formulation.

- *Viscosity of solution*

Viscosity is an important factor which helps to retain the drug at ocular sight for a longer time, thereby increasing the contact time. With increasing the viscosity of formulation, rate of solution drainage can be reduced. Viscosity below a certain level does not significantly improve intraocular drug availability, while a further increase in viscosity interferes with visual field and hence is not used. Acceptable viscosity level is about 20–30 centipoises [33]. Formulation with higher viscosity is difficult to filter and sterilize. Polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose and polyacrylic acid, etc. are the variety of polymers used to increase viscosity of topical formulations [34], for example, ketorolac 0.45% solution containing carboxy methylcellulose as viscosity enhancer.

- *Optimum lipophilicity/hydrophilicity*

An increase in lipophilicity restricts drug diffusion. Lipid prodrugs are developed to increase lipophilicity of poorly soluble drugs, e.g., lipid derivatives of 5-FU (5-fluorouracil) to treat proliferative vitreoretinopathy [35]. Likewise, cyclodextrins can be used to improve aqueous solubility of poorly water-soluble drugs, e.g., cyclodextrin-based solutions of pilocarpine, prostaglandins, acetazolamide, or cyclosporine [36].

- *Particle size and shape*

Dissolution of drug is a fundamental property that determines the drug concentration in solution actually exists for diffusion across ocular barriers. The smaller the particle size along with greater surface area, the greater will be the surface-specific dissolution rate and permeation across the cornea [29].

- *Surface charge of molecules*

The mucin layer of the cornea presents a negative charge and normally repels anionic drugs. Pores in the corneal epithelium show a negative charge, and hence, penetration of positively charged molecules will be better through the cornea. Corneal penetration by PnG liposomes is detected in order of positive > negative > neutral. Cationic liposomes deliver a higher concentration of acyclovir to aqueous humor when compared to anionic liposomes and acyclovir solutions in in vivo models. Further, positively charged emulsions demonstrate a higher spreading coefficient on surface with improved precorneal retention and enhanced delivery to posterior segment when compared to anionic emulsion. Chitosan-coated nanoparticles, having a positive surface charge, are shown to increase indomethacin concentration twofold in the cornea and aqueous humor. Chitosan can also be used as

matrix to improve delivery of anionic drugs such as naproxen [37]. Positively charged molecules get bound to negatively charged proteoglycan matrix of the sclera and exhibit poor penetration via transcleral route. Choroid-Bruch's membrane is also less permeable to cationic molecules. These complexes aggregate and reduce the drug delivery to the retina. This is observed in cases of polymeric and liposomal gene delivery to the retina and can be overcome to a significant extent by PEGylating the particles. Negatively charged albumin nanoparticles diffuse more freely in vitreous than cationic nanoparticles [38].

- *Melanin binding*

Melanin is normally present in the uvea and retinal pigment epithelium (RPE). Generally, basic and lipophilic drugs have affinity for it. Melanin binding significantly reduces drug available for therapeutic action and warrants use of larger doses. Melanin binding in iris-ciliary body affects drug response in anterior segment, while that in choroid and retinal pigment epithelium (RPE) affects penetration of drug in the retina and vitreous. Lipophilic beta-blockers are expected to have significant binding to melanin in human choroid-RPE. The sclera, devoid of melanin, does not pose this problem [39]. Choroid-Bruch's membrane demonstrates high resistance to permeation of lipophilic drugs due to presence of melanin.

10.1.3 Ideal Characteristics of Ocular Drug Delivery Systems

- It should be easy to self-administer.
- It should be sterile.
- It should be isotonic with tear fluid.
- It should not induce bad taste after administration.
- It should provide good corneal penetration.
- It should possess more local activity than systemic effects.
- It should deliver the drug to the right place.
- It should be nonirritant.
- It should reduce the number of administration per day.

10.1.4 Conventional Dosage Forms for Ocular Drug Delivery with Their Limitations

Eye drop instillation is a widely suggested and patient-compliant route of drug delivery. However, only 20% of the dose instilled is remained in the precorneal pocket, as much of the instilled dose is lost since the eyes normally blink frequently. However, for effective drug delivery with ocular solution, higher corneal permeation with longer drug residence time is requisite. There are a variety of eye formulations presented in the market, of which conventional eye drops share around 70%

of the recommendations. The reasons include ease in large-scale manufacturing and improved patient satisfactoriness.

10.1.4.1 Topical Eye Drops

These are the utmost suitable, harmless, noninvasive, fast acting, and patient-friendly mode of drug administration to the ocular cavity. Eye drop formulation offers a rhythmic drug infiltration after the administration of drop, subsequently rapidly declining its concentration. This decline in drug concentration might follow near dose-dependent kinetics. Consequently, to advance residence time, permeability, and ophthalmic bioavailability, numerous excipients may be supplemented such as viscosity and permeation enhancers and cyclodextrins. Viscosity enhancers advance the habitation time and ocular availability by administration of topical drop with high viscosity. Various viscosity builders that can be used are HMC, HEC, sodium CMC, HPMC, and polyalcohol.

Permeation enhancers progress corneal uptake by altering the corneal integrity. Other excipients such as preservatives, surfactants, complexing agents, and bile salts can be considered for permeation enhancers. Examples of permeation enhancers include sodium taurocholate, ethylene diamine tetra acetic acid sodium salt, polyoxyethylene glycol ethers (lauryl, stearyl, and oleyl), saponins, benzalkonium chloride, and cremophor EL which have been investigated for enhancing the ocular delivery. Permeation enhancers improve the bioavailability of ocular solutions, but some research has exposed the toxicity occurred through the use of permeation enhancers. Therefore, research is continual phase in order to alter the influence of permeation enhancers to assess their safety over the corneal tissues. Cyclodextrins behave as transporters for lipophilic drug moieties in the aqueous medium. This facilitates transport of drugs to the outer surface. Hydrophilic cyclodextrins have far lower affinity to highly lipophilic biological membrane. Among these methodologies, cyclodextrins and viscosity enhancers show the demerits of precorneal loss.

Examples

DuraSite® DDS (InSite Vision Inc., Alameda, CA, USA) is a polycarbophil-based aqueous solution [40]. Polycarbophil is a polyacrylic acid which is cross-linked with the divinyl glycol and forms a hydrogen bonding with the mucus, conjunctival, and corneal epitheliums, all of which are negatively charged, to prolong the effects of treatment to several hours.

AzaSite® (azithromomycin 1.0%) ophthalmic solution was approved by the US Food and Drug Administration (FDA) in 2007 as the first commercially available formulation for the treatment of bacterial conjunctivitis containing azithromycin [41]. AzaSite® is a wide-spectrum antibiotic, effective against Gram-negative, Gram-positive, and atypical bacteria. AzaSite® has also been explored beyond its clinical indication for the treatment of ocular conditions. Numerous clinical studies have assessed its efficacy and safety in the treatment of the ocular conditions like blepharitis on both the adult and pediatric populations.

10.1.4.2 Emulsions

Emulsions are made up of two immiscible liquids having fine dispersion of droplets. Nano-emulsions have a globule size in the submicron to nanometer range. This comprises of amphiphilic lipids or surfactants. Surfactants are a bipolar molecular structure comprising hydrophilic as well as hydrophobic portion. Owing to their small globule sizes, nano-emulsions are unstable thermodynamically and require higher concentration of surfactants for their stabilization as it can cause a sticky feeling when used on the eye. Microemulsions are promising drug formulations, which are economical to produce, and have ease in sterilization with stability, providing the prospect of introducing larger quantities of active ingredient.

Examples

Restasis®, 0.05% cyclosporine (CsA): The first nano-emulsion that was permitted by the FDA is 0.05% CsA (Restasis®); it delivers 0.05% cyclosporine for the management of dry eye. CsA is a potent immune modulator which is extensively used in the management of ocular disorders like immune-mediated keratitis [42]. Furthermore, systemic administration of CsA can manage various ocular conditions such as uveitis [43]. Restasis is an ophthalmic castor oil-water 0.05% CsA emulsion which was recognized by the US FDA in 2002 for KCS treatment. Outcomes of 0.05% CsA phase II clinical trials have shown it to be the most consistent in the successful treatment of patient's symptoms [42]. Restasis® displayed satisfactory physicochemical properties.

Cyclokat® is a nano-emulsion containing CsA utilizing Novasorb®, a technology exploring interaction between cationic nano-emulsion and anionic eye surface, hence improving the bioavailability to treat the dry eye. Prostaglandins (PGs) used for the treatment of glaucoma are oxygenated cyclic fatty acids. Available PG substitutes are latanoprost, bimatoprost, travoprost, etc. However, several of these drugs are chemically unstable in aqueous solution due to poor water solubility.

10.1.4.3 Suspensions

Aqueous suspensions have few pharmaceutical problems with regard to the poorly water-soluble drugs which include caking and poor redispersibility; this may affect bioavailability because of error in dosing and difficulty with filtration sterilization owing to its wider range of particle size.

Examples

Succeeding single instillation of indomethacin-HPMC and indomethacin-CD into the rabbit's eye, peak drug concentrations in the aqueous and vitreous humor were found to be T_{max} (30 min) and T_{max} (60 min), respectively. Advanced drug levels in different ocular tissues after administration of indomethacin-HPMC in comparison to indomethacin-CD showed the effectiveness of HPMC in treating various ocular disorders. In contrast, HPMC's bioadhesive nature has a vital role in the improvement of ocular drug bioavailability [44].

10.1.4.4 Semisolid Ophthalmic Drug Forms: Eye Ointments

Ointments consist of a solid or semisolid part which is made up of hydrocarbon base and have a softening or melting point near to the physiological temperature. They are semisolid in nature and are purported for external use. After their application to the eye, they break into small droplets that have a longer stay in the conjunctival sac due to their higher viscosity, hence increasing bioavailability. They too have certain shortcomings although they are well borne and safe, and they have the tendency of causing blurred vision and occasional irritation; therefore they are mainly applied during the nighttime (Table 10.1).

10.1.5 Novel Strategies/Approaches to Enhance Ocular Bioavailability

Novel ophthalmic formulations for the drug delivery to the posterior segment have been explored especially to bypass the ocular barriers and various limitation offered by conventional dosage forms. Examples include microparticles, dendrimers, nanomicelles, in situ thermosensitive gels, liposomes, microneedles, implants, nanoparticles, and contact lenses.

10.1.5.1 Nanotechnology-Based Ocular Drug Delivery

10.1.5.1.1 Nanomicelles

Nanomicelles are self-assembled arrangements of about 10–100 μm size range comprising of a hydrophobic core and a hydrophilic shell [45]. Surfactant-based micelles have greater critical micelle concentration (CMC) value, thus remaining unbalanced, whereas polymeric micelles are stable with low CMC upon dilution [46]. PIC has a core-forming block which is charged and is water soluble. The stimulating force for the formation of micelle is the interaction between the core block which has an electrostatic charge and the drug which is oppositely charged aids micelle stabilization. Selection of the drug carrier depends upon its physicochemical properties, active site, interaction between carrier and drug, as well as their biocompatibility [46]. The size and shape of surfactant-based micelles depend upon the amount of surfactants, temperature, pH, as well as the ionic strength of the surfactant. Nanomicelles take the following edges above other systems: ease in permeation, enhanced bioavailability, minimal drug degradation, and no irritation [47].

Table 10.1 Disadvantages of conventional ophthalmic drug delivery system

Solution	Suspension	Ointment
Faster drug elimination from precorneal route	Performance is decided by properties of drug	Non-patient compliance
Drug loss by nasolacrimal drainage	Loss of solid from solution and suspended solid	Unclear vision
		Limitation in drug selection due to partition coefficient

10.1.5.1.2 Nanoparticles and Microparticles

Solid, polymeric, multi-compartment delivery systems are favorable dosage forms for application of drug to the eyeball. Microparticles and nanoparticles can be distinguished from polymeric microvessels with respect to their size, the former between 1 μm and 5–10 μm while the latter from 10 nm to 1000 nm in the case of application to the eyeball [48]. Nanoparticles are a kind of synthetic or natural polymers which are biocompatible and biodegradable, with mucoadhesive properties.

They can be classified into two groups: nanospheres and nanocapsules. Nanospheres are small solid material spheres constituting of dense solid polymeric network, developing over a large specific area. Drugs can either be incorporated in the matrix of the nanospheres or adsorbed onto the surface of the colloidal carrier. Nanocapsules are small capsules formed of a central cavity (oily droplet) surrounded by a polymeric membrane. Ingredients utilized in its development, for the purpose of administration to the eyeball, include polylactic acid, poly(lactic-co-glycolic acid), poly(alkyl cyanoacrylate), chitosan, poly(epsilon-caprolactone), gelatin, and albumin. The drug absorption mechanism from nanocapsules or nanospheres next to their application in conjunctival sac includes degradation or diffusion of the polymer.

The benefits of using nanoparticles in the ophthalmic formulations include enhanced corneal permeation and a larger surface area, which leads to the enhancement of the drugs bioavailability in contrast to conventional formulations. Additionally, low capacity is the key drawback of nanoparticles. Nanoparticulate systems were prepared for sparfloxacin, flurbiprofen, sulfacetamide, cyclosporine A, levofloxacin, piroxicam, acyclovir, and pilocarpine [49].

Initial studies involved Piloplex systems, consisting nanospheres loaded with pilocarpine [50]. Clinical data shows Piloplex lowering the intraocular pressure. Zhang et al. [51] validated better tolerance and pharmacokinetics for PLGA-based nanoparticles loaded with dexamethasone in rabbits after intravitreal injection. Concentration of dexamethasone was sustained in vitreous humor at a steady state for more than a month, with average concentration of 3.85 mg/L. In contrast, on day 7, only rare quantities of dexamethasone with intravitreal injection were detected. Dexamethasone nanoparticles reduced dosing frequency by providing sustained release. Surface charge of the nanoparticles does play its role in ocular drug delivery. Kim et al. [52] demonstrated that human serum albumin (HSA) nanoparticles with anionic surface charge permeated by forming a depot inside the RPE comparative to their cationic counterparts, after intravitreal application. Also, their movement depends on the retinal injury. The site disrupted in the Bruch's membrane and RPE due to the injury in the retina paves way for the HSA nanoparticles to reach the choroid. Hence, more permeability through the ocular tissues like the choroid area is obtained by the presence of anionic charge on the surface of the nanoparticles which provides an efficient treatment of choroidal neovascularization (Fig. 10.3).

10.1.5.1.3 Nanosuspensions

Nanosuspensions are colloidal systems having dispersed particles of submicron size which are stabilized with the help of surfactants or polymers. Nanosuspension

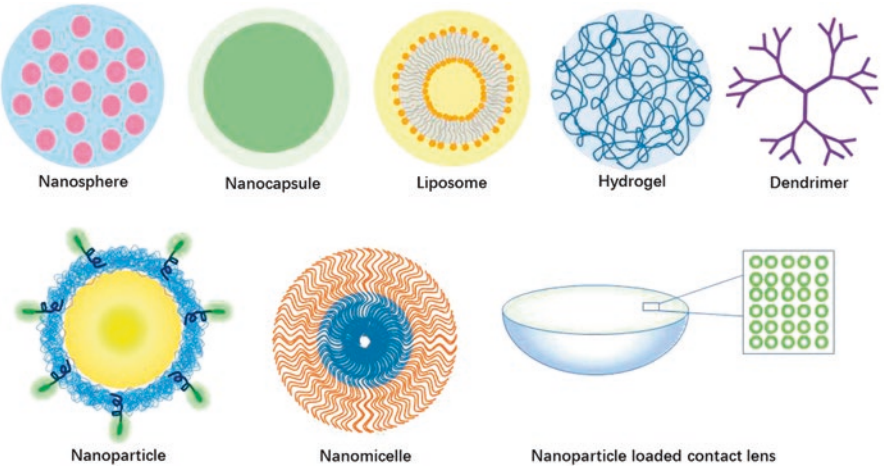

Fig. 10.3 Nano-based/novel ocular drug delivery systems

offers a favorable delivery condition for lipophilic drugs. They come with numerous benefits while dealing with ocular formulations, such as enhanced bioavailability for molecules having poor or no solubility in tear fluid, increased drug retention time, reduced irritation, and ease in manufacturing [53].

For the delivery of ibuprofen (IBU) through the ophthalmic route, a nanosuspension system using Eudragit RS100 was formulated. The formulation had a positive surface charge with mean particle size less than 100 nm, displaying controlled release. Inhibition of meiosis was observed in the rabbit's eye during in vivo studies. After instillation, only a meager amount of free drug entered into the conjunctival sac through the nanosuspension system. In post application of the IBU formulation, enhanced concentration was observed in the aqueous humor with no irritancy or toxicity [54]. Polymeric nanosuspensions were formulated using biocompatible Eudragit RL100R and RS100. Nanosuspensions with RL and RS reflected small particle size through photon correlation spectroscopy making it suitable for ophthalmic administration. Moreover, controlled release and enhanced corneal retention were observed.

To deliver acyclovir (ACV), a novel nanosuspension with controlled release was formulated. Controlled drug release profile can be observed while looking over the in vitro release data [55]. For increasing the bioavailability of glucocorticoids, efforts in the area of nanosuspension have been made. For example, Kassem et al. compared the bioavailability of a number of glucocorticoids in the ocular tissues from solutions, microcrystalline suspensions, and nanosuspensions. IOP in the rabbit eye was measured after instillation of the formulations into the cul-de-sac at predetermined time intervals up to 12 h. The AUC value in IOP vs. time curve for drug solutions was lower compared to all their suspensions. Similarly, more amount of drug absorption and its effects were detected in nanosuspensions [56]. In a separate study, Ali et al. have evaluated hydrocortisone (HC) nanosuspensions which

were formulated by milling and precipitation method with HC solution in the rabbit eye. Significantly higher AUC values were observed with the nanosuspensions by precipitation and milling method compared to that of HC solution which showed AUC value of 15.86 ± 2.7 μg/mL in 0–9 h time period [57] (Table 10.2).

10.1.5.1.4 Liposomes

An ideal ophthalmic drug delivery having convenience of utilization as a drop while localizing and preserving the molecules activity at the active site is being offered promisingly by liposomes. Liposomes are made up of membrane-like bilayer microscopic vesicles surrounded by aqueous compartments. They are expected to be biodegradable and biocompatible owing to their similarity in the lipid structure with the composition of biological membranes. While formulating drug-loaded liposomes, localization of drug into either aqueous or lipid compartments will depend upon its solubility characteristics. Therefore, they have the capacity to accommodate both hydrophobic and hydrophilic molecules, making it possible for hydrophobic drugs to be applied using liquid dosage form. Based on the sizes, liposomes are classified as either SUV (small unilamellar vesicles) for size range of 10–100 nm or LUV (large unilamellar vesicles) having 100–3000 nm size range. MLV (multilamellar vesicles) are those having more bilayers than the above two [58].

As stated in literature "coating of liposomes with high molecular weight chitosan has been shown to reduce aggregation, increase viscosity thus improving residence time in the cornea" [59]. Positively charged liposomes demonstrate higher affinity with the conjunctival muco-/glycoproteins and cornea compared to neutral as well as negatively charged liposomes, hence decreasing the pace of elimination of active molecule from the site of action. Alternatively, suspensions of liposomes or

Table 10.2 Novel ocular formulations approved or under clinical trials

Sr. no	Brand name	Therapeutic ingredient	Indication
1	Visudyne®	Verteporfin (photosensitizer)	Used in subfoveal choroidal neovascularization
			Photodynamic therapy for age-related macular degeneration
2	Tears Again®	Phospholipid	Dry eye syndrome
3	Photrex®	Rostaporfin	Photosensitizing agent with the aim to treat age-related macular degeneration (currently FDA approval pending)
4	AzaSite Plus™	Azithromycin/ dexamethasone (ISV-502)	Blepharoconjunctivitis (under clinical trial= P3)
5	EyeGate II®	Dexamethasone phosphate (EGP-437)	Dry eye (under clinical trial= P3)
6	Iluvien®	Fluocinolone acetonide	Diabetic macular edema (under clinical trial= P3)
7	Cortiject®	Corticosteroid prodrug (NOVA-63035)	Diabetic macular edema (under clinical trial= P1)

mucoadhesive polymer-coated liposome are proposed to increase the bioadhesion of neutral and negatively charged liposome.

Liposomal formulations for ophthalmic delivery are in pipeline for pilocarpine, acyclovir, chloramphenicol, acetazolamide, and ciprofloxacin. Targeting posterior segment, liposomes are being coated with penetration enhancers and bioadhesive polymers for improving permeability as well as conjunctival and corneal adhesion [18, 60]. Liposomal technology has attracted several patents [61, 62].

10.1.5.1.5 Dendrimers

The macromolecular structure having a central core which is been encircled by a sequence of branches are termed as dendrimers. Dendrimers are of nanometer size and have the capability of presenting numerous surface groups to the cell for biological recognition [63]. Due to the presence of −NH2, −COOH, and –OH at the terminal, dendrimers can be termed as positive, negative, or neutral, and this property aids drug to form covalence or electrostatic bonds with it, therefore, making it suitable for ophthalmic drug delivery [64, 65]. Being nano-sized, heavily branched, and star-shaped system, their molecular weight varies and thus can be used in conjugating target moieties.

Dendrimers are of different types:

(a) PAMAM (polyamidoamine) dendrimers have large surface groups and are highly soluble in aqueous system and thus considered as an ideal drug carrier. They have the size range between 1.1 nm and 12.4 nm. Alternative form of PAMAM is made of silicon inverted unimolecular micelles and comprises hydrophobic organosilicon as an external part and hydrophilic, nucleophilic polyamidoamine as the internal part, which is called PAMAMOS (polyamidoamine organosilicon).
(b) PPI (polypropylene-imine) dendrimers are made up of poly-alkyl amines and are toxic; hence they are not used.
(c) Poly aryl ether dendrimers are poorly hydrophilic in nature.
(d) Polydisulfide, polylysine, polyester, or polyether amines are biodegradable dendrimers which act as suitable candidates as antibacterial and antiviral agents and vaccine in ocular drug delivery.

Ophthalmic drugs delivered through dendritic carrier have been successful in enhancing corneal residence time, reducing IOP, and enhancing corneal transport with reduced toxicity; it endorses proliferation of epithelial cells and bioadhesion, with increase in drug uptake which results in increased half-life and ultimately increased bioavailability in order to expedite healing. Numerous systems have been used in ocular for the treatment of mydriasis, meiosis, retinoblastoma, retinal neuro-inflammation, glaucoma, intraocular infections, cataract incisions, and conjunctivitis.

Vandamme et al. successfully established PAMAM dendrimers as systems for pilocarpine for ocular use. They have studied ocular residence time of fluorescein in saline and compared it with that of PAMAM solutions in the rabbit model. Carbopol

solution containing fluorescein was utilized as a reference. The MRT (mean residence time) of drug at ocular surface using PAMAM and Carbopol vehicle was significantly higher than to saline. Hence, for the enhancement of ocular bioavailability, residence time and realizing improved therapeutic outcomes dendrimers could be an alternative method. For example, PAMAM dendrimers containing tropicamide and pilocarpine nitrate showed higher mydriatic and meiotic action in rabbits [65]. Scientists have developed and assessed the potential of PAMAM complexes with puerarin in the ocular drug delivery, and results proved that their complexes were organized through hydrogen bonds. Release profile shows puerarin release to be faster in free-state compared to its complex. Enhanced retention in the rabbit eye cavity was also observed with the puerarin complexes, without any sign of ocular irritation or tissue damage [66] (Table 10.3).

10.1.5.2 Polymer Gels

10.1.5.2.1 In Situ Gelling Systems

The most anticipated dosage form for ocular drug delivery is a one, which has a property of an eye drop, single dosing and no hindrance on vision. In situ gelling system can be termed as a viscous liquid which on exposure to bodily conditions converts to gel form. The prime benefit of the system is accuracy and reproducible dose administration comparing to already gelled systems, besides enhanced precorneal retention. This unique concept was first introduced in the early 1980s. Methods engaged in phase transition onto the surface of the eye are change in the viscosity of solution triggered by temperature difference [74], pH [75], or electrolyte composition [76]. This property reduces drug drainage from the surface of the eyeball and escalates bioavailability of the active ingredient. Polymers used in formulating these dosage forms include poloxamer, gellan gum, and cellulose acetate phthalate, while active molecules in research for in situ gel systems contain timolol maleate, pilocarpine, fluconazole, and ciprofloxacin hydrochloride [60].

Poloxamers have weak mechanical strength and are utilized in thermosensitive in situ gel-forming system. Once blended with alginate, polyacrylic acid, and chitosan, these gels stay longer on the surface of the eye. Sodium alginate gets transformed into gel when contacted with the calcium existing in the lachrymal liquid. Moxifloxacin formulated along with HPMC and sodium alginate was used to sustain the drug release (more than 10 h) in the hydrogel system. Poloxamers are described to be nontoxic and well tolerated even though their larger concentrations (20–30%) are required to acquire a gel. Cellulose acetate phthalate (CAP) is a polymer with potentially useful properties for sustained drug delivery to the eye, since latex is a free running solution at a pH of 4.4 which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4.

Owing to their similarity to the eye drop therapy with regard to dose accuracy and precision, in situ gelling systems seem favorable for achieving continuous release. Gelrite has been studied widely and appears to be favored over the temperature setting systems or pH-sensitive. Poloxamer and chitosan together provide gel strength and mucoadhesive properties along with site-specificity. Molecules used in

Table 10.3 Patents for ophthalmic drug delivery and therapeutics [67–73]

Patent no.	Year	Inventor	Formulation/delivery system	Specification and application
US20110008421	2011	Hara H et al.	Liposome	Liposome to target posterior segment of the eye and prepared by phospholipid, a charged substance and a membrane reinforcing substance
				Drug: 6-cumarin
				Indication: posterior segment
				Inorganic
US8298568	2012	Bague S et al.	Nano-emulsion	Oil-in-water-type emulsion (cetalkonium chloride, tyloxapol, and poloxamer) with average particle size of about 300 nm and positive zeta potential
				Drug: sirolimus
				Indication: uveitis
US8097270	2012	Ketelson HA et al.	Nanoparticles	Nanoparticles (hydrous clays and silica) composed of contact lenses containing surface-active biocide
				Drug: polyquaternium-1
				Indications: antimicrobial, glaucoma
US8153156B2	2012	Ravi N et al.	Nanocomposite by reversible hydrogel embedded nanoparticles	Reversible hydrogel system containing nanoparticles and nanospheres
				Indication: posterior segment
				Inorganic
US8414904B2	2013	Carli F et al.	Nano-emulsion	Oil-in-water emulsion with neutral zeta potential
				Drug: prostaglandins
				Indication: glaucoma
EP2659903 A2	2016	Lee SI et al.	Nano-emulsion	An ophthalmic composition provided in the form of a nano-emulsion
				Drug: cyclosporine
				Indication: keratoconjunctivitis sicca/dry eye
WO2017025588A1	2018	Gaillard PJ et al.	Pegylated lipid nanoparticle	Nanoparticles for the systemic or topical delivery of lipophilic diagnostic or therapeutic agents
				Drug: Macrolides such as cyclosporine, sirolimus/tacrolimus
				Indication: keratoconjunctivitis sicca/dry eye

in situ gel system permitted by the FDA include fluconazole, pilocarpine, ciprofloxacin, tobramycin (Tobradex-ST®), timolol (Timoptic-XE®), and ganciclovir useful for various ocular diseases. Excipients like dextran, Carbopol gels, polyethylene glycol (PG), gelatin, cellulose derivatives, polyvinylpyrrolidone, glycerine, etc. are supplemented due to their bioadhesive and viscosity improving properties that can pointedly improve the retention time at ocular surface [60, 77, 78].

10.1.5.2.2 Contact Lens

Curve-shaped, thin plastic discs intended to be placed on the surface of the cornea are contact lenses [16]. On its application to the cornea, adherence over its surface is owing to the corneal surface tension. Drug-laden contact lenses have been prepared over the years for the treatment of ophthalmic diseases, to deliver β-blockers and antihistamines among others. Post-lens tear film is the region separating the cornea and contact lens from each other. Generally, poly(hydroxyethyl methacrylate) (p-HEMA), 3-methacryl oxypropyl tris [trimethylsiloxy] silane, *N*,*N*-*N*,*N*-dimethyl acrylamide, omega-[methacryloxypropyl] poly dimethyl siloxane, ethylene glycol dimethacrylate, and 1-vinyl-2-pyrrolidone are the key polymers for contact lens manufacturing [79, 80].

Drug-laden contact lenses and/or nanocarriers loaded with drug and incorporated into the contact lens have been a successful development in the area. Over the years for drug delivery to the anterior segment, beta-blockers, antihistamines, timolol, dexamethasone 21-acetate, dexamethasone, and several antimicrobials have been developed [80]. Owing to the increased residence time over the corneal surface, high drug flux occurs between it and the POLTF which minimizes the drug loss through nasolacrimal duct. Mostly contact lenses are being soaked into the drug solution, show minimal drug loss with slow release due to prolonged residence time, and also improve bioavailability and efficiency relative to the conventional drops. For example, p-HEMA-based contact lenses loaded with dexamethasone provide higher bioavailability in the ocular tissues when compared with the eye drops [81].

To obtain increased drug loading and sustained release, surfactant coating over the contact lenses has been done. It is achieved by optimizing the interfacial tension between hydrophobic tail of ionic surfactant and the contact lens matrix, aiding adsorption of more surfactant molecules to the polymer surface. Surfactant-coated contact lenses have high surface charge which helps in the adsorption of the ionic compounds over its surface with high affinity, which decreases the transport rate leading to extended release. For example, anionic drug like dexamethasone 21-disodium phosphate interacts and remains localized to the p-HEMA contact lenses with cetalkonium chloride (cationic surfactant). Slow diffusion rate was observed with molecules which are adsorbed on the surfactant-coated polymer and offers lower diffusivity than free drug. Loading of surfactant boosted the release duration in Acuvue® contact lenses from about 2 to 50 h [79].

Although offering several benefits over and above the conventional ocular drops, contact lenses too suffer from few drawbacks such as insufficient drug loading and short-term drug release. Further improving the drug loading and release duration,

various colloidal systems like liposomes or nanoparticles are being laden into contact lenses along with molecular imprinting. For such systems, the active molecule is first entrapped into the colloidal systems and then dispersed in the contact lens material. There are studies reported where lidocaine entrapped in the microemulsion and/or liposomes is incorporated into the p-HEMA-based hydrogels demonstrated release over 8 days [82, 83]. Also, drug loss during storage is to be avoided by storing the contact lenses into solution saturated with drug. Smart contact lenses which release drug upon stimuli or contact with the corneal surface may overcome such issues.

The implantation technology could serve as a novel ocular drug delivery platform capable of alleviating many ocular diseases. To treat the chronic disease like glaucoma, Maulvi et al. have prepared timolol nanoparticle implant-laden contact lenses using this novel approach, which is capable of showing reduction in intraocular pressure (IOP) for 192 h in rabbit model [84]. Using this same technology, for the treatment of dry eye, researchers have prepared hyaluronic acid (HA)-laden ring implant contact lenses that showed greater efficacy to treat dry eye syndrome [85]. Timolol and HA (comfort agent) implant-laden contact lenses were prepared using implantation technology which showed the presence of timolol in tear fluid of rabbit till 72 h and significant reduction in IOP compared to high-dose eye drop therapy [86]. Again to treat bacterial conjunctivitis, moxifloxacin and HA (comfort agent) implant-laden contact lens were prepared using this platform technology that showed equivalent healing effect against *S. aureus*-induced conjunctivitis in comparison to the frequent high-dose eye drop therapy [87].

10.1.5.3 Other Drug Delivery Systems

10.1.5.3.1 Implants

Implants are polymeric devices which are being employed to prolong the drug release by inserting them into the eye surgically. These implants are capable of transporting the drug over a period of months or years. There are numerous types of implants: biodegradable, nonbiodegradable, and stimuli-responsive. Nonbiodegradable implants trapped molecules by dispersion in the polymer matrix and enclosed by the polymer membrane that controls the drug release. Ethylene vinyl acetate, polyvinyl alcohol (PVA), silicon, etc. are generally used as nonbiodegradable ophthalmic implants. FDA permitted ganciclovir containing Vitracert® for cytomegalovirus and fluocinolone containing Retisert® for uveitis. These implants are inserted surgically and sutured to the sclera. They are implanted for a period of 5–8 months for Vitracert® and about 2.5 years for Retisert® [88, 89].

These biodegradable ophthalmic implants comprised of PLGA and PLA which get degraded to CO_2 and water into the body by water or enzyme. Dexamethasone containing Ozurdex® is permitted by the FDA for diabetic macular edema and is being implanted for up to 6 months. For example, biodegradable implants are Ozurdex® and Surodex® [90]. The trick behind it is the carrier residue which needs to be removed surgically once the drug has been depleted, leading to non-compliance. If not removed, the accumulation could lead to cataract, hemorrhage, and other complications.

10.1.5.3.2 Microneedles

These are minute separate needles or arrangement of micron-sized needles, prepared by using the tools from microelectronics industry. Microneedles were actually formulated for transdermal-type drug delivery. Microneedles made from stainless sheet metals are solid, hollow, and 500 to 750 μm in length, whereas glass microneedles were prepared from borosilicate material [91]. Nowadays microneedles have been utilized for drug administration into ocular tissues especially to the back of the eye in minimally invasive manner. Microneedle-based drug delivery reduces the risk as well as the associated complications with intravitreal injections, like hemorrhage, detachment of the retina, endophthalmitis, cataract, or pseudo-endophthalmitis. It can bypass the blood-retinal barrier and offers an effective treatment approach specifically for age-related macular degeneration (AMD), posterior uveitis, and diabetic retinopathy (DR). Microneedles are specially designed to penetrate directly to the sclera or suprachoroidal space (SCS), the area between sclera and choroid; therefore injury to inner ocular tissues may be circumvented [92]. Either drug solution or carrier system (nano-/microparticles) deposited in this region may assist diffusion of drugs into inner tissues (like neural retina and choroid). Drug molecules dissolve rapidly following insertion of microneedles, following which microneedles are removed, e.g., pilocarpine-coated microneedles. With the use of microneedles, in vivo concentration of fluorescein in anterior segment was detected to be 60 times higher as compared to topical application [93].

Surface covered microneedles were studied to deliver the active compound to posterior chamber in rabbit and cadaver eyes. In vivo studies of microneedles loaded with pilocarpine in rabbit model provide faster drug dissolution and also depot formation. The depot formed by such system increases the bioavailability of drug (pilocarpine) by providing the sustained release of drug from the cornea, causing faster pupil constriction [94]. Microneedles have been utilized as a method of drug delivery to infuse and deposit drug microparticles, solutions, and nanoparticles into the sclera. Micro-carrier drug delivery systems if located near the posterior part (the back of the eye) tissues (i.e., in SCS) can bring high concentrations of drugs to the retina-choroid. Researchers have tried to administer nanoparticles, microparticles, and drug solution using these microneedles in various animal models (pig, rabbit, cadaver, etc.) and proved to be safe and less invasive and also form drug depot at the application site. The pharmacokinetics study of SCS deposited suspension or solution confirmed the long half-lives for soluble/dissolve molecules, nanoparticles, macromolecules, and microparticulates [3]. However, the thorough pathway or mechanism for drug solution/microparticles/nanoparticles clearance from SCS has yet not been defined well; hence further studies are required. Microneedle-based drug administration may act as minimally invasive means of drug delivery to the back/posterior segments of the eye (i.e., choroid, neural retina, Bruch's membrane).

10.1.6 New Trends/Emerging Technologies for Ocular Drug Delivery

10.1.6.1 Punctal Plug Delivery System (PPDS) or Evolute®

By combination of innovative punctal plug with drug-eluting central core (Fig. 10.4), Mati has industrialized an absolutely noninvasive and sustained release platform which is identified as the Evolute® or Punctal Plug Delivery System (PPDS). The Evolute® is introduced into the individual's punctal duct using a noninvasive method. Once placed at application site, the Evolute® is capable of transporting the drug to the ocular site or to the tear film over a predetermined time. After completion of the treatment, Evolute® is detached with no additional follow-up, in the case of acute conditions. For chronic conditions, patients have to reach the clinic for removal of the exhausted Evolute®, and for the continuation of treatment, a new Evolute® is inserted. The advantage of this system is easy removal without any surgical procedure. The unique conformation of PPDS produces a unidirectional system for the effective therapy at application site. The most important advantage offered by PPDS is the non-bioerodible and nonbiodegradable nature of punctal plug and the drug core. So it becomes easy to predict precisely the quantity of drug formulation transported during the period of therapy. It is possible to achieve high retention rates with PPDS as the retention features of punctal plug will remain unchanged during the course of therapy. Clinical experiments have established a repeated and expected retention rate with the range of 92–96% above a 90-day period of treatment.

It is a platform technique that can be customized for the treatment of multiple anterior chamber-related disease conditions of the eye. Based on the ophthalmic disorder, the period of drug delivery with release rate can be adjusted like low level

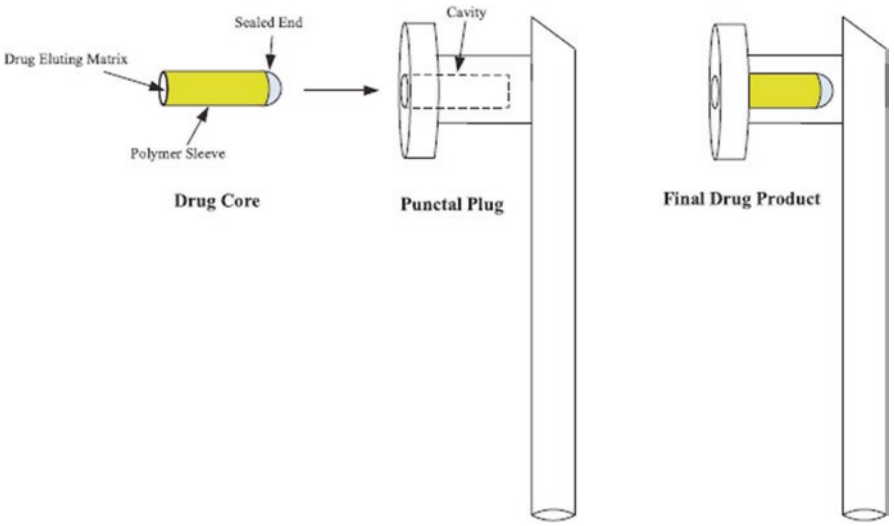

Fig. 10.4 Evolute® or Punctal Plug Delivery System (PPDS)

and high level (for treatment of post-cataract surgery), for short or long term (for chronic disease) [95]. Numerous products like for allergy medications, anti-inflammatories, glaucoma therapies, and post-cataract surgery have been developed using Evolute® technology.

For instance, the Evolute® can be considered to transport higher amount of medication at initial stage followed by a lower steady concentration over a long period of time. The other advantages with Evolute® system are as follows: (1) it allows both lipophilic and hydrophilic compound formulation, and (2) it does not contain any preservative, so adverse effects related to long-term use of preservatives could be eliminated. Preservatives like benzalkonium chloride have been proved to cause the unwanted effects like conjunctival inflammation, toxicity to the cornea, instability of tear film, and cataract development. Since the PPDS prevents drug loss into the canaliculus, it resulted in less systemic absorption and hence greatly decreased the unwanted systemic effects related to some of the ophthalmic medications (Fig. 10.5).

Many of the patients choose PPDS over the eye drop therapy during the clinical studies as benefit provided by system is that one has not to do anything after insertion of the device. Assuring enhanced adherence and more steady management of the disease conditions can lead to superior outcomes.

10.1.6.2 DelSiTech®

The proprietary technology is based on silica matrix which is non-mesoporous and biodegradable in nature where the active molecule is released by the dissolution of silica matrix in tissue, i.e., the mechanism of drug release is through the bulk matrix erosion and not by diffusion. It is possible to adjust the properties of silica (sol-gel derived) which could be used for accurate APIs encapsulation/loading, and the required rate of degradation by the dissolution of silica in tissues could be achieved from days to months or up to a year. DelSiTech® has established various formulations which could be used for ocular drug delivery like injectable, silica-based matrix formulation, etc. The silica microspheres encapsulated in silica hydrogel are the first drug delivery system developed successfully. The active molecule is embedded in silica microspheres that act as the reservoir for drug molecule elution and also control the release of drug by dissolution of matrix. As one can control the rate of degradation from silica microsphere, an accurate drug release could be achieved. Silica matrix is hydrophilic in nature, and once positioned inside the body, silica

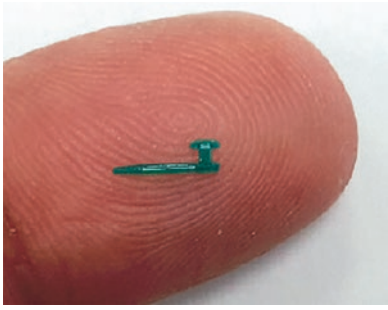

Fig. 10.5 Tiny Evolute® device

gets solubilized in tissue liquids. Hydrophilicity (water solubility) of these microspheres is a fundamental characteristic which can be tuned easily, as hydrophilicity of any molecule is governed by the OH-group density and the number of OH groups on the exterior surface of the silica matrix. It is also possible to produce microsphere with different surface properties with just simple adjustment in the reaction parameter ad composition like concentrations of chief precursors that are tetraethyl orthosilicate (TEOS) and water. These silica-based hydrogels could be delivered either through subconjunctival route or by IVT route and can be used for the treatment of disease where sustained release of drug molecule is desired for a minimum of 1 month. With such system, it is possible to prepare longer-acting formulations which could provide the prolonged release of the drug for about 3–6 months. The formulation of an ultra-long-acting silica matrix system is limited due to the desired dose of drug that directly affects the injection volume (normally maximum 0.1 ml).

Using the potent drug molecule, it is easy to design such dosage form that releases the drug for about 12 months [96]. For the treatment of conditions related to the frontal part of the eye, silica hydrogel formulation placed under conjunctival cul-de-sac represents the opportunity for such condition as the material used for formulation composites adheres well to the conjunctiva and releases the drug molecule in a controlled manner. Model composite has been prepared using fluorescein molecule embedded in silica microspheres which are further encapsulated in silica-based hydrogels. The administration of these composites in the form of "eye drops" to rabbit eye releases the fluorescein for about 24 h from hydrogels system without any signs of discomfort and irritation (Fig. 10.6).

Fig. 10.6 Silica-silica hydrogel composite

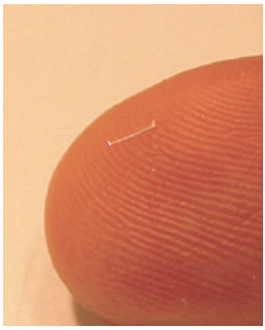

Fig. 10.7 Silica micro-implant with 0.4 mm diameter

10.1.6.2.1 Silica Ocular Micro-implants

For the ophthalmic drug delivery, the drug-eluting implants are the first dosage forms that release the drug in controlled manner. Majority of implants have limitations particularly for repeated use, as they are made up of nonbiodegradable type of materials and hence need to be removed once used. DelSiTech has also established micro-implant-based technology (Fig. 10.7) using silica matrix that is biodegradable in nature (for IVT injection). Micro-implants which are made up of silica are usually transparent specifically when it comes in contact with water. The therapeutic action of viral vectors and biomedicines can be preserved as it is easy to control the water content of micro-implants. The formulation of silica micro-implants includes the casting of drug-containing silica solution into a mold/die before formation of sol to gel. Then the gel is formed in the die after controlled drying. These implants provide an alternative approach to injectable in case of sensitive APIs, which are not appropriate for spray-drying.

10.1.6.3 OpsiSporin

OpsiSporin is a long-acting treatment approach for uveitis development by Midatech. It contains encapsulated cyclosporine that is traditionally used for organ transplantation as an immunosuppressant agent. The mechanism of drug molecule includes the interleukin-2 inhibition during T-cell activation, thereby suppressing the cell-mediated immune response. This cyclic peptide drug molecule forms a complex with T-cell protein called cyclophilin, which inhibits calcineurin (responsible for the activation of interleukin-2). That causes a reversible immunosuppressive action, when treatment is terminated. So, immune-related disorders or diseases involving the cytokines, like noninfectious uveitis, are the possible candidate disease for cyclosporine. Cyclosporine has been speculated as the best treatment option for noninfectious uveitis by preventing activation and proliferation of T cell. Sustained delivery of cyclosporine to the posterior chamber of the eye is likely to decrease the requirement of oral drugs used for the management of uveitis, especially oral glucocorticosteroids and immune-suppressing agents; further by the literature survey, intravitreal cyclosporine is proved to be effective, well tolerated, and safe. Therefore, OpsiSporin is likely to be efficacious for the treatment of posterior chamber disease like uveitis. For the treatment and prevention of recurrence, the use

of this approach can eliminate the requirement/need of steroids for long-term treatment of inflammation, bypassing the chronic systemic corticosteroid complications. Sustained cyclosporine delivery is attained by the use of bio-resorbable polymer excipients. Cyclosporine release is mediated by the hydrolysis of the polyester backbone and that broken down to its component monomers leads to the gradual erosion of polymer matrix. OpsiSporin is available in the form of a powder that needs to be resuspended to a suspension prior to its use. There is still a need for significant development for simple and reproducible injectable suspension as it is to be given by intravitreal route where volume is limited to small quantity, also the hydrophobicity of drug-laden microspheres, etc. The company Midatech is working for the development of formulation which rapidly reconstitutes and is safe and consistent.

For chronic ocular conditions like noninfectious posterior uveitis, solid preparations that are easy to administer, precisely defined, and able to deliver drug release in a controlled manner to the eye over a period of 3–6 months are ideal substitutions [97]. In the development of this drug delivery platform, Midatech technology may bring significant benefits to the uveitis patients by producing easy-to-use, long-acting, and effective products that can bypass the unwanted adverse effects of systemic/local steroids or immune-suppressing agents.

10.1.6.4 ForSight VISION5®

ForSight VISION5® is an ocular ring intended for topical application as a substitute of eye drop use to treat glaucoma. ForSight VISION5® is focused on developing noninvasive drug delivery products that replace eye drops and provide sustained therapy for major eye diseases including glaucoma, dry eye, and allergy. The insert of bimatoprost is an ocular ring without any preservative, containing 13 mg of drug (bimatoprost) mixed with silicone matrix positioned above polypropylene support, having the thickness of 1 mm and diameter in the range of 24–29 mm (Fig. 10.8) [98]. Release of drug depends on various factors like concentration gradient and drug molecular diffusion through the matrix structure. The rate of drug release into the tear film is mainly governed by the concentration of drug in silicone matrix, surface area of matrix, and the physicochemical properties of silicone. The bimatoprost insert provides the release of drug in a declining manner like high drug release at 0 day (insertion) than at 180 days (removal period) [98]. Bimatoprost was just selected as a model drug; one can also incorporate other drugs of this class

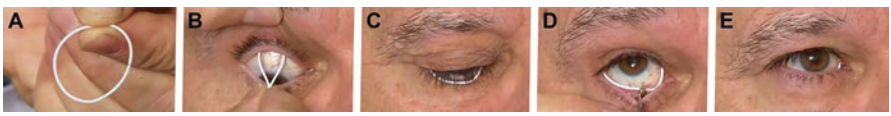

Fig. 10.8 (**a**) Bimatoprost ocular insert. (**b**) For the placement of insert, the upper lid is retracted, and the insert is placed in the upper fornix by the physician. (**c**) Placement of the top half of the insert in the upper fornix. (**d**) The lower lid margin is retracted manually or using a scleral depressor to seat the bottom half of insert into the lower fornix. (**e**) Insert in situ with a small portion of the insert visible in the medial canthus

(prostaglandin) like latanoprost or travoprost without any further difficulty into silicone matrix. The insert of bimatoprost is an answer for controlling glaucoma (reduction in IOP), which can provide the sustained release of the drug for 6 months. The ring offers benefits like it is well-retained, noninvasive, and well accepted by patients. About 90% of the patient population were happy while wearing a blank (non-medicated) ring, and excellent retention was found in both the eyes for a period of about 6 months during Phase I clinical studies. First Phase II trial results showed sustained reduction of intraocular pressure (IOP) of 4–6 mmHg (or ~20% IOP reduction) for 6 months, high retention, and excellent safety profile. After the successful trials in Phase II studies, it is now going to enter in Phase III.

10.1.6.5 OcuSurf™

OcuSurf™ is a water-based nano-dispersion of soluble lipophilic drug molecule in nanostructured "cores" that quickly get absorbed into the phospholipid layers of ocular muscles. The components of nano-dispersion permit the interaction and adhesion with biological membrane, nano-core melting, drug release, and quick absorption. OcuSurf™-LP, OcuSurf™-MOX, OcuSurf™-DX, and OcuSurf™-FP are the several products for drug delivery using this technology [99] (Fig. 10.9).

To be more specific, research on topical product (OcuSurf™-LP) for the treatment of inflammation caused after cataract surgery is ongoing. Loteprednol etabonate a corticosteroid 6 ester with C-20 has a well-designed structure and developed as an OcuSurf™ to treat ocular inflammation. OcuSurf™-LP has certain characteristics like membrane-adherent, non-settling, and stable on storage at room temperature and exhibits better bioavailability. The central core contains the dissolved drug that releases at ocular temperature. The drug holding cores are distributed in a hydrophilic and bioadhesive polymeric phase that constitutes continuous phase, with 350 cps viscosity (Table 10.4).

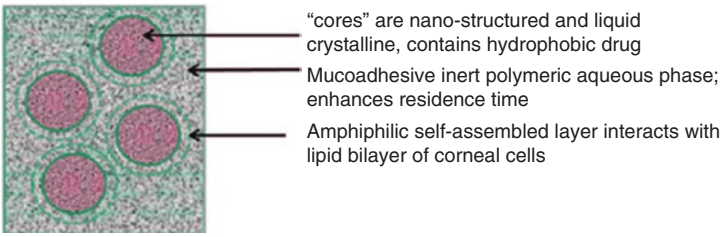

Fig. 10.9 OcuSurf (aqueous nano-dispersion)

Table 10.4 Various ocular formulations under clinical trial

Study title	Indication/condition	Interventions/ treatment	Status	Identification no.
An Open-label Extended Clinical Protocol of Ranibizumab to Evaluate Safety and Efficacy in Rare VEGF Driven Ocular Diseases (ECLIPSE)	Glaucoma, diabetic retinopathy	Drug: ranibizumab	Phase III	NCT01908816
Ziv-aflibercept in Ocular Disease Requiring Anti-VEGF Injection (Zaltrap)	Macular degeneration, diabetic retinopathy, retinal vein occlusion, cystoid macular edema	Drug: ziv-aflibercept	Phase II	NCT02486484
EYE001 to Treat Retinal Tumors in Patients With Von Hippel-Lindau Syndrome	Hippel-Lindau disease	Drug: EYE001 (intravitreal injection of anti-VEGF pegylated aptamer	Phase I	NCT00056199
Ranibizumab Injections to Treat Retinal Tumors in Patients With Von Hippel-Lindau Syndrome	Von Hippel-Lindau syndrome	Drug: ranibizumab	Phase I	NCT00089765
Comparative Study of Thymosin Beta 4 Eye Drops vs. Vehicle in the Treatment of Severe Dry Eye	Dry eye syndrome, Sjögren's syndrome, graft-versus-host disease	Drug: thymosin beta 4 eye drops Drug: vehicle control	Phase II	NCT01393132
Prophylactic Effect of Ketorolac Tromethamine on the Cystoid Macular Edema After Phacoemulsification in Diabetic Patients	Cystoid macular edema after phacoemulsification	Drug: using of ketorolac tromethamine eye drop	Phase II	NCT03551808
Treatment of Dry Eye Using 0.03% Tacrolimus Eye Drops	Sjögren's syndrome, dry eye syndrome	Drug: tacrolimus Drug: olive oil	Phase IV	NCT01850979
Intravitreal vs. Sub-tenon Injections of Triamcinolone Acetonide for Macular Edema in Retinal Disorders	Macular degeneration, retinal vein occlusion, diabetic retinopathy	Drug: triamcinolone acetonide	Phase I	NCT00101764

10.1.7 Biodegradable Polymers for Ophthalmic Applications

10.1.7.1 Natural Biodegradable Polymers

10.1.7.1.1 Gelatin

Gelatin is a natural polymer derived from the purified fraction of protein collagen. Commercially gelatin is available in two types: designated as type A (partial acid hydrolysis) and type B (partial alkaline hydrolysis) of animal collagen. By changing the polymer physical and electrical properties, ophthalmic drug delivery systems using gelatin can be optimized [100]. Gelatin in an aqueous solution acts as a hydrogel with thermo-reversible properties. These thermo-reversible hydrogels break at 30 °C as they have lower mechanical strength, which leads to drug loss. To provide thermal stability to gelatin, polymer chains can be chemically cross-linked, e.g., pilocarpine hydrochloride laden carbodiimide cross-linked hydrogels to treat glaucoma. Gelatin as a polymeric carrier has an advantage of prolonged residence time at the application site (ocular surface). Vandervoort et al. have formulated the gelatin nanoparticles capturing hydrocortisone and pilocarpine HCl for ophthalmic applications. They have investigated the effect of important parameters (like type of gelatin and pH) on the nanoparticle preparation [101]. Gelatin was widely engaged for the preparation of various ocular devices like microspheres [102] and microcapsules [103].

10.1.7.1.2 Collagen

Collagen is a natural polymer which is biodegradable and biocompatible in nature, commonly found in ocular tissues like the stroma, cornea, and sclera. Collagens distributed in human tissues are normally 300 nm long with a molecular weight of 300,000. Type I collagen is the commonly existing protein in the mammals. Due to structural similarity (secondary and tertiary) of animal collagen (derived from porcine and bovine) with human collagen, animal collagen could also be utilized for human use. In vivo, collagenase and metalloproteinase enzymes are involved in the degradation of polymers and conversion to corresponding amino acids. The degradation rate of polymer can be controlled by cross-linking agents and the enzymatic treatment. Collagen is extensively used to prepare collagen shields because of excellent absorption capacity, biocompatibility, and low immunogenicity [104]. These collagen shields act as drug reservoir and thereby boost the bioavailability of drug and also provide prolonged contact time to corneal surface. As polymer is capable of forming the gel-like structure onto the dry eye surface, shield can be utilized for treatment of dry eye syndrome. These polymeric structures were also used for delivery of antiviral, antifungal, antibacterial, anti-inflammation, anticoagulant, and immunosuppressive agents [105].

10.1.7.1.3 Chitosan

Chitosan (CS) is derivative of chitin that upon deacetylation produces the natural polymer chitosan. Degradation of chitosan occurs through various enzymes like lysozyme, papain, and chitosanase in vitro, but in vivo degradation occurs mainly

through lysozyme enzyme. The degradation rate of CS is proportional to the degree of acetylation and polymer crystallinity in inverse order. CS holds several properties like mucoadhesiveness and penetration enhancer, which render its application for ocular use. Both nanoparticles and nanocarriers coated with chitosan showed high affinity for corneal and conjunctival cells. Chitosan increases the penetrability of drug molecules by modifying the tight junctions of epithelial cells of the cornea in reversible manner. The ocular bioavailability of drug molecules was found two- to tenfold higher with chitosan nanoparticles compared to drug suspension in chitosan solution [106]. Nanocapsules coated with chitosan were found more efficacious than nanocapsules coated with PEG. CS enhances the nanocapsule retention in the outer layers of the epithelium, while PEG quickens the diffusion of carrier/nanocapsules throughout the epithelium [107].

10.1.7.2 Synthetic Biodegradable Polymers Used for Ocular Drug Delivery

10.1.7.2.1 Poly N-Vinylpyrrolidone (PVP)

PVP is a biocompatible polymer widely used for vitreoretinal delivery systems. It is mostly engaged for the preparation of hydrogels showing viscoelastic characteristics [108]. Decomposed products of PVP-based hydrogels are eliminated easily through phagocytosis from the vitreous humor. Hydrogels were transparent and remain accumulated at injection site for loner period (several weeks). However, breaking up of the hydrogels generates an inflammatory response forming the vacuole in the retinal pigment epithelium [109]. Clinical studies prove that PVP-based hydrogels cause hazy cornea, intravitreal opacity, and also an inflammation. Hence they are not considered appropriate as alternatives for vitreous applications. Studies also suggest the use of implants made up of PVP as valuable approach for the treatment of glaucoma, which could provide controlled release of APIs for a period of 300 days.

10.1.7.2.2 Poly(lactide) (PLA), Poly(glycolide) (PGA), and Their Copolymers Polylactide Co-glycolide (PLGA)

Both of these polymers are the most promising to use because of their unique property, biodegradation [110]. Alone poly(glycolide) (PGA) is extremely susceptible to hydrolysis; in addition it is insoluble in organic solvents, hence not widely suitable for the controlled release formulations, while alone poly(lactide) and poly(glycolide) in different ratios are generally used in different formulations. Both the polymers upon nonenzymatic or enzymatic hydrolysis produce hydrophilic metabolites that are harmless to living tissues. These polymers mainly degrade through bulk erosion. For instance, using different ratios of lactide and glycolide, PLGAs with a variety of diffusion and degradation profiles can be achieved. PLA and PGA alone degrade at slower rate compared to PLGA with 50% PLA and 50% PGA [111]. The methyl group present in PLA provides more lipophilicity and hence degrades at slower rate while comparing with PGA. Dillen et al. have developed a PLGA nanoparticle coated with cationic Eudragit® loaded with a commonly used fluoroquinolone, ciprofloxacin, for ophthalmic infections. They have found that drug-loaded

nanoparticles which are positively charged can adhere well to the negatively charged surface of bacteria. By providing extended diffusion controlled release, this system improves the drug concentration at target ocular site [112].

10.1.7.2.3 Poly-ε-Caprolactone (PCL)

PCL is a polyester produced using monomer ε-caprolactone through ring-opening polymerization with stannous octoate as catalyst at 140 °C. Modification in permeability and crystallinity can be achieved by copolymerizing PCL with PLA or PGA. PCL is degraded in two phases. In the first phase, cleavage of ester linkage leads to the loss of molecular weight up to 5000 (chain scission), producing ε-hydroxyl caproic acid, and leads to reduction in the intrinsic viscosity of polymer. The second phase involves the production of small fragments from low molecular weight polymer (observed commonly in vivo) that diffuse out from the bulk of polymer and undergo phagocytosis. It is used to prepare sustained release formulation because of its higher permeability toward drug molecules as well as slower rate of degradation compared to other polymers. Rate of degradation can be enhanced by copolymerizing it with additional polymers, i.e., faster degrading polymers. Dexamethasone-loaded PCL implant was found well tolerated in rabbit eye and also releases the drug for a period of 1 year within the therapeutic range. Researchers have found the cyclosporine bioavailability 10–15-folds higher with nanospheres compared to cyclosporine solution in oil (castor oil). PCL can also be used for preparing in situ gel-forming systems that provide sustained drug delivery. Triblock polymer of PCL was characterized recently for ophthalmic preparations. Gong et al. have evaluated the potential toxicity of the triblock copolymer (PEG-PCL-PEG) hydrogel that was found biocompatible with all the ocular tissues and seemed to be promising for controlled drug delivery system for chronic diseases [113].

10.1.7.2.4 Polyanhydrides

Hydrolytically labile linkages of polyanhydrides provide biodegradability and regulate degradation rate. Degradation of polyanhydrides depends on pH, which can be modified by the use of additives. Basic additives mainly stimulate bulk erosion, while acid additives showed surface erosion and generate acetic acid on degradation. Further, by changing the polymeric backbone, drug release rate can be modified. Mostly copolymer of bis(p-carboxy phenoxy propane) and sebacic acid is used for drug delivery. Release of drug from polymer-based system happens mostly by surface erosion rather than simple diffusion. Microspheres formulated using poly(adipic anhydride) (PAA) showed the surface degradation. Sustained release for about 7 h could be achieved using timolol maleate-loaded microspheres and is primarily controlled by degradation of the polymer. Additionally for the improvement in bioavailability of timolol maleate, these microspheres were added into an in situ forming gel called Gelrite® [114].

10.1.8 In Vivo Examinations

10.1.8.1 Draize Test

Draize eye irritation test is a standard international method in which New Zealand white rabbits are used commonly as they are easily available/obtainable and relatively cheap. Study protocol includes the application of test substance (volume 0.1 ml) only to the one eye of the rabbit, and the second eye acts as a control eye. An evaluation of eyeball before and after introduction of the formulation is done by suitable light source, either using a slit lamp or magnifying glass that guarantees more accurate evaluation. Secondary techniques include dyeing with fluorescein and taking photographs of the eyeball, thereby visualizing the changes in the eyeball.

Furthermore, the level of discomfort after application is indicated by the blinking rate or rubbings of the eye. The assessment was done usually after 1 h, 24 h, 48 h, and 72 h from the application of drug on the eyeball and, if crucial, then also after 7 or 21 days [115]. Despite its gold standard status and being the only validated test for evaluating irritation severity in full range, the Draize test has numerous limitations, including its time-consuming and subjective nature of assessment, its lack of repeatability and reproducibility, high dosage of test materials using variable estimation of results, and overprediction of human response, which is mainly related to interspecies differences.

10.1.8.2 Transcorneal Permeation Study

For transcorneal permeation study, healthy New Zealand albino rabbits are chosen for obtaining reliable data. The prescribed quantity of active substance is introduced into the conjunctival sac at given time intervals and aqueous humor as sample is collected after the anesthesia. Xylazine hydrochloride, ketamine hydrochloride, or pentobarbital sodium might be used as anesthetic agents given either through intravenous or intramuscular route. At times, further inhalation anesthesia is used like in the form of mixture of around 4% isoflurane oxygen, shortly during paracentesis. Regional/local anesthesia like xylocaine solution may also be used. An aqueous humor sample is collected using syringe (amount approximately 150–200 μL) and stored at a temperature around −20 °C, before performing HPLC analysis.

10.1.9 Challenges and Perspective

There are several challenges that need to be focused in future studies, like the following: (1) Rather than focusing more on in vitro studies, efforts should be made in the area of in vivo study using animal models for better ocular therapy. (2) However, New Zealand albino rabbits are commonly used as animal model due to similarity in size of the eye, but there is an existence of dissimilarities compared to human like high surface sensitivity, lower blinking rate, high mucus production, and tear production which would result in better bioadhesion and retention at ocular surface consequently making the systems unauthentic for humans. (3) To provide accurate

information regarding the development of new ocular formulation, more clinical studies are essential. (4) Combination of drug delivery systems can lead to new direction for improvement in therapeutic action. But combination drug delivery systems lead to complexity. Also it becomes difficult to understand the actual mechanism of action behind it. Even though extensive research is ongoing in the field of ocular therapeutics, lack of clear understanding regarding the complexities in normal and diseased condition/state and various barriers to drug delivery and pharmacokinetics would considerably affect the further development in ocular field. Better understanding of fundamentals of human eye and biomarkers can enable the drug development for novel delivery systems with high retention time and penetration.

10.1.10 Conclusions

Targeted drug delivery to ophthalmic tissues serves a major challenge for ocular scientist. Conventional topical drug administration using eye drops has certain limitations like drug wastage, frequent instillations, patient non-compliance, etc., which initiated the development of other systems for ophthalmic drug delivery. Great efforts are made for the development of more safe, efficacious, cost-effective, and patient-compliant novel/new drug delivery approaches for ocular use. Researchers nowadays are trying hard to improve the conventional dosage form performance in vivo. Further, introduction of nanotechnology, novel techniques, new devices, and their use in ocular drug delivery is creating vast curiosity to scientists. Using the nanotechnology approach, drug substance is encapsulated into nanocarriers or nano-devices that can be delivered using invasive and/or minimally invasive mode of drug administration. The systems being explored and researched based on nanotechnology are nanomicelles, nanoparticles, nanosuspensions, liposomes, and dendrimers. Some of these systems are devised at commercial scale and are used in healthcare industry. Nanotechnology is helping the patient by reducing the associated drug toxicities and vision loss. With the use of nano-based carriers and devices, sustained drug release can be achieved along with reduced dosing frequency with improved specificity, though there is a need of carrier systems for targeted ocular delivery which can target the back of the eye (posterior chamber). With the current investigation, it is estimated to overcome the limitations of topical solution (eye drop) by the nano-formulation which retains high residence time in the cornea, transports drug into targeted tissues (both anterior and posterior) at therapeutic rate, and also circumvents the non-specific accumulation of drug in various tissues. In the future, nano-based drug delivery system may substitute/eliminate the invasive method of drug administration (such as intravitreal and periocular injection) to the posterior chamber of the eye.

10.2 Otic Drug Delivery

10.2.1 Introduction to Otic Drug Delivery

Hearing loss, otitis media, tinnitus, and Meniere's disease are the ear disease/conditions which affect millions of people worldwide. For instance, 3–5% of the US people suffer from the condition called chronic otitis media/otitis externa that leads to a therapeutic cost of around $2.98 billion [116–118]. With immunocompromised patients, lethal infection can spread to the neighboring tissues if diseases are not treated optimally. Around 250 million of the population worldwide suffers from moderate to severe hearing loss according to the survey of WHO. The other common ear disorders are Meniere's disease, tinnitus, and autoimmune inner ear disease, which expressively reduce the quality of life. The actual and safe management of auditory and vestibular diseases mainly depends on the efficacy of the drug delivery to inner ear. Various new drug delivery systems and technologies for the treatment of ear disease were developed in the past few years. The occurrence of ear disorders has encouraged efforts for the development of new therapeutic technologies leading towards the development of the novel drug delivery systems and to improve the effectiveness of the treatment, as per the cited literature, "the demand for management of ear disorder has a market of around $10 billion" [119]. If these diseases are identified and managed in the early stage, then hearing damages can be treated effectively [120]. The ear is an organ that is structurally and anatomically protected, which hindered the delivery of drugs to the affected site, especially to the disease conditions of the inner ear. As per the anatomical structure of the ear, "three major physical barriers for the delivery of drug to the ear are the tympanic membrane, the round and oval windows, and the blood–perilymph barrier" [121, 122]. For the management of inner ear disease, conventional routes of the drug administration like oral routes, injection, topical routes, etc. have been proved to be unsuccessful.

Based on the disease condition, local drug application may have major benefit over systemic drug delivery as systemic drug delivery may lead to systemic side effects and using the local drug delivery, the systemic exposure can be reduced. Since "pharmacokinetic advantage" is achieved by local delivery systems, they are the most common mode of treatment for inner ear ailments. Two methods are used for the local delivery to the inner ear: (1) intratympanic administration (delivery to the middle ear) and (2) intracochlear administration (delivery to the inner ear).

10.2.2 Anatomical and Physiological Barriers for Otic Drug Delivery

10.2.2.1 Blood-Perilymph Barrier

The blood-cochlear barrier, also called as blood-perilymph barrier (BPLB), is made up of blood vessels that line the capillary endothelium in the cochlea. Because of the presence of tight junction connecting the endothelial cells, there

are no fenestrations [123]. The inner ear integrity is protected by this structure and also maintains the micro-homeostasis of the inner ear fluids and cells. The blood-cochlear barrier acts as a physical barrier as well as biochemical one with efflux pump structure [124]. The blood-cochlear barrier only allows small liposoluble molecules to penetrate, whereas it is non-permeable to water-soluble, charged, and high molecular weight molecules. These are the reasons; BPLB is a chief obstacle for the transport of active substance from systemic passage to cochlea. The blood-cochlear barrier also prevents the damage to the ear caused by various toxins like exo-/endogenous present in systemic circulation, but at the same time, it poses a major challenge for efficacious drug delivery from systemic passage to the cochlea. For example, the cited article suggests "very low concentrations (0.03 μg/mL in perilymph after 1 h versus 2.76 mg/mL in plasma) in guinea pig model after the single intracardial injection of dexamethasone (0.2 mg/mL)" [125], whereas fivefold higher amount of the compound was achieved after intratympanic injection. However, the path of molecules across the BPLB depends on a variety of conditions like noise exposure, diuretics, inflammation, and osmotic agents such as glycerol (Fig. 10.10).

10.2.2.2 Tympanic Membrane

The principal barrier for the delivery of active molecules to both the middle and inner ear is the tympanic membrane. Thus for the delivery of drugs through intratympanic/intracochlear injection, it must be breached. The tympanic membrane or eardrum is the barrier that separates the middle ear from the external ear and is oval and somewhat conical in shape. The thickness of the membrane is around 600 μm and made up of three layers: (1) an epidermal layer (outermost), (2) a mucosal layer (innermost), and (3) a layer composed of fibrous layer with collagen that provides

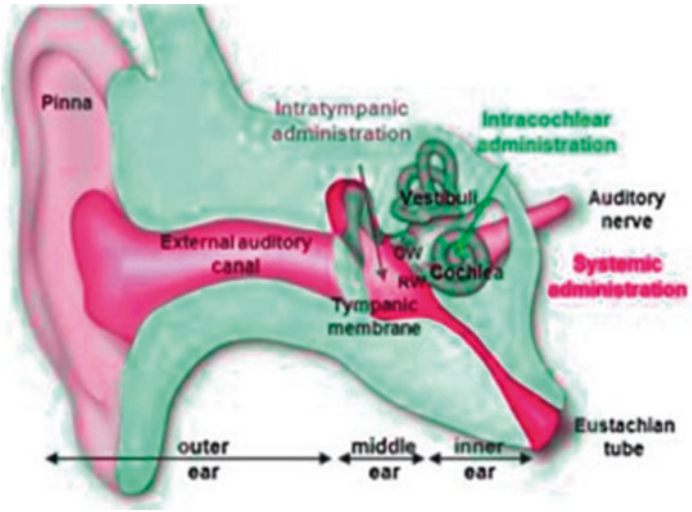

Fig. 10.10 Anatomical barriers of ear

the structural integrity to tympanic membrane [126]. The transmission of sound waves to the ossicular chain is the main function of the tympanic membrane. Because of the similarity in structure of the membrane to the skin, it is possible to transport an active substance through transtympanic delivery into the middle and inner ear.

10.2.2.3 Round and Oval Windows

The membranous boundaries between the cochlea and the middle ear which are semipermeable in nature, called the round window and the oval window, are located at the base of the cochlea. Both the windows can act either as hurdles or as pathways for the delivery of active substance to the cochlea. The round window is composed of three layers: outer and inner epithelium with middle connective tissue. The connective tissue is comprised of blood vessels, collagen, fibroblasts, and elastic fibers. The surface area of the round window is about 2.2 mm^2 with normal thickness of 70 micrometers in humans [127]. For the drugs entering to the perilymph of the vestibule, this structure is considered as secondary route, though quantification of the drug reaching the inner ear by this route is very tough/difficult.

10.2.3 Administration Routes for Otic Drug Delivery

10.2.3.1 Systemic Drug Delivery

Oral and i.m are the most suitable route of drug administration for transport to the systemic circulation to different segments of the ear, though the drug transport by this method suffers from many drawbacks like blood-cochlear barrier and unwanted secondary response. For the disease conditions related to the inner part of the ear, this mode of drug transport is at present believed to be the first-line treatment methodology [121]. Basically, this mode of drug transport is of two types either by oral or i.v. route. Advantages offered by the oral mode of drug transport are easy acceptance by the patient and convenience of the approach, hence usually utilized for the treatment of disorders related to the central part and inner part of the ear. Though bioavailability is limiting factor for oral route while comparing with local route of drug transport, but still it has wide acceptance. Antibiotics are normally recommended for treatment of severe peripheral otitis and otitis media [117]. But, the difficulties with antibiotics given orally are the chances of drug resistance and loss of balance in intestinal flora. Steroidal drugs, antioxidant agents, as well as agents providing neuroprotection are generally prescribed orally for the treatment of sudden sensorineural hearing loss (SSNHL) for the recovery of the same. The extreme infections related to the middle ear like severe mastoiditis and necrotizing otitis externa are treated with the other mode like intravenous injections (i.v.). The i.v. injection of steroidal drugs has also been used for the management of acute hearing loss and Meniere's disease [128]. Both the modes of drug administration have suffered from same unwanted effects provided by steroids. Researchers have shown to decrease the unwanted side effects using the nanoparticles of the steroidal drugs by enhancing the oral bioavailability [129]. For the treatment of the conditions like

SSNHL and Meniere's disease, i.v. route of drug delivery for steroidal drugs is preferable. The animal studies of the steroidal drug encapsulated in synthetic polymer nanoparticles showed to improve the extent of drug transport after systemic mode of administration to various parts of the inner ear.

10.2.3.2 Local Drug Delivery

For otic disorders, the effective approach is local mode of drug transport, as it offers several benefits over the systemic mode, basically for the drugs having narrow therapeutic index, adverse effects, and the drugs undergoing extensive first-pass metabolism. The benefits of local mode of drug application include (1) the capability to avoid the blood-cochlear barrier, (2) high drug accumulation at application site, and (3) lesser unwanted effects. There are four different methods used for the transport of molecule locally and that are currently in use like intratympanic, transtympanic, cochlear, and topical route of delivery.

10.2.3.2.1 Intratympanic Administration

In intratympanic administration, drug molecule is injected in the cavity of the middle ear, and then the molecule diffuses to the cochlea from the cavity. The middle ear acts as a pool of drug molecule through which the molecule then diffuses out to the inner part of the ear across the round window. The distribution of drugs through/by the round window is dependent on the existing drug concentration between the center part of the ear and the perilymph-filled scala tympani. The diffusion rate of molecule across the membrane depends on several factors like charge, hydrophilicity/hydrophobicity, concentration, and molecular mass, on the conformation of molecule, and also on the width of the round window. The capacity of intratympanic injection varies from 300 to 500 μl according to literature survey [130]. Various obstacles that might cause influence in the transport of molecules through round window membrane are thickness of RWM, occurrence of tissue plugs, existence of pseudomembranes, and destruction of the bones. It is very important to understand the effect of interspecies alterations while carrying out clinical trials on human using intratympanic drug transport route. Various devices used for intratympanic delivery include MicroWick®, osmotic pump, and microcatheter.

The Silverstein MicroWick® is an absorbent wick made up of polyvinyl acetate, which is 9 mm long and 1 mm in diameter. Ventilation tube is used for the insertion of device in the tympanic membrane and positioned covering the round window. Local anesthesia is necessity for the insertion of the device. After insertion of device to the tympanic membrane, one can instill the solution of drugs (for several times a week) into the external ear passage. The absorbed drug by the MicroWick® is then transported to the inner ear by passive transport [131]. The intratympanic injection of steroids has also been studied clinically for the acute/chronic hearing loss and Meniere's disease management. The intratympanic delivery also suffers from limitations like the various structural barriers for the absorption of drug to the inner ear from the center ear, the drug loss through the Eustachian tube, and drugs with unidentified pharmacokinetic profiles. Potential ototoxicity is another

limitation of this route, seen in more than 30% of patient population due to change in uptake profile of drugs to the inner ear. Several factors that influence ototoxicity are the thickness of the round window, mucosal status of the middle ear, obstruction in the Eustachian tube, and alteration in endolymphatic fluid. Nanoparticles and biodegradable hydrogel controlled systems were also developed to bypass the limitations offered by intratympanic administration.

For the treatment of otitis media though intratympanic route, Otiprio® is the first commercial injection developed by Otonomy Inc. It is the suspension of ciprofloxacin with thermosensitive characteristic to convert gel from liquid using poloxamer 407 as a thermo-responsive polymer, as poloxamer 407 forms a gel at physiological (body) temperature. An alternative product with the same technology developed by Otonomy is Otividex®, which is in clinical trial Phase III for the management of Meniere's disease [132].

10.2.3.2.2 Transtympanic Administration

The tympanic membrane is the principal obstacle involved in transport of molecules to the middle and inner ear. Efficacious delivery through transtympanic mode depends mainly on diffusion of drug through tympanic membrane into the middle and inner ear from ear passage. Permeation enhancers can be used to facilitate the process of drug transport by this route. Local and continuous delivery of antibiotic was achieved using chemical enhancers for the treatment of otitis media by transtympanic mode to the middle ear. Magnetic drug nanoparticles utilizing magnetic field proved to be a feasible method for permeation of drug molecule though tympanic membrane. Pain and vertigo are the main side effects associated with transtympanic injection. However, they are for a limited period of time like 1–2 h after injection. Unwanted effects also depend on several factors like drug concentration, temperature, and the individual's sensitivity [133]. Conventional solution of drug like corticosteroids given by transtympanic injection is normally used in clinical studies. As the administered liquid solution is eliminated quickly from the middle ear through the Eustachian tube. Hence, the technique requires frequent administration like two to five times a week. Hydrogels possesses viscoelastic properties, which can be utilized to avoid quick loss of drug through the Eustachian tube, thereby improving the retention time of drug in the middle ear. So, hydrogels can be used as an interesting approach for transtympanic injection by reducing the frequency of administration. Investigations on hydrogel-based drug delivery for otic disorders include a variety of polymers with diverse natures like synthetic thermosensitive block polymers such as Pluronic F-127 and natural polymers like gelatin, hyaluronic acid, chitosan, or collagen (Table 10.5).

10.2.3.2.3 Intracochlear Administration

In intracochlear drug delivery, the drug molecule is administered straight to cochlea via injection to bypass the middle ear barriers. The solution administered via intracochlear route should be isotonic and sterile and should have a pH in the range of 7.1–7.4 and preservative-free, as very small fluctuations in the ear fluids (like change

Table 10.5 Local otic drug delivery products under clinical trial

Study title	Status	Product/ description	Indication	Identification no.
Latanoprost for the Treatment of Meniere's Disease	Phase II	Latanoprost	Meniere's disease	NCT01973114
Safety and Efficacy of STR001-IT and STR001-ER in Patients With SSHL	Phase III	Drug: STR001-IT and STR001-ER	Acute hearing loss	NCT03331627
Efficacy and Safety of Once-Daily Ciprodexa Otic Foam Compared to Twice-daily Ciprodex Ear Drops in Acute Otitis Externa (Ciprodexa Foam)	Phase II	Drugs: Ciprodex Otic suspension, Ciprodexa Otic Foam	Otitis media, otitis externa, otorhinolaryngology diseases	NCT01359098
OTO-104 for the Treatment of Meniere's Disease	Phase II	Drug: OTO-104	Meniere's disease	NCT01412177
FX-322 in Sensorineural Hearing Loss	Phase I	Drug: FX-322	Sensorineural hearing loss	NCT03616223

in pH, composition, volume, or osmolality) can even lead to ototoxicity and hearing loss. The drug delivery through intracochlear route is of two types, either passive or active, based on the need of power and electrical controls set inside the device used. Intracochlear mode of drug administration is the most suitable approach for the treatment of stubborn ailments of the inner ear, like auditory conditions (hearing loss) to vestibular disorders and tinnitus.

The miniaturized osmotic device and continuous infusion micropumps are considered as a primary device for the intracochlear administration as they have the ability to reach the target like hair cells of the inner ear. Limitation of these devices includes short effective life and absence of the programmable control that diminishes the effectiveness. Nowadays, the new generations of intracochlear devices include micropumps with high accuracy, automated controls, and miniaturized power [121]. To treat the disease related to the inner ear, these devices/systems will eventually assist as fully implantable devices for prolonged therapeutic delivery. In other terms, these devices will find usefulness as implantable and wearable systems for various animal models which boost the speed of drug development, thereby allowing individuals to understand the fundamental mechanisms behind the inner ear diseases' treatment strategies and regeneration.

10.2.4 Challenges and Perspective

There is significant progress in the field of otic delivery, but still many challenges have to be addressed. The biggest challenge for drug delivery is limited approachability of the inner ear, which prevents the precise drug delivery to the inner part of the ear without affecting/damaging the delicate organ. Local approaches for drug delivery are invasive (intracochlear) and/or minimally invasive (intratympanic), but they can lead to temporary or permanent hearing loss. There is a need to develop a less invasive or noninvasive method of drug delivery to the inner ear with significant advantages and also preventing the loss of hearing related to the treatment technique. Additionally the inner ear contains very small amounts of fluid that could lead to the problem like inadequate sample volume required for examination/quantification by traditional methods of analysis. Extremely sensitive method like LC-MS could be used for performing assay of perilymph samples, but the method is expensive and complicated. Quantification of drugs that accumulate in various parts of the cochlea represents the major task/challenge to understand the perilymph pharmacokinetics.

Through use of specific biomarkers and various pathways, nano-based approaches along with targeting entity will increase the drug residence as well as targeting of the cochlea. Combining the cell targeting characteristics and sustained drug release profile will provide a method for improving the safety and efficacy of therapy to the inner ear without causing trauma. There are major progresses for delivery of charged particles across the tympanic membrane after crossing the middle ear utilizing the concept of iontophoresis upon application of magnetic field. The molecules could then be diffused via RWM into the inner ear, hence utilized to target the cochlea. The best future option to treat the pathologies related to the middle and inner ear would be an ideal carrier loaded with the drug molecule that could cross the anatomical barriers of the ear.

10.2.5 Conclusion

There are numerous methods of drug delivery to the ear which can be categorized as topical, systemic (intravenous), transtympanic, and via the Eustachian tube. Localized treatments have the advantages of allowing higher therapeutic doses and minimizing systemic side effects, which are mainly vital while considering the administration of potential ototoxic medication like steroids and antibiotics. Treatments of the inner ear vestibule and auditory diseases with high safety and efficacy profile will remain a challenge. Current approaches for the development include strategies for improvement in drug permeation, targeting, residence, safety, monitoring, and pharmacokinetic profile/modeling. The intratympanic and intracochlear drug delivery with precise control and minimum shock to the delicate part of the inner ear represents the research concerns for the future. Direct delivery of drug to the vestibule in the case of vestibular disease is only possible using trans-oval window delivery and may represent a favorable methodology by circumventing the

unwanted effects arising due to circulation of drug to the cochlea. In particular, patient acceptability and the successful systemic delivery of large molecules (proteins, oligonucleotides, and polysaccharides) via this route remain both a significant opportunity and challenge, and new/improved technologies may be required to address these.

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11 Approaches in Barriers, Modifications, Route of Administrations, and Formulations of Therapeutic Agents for Brain Delivery

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_11

Abstract

The barriers in the delivery of the therapeutic agent to brain diseases are blood–brain barrier (BBB), blood-cerebrospinal fluid barrier, and cellular barriers. The above mentioned barriers limit the distribution of the therapeutic agent or drug delivery system, thereby affects the therapeutic efficacy. The route of administration is also an important factor in the drug delivery to the brain diseases. Therefore, there is unmet need for the development of drug delivery systems which will overcome the barriers and delivers the therapeutic agent to the brain diseases. This chapter is focused on various strategies used to overcome the barriers in drug delivery to the brain diseases. The application of energy and chemical substances such as osmotic agent and permeation enhancers has been studied. Other strategies, such as developing the prodrug and inclusion complex of therapeutic agents, have been explained. The application and limitations of the different routes of administration such as intravenous, intra-arterial, intranasal, intracerebral, and intracerebroventricular have been described. The drug delivery system in the nanoscale such as liposomes, nanoemulsion, polymeric nanoparticles, and dendrimer have been explored to overcome the limitations associated with drug delivery to the brain diseases. Specific examples are described in this chapter. Lastly, various ongoing clinical trials for drug targeting to the brain are listed.

Keywords

Blood brain barrier · Brain drug delivery · Nanocarrier systems

11.1 Introduction

The brain is one of the most vital organs, acting as the control center of the body. It is the key component of the central nervous system (CNS). Any small irregularities to this vital system might pose devastating consequences in one's lifestyle, leading to diseases or disorders. Some of those conditions include epilepsy, Alzheimer's, cerebrovascular diseases, neurodegenerative disorders such as Parkinson's, HIV encephalopathy, and brain tumors. Most of these disease conditions require the drug substance to reach the intracranial target site for potential therapeutic effect. Despite

billion-dollar investments and aggressive research for the cure, patients suffering from such brain relevant diseases/disorders outnumber those dying of heart diseases or other types of cancers [1, 2]. An arsenal of potent therapeutic agents developed over the last 50 years demonstrated promising effects in the laboratory, but their translation to the clinic has been very less successful. This failure is often not due to lack of drug potency but due to associated limitations in the therapeutic agent pharmacokinetics, off-target effects, and in the drug delivery methods. Some formidable impediments that regularly hamper effective drug delivery to the brain were identified in the early twentieth century, with blood-brain barrier (BBB) being the first [3]. Several novel research strategies have been proposed and investigated, since then, to overcome the deficiencies and challenges associated with conventional delivery mechanisms. This chapter briefly discusses those barriers impeding brain delivery followed by strategies to overcome associated challenges and concludes with summary of approved drug products as well as ongoing clinical trials.

11.2 Barriers and Approaches to Tailor BBB

The BBB is the first physiological impediment to the delivery of drug molecules from the systemic circulation to the brain. It acts as a selectively permeable membrane, separating from the peripheral systemic circulation, to control and protect the brain microenvironment, i.e., neurons that are highly susceptible to changes in signaling neurotransmitters as well as extracellular ions. The same selectively hamper drug molecule's penetration through the endothelium lining. This led to aggressive research to study distinguishable physiological characteristics between the capillary endothelial cell linings of the cerebral and systemic microvasculature. The first characteristic is the absence of pores and fenestrations with gaps in the cerebral endothelial cells when compared with systemic capillaries. Exchange of ions or therapeutic agents between blood and surrounding interstitium is commonly abetted by the membrane transporters. Tight penta-laminar arrangement of adjacent cerebral capillary endothelial cells are responsible for limited permeability of ions and small molecules and practically impermeable to peptides and macromolecules [4]. This was further confirmed by the measurements of ionic current flow across most systemic and cerebral capillary endothelium microvasculature [5]. In BBB disruption approach, the therapeutic agents are directly delivered to CNS by amending the integrity of tight junctions of BBB causing transient disruption of BBB. This BBB disruption can be achieved by two methods: (i) application of energy and (ii) use of chemical substances.

11.2.1 By Application of Energy

Electromagnetic radiations or ultrasound is used for disrupting BBB. These approaches offer the advantage of targeting a specific area of the brain. The radiation was used to tailor the properties of BBB which can be explored for drug or gene delivery [6]. The use of ultrasound for tailoring the properties of BBB for drug or gene therapy was summarized in the reported article [7]. Focused ultrasound

when combined with microbubbles resulted in increase in permeability of BBB and the blood-tumor barrier (BTB), which helps in enhancing delivery of doxorubicin across BBB and BTB and increased the retention of the drug in the tissue up to 24 h [8].

The path of entry of drug molecules by ultrasound occurs by the following mechanisms:

(i) Thermal lesions are formed which leads to alteration of permeability and opening of BBB.
(ii) Small air-filled cavities are formed by the injected fluid in the luminal membrane of BBB which allows the drug to pass through them easily.
(iii) Microbubbles are formed by ultrasound contrast agents, which increase in size and finally burst causing the opening of tight junctions.

This method is mostly used as a diagnostic tool for imaging brain and brain tumors [9].

11.2.2 By the Usage of Chemical Substances

11.2.2.1 Osmosis-Mediated BBB Disruptions

In this method, chemical substances that are hyperosmolar/hypertonic to BBB cells are used. When the cells are in hypertonic solutions, the cellular fluids come out of the cells to maintain equilibrium, and as a result, cells shrivel leading to the opening of tight junctions in capillary endothelial cells. The most common osmotic agent used for this is mannitol, which has the potential to help drugs to cross BBB. It was also shown that mannitol increased the delivery of stem cells and growth factors across BBB [10].

However, this technique is limited due to the prolonged recovery period of BBB after disruption, which leads to an increase in intracranial pressure due to influx of macrophages and other molecules [11]. Increased intracranial pressure is a contraindication for brain tumor treatments. Other disadvantages are hemodynamic variability between patients and variable BBB disruption after repeated exposure to osmosis- or radiation-mediated disruption [12].

11.2.2.2 By Permeation Enhancers

The chemical substances such as bradykinin analogs and alkylglycerol act by increasing the permeability of BBB. The few examples are given below.

(a) Bradykinin analogs: These substances stimulate B2 receptors, which lead to increase in intracellular calcium levels. This calcium activates actin/myosin fibers leading to leaching out junctional proteins and thereby loosens the tight junctions [13]. Cereport (RMP-7) is a bradykinin analog, which increased the delivery of loperamide to the brain resulting in the induction of analgesic effect [14].

(b) Alkylglycerols: These are surfactant-like molecules. These agents disrupt BBB by destabilizing the membrane. Despite being a successful strategy, disrupting the BBB increases the risk of infection [15]. In normal brain and brain tumors, alkylglycerols enhanced the delivery of small and large compounds [16].

11.3 Approaches to Modify Therapeutic Agents

Despite being a successful strategy, disrupting the BBB increases the risk of infections. Various strategies have been exploited to achieve the goal of delivering the drug into the brain, which can be broadly classified into four parts: (i) bypassing the BBB, (ii) BBB disruption, (iii) modification of drug, and (iv) nanocarrier systems. For bypassing BBB, altering route of administration for both direct delivery and nasal pathway was studied. Physical and chemical approaches were utilized for disrupting BBB. Drug modifications including prodrug and inclusion complex followed by novel drug carrier systems were summarized below.

11.3.1 Drug Modification

11.3.1.1 Prodrug

Prodrugs are inactive drug or precursor of pharmacologically active substances which after enzymatic degradation releases or get converted into the active form of the drug within the body. A prodrug is developed by covering, masking, or altering the functional group of the parent molecule with another functional group and results in a new entity with unique physicochemical properties [17, 18]. These entities are acted upon by the enzymes present on the BBB to give active agents. It is a unique drug delivery strategy that improves the drugs' solubility, stability, and absorption through the biological membrane and reduces premature metabolism. The prodrug was initially explored for hydrophilic drugs to enhance the nasal permeability of drug thus the nasal drug absorption and also to protect the drug from enzymatic degradation in the nasal cavity [19]. The lipophilic and biocompatible nature of promoiety makes it more suitable for nasal administration. Gambaryan and coworkers evaluated the delivery of antiparkinsonian drug dopamine in its prodrug form L-DOPA through nasal route by incorporation into the PLGA nanoparticles. The prodrug gets converted into the parent drug by enzymatic degradation with L-amino decarboxylase enzyme inside the brain. The in vivo investigation on animal model exhibited a significant improvement in the therapeutic potency of the drug and sustained drug action [20].

11.3.1.2 Inclusion Complex

The complexation between two molecules in which one serves as a cavity for the inclusion of another compound is known as an inclusion complex. It is based on the host-guest chemistry: the one who has the cavity or hole is called the host molecule, while the other which gets encapsulated into the cavity is known as guest molecule

[21, 22]. Cyclodextrins are most commonly used host molecule in drug development. Owing to the unique characteristic feature, the hydrophilic outer surface and hydrophobic internal cavity, it can form a complex with a wide variety of drugs, both hydrophilic and lipophilic [23]. Furthermore, this approach overcomes the limitations of intranasal route solubility and enzymatic degradation and thus increases the bioavailability. Zhang formulated poloxamer/chitosan thermosensitive gel containing hydroxypropyl-β-cyclodextrin (HP-β-CD)-curcumin inclusion complex, to enhance the brain availability and antidepressant effect of curcumin through i.n. administration [24]. In pharmacokinetic studies, from thermoresponsive gel, AUC_{0-8} of curcumin was 1.62 and 1.28 times higher in plasma and hippocampus, respectively, when compared to i.v. administration, which shows that the system has high potential for clinical application.

11.4 Drug Products and Formulations Explored in Various Routes of Administration

The route of administration such as intravenous (i.v.), intra-arterial, intranasal (i.n), and intracerebroventricular has been used to deliver the therapeutic agent to the brain. The summary of commercially available drug products used for brain diseases via various route administrations is provided in Table 11.1.

Table 11.1 Commercially available drug products for brain targeting

Product name	Type of formulation	Active ingredient	Company	Route of administration	Disease condition
Radicava	Suspension	Edaravone	MT Pharma America, Inc.	i.v.	Amyotrophic lateral sclerosis
Ingrezza	Powder in capsule	Valbenazine	Neurocrine Biosciences, Inc.	Oral (capsule)	Tardive dyskinesia
Ocrevus	Solution	Ocrelizumab	Genentech	i.v. infusion	Multiple sclerosis
Spinraza	Solution	Nusinersen	Biogen, Inc.	Intrathecal	Spinal muscular atrophy
Zinbryta	Solution	Daclizumab	Biogen, Inc.	Subcutaneous injection	Multiple sclerosis
Aristada	Suspension	Aripiprazole lauroxil	Alkermes Plc	Intramuscular injection	Schizophrenia
Synarel	Solution	Nafarelin	Pfizer Ltd	Nasal spray	Endometriosis
Imitrex	Liposome	Sumatriptan	GSK	Nasal spray	Migraine
Estredox	Cyclodextrin complex	Estradiol (prodrug)	Teva pharmaceuticals	i.v. injection	Menopause symptoms
Bidopar	Suspension	Levodopa (dopamine prodrug)	GSK	Oral	Parkinson's disease

11.4.1 Intravenous Delivery

The brain has extensive blood supply with a network of capillaries constituting around 20 m^2 area. The neurons are also well connected with the blood vessels. Hence this approach is considered to have great potential to deliver drugs to the brain.

This route also bypasses first-pass metabolism. However, due to rapid metabolism and clearance of drugs from extracellular fluid, there is little accumulation of drug in the brain. Thus, drug accessibility to the brain by this route is significantly affected by its half-life, metabolism rate, permeability across BBB (Fig. 11.1, [25]), and level of nonspecific binding to plasma proteins. In addition to the conventional methods, several strategies such as nanoparticles, liposomes, polymeric micelles, and nanoemulsions were proposed to overcome the difficulties posed by BBB (Fig. 11.1, [25]). The delivery of drugs to the brain using nanoparticle systems is influenced by the physicochemical properties (composition, nature of entrapped drug, shape), modification of surface, and pharmacokinetic parameters. The characteristics of nanoparticles were represented in Fig. 11.2. Few strategies were elaborated below in which liposomes were applied via i.v. delivery. The other types of

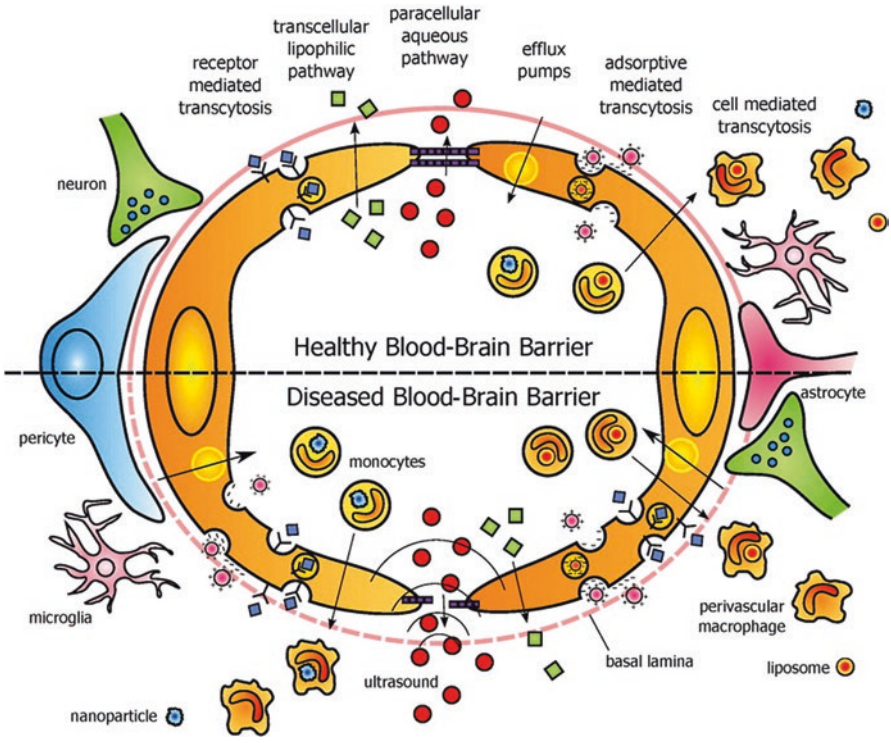

Fig. 11.1 Schematic of different mechanisms for BBB crossing. (Figure reproduced with permission from [25])

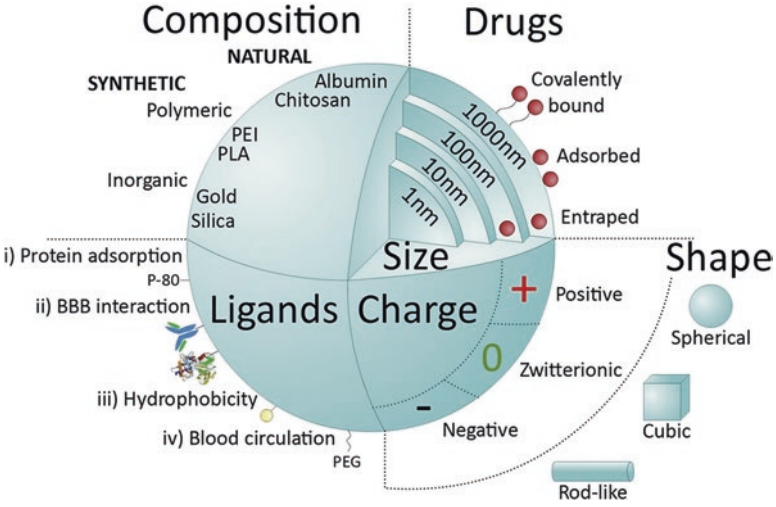

Fig. 11.2 Nanoparticle characteristics influencing systemic delivery and blood-brain barrier (BBB) passage. (Figure reproduced with permission from [29])

nanocarriers such as polymeric nanoparticles [26], polymeric micelles [27], and nanoemulsions [28] administered via i.v. route were reported.

Chen Z-L et al. showed liposomes modified with transferrin (Tf) promote α-mangostin (α-M) to overcome the BBB [30]. α-M is used for the treatment of Alzheimer's disease (AD) [31]. But its activity is compromised due to poor penetration of drug through the BBB. Liposomes were prepared by thin-film hydration method. The average particle size of the Tf(α-M) liposome was 196.3 ± 7.09 nm, PDI of 0.211 ± 0.034, and zeta potential of −22.23 ± 2.87 mV. In brain imaging studies, in place of α-M, dye DiR was used and injected into the rats via the tail vein. It was observed that after 2 h of treatment, Tf-DiR liposomes showed higher fluorescence in the brain than only DiR liposomes and DiR solution groups.

When compared to unmodified liposomes and α-M solution, Tf-modified liposomes delivered more α-M into the brain, which suggests the role of Tf in the transportation of α-M into the brain. In pharmacokinetic studies, it was observed that Tf (α-M) liposome group (Dose 5mg/kg) that the $t_{1/2}$, MRT, AUC $_{O\text{-}T}$, and AUC $_{O\text{-}\alpha}$ values were higher when compared with α-M solution, which shows that it is a suitable dosage form for α-M delivery.

Glutathione targeted pegylated (GSH-PEG) liposomes were formulated to deliver amyloid-targeting antibody fragments (VHH-pa2H) to the brain by bypassing BBB. 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and egg-yolk phosphatidylcholine (EYPC) were used to formulate two different GSH-PEG liposomes by post-insertion method [32]. The average size of the GSH-PEG DMPC liposomal VHH-pa2H-DTPA was ~110 nm and PDI of ~0.105, and the size of GSH-PEG EYPC liposomal VHH-pa2H-DTPA was ~108 nm and PDI of ~0.061. Unencapsulated VHH-pa2H-DTPA-^{111}In showed significantly lower AUC

($P < 0.05$) when compared to encapsulated VHH-pa2H-DTPA-^{111}In GSH-PEG DMPC and GSH-PEG-EYPC. In later liposomes, VHH-pa2H-DTPA-^{111}In GSH-PEG-EYPC showed higher AUC ($P < 0.05$), against VHH-pa2H-DTPA-^{111}In GSH-PEG-DMPC. Biodistribution studies are carried out in APP/PS1 and wild-type animals. Both liposomal formulations showed significant higher retention of the tracer in excised perfused brain when compared with free VHH-pa2H ($P < 0.05$). In these two tested phospholipids, GSH-PEG EYPC showed better activity than GSH-PEG DMPC. Only after single injection of the tracer VHH-pa2H encapsulated GSH-PEG-EYPC liposomes showed high cellular uptake in the brain.

Jiang and coworkers conjugated glioma-homing peptide (Pep-1) to pegylated polyamidoamine (PAMAM) dendrimer nanoparticles which were evaluated in glioblastoma multiforme (GBM) as targeted delivery system [26]. In U87MG tumor-bearing mice, targeted nanoparticles fluorescence intensity at glioma site was 2.02 times higher than nontargeted system, and also they concluded that targeted delivery system showed high accumulation and penetration into the tumor.

11.4.2 Intra-arterial Delivery

The brain has a predominantly high oxygen demand. It denotes almost one-fifth of the body's total oxygen consumption at rest. Therefore, the brain is abundantly furnished by arteries. There are mainly two paired arteries that are responsible for blood supply to the brain: the vertebral arteries and internal carotid arteries. They arise in the neck and ascend to the cranium.

Intra-arterial drug delivery across the BBB may offer the advantages, i.e., reduction in the dose of the drug to be delivered, targeted drug delivery, higher drug availability to the site of action, as well as the decreased drug exposure to the unintended sites as compared to the i.v. route [33]. Despite these advantages, BBB targeting has been limited due to the cerebral blood movement as well as the varying degree of intactness of the BBB in the diseases when presented with the drug solution. Nanoparticulate drug delivery through the carotid artery may help in overcoming the shortcomings of conventional drug delivery. The important factors affecting the efficiency of such delivery systems involve an interplay between the pharmacokinetic, pharmacodynamic, and hydrodynamic factors.

Liposome-encapsulated antibody against ICAM-1 (intercellular adhesion molecule-1) when administered through the carotid artery resulting in a significant increase in uptake in TNFα induced inflamed areas of the mice brain (much higher than the healthy brain) as compared to the vehicle delivery through the jugular vein. Additionally, these ~150 nm nanoparticles showed more than 100-fold higher uptake as compared to the anti-IgG tagged liposome besides being significantly biodistributed into the brain as compared to lungs. The specific uptake of the immuno-targeted nanocarrier may be attributed to the overexpression of the ICAM-1 on the luminal surface of the inflamed tissue of the brain. This approach of combining the targeted nanocarrier along with the intra-arterial catheter-based local delivery may be utilized for the delivery of the therapeutics against the inflamed brain etiologies [34].

PAMAM (polyamidoamine)-based generation 4 dendrimers loaded with deferoxamine tuned to 5 nm in size, and the neutral surface charge was tested for their uptake in the mice glioma brain via intra-arterial as well as i.v. The intra-arterial route-based delivery showed a significant improvement in the brain uptake of these carriers (after 1 h and after 24 h) than the i.v. delivery in case of intact BBB as well as mannitol-induced disrupted BBB. Such dendrimer-based approaches may be utilized for the delivery of the chemotherapeutic agents as well as other therapeutic agents across the BBB [35]. However, the design of such delivery vehicles needs to establish a careful balance between the physicochemical components as well as the associated physiological risks (such as cerebral lesions) of this delivery route [36].

11.4.3 Intranasal

The intranasal (i.n.) route of administration of drugs for drug delivery to the brain is being used extensively due to direct transport of drug from the submucosa of the nose to cerebrospinal fluid (CSF) compartment of the brain. This route offers advantages of evading BBB and first-pass metabolism. The nasal epithelium is highly permeable and allows rapid drug absorption to the brain due to high blood flow owing to its large surface area and porous membrane. This route delivers many advantages like reduced dose, self-administration, improved patient compliance (noninvasive), and compatibility for the delivery of wide variety of therapeutic agents. However, it has some limitations like damaging nasal mucosa, irritation, rapid clearance by mucociliary clearance system, elimination by systemic absorption, and interference due to patient conditions like nasal congestion.

The nasal cavity is divided into three regions: vestibular, respiratory, and olfactory region. The vestibular region is the first region that is highly enriched with ciliated cells and mucus, which are engaged in mucociliary clearance. Most of the drug administered in this region is lost due to mucociliary clearance. The respiratory region, which covers the major portion of the nasal cavity, is highly vascularized, and it is the major site of drug absorption into systemic circulation. Compounds enter the bloodstream by transcellular/paracellular passive absorption−/carrier-mediated transport/transcytosis pathways. The olfactory region, next to respiratory region, is the foremost site, from which drug can be absorbed directly into the brain by different mechanisms like transcellular, paracellular, olfactory, and trigeminal neural pathways.

Zheng and coworkers encapsulated novel β-sheet breaker peptide, H102 into liposomes and administered i.n. in mice for the treatment of Alzheimer's disease [37]. H102 liposomes were prepared by thin-film hydration method. Liposomes have a mean particle size of 112.2 ± 6.4 nm, surface charge of −2.96 ± 0.38 mV, and PDI of 0.185 ± 0.012.

In plasma, after administering i.n. H102 liposome, H102 was found after 90 min, whereas for i.n. H102 solution, it was found only up to 45 min, and it was not detectable after 5 min by i.v. route. The i.n. H102 liposomes significantly increased the absolute and relative bioavailabilities, thereby suggesting increased the nasal

absorption of H102. In hippocampus, the AUC of H102 liposomes was 2.92 times higher than that of the i.n. H102 solution group which shows that the formulation can cross BBB. In Morris water maze test, compared to i.v., i.n. H102 solution, i.n. H102 liposomes effectively amended spatial memory. In Alzheimer's disease, typical pathological indication is formation of Aβ plaque. After i.n. H102 liposome injection, the size and quantity of Aβ plaque were decreased and were close to that of sham group.

Cationic liposomes made from L-α-phosphatidylcholine and dihexadecylmethylhydroxyethylammonium bromide were analyzed for BBB crossing by utilizing the i.n. route [38]. Cationic liposomes were used to treat organophosphorus poisoning, which results from exposure to organophosphorus agents (OP). The acute toxicity of OP agents was observed due to the inhibition of acetylcholinesterase. They used 2-PAM which is cholinesterase reactivator as a model drug in formulation of cationic liposome for the treatment of organophosphorus poisoning. The hydrodynamic diameter of 2-PAM loaded liposomes was 1142 ± 2 nm with zeta potential of +6 ± 0.2 mV and PDI of 0.2 ± 0.03. Rhodamine B encapsulated cationic liposomes applied i.n. showed higher rhodamine absorption in the brain.

For the reactivation of brain AChE, rat model was used. Organophosphate paraoxon (POX) (0.8 × LD50) was used as AChE inhibitor. 2-PAM (7 mg/kg) loaded cationic liposomes when introduced i.n. showed 12 ± 1% reactivation of brain AChE, whereas the free 2PAM was failed in reactivation of AChE.

In other studies, paroxetine was delivered i.n. in rats using nanoemulsion formulation, which showed 2.57 times in an increase in permeation when delivered using nanosuspension orally [39]. Behavior activities also improved drastically when nanoformulation applied i.n. by increasing glutathione levels and decreasing the increased TBARS in Wistar rats. Also, efavirenz, which is an antiretroviral drug, was formulated in solid lipid nanoparticles and administered i.n. in adult Wistar albino rats, which showed 150-fold increase in brain targeting and 70 times higher absorption potential when compared with orally administered marketed formulation [40].

11.4.4 Intracerebral

Drugs can be directly administered in the brain by intracerebral administration by injection and implants. Drugs can be injected as bolus or infusion. However, the bolus injection is hampered by the limited diffusion coefficient of drugs through brain parenchyma which results in slower movement of compounds. Intracerebral infusion requires the insertion of a catheter into the brain. This strategy can be improved by convection-enhanced delivery, which involves positive hydrostatic pressure. A positive pressure gradient is created through an infusion pump, which enables the administration of drug through catheter and helps the administered drug to penetrate further into target tissue.

Although the intracerebral route of administration results in high local concentrations of the drug, the drug release kinetics from the carrier, physiochemical microenvironment at the injection site, as well as diffusion-based uptake through

the brain parenchyma govern the efficacy of the product. Drug delivery through this approach not only reduces the systemic toxicity of drug by avoiding the BBB path but also may be associated with neurotoxicity at the site of delivery due to the lack of efficient diffusion-based drug uptake and presence of high localized concentrations of the drug [41].

Surface decoration of PLGA nanoparticles with high degree of pegylation and loaded with paclitaxel was evaluated against 9 L gliosarcoma-bearing Harlan F344 rats. These nanoparticles having a size of 70 nm and near zeta potential (−2 mV) exhibited 100-fold increase in the tumor uptake with a significant reduction in the tumor growth as well as improved bio-distribution in the tumor parenchymal cells as compared to the non-pegylated components. This improved intra-tumor distribution may serve in development of better treatment of brain tumors as well as other brain disorders [42].

The immune cell components of the central nervous system, microglia, have been implicated for their role in the destruction and degeneration of the neurons in brain diseases such as multiple sclerosis, Parkinsonian disease, and Alzheimer's disease [43]. The progress of the disease may be arrested by the use of clodronate, which propagates the apoptosis of the microglia and microglia-induced activation of chemokines, cytokines, and proteases. The intracerebral injection of the liposomal clodronate resulted in a significant improvement in the uptake by the parenchymal cells with the subsequent reduction in the microglial population as compared with i.v. injection. However, the liposomal drug delivery through this route showed the toxicity to brain cells [44].

Additionally, the controlled release of the drug delivered through intracerebral delivery may be achieved by the use of polymeric biodegradable wafers, nanofibers, and depots [45]. The USFDA and EMEA approved product Gliadel™ (carmustine wafer) prepared using polifeprosan 20 copolymer is one such example used as an adjunct to other chemotherapeutics in newly diagnosed gliomas as well as glioblastoma [46]. The blood carmustine levels are detected 24 h postimplantation with the drug reaching C_{max} within 3 h after carmustine release [47].

11.4.5 Intracerebroventricular Injection

The drug is directly introduced into the ventricles of the brain after intracerebroventricular (ICV) injection. The ventricles of the brain allow the diffusion of drug into parenchymal cells of the brain through the interaction of CSF contents with interstitial fluid. However, as the rate of CSF turnover is much faster than the drug diffusion, drug is more prone to enter general circulation than targeted cites in the brain. This CSF turnover depends on size of the individual and volume of CSF. For instance, adults have more CSF than children and thus longer turnover time. Therefore, the drug concentrations vary largely with individuals. Furthermore, this route leads to higher drug exposure at the ependymal surface and is effective if the target receptor is located near the ependymal surface.

Finan and coworkers tested intracerebroventricular route for the treatment of edema in mice [48]. They have used the chondroitinase ABC enzyme, which degrades

chondroitin sulfate proteoglycan, which is responsible for edema. After the treatment, the ipsilateral water fraction was decreased to 0.54%, which indicates more than half of the edema induced by trauma was overcome. The treatment was selective as water fraction is not effected in uninjured animals when compared to injured animals. ICV method was far superior due to its improved patient compliance and efficient when compared to intraparenchymal injection and i.v. delivery. There are certain limitations for this method, such as murine brain is smaller than human brain, and here treatment was given within 5 min, which is impractical in treating humans.

Mutations in SMN1 gene result in spinal muscular atrophy, which is an autosomal recessive neuromuscular disease. In neonatal SMNΔ7mice, by administering scAAV9 vector, which is expressing a codon-optimized version of the human *SMN1* cDNA under the control of PGK promotor in ICV space, therapeutic efficiency was measured [49]. All tested mice showed enhanced life span and growth in a dose-dependent manner with longest median survival of 346 days at dose of 3×10^{13} vg/kg. When ICV dose is co-administered with i.v. injection at different ratios, it didn't improve survival. In biodistribution studies, after 90 days of postinjection, it was observed that CNS transduction is achieved through vector release by ICV route, while i.v. administration transudes principally in peripheral organs (lung and heart). One more critical advantage of gene therapy by ICV route is need of steroid treatment or immune suppression is hugely reduced. Different routes of brain targeting methods outlined in Table 11.2.

11.5 Clinical Advancements and Ongoing Clinical Trials

The nanocarrier systems have been studied in clinical trials. List of some ongoing clinical trials for brain targeting of the drug using various delivery approaches is mentioned in Table 11.3.

The ongoing clinical trials for the delivery of drugs to the brain and preclinical studies suggest that these delivery systems or approaches will be promising for the treatment of brain disorders.

11.6 Summary

The brain is almost inaccessible for most of the drugs, macromolecules, and other foreign materials due to the presence of BBB. This reduces the drug concentrations at the site of action and thereby the effectiveness of therapies and makes the treatment of CNS/brain disorders challenging. The use of chemical agents and prodrug showed promising results. Currently, the targeted drug delivery system-based therapies administered via different routes demonstrated promising findings while overcoming the BBB. The extensive work has been done in the last two decades on the use of different drug carrier systems, route of administration, and various surface-acting ligands specific to the brain receptors to successfully deliver the drugs to the brain. In this chapter, we have discussed the strategies to overcome

Table 11.2 Summary of various routes of drug administration for brain targeting

Route of administration	Therapeutic agent	Type of formulation	Key findings	References
Intravascular	VHH-pa2H	Pegylated liposome	In the brains of transgenic animals, GSH-PEG EYPC liposomes showed significant increase in SUV	[32]
Intravascular	α-Mangostin	Tf liposome	Tf-modified liposomes improved the brain delivery of α-mangostin	[30]
Intravascular	ZL006	T7-pegylated liposome	T7-conjugated pegylated, ZL006 loaded liposomes highly accumulated in the brain and decreased infarct volume, improved neurological deficit when compared to unmodified liposomes	[50]
Intra-arterial	ICAM-1	Liposome	The combination of first-pass cerebral blood flow effect and IgG immunotargeting against ICAM-1 resulted in significantly improved and effective local drug delivery	[34]
Intra-arterial	Deferoxamine	Dendrimer	Generation 4 PAMAM dendrimer resulted in the significantly higher brain accumulation of the drug on intra-arterial delivery as compared to the intravenous route	[35]
Intranasal	H102	Liposome	AUC of H102 liposomes in the hippocampus was 2.92-fold higher than that of solution group H102 liposomes could effectively ameliorate spatial memory impairment of AD model rats	[37]
Intranasal	2-PAM	Cationic liposome	Rat challenged with paraoxon (0.8 × LD50) shown to reactivate central AChE (12%)	[38]
Intranasal	Quetiapine fumarate (QTP)	Nanoemulsion	High drug transport efficiency percentage and direct nose to the percentage of brain drug transport were obtained when compared to i.v.	[51]
Intracerebral	PTX	Polymeric nanoparticle	Pegylated PLGA copolymer-based nanoparticle upon delivery was able to provide higher concentration of the drug in the gliomas as well as with improvement in the tumor reduction as compared to non-pegylated components	[42]
Intracerebral	Clodronate	Liposome	Clodronate-loaded liposomes on intracerebral administration resulted in better depletion of microglial population a key component of the neurological diseases as well as neuro-inflammation as well as improved tumor outcomes	[44]

Table 11.3 Ongoing clinical trials of nanocarrier systems or delivery approaches for the brain targeting of the drug

Official title	ClinicalTrials.gov identifier[a]	Condition	Treatment	Phase
Overcoming membrane transporters to improve CNS drug delivery	NCT01322009	Pediatric traumatic brain injury	Probenecid and N-acetyl cysteine	Phase I and II
Combination chemotherapy delivered in conjunction with osmotic BBB disruption, with intraventricular cytarabine +/− intraocular chemotherapy	NCT00074178	Primary CNS lymphoma	Filgrastim, pegfilgrastim, cyclophosphamide Cytarabine, dexamethasone, etoposide phosphate, methotrexate	Phase II
A randomized study on CNS prophylaxis with liposome-encapsulated cytarabine in association with a lineage-targeted and MRD-oriented postremission strategy in adult ALL	NCT00795756	Acute lymphoblastic leukemia	Liposome-encapsulated cytarabine (DepoCyt®), triple intrathecal therapy (TIT)	Phase II and III
Combination of high-dose methotrexate and intrathecal liposomal cytarabine in patients with leptomeningeal metastases with or without parenchymal brain involvement	NCT00992602	CNS metastases; leptomeningeal metastases; recurrent breast cancer; stage IV breast cancer; tumors metastatic to the brain	Methotrexate, liposomal cytarabine	Phase II
RNOP-09: Pegylated liposomal doxorubicin and prolonged temozolomide in addition to radiotherapy in newly diagnosed glioblastoma	NCT00944891	Glioblastoma	Pegylated liposomal doxorubicin	Phase I and II
Combined chemotherapy as initial induction regimen in adults with acute lymphoblastic leukemia	NCT02072785	Adult acute lymphoblastic leukemia	Vincristine sulfate (liposome and non-liposomal)	Phase III

(continued)

Table 11.3 (continued)

Official title	ClinicalTrials.gov identifier[a]	Condition	Treatment	Phase
A prospective study of a high-dose, short-course regimen (R-CODOX-M/IVAC) including CNS penetration and intensive IT prophylaxis in HIV-associated Burkitt's and atypical Burkitt's lymphoma	NCT00392834	Lymphoma	Filgrastim, pegfilgrastim Rituximab, cyclophosphamide, cytarabine (liposomal and non-liposomal), doxorubicin hydrochloride, etoposide, ifosfamide, leucovorin calcium, methotrexate, therapeutic hydrocortisone, vincristine sulfate	Phase II
Multicenter, prospective, open-label trial, uncontrolled to determine the efficacy and safety of DepoCyt® for CNS relapse in adult patients with lymphoblastic leukemia or very aggressive lymphoma	NCT00388531	Lymphoblastic leukemia; lymphoma	DepoCyt®	Phase II
A randomized clinical study to determine the patient benefit and safety of DepoCyt® for the treatment of neoplastic meningitis	NCT00029523	Meningeal neoplasms	DepoCyt, methotrexate, cytarabine (aka ara-C)	Phase IV

[a]Completed studies compiled from ClinicalTrials.gov; NIH US National Library of Medicine (Accessed on December 08, 2018)

the challenges associated with the delivery of drug/s and use of route of administration. After all such claims of numerous drug delivery strategies, till now not even one is commercially available for clinical application. However, newer strategies are being tested in ongoing clinical trials. The reason behind is most of the drug delivery approaches are successful in preliminary trials and do not show promising results in the clinical trials. Along with this, the safety profile of the carrier system, drug release behavior, encapsulation efficiency, permeability across BBB, and bioavailability are the major challenges to resolve.

Acknowledgments The authors would like to acknowledge the Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, USA, for providing start-up support to Dr. Chougule's lab.

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12 Opportunities and Challenges in Targeted Carrier-Based Intracellular Drug Delivery: Increased Efficacy and Reduced Toxicity

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Contents

Abstract

The discovery of new therapeutic agents and targets depending upon the pathophysiology of various diseases has necessitated the delivery of therapeutic

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A. Misra, A. Shahiwala (eds.), *Novel Drug Delivery Technologies*,
https://doi.org/10.1007/978-981-13-3642-3_12

molecules to specific cellular sub-compartments. The efficiency of various treatments can be improved by carefully designing new therapeutic strategies involving modifications of nanocarriers enabling organelle-specific targeting of bioactives. In order to do that, in-depth studies to unravel the pathophysiology of diseases, internalization and intracellular trafficking pathways, as well as the time-dependent fate and release of encapsulated cargo from nanocarriers within the organelles are much needed. Despite the interdisciplinary efforts from the fields of medicine, materials science, and engineering, and the development of various nanomedicines with a precise control over their physical and chemical attributes, the subcellular targeted delivery still presents formidable challenges. Further, considering the fact that drug repurposing is now gaining interest, an intersection of nanocarriers and drug repurposing would provide key benefits like reduced time, cost, and risk in developing safer and more effective treatments for several indications. The significant opportunities and challenges in further progress toward bench-to-bedside translation of organelle-targeted nanomedicines are discussed in this chapter.

Keywords
Targeted delivery · Organelle targeting · Nanocarriers · Intracellular delivery

12.1 Introduction

The concept of targeted delivery of a drug to a desired region was envisioned as early as the 1900s when Nobel laureate Paul Ehrlich proposed the "magischekugel" or "magic bullet," which embodied a targeting agent along with the drug [1]. Later with the increase in the use of nanomaterials for biomedical applications, the research in the field of targeted drug delivery experienced an exponential surge. Targeted drug delivery involves directing a therapeutic molecule or drug specifically and preferably only to its site of action. Therapeutic index of a drug molecule depends on its effective delivery in the active form to the target site. But in most of the cases, it is associated with the lack of target site affinity toward the pathological site causing off-target side effects and toxicity issues as well as high-dose requirement for efficacy. Nanosized drug delivery systems play a vital role as carriers for the delivery of active molecules to their target sites. The main requirements of an ideal targeted drug delivery system include retention, evasion, target specificity, and release. The drug/gene should be properly loaded into an appropriate delivery vehicle and protected from degradation in vivo, and in case of intravenous administration, it should possess a longer circulation time. The chemical conjugation or physical encapsulation of the active molecules within a carrier should not inactivate the cargo and the targeting ligand employed. Further, the drug delivery vehicle should be stable in vivo and reach the desired site of action before effectively releasing the encapsulated drug at a predetermined rate of release with minimal

nonspecific accumulation. The drug carrier employed should be nontoxic, nonimmunogenic, preferably biodegradable, and easily eliminated from the body. The synthesis or fabrication of the targeted nanocarriers should be reasonably simple, reproducible, cost-effective, and industrially feasible [2–4].

Drug targeting may be broadly classified into first, second, and third order of targeting based on the target. First-order targeting or organ-level targeting utilizes a tissue or organ as the target, e.g., lymphatics, eyes, cerebral ventricles, etc. When the target is a specific cell like a tumor cell, macrophage, or Kupffer cell, it is referred as second-order targeting or cell-level targeting. Majority of the nanocarrier systems are designed for second-order targeting against specific cells. The third-order targeting involves targeting intracellular organelles and specific intracellular molecules like DNA inside the nucleus, mitochondria, Golgi apparatus, lysosomes, etc. Each level of targeting is associated with its own advantages and complexities. For instance, if all the cells in the targeted organ require therapeutic intervention, then organ-specific delivery may be preferred, whereas to target only specific diseased cells in an organ, cell targeting may be useful [2, 5, 6].

Intracellular targeting or the third level of targeting poses tremendous research opportunities as the site of action of most of the drugs are within specific organelles. For instance, pro-apoptotic drugs are targeted to mitochondria and lysosomes, anticancer drugs interfering DNA replication need to reach the nucleus, drugs interfering protein metabolism are targeted to endoplasmic reticulum (ER), and many other active pharmaceutical agents, including large molecules like proteins, antibodies, enzymes, etc., are to be delivered subcellularly for their therapeutic effect. In addition, gene delivery against several genetic disorders also demands delivery of specific DNA sequences or protein/nonprotein drugs to specific intracellular compartments. It is postulated that efficient localization of drugs in specific organelles can enhance treatment efficiency and reduce adverse effects. Passive accumulation of drugs within cells often leads to a nonuniform distribution between organelles. However, smart drug delivery systems equipped with specific residues like nuclear localization sequences/signals (NLS), organelle-specific signal peptides, mitochondriotropic residues, etc., which can alter the intracellular trafficking, can be envisioned to deliver their cargo at specific organelles. In-depth knowledge of molecular and cell biology, cellular uptake, as well as trafficking mechanisms is of prime importance while designing subcellular targeted drug carriers [7–9].

Another perspective to address the urgent need for overcoming drug resistance and improved efficacy is drug repurposing, which refers to the identification and discovery of novel therapeutic uses for already clinically approved drugs by screening them against relevant disease targets. A repositioned drug goes directly to preclinical and clinical trials, thus reducing risk and costs. The structural optimization, preclinical and/or clinical trials, and clinical safety analysis of such drugs have already been completed, and the toxicological, pharmacological, and clinical safety information is already available [10, 11]. Majority of the studies investigating nanocarriers for repurposed drugs are preclinical studies for antimicrobial and anticancer applications. One such drug is disulfiram, an anti-alcoholism drug that shows anticancer properties. However, its clinical application in cancer treatment is limited

due to its very short circulation half-life. Several nanocarriers have been designed to improve the pharmacokinetic properties of disulfiram and enhance its anticancer efficacy [12–14]. The use of targeted nanocarriers for the repurposed drugs would reduce the risks and costs related to the failures in early stages of development and warrant enhanced clinical efficacy.

Currently, nanocarriers that have been clinically approved or under clinical trial are primarily developed to enhance pharmacokinetic and/or pharmacodynamic properties of drugs. In the majority of cases, these nanocarriers employ passive targeting, which involves nonspecific accumulation in the diseased tissue. Since 1995, about 50 nanopharmaceuticals are in clinical use after receiving the FDA approval. Table 12.1 provides few examples of the FDA-approved nanodrugs in clinical use with intracellular targets. Table 12.2 provides some of the nanomedicines undergoing clinical trials, while Table 12.3 provides examples of patents for intracellularly targeted nanocarriers.

12.2 Advantages of Targeted Drug Delivery

- The main advantage of targeted drug delivery is that it enables preferential accumulation of the therapeutics in target cells versus normal cells, thereby minimizing the potential side effects and enhancing therapeutic efficacy as well.
- Some of the pharmacokinetic shortcomings in terms of bioavailability, short half-life, large volume of distribution, etc. can be overcome as the pharmacokinetic behavior of the drug-loaded carriers depends on the delivery system as opposed to the encapsulated drugs.

Table 12.1 Examples of the FDA-approved nanodrugs in clinical use [15]

Nanocarrier (manufacturer, formulation)	Indication	Intracellular site of action
DOXIL® (Janssen, doxorubicin HCl liposome injection)	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	DNA
DepoCyt (Sigma-Tau, liposomal cytarabine)	Lymphomatous meningitis	DNA
Onivyde (Ipsen Biopharmaceuticals, liposomal irinotecan)	Pancreatic cancer	Topoisomerase 1-DNA complex
Vyxeos (Jazz Pharmaceuticals, liposomal daunorubicin, and cytarabine)	Acute myeloid leukemia (AML), AML with myelodysplasia related changes	Topoisomerase
Ryanodex (Eagle Pharmaceuticals, dantrolene sodium)	Malignant hypothermia	Sarcoplasmic reticulum
Abraxane (Celgene, albumin-bound paclitaxel)	Breast cancer, non-small-cell lung carcinoma (NSCLC), pancreatic cancer	Microtubules
Ontak (Eisai, denileukin diftitox)	Cutaneous T-cell lymphoma	Cytoplasm

Table 12.2 Examples of nanomedicines under clinical trial [15]

Name of formulation	Drug	Clinical trial phase	Intracellular target	Indication
Arikayce (Insmed, Inc., liposomes)	Amikacin	Phase 3	Bacterial 30S ribosomal subunit	Chronic lung infections
Promitil (LipoMedix Pharmaceutical, Inc., PEGylated liposomes)	Mitomycin C	Phase 1	DNA	Anal squamous cell carcinoma
MM-302 (Merrimack Pharmaceuticals, Inc., liposomes)	Doxorubicin	Phase 1	HER2 receptor targeted	HER2-positive breast cancer
NKTR-102 (Nektar Therapeutics, PEGylated polymer nanoparticles)	Etirinotecan	Phase 3	Topoisomerase I inhibitor	Metastatic breast cancer
CRLX101 (drug, cyclodextrin-PEG conjugate)	Camptothecin	Phase 2a	Topoisomerase inhibitor	Relapsed/refractory small cell lung cancer
Nanoplatin (NC-6004, NanoCarrier Co., Ltd., micellar formulation)	Cisplatin	Phase 3	DNA	Pancreatic cancer
SN-38 (micellar formulation)	Active metabolite of irinotecan	Phase 2	Topoisomerase I inhibitor	NSCLC and triple-negative breast cancer
Genexol-PM (Samyang Biopharm, mPEG-block-D,L-PLA micellar formulation)	Paclitaxel	Phase 2	Microtubule assembly	Hepatocellular carcinoma
MAT2203 (Matinas BioPharma, nanocrystal)	Amphotericin B	Phase 2	Fungal cell membrane	Invasive fungal infections
MAT2501 (Matinas Biopharma, Nanocrystal)	Amikacin	Phase 1	Bacterial 30S ribosomal subunit	Non-tuberculous Mycobacterium infections
Aurimune (CytImmune, gold nanoparticles with a PEG linker)	Recombinant human TNF	Phase 1	Mononuclear phagocyte system	Advanced cancer
RSV-F Vaccine (Novavax, protein nanoparticle)	(RSV) fusion protein	Phase 2	–	Respiratory syncytial virus
DTXSPL8783 (Dendrimer)	Docetaxel	Phase 1	Microtubule assembly	Advanced solid tumor and NSCLC
VivaGel (Starpharma, dendrimer-based gel)	SPL7013 or astodrimer sodium	Phase 3	gp120 proteins on the viral surface	Prevention of HIV and HSV-2 genital infections in women

Table 12.3 Representative patented intracellular drug delivery system

Patent no	Formulation	Targeting ligand	References
US20050163832A1	Cationic liposome	Transducing polypeptides	[16]
WO2017049245	Liposome	Modified PEG	[17]
US20020192275A1	Liposome	Antibody fragment	[18]
WO2006007560A2	Liposome, microbubble, dendrimer, or micelle	Mammalian lysosomal protein	[19]
US5711964A	Liposome	Thiocationic lipid	[20]
US5459127A	Cationic liposome	Lysophosphatide	[21]
US20060083711A1	Cationic polymer nanoparticle	Glycosaminoglycan	[22]
US20070292494A1	Liposome	CTL/CTLD receptor-specific anchor	[23]
US20030026831A1	Anionic liposome	Low-density lipoprotein	[24]
JP2009286709A	Liposomes	Peptide containing basic amino acid residues	[25]

- Intracellular drug delivery via nanocarriers, in particular, is beneficial because the amount of drug required to exert therapeutic action is reduced significantly, which in turn reduces the side effects [26].
- Multidrug resistance, a major hurdle in chemotherapeutic and antimicrobial drug therapy, can be to an extent overcome using intracellularly targeted nanocarriers. Since most of the transporter proteins recognize and expel drugs at the plasma membrane, internalized nanocarriers bypass this mechanism, thereby improving the efficacy of the drugs [27, 28].
- When compared with drug conjugates, a nanocarrier system can simultaneously incorporate high density of drug and present targeting ligands at its surface. This enhances the ligand-target interaction through multivalency and subsequent internalization of the targeted carrier.
- Targeted carriers can be designed to simultaneously deliver synergistic ligand molecules along with the encapsulated drug. This has been particularly advantageous in anticancer nanopreparations combining monoclonal antibodies with a chemotherapeutic drug, which were proven more beneficial than the drug alone or antibody alone [29–31].

12.3 Targeted Delivery Approaches

Active and passive targeting are the two key approaches explored for the targeted delivery of drug by nanosystems.

12.3.1 Passive Targeting Opportunities

The accumulation of drug or carrier system at the desired site of action owing to specific pathophysiological or anatomical factors is considered as passive targeting.

12.3.1.1 Pathophysiological Factors

Many diseases alter physiology and physiological functions of the diseased tissue, which can be used as a tool for intracellular targeting. Infection/inflammation leads to the release of various chemotactic mediators during tissue remodelling, which causes increased leukocyte extravasation. This pathophysiological abnormality leads to the increased vascular permeability of drug and drug carriers allowing extravasation and selective localization of the nanocarrier at the damaged tissue. This phenomenon, known as the enhanced permeation and retention (EPR) effect, is more pronouncedly used in anticancer drug targeting where solid tumors present more preferable conditions for drug accumulation [32, 33]. Angiogenesis recruits new blood vessels around the tumor to meet the demand of nutrition for the cells. But unlike the normal vasculature, this endothelium is leaky in between the adjacent cells leading to increased vascular permeability and reduced lymphatic drainage in tumors. However, a drug carrier system should have a longer circulation time to attain the EPR effect for passive targeting. Many nanosystems like liposomes, polymeric micelles, and nanoparticles target the tumor vasculature passively using EPR effect [34–36].

12.3.1.2 Anatomical Factors

These factors involve the delivery of the drug or drug carrier system directly into the anatomical region where the action of drug is desired. This is an indirect method of targeting the cells of a particular region like lungs, knee joints, eyes, etc. Here, the advantage of the anatomical entry of the drug has been taken into consideration in comparison with the traditional drug delivery system like tablets and capsules. This site-specific drug delivery prevents the unwanted exposure to the other tissues, which in turn avoids side effects [37, 38].

A classic example is delivery to the brain, which is limited due to the tight barrier of the blood-brain barrier (BBB) making the permeation of drug molecules difficult. Although various selective transport mechanisms like diffusion amd receptor-mediated or fluid-phase endocytosis play important roles in the absorption and transport of drugs via the BBB, the systemic administration and subsequent transport of therapeutic agents to the brain are still challenging. Efflux mechanisms are mainly responsible for preventing the drug delivery systems from reaching the target site. To overcome these challenges in brain drug delivery, microinjection technique or nose-to-brain drug delivery has been researched as alternatives. Microinjection technique involves the direct injection of the drug solution or nanocarrier system into the cerebrospinal fluid, which takes the drug to the brain. Nose-to-brain delivery utilizes the nasal pathway for the drug delivery to the brain. This leads to higher drug concentrations in the brain owing to bypassing of the BBB

[39–41]. As an example, R Jain et al. developed and characterized micellar nanosystems of sumatriptan for intranasal delivery and further evaluated the biodistribution in rats. The nanomicellar carriers were found to be homogenous and spherical in shape. In vivo biodistribution and radiography studies revealed significantly higher sumatriptan brain uptake from the micelles as compared to sumatriptan drug solution given by nasal route. This investigation thus indicated the potential to target nanocarriers for brain drug delivery via nasal pathway [42].

12.3.1.3 Physicochemical Factors

Various physiological factors like size, surface charge, and hydrophilicity, which play an important role in the biodistribution and clearance of the nanocarriers, can be manipulated for passive targeting of the drug. Reticuloendothelial system (RES) clears 90% of the nanosystems out of the systemic circulation when injected intravenously from liver and spleen. This inherent tendency of nanosystems having size less than 100 nm to accumulate in the liver and spleen presents excellent opportunities for passive targeting to these organs. This has been utilized for the intracellular passive targeting of antiviral and antimicrobial agents. Although this approach is more promising for targeting to highly perfused organs, it holds the drawback of rapid clearance of the drug from the circulation. Many approaches have been researched and optimized to escape the RES uptake, improve the circulation of the nanosystems, and exhibit the action of the drug molecule at the desired site of action [43–45].

12.3.2 Active Targeting Opportunities

Passive targeting presents limited scope in drug delivery, and hence immense efforts have been directed toward active targeting of the drug or nanocarrier via modification with active ligands having selective affinity toward specific receptors or proteins on the cell membrane or lipid components of the cell compartments. A wide number of studies were carried on by direct coupling of a ligand to nanosystems like polymeric nanoparticles, liposomes, dendrimers, micellar systems, etc. to enhance the efficacy and minimize the off-target side effects of the drug. In many cases, the active-targeted nanosystems act as carriers to deliver the cargo to the inner compartments of the cell where they lack the entry phenomenon. In many diseased states, some receptors or surface antigens/proteins are expressed uniquely, or there is a structural or molecular change in the cellular membrane structure as compared to normal cells. Taking benefit of these changes, active agents like ligands, antibodies, or antigens have been extensively employed for active targeting. Various drugs are delivered by the active targeting approach at different receptors like folic acid receptors, LDL receptors, peptide receptors, G-protein-coupled receptors, etc. The following agents can be used as targeting moieties: antibodies and their fragments; lipoproteins; hormones; lectins; mono-, oligo-, and polysaccharides; and low molecular weight ligands like folate. Recently, monoclonal antibodies are the most commonly used vector molecules against characteristic tissue components.

The major targets involve different body compartments and pathologies like components of cardiovascular system, RES, lymphatic system, tumors, infarcts, inflammations, infections, transplants, etc. Currently, coupling a drug directly to the targeting ligand seems the easiest method for active targeting, for example, the development of direct drug-antibody conjugates has been explored for treatment of malignant diseases, such as cancer [46].

12.4 Design Considerations for Carrier-Mediated Intracellular Drug Targeting

Carrier-mediated passive targeting for intracellular delivery can be possible by utilizing pharmacological and physicochemical factors. Pathophysiological conditions such as leaky vasculature and change in pH of cancerous cells pave the way for passive targeting, specifically by modulating size, shape, surface charge, or composition of carrier.

12.4.1 Shape and Size

Particle size plays a vital role in pharmacokinetics of the drug-loaded carrier. Particle size affects the attachment, adhesion, cellular uptake, circulation half-life, and accumulation of the carrier [47]. Modulation of particle size can also help in avoiding or encouraging cellular uptake by endocytosis [48, 49]. Small nanoparticles having size 10–20 nm exhibit extensive accumulation in several organs by crossing the tight endothelial junctions and show rapid hepatic as well as renal clearance. Thus, having carrier particle size greater than 20 nm can ensure avoidance of clearance by filtration through the kidneys [50, 51]. Polymeric particles and liposomes with higher particle size (200 nm–few μm) generally exhibit phagocytic uptake. So nanocarriers of size between 10 and 100 nm are ideal [52]. Particle size not only affects the mode of cellular uptake but can also mediate the essential molecular processes for regulating cellular functions [53]. The smaller molecules easily diffuse, while EPR effect dominates in the case of larger and long-circulating nanocarriers (> 100 nm) due to lack of effective lymphatic system [54].

Apart from size, particle shape is also a strong determinant of cellular uptake of the carrier. Although traditionally, spherical nanocarriers such as polymeric nanoparticles, liposomes, and micelles dominated the targeted delivery research, lately it has been observed that non-spherical shapes have great potential as drug delivery vectors. Non-spherical carriers of ellipsoid, rod, and worm shapes offer several advantages in terms of improved drug delivery efficiency owing to high drug loading efficiency, long circulation time, enhanced attachment and binding affinity to target cells, and better cellular uptake [55, 56]. Sharma et al. showed that nanoparticles with at least one extended axis, like prolate ellipsoids, are promising long-circulating drug carriers. Non-spherical particles bypassed phagocytosis because of incomplete actin structure formation [57]. Particle shape was also found to

influence attachment and internalization during phagocytosis [58]. Yoo et al. compared non-spherical geometry of elliptical disks with spherical geometry and showed that the former exhibits slow uptake kinetics with equilibrium distribution of particles in cells [59].

12.4.2 Composition

The composition of subcellular targeted nanocarriers designed to deliver drug intracellularly through either passive or active means has also shown to influence their trafficking. Inclusion of negatively charged phospholipids such as phosphatidylserine and phosphatidyl glycerol in multilamellar vesicles containing phosphatidylcholine greatly favored the binding and phagocytosis by macrophages as compared to neutral phospholipids [60]. However, nanocarriers internalized via the endocytic pathway get entrapped in the endosome and lysosome and eventually get degraded by the action of the lysosomal enzymes. Therefore, several strategies have been attempted to achieve delivery of nanocarriers like liposomes, micelles, etc. into the cell cytoplasm, circumventing the endocytic pathway.

Torchilin et al. showed that incorporation of different polymers into liposomes can result in enhanced circulation time as a function of concentration. In addition, the use of pH-sensitive carriers, which destabilize endosomal membrane at low pH and liberate the loaded cargo into the cytoplasm, is a promising approach to avoid lysosomal degradation. [61, 62] Micelles, including polymeric micelles, are also widely studied pharmaceutical carriers owing to their smaller size, in vivo stability, feasibility to load water insoluble anticancer drugs, and prolonged circulation times [63]. Passive targeting of micelle is possible due to the small micellar size and the EPR effect. Modification of composition of amphiphilic polymer micelles with phosphatidyl ethanolamine and lipid moieties as hydrophobic blocks that cap hydrophilic polymer chains endows additional advantages like particle stability and enhanced accumulation [64]. Further modification of these micelles with cationic lipids may improve the internalization of drug-loaded micelles within cells and facilitate the escape from endosomes to enter the cytoplasm [65].

12.4.3 Surface Characteristics

Surface charge of nanoparticles shows significant impact on the circulation, biodistribution, internalization, and trafficking. It also effects the opsonization by macrophages, which further affects their biodistribution [47]. Anionic cell membrane shows better interaction with positively charged nanocarriers leading to higher phagocytic uptake and less circulation time than negatively charged nanocarriers [66, 67]. Conversely, it has also been demonstrated that neutral and cationic nanoparticles exhibit limited internalization of particles by RES and are cleared less rapidly than the anionic ones [68]. Xiao et al. studied both cationic and anionic nanocarriers for their in vivo fate. This study demonstrated that nanocarriers with

high positive or negative surface charge get internalized nonspecifically by macrophages in vitro and in vivo, resulting in high liver uptake after systematic administration [69]. Further, upon investigating the uptake of both cationic and anionic nanocarriers in phagocytic and non-phagocytic cells, it was observed that a slightly negative surface charge of nanocarriers was optimal for use as drug delivery carriers in cancer therapy [68].

Apart from charge, surface hydrophobicity can also affect the opsonization, phagocytosis, blood circulation, and biodistribution of nanocarriers [47]. As hydrophobic nanocarriers are preferentially coated and scavenged by RES, increasing the surface hydrophilicity is seen as a promising strategy to evade RES. PEGylation of nanocarriers such as dendrimers, polymeric nanoparticles, liposomes, etc. is one of the most explored strategies to prolong circulation half-life and improve the accumulation of nanocarriers in tumor cells [70]. PEGylated proteins, micelles, and low molecular weight drugs showed improved therapeutic efficacy by passive targeting in a novel way [71].

12.4.4 Target Specificity

Active targeting is preferred for the subcellular targeted delivery of macromolecular drugs such as DNA, siRNA, and proteins. However, nanocarriers upon endocytosis may undergo degradation, which may not be desirable for nucleic acid or macromolecules delivery. Such drugs must be thus delivered to specific cellular organelles like nuclei, lysosomes, mitochondria, etc. to exert their therapeutic action. For example, to overcome the enzymatic degradation as well as poor cellular uptake and endosomal escape of nucleic acid therapeutics like antisense oligonucleotides, small interfering RNA, etc., viral vectors have been employed. Viral vectors such as adenoviruses, herpesviruses, hepadnaviruses, influenza viruses, etc. have been investigated for gene therapy, but these showed several drawbacks such as toxicity, immunogenicity, and limitation in the size of the plasmid to be inserted. Polyelectrolytes diffuse passively into the nucleus and tend to be retained due to cationic histone and anionic nucleic acids [72]. Complexes with cationic polymers like chitosan, poly-L-lysine and poly(ethyleneimine), and lipoplexes (complexes with cationic lipids) have also been employed for nucleus targeting [73].

Lysosomal targeting strategies mainly revolve around two main objectives: (i) to directly target lysosomes through receptor-mediated endocytosis and (ii) to protect the cargo molecule from lysosomal degradation and make it available in the cytoplasm for further action [74]. Similarly, the distinct mitochondrial features including high membrane potential across the inner mitochondrial membrane, the organelle's protein import machinery, and the mitochondrial fusion process have been exploited for developing a targeting strategy to the mitochondria within living mammalian cells [75]. Lipophilic cations owing to their cationic charge and hydrophobic surface area possess low activation energy for their movement across the membrane and, hence, can easily transverse across the plasma membrane and the mitochondrial membranes. Triphenylphosphonium (TPP) cation was originally

used to assess the mitochondrial membrane potential, and its uptake into mitochondria is well recognized. It can be easily incorporated into a compound late in the chemical synthesis scheme, typically by displacing a leaving group [76]. Mitochondrial targeting signal (MTS) peptide can be used to deliver proteins to the mitochondrial matrix. The MTS sequence leads the cargo protein to the mitochondria and is then cleaved enabling localization and function of the fused protein [77].

The various opportunities for subcellular targeting to the different organelles have been discussed in detail in the following sections.

12.5 Opportunities in Intracellular Drug Delivery

Recent advances in molecular biological techniques have led to the detailed understanding of the pathophysiology of diseases. This lead to the identification of newer cellular and molecular targets for drug discovery and imaging purposes. Further, the integration of the computer-aided drug designing along with molecular biology has opened paths for the target-specific drug molecules or drug delivery carriers. However, the molecular complexity and inaccessible drug targets lead to the evolvement of novel nanodrug carrier systems as the most desirable option. Several nanodrug delivery systems were designed to target intracellular organelles. Treatment strategies against a host of diseases have been explored by targeting the cellular organelles like mitochondria (cancer, diabetes mellitus, cardiomyopathy), Golgi apparatus (Alzheimer's disease, CDG syndrome), ER (cystic fibrosis), lysosomes (Tay-Sachs diseases, autoimmune diseases), plasma membrane (familial hypercholesterolemia, infectious diseases), as well as the nuclear envelope (progeria, muscular dystrophy) (Fig. 12.1).

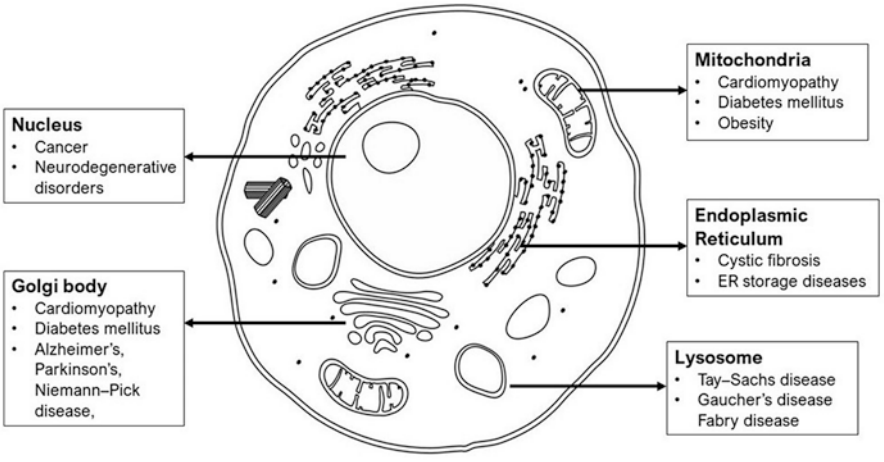

Fig. 12.1 Examples of cell organelle-associated diseases

12.5.1 Nuclear Targeting

Nucleus is the eukaryotic cell controller responsible for the regulation of gene expression, transcription, and translocation of proteins from nucleus to cytoplasm for various cellular processes. The human nuclear genome database contains two copies each of 3.2 billion base pairs, of which only 2% codes for 30,000 diverse proteins. Several disorders like cancer, heart dysfunction, and neurodegenerative and other brain diseases are manifestations of mutations in the promoter/enhancer regions of these genes and their splice sites. Various drugs used in the treatments of cancer act at the DNA to prevent the transcription of genes. However, only some of the total drug administered translocate into the nucleus from the cytoplasm to exert its action, which ultimately warrants a higher dose of the drug to be administered. In addition, proliferating cells develop genetic changes, which may lead to resistance to a particular drug. This may also result in the generation of new drug-resistant daughter cells, which have the properties of the parent cells. This necessitates the need for nanoparticle-based delivery systems for direct and effective nuclear delivery of drugs or plasmids to avoid the adverse drug reactions [78–82].

The main barriers for nuclear-targeted carriers are in the form of cell membrane, entrapment and degradation in endo-/lysosomes, cytoplasmic trafficking, and nuclear membrane. The smaller nanoparticles (< 25 nm) have been found to enter the cells passively, while the larger nanocarriers are taken up by endocytosis and traverse the endolysosomal pathway or get trafficked to other organelles or exocytosed. Nanocarriers modified with ligands targeting LDL receptors, transferrin receptors, epidermal growth factor receptors, etc. undergo clathrin-mediated endocytosis and ultimately get degraded in the lysosomes. Ligands like folic acid, albumin, cholesterol, etc. have been found to assist in caveolae-mediated and lipid raft endocytosis that allow bypassing of endosomal pathway, cytoplasmic trafficking, and delivery to non-lysosomal compartments by activating signal transduction cascade [83]. Nuclear pore complex (NPC), a central perforated channel of 9 nm, plays a vital role in all the passive and active transport of the molecules measuring less than 50 kDa across the nuclear envelope. Molecules larger than 50 kDa need assistance from NLS and NPC. NLS specifically interacts with the NLS receptor in an energy-dependent recognition successively docking the cargo by an energy-dependent translocation and subsequent release into the nucleus [84]. Several viral-mediated gene delivery strategies have been developed following the advances in the field of viral infection mechanisms. Adenovirus type 2 and type 5, the most commonly studied virus for gene delivery, get endocytosed by the epithelial cells, enter the cytosol in an integrin-dependent manner, and are translocated to a microtubule organizing complex and then nucleus [85]. Simian virus has also been investigated to facilitate caveolae-mediated endocytosis, and simian virus NLS have been employed to assist nanocarriers in nuclear localization [86]. Viral-mediated nuclear delivery offers an advantage of high translocation efficiency, but their use in drug delivery is limited owing to the considerable toxicity associated with the viral components. Various non-viral vectors (liposomes, nanoparticles) have also been

surface modified with the identified NLS sequences for nuclear-targeted gene delivery. The NLS-modified carriers bind and interact with the NLS binding domain of a cytoplasmic transporter, importin-α, and the resultant complex then binds to importin-β. The final complex then interacts with nucleoporins and docks into the NPC effecting nuclear entry [87].

Liposomes, with their phospholipid bilayer nature, are unique because of their ability to fuse with cell membrane. Upon entering the cell by fusion, the liposomes avoid endosomal entrapment and deliver their cargo to the cytoplasm. However, liposomes also get endocytosed, fuse with the endosomal membrane, and release their cargo in the cytoplasm after endosomal escape [88, 89]. The chances of nuclear delivery have been found to increase if the nanocarrier is modified to avoid the endolysosomal pathway. Cell-penetrating peptides and various small viral peptides, like KKKRKV from SV40 large T antigen, fusogenic peptides like HA2 peptide from influenza virus hemagglutinin, etc., have also shown effective nuclear localization and, hence, are used for nuclear delivery [84, 90]. Certain cationic lipids and polymers complexed with DNA, known as lipoplexes and polyplexes, respectively, have also been developed to deliver DNA into the nucleus and are in the clinical trials for the treatment of melanoma [91, 92]. Another study showed that a complex of plasmid DNA and low molecular weight protamine efficiently translocated into the cell and then entered the nucleus due to the structural similarity of protamine with HIV-TAT peptide [93]. Few examples of nuclear-targeted nanocarriers are given in Table 12.4.

12.5.2 Mitochondrial Targeting

Mitochondria, known as the powerhouse of the cell, provide adenosine triphosphate, ATP, to the cell by oxidative phosphorylation. They are also associated with other metabolic pathways, like the citrate cycle, fatty acids oxidation, and the

Table 12.4 Few examples of nuclear-targeted nanocarriers

Nanocarrier	Purpose	Therapeutic effect
TAT-HA2 gelatin-silica nanoparticles	Gene therapy	Efficient gene transfection [94]
NLS-poly(lactic-co-glycolic acid) (PLGA) nanoparticles	Gene therapy	Efficient gene transfection [95]
Ultrasmall gold nanoparticles	Gene therapy	Downregulation of gene and further reduction in cell viability [96]
Cationic polyplexes	Gene therapy	Successful gene transfection [97]
NLS/RGD-silver nanoparticles	Cancer therapy	Cytotoxicity, induction of apoptosis [98]
Mesoporous silica nanoparticle TAT	Cancer therapy	Cytotoxicity, induction of apoptosis, inhibition of in vivo tumor growth [99]

Reprinted with permission from Tammam SN, Azzazy HME, Lamprecht A (2016) How successful is nuclear targeting by nanocarriers? J Control Release 229:140–53

synthesis of hormones and gluconeogenesis. Mitochondrial dysfunction and somatic mutations contribute to various human disorders, like obesity, diabetes, cardiomyopathy, Parkinson's, kidney and liver diseases, and stroke to name a few. Mitochondria have a vital role in apoptosis, and the mutations in apoptosis-related genes, viz., p53, PTEN, and Bcl-2, and their homologues cause chemoresistance in most cancers. They also regulate the concentration of intracellular calcium ion and reduce the oxidative stress by oxidative phosphorylation via the mitochondrial respiratory chain. The multiple functionality of mitochondria thus makes them a major target in pharmacological interventions. Reduction in oxidative damage and calcium overload could prevent mitochondrial damage. Several strategies for targeting the mitochondria and nullifying the effect of mutant genes have been employed for treating mitochondrial gene mutations [100–104].

Several clinically used drugs, such as paclitaxel, etoposide, lonidamine, ceramide, etc., act on mitochondria directly and cause apoptosis. One of the attempts to target the mitochondria is through transmembrane electrochemical gradient, contributed from both negative membrane potential and pH difference (acidic outside). Owing to the negative membrane potential, cationic molecules get attracted by the mitochondria. Vitamin E covalently coupled to a mitochondrotropic molecule, TPP cation, was driven across the mitochondrial inner membrane due to a large membrane potential ranging from –150 to –180 mV. This leads to higher accumulation of vitamin E in mitochondrial matrix as compared to its native form. TPP cation has also been explored to realize mitochondrial delivery of antioxidants like coenzyme Q, ubiquinone, nitroxides, peptide nucleic acids, cyclosporin A, etc. [105, 106]. Another strategy for mitochondrial targeting involves MTS, i.e., mitochondrial targeting sequence. MTS are nonspecific and have similar physiochemical properties of the mature protein of which they are a part of. There are several studies attempting gene therapy involving restriction enzymes that are targeted to the mitochondria using MTS. An example of such an attempt involves targeted delivery of the restriction endonuclease Sma1 to mitochondria and consequent removal of mutant mitochondrial DNA [107].

Another approach involves a molecule or nanocarrier that possesses specific mitochondrial affinity. Dequalinium chloride (DQA), a single-chain bola mitochondriotropic amphiphile having two delocalized positive charge centers, has been found to specifically accumulate in the mitochondria of cancer cells. Weissig et al., in 1998, first proposed DQA-based liposome-like vesicles (DQAsomes) as a mitochondrial-specific drug delivery system. These bola-like amphiphiles (bolasomes) form cationic vesicles with diameters between 70 and 700 nm entrapping various drugs and DNA and transport them to mitochondrion. Later, it was demonstrated that DQAsomes conjugate with DNA and release it in mitochondria after entering the cells [108–112]. It was also attempted to target liposomes to mitochondria by modifying with a mitochondrial membrane fraction. The incorporation of stearyl triphenylphosphonium (STPP) in liposomes enabled the stearyl residue of STPP to act as an anchor for the TPP residue that would result in a liposomal formulation having an inherent predisposition for mitochondria [113]. In another study, the octaarginine residues used to modify liposomes enabled cell entry via

macropinocytosis, while the lipid composition of the liposomes facilitated preferential fusion with the mitochondrial membrane and release of the encapsulated cargo in mitochondria [114, 115]. TPP modified N-(2-hydroxylpropyl) methacrylamide nanoparticles and inorganic nanoparticles like amorphous silica nanocages were also explored for mitochondria-specific delivery although the exact mechanism of mitochondrial accumulation of silica nanocages was not clear [116, 117].

12.5.3 Lysosomal Targeting

Lysosomes are single membrane-bound, subcellular organelles with acidic pH and approximately 60 hydrolases that can degrade various biological molecules. They also play a role in the recycling of cell surface molecules and receptors. Macromolecules reach the lysosome exogenously via phagosomes or endosomes and endogenously via autophagy. Certain inherited diseases like Tay-Sachs disease, Gaucher's disease, Fabry disease, Niemann-Pick disease, etc. are manifestations of the deficiency of some lysosomal enzymes (lysosomal storage diseases) and can be treated only by administering exogenous enzymes. Several glucosidases, glucocerebrosidase, phenylalanine ammonia lyase, and other enzymes are used for treating lysosomal storage diseases. For many disease conditions, the treatment with purified exogenous enzymes shows very encouraging results than with native enzymes. Treatment with native enzymes gives short-term relief only because of short biological half-life and relatively inefficient lysosomal transport [118–120]. Liposomes were researched as carriers for replacement enzymes that could avoid inactivation of enzymes and improve their intracellular delivery and lysosomal transport. G Gregoriadis studied the biodistribution of β-fructofuranosidase entrapped in liposomes composed of phosphatidylcholine, phosphatidic acid, and cholesterol. It was shown that after 6 h and 48 h, 45% and 25% of the administered enzyme activity, respectively, was shown to be accumulated in the liver. It is of prime importance that about 50% of the intracellular enzyme activity is localized within the lysosomal fraction. Similar kind of study attempted the intravenous administration of α-mannosidase and neuraminidase encapsulated in liposomes [121, 122]. Recently, several targeting ligands like folate, RGD, rhodamine, transferrin, etc. were also employed to functionalize liposomes and enhance their lysosomal delivery [123, 124].

A transmembrane glycoprotein called intercellular adhesion molecule-1 (ICAM-1) has been widely explored to facilitate lysosomal delivery of nanocarriers. Anti-ICAM-1 antibody-functionalized polymeric nanoparticles, solid-lipid nanoparticles, polyelectrolyte complexes, etc. were developed against Pompe disease, Gaucher's disease, and Fabry disease [125–128]. Lysosomotropic agents like octadecyl rhodamine B, anti-LAMP1 antibodies, Gly-Leu-Phe-Gly peptide, etc. induce permeability of lysosomal membrane and release of hydrolytic enzymes and reactive oxygen species resulting in apoptosis of cells. Such agents have been used to functionalize nanocarriers and enable their preferential accumulation in lysosomes and release of their cargo, eventually leading to cell death [129–131]. Lysosomal targeting has

also been explored to direct nanocarriers like single-wall carbon nanotubes, polybutylcyanoacrylate nanoparticles, gold nanoparticles, etc. and induce autophagy in neurodegenerative diseases, infectious diseases, as well as autoimmune disorders [132–134]. For several therapies, it is required that the drug/nanoencapsulated cargo need to escape from the endo-/lysosome and get released to the cytoplasm. In such cases, "pH buffering" or "proton sponge" effect caused by polyethylene imine, polyamidoamines, lipopolyamines, etc. is employed to cause endo-/lysosomal escape. Membrane disruptive agents like poly(acrylic acid), polyethylacrylic acid, pyridyldisulfide acrylate, etc. can also be employed to achieve the same [135–137].

12.5.4 Golgi/ER Targeting

Golgi apparatus is one of the key organelles of the cell secretory pathway and has functions similar to ER. It is mainly involved in the posttranslational modification of newly synthesized proteins and synthesis of carbohydrate and proteoglycans structures like glycosaminoglycans and polysaccharides. Certain alterations in the Golgi apparatus caused by pharmacological agents, pathological changes, and overexpression of associated proteins result in various neurodegenerative disorders including Alzheimer's, Parkinson's, Niemann-Pick disease, etc. Further, the Golgi apparatus and the ER are also involved in development of targeted anticancer therapy against androgen-dependent and androgen-independent prostate cancer [138–140].

The ER, a system of folded membrane tubules and sacs extending from the nuclear membrane, is responsible for the folding of secretory and membrane proteins, calcium storage, calcium signalling, and apoptosis regulation. The absence or misfolding of a protein or the presence of a mutant protein can lead to ER storage diseases like familial hypoparathyroidism, familial central diabetes insipidus, chronic pancreatitis, etc. [141, 142]. Targeting mammalian target of rapamycin (mTOR), the central regulator of cell growth and proliferation (e.g., by rapamycin), is an example of targeting Golgi body or ER as an anticancer therapy [143, 144]. Some polymeric nanocarriers like polycaprolactone and PLGA nanoparticles were found to accumulate in the Golgi-associated vesicles of late endosomes and hence can be used for Golgi/ER targeting [145, 146].

12.6 Challenges in Intracellular Drug Delivery

The key problem in targeted delivery of different pharmaceutical active molecules is the intracellular transport, especially to the subcellular organelles. Successful drug targeting requires not just performance at the target site and drug receptor interactions but also (a) high drug loading, (b) drug retention in active form within the carrier until it reaches the target site, and (c) the pharmacodynamically appropriate drug release upon reaching the desired site of action. The drug loss from the

carrier due to release or degradation, uptake into nontarget sites, or reduction in drug activity due to protein sequestration may result in failure of the drug delivery system to deliver its cargo in sufficient quantities at the site of action or suboptimal drug release rate limiting therapeutic effects. Further, limited knowledge about the physical, biophysical, or biological nature of the target sites and the therapeutic drug levels required at the individual organ or cell level may result in failure of in vivo experiments. Although it is necessary that the drug remains encapsulated during circulation, conversely, it may bind so tightly that it is not released at the target site. The recirculation of drug carriers further increases opportunities to interact with the target but also sustains the duration of the carrier in the circulation, increasing the risk of drug leakage. In addition, there is untimely drug loss in the case of time-dependent drug release, rather than triggered by some mechanisms (pH change or enzymatic reaction) [147]. Further, if it is difficult for free drug molecules in accessing tissues, the same problem may exist for the drug within a carrier, even if it is taken in considerable quantities to the core of the target and then released. Even after safe delivery of drugs into the cytoplasm, it is still challenging to reach the specific organelles like nuclei, lysosomes, mitochondria, etc., where they are expected to exert their therapeutic effect [148]. This is the main hurdle in the case of gene delivery where the prime requirement is to release the cargo inside the nucleus. In both non-viral and viral vector-mediated gene delivery, uptake and movement toward the nucleus are decisive. Some early initial trials with different vectors were encouraging; however, the latest results have posed certain concerns. In many instances, aggregation of nanocarriers in circulation may happen, resulting in the change of the desired particle size critical to reach targets or interact with receptors. Studies on the oral delivery and uptake of nanoparticles have clearly shown the limited size-dependent internalization of particles below 100 nm by endothelial enterocytes and the M cells in Peyer's patches in the order of 5% of the administered dose. There is little success to increase the uptake and bioavailability in turn by using absorption enhancers or efflux inhibitors [149]. The probability of an individual nanoparticle recognizing and attaching to a receptor is also low, especially in dynamic blood circulation interactions. To counteract this, a large numbers of particles may be administered, and a specific number of particles need to be engaged to bring about a therapeutic effect [150]. Further, adhesion of the nanocarrier to the target does not necessarily lead to cellular uptake. Even if it does, the carrier may not release the cargo within the cytoplasm or may be thrown out of the cell. Therefore, the probabilities of adhesion, uptake, diffusion, and escape from the cell into the adjacent ones should be taken into consideration [151, 152]. Another factor to be considered while designing the targeted carrier is the fact that targets can also change; tumors grow and are heterogeneous depending on their susceptibility to chemotherapy [153]. The properties of nanosystems also undergo continuous phase changes when they are administered. For example, the stability of an aqueous formulation is altered when injected into the blood. The differences in the viscosity of bimodal dispersions from that of monodisperse and polydisperse colloidal suspensions have also been established [154, 155]. Further, the particle flow profile is also dependent on the pressure during flow in circulation, the particle size

and distribution, the flocculation tendency, and the tube diameter. Several studies of particle flow have been conducted to analyze the interaction of nanoparticles with surface receptors without considering biological applications in mind. In concentrated Brownian suspensions, an initially uniform suspension can become less concentrated near the walls and more concentrated near the axis of the channel. On the other hand, the circulating particles drift toward the vessel walls in the microcirculation due to margination [156, 157]. Unlike cellular uptake, which may be a size-dependent process, the diffusion in the cytoplasm is dependent on various factors like concentration gradients, particle diameter, physical obstruction effects, and the gel-like nature of some regions [53]. The NPC with its 8-nm-diameter limit for passage of particles presents the final barrier for gene delivery. Thus, multistage drug delivery involving the use of micro- and nanosystems nested together may help in successful delivery and targeting by overcoming some of the barriers. While the inclusion of nanosystems within microsystems may protect the former while in circulation, the downstream events may be affected by other variables [158, 159].

12.7 Toxicological Considerations in Intracellular Nanoparticulate Delivery

The nanotechnology-based drugs are either aimed to improve release or uptake of agents into target cells or to reduce toxicity associated with the agents. Although a nanoparticle delivers the drug into or at the vicinity of target organs, recently several findings have reported unexpected toxicities owing to nanoparticles, leading to the origin of the field of nanotoxicology. However, the fundamental cause-effect relationships are not very well defined or explored in detail. Hence, there is an urgent need of studies to demonstrate and identify different structural elements causing cyto- and organ toxicity. Nanomaterial first interacts with proteins or cellular components of cells and causes deleterious toxic effects. Several in vitro and in vivo experimental studies have reported the potentially harmful effects of nanoparticles and identified key physicochemical properties like particle size, composition, charge, surface area, agglomeration, and dispensability influencing nanoparticle toxicity [160, 161]. Particle size is one of the significant factors influencing nanoparticle toxicity, and it varies in different dispersion mediums such as deionized water and cell culture media. The nanoparticles having size less than 100 nm are postulated to possess suitable mechanical, electrical, and chemical properties that are essential for drug delivery. These smaller particles can pass through the BBB and also trigger immune reactions as well as damage cell membranes. For example, in vitro cytotoxicity study with 1.4 nm and 15 nm gold nanoparticles in connective tissue fibroblasts, epithelial cells, macrophages, and melanoma cells showed that particles of 15 nm size are nontoxic, but 1.4 nm gold particles efficiently inhibited the growth at the same concentration [162]. Owing to their small size, the nanoparticles offer higher surface area for the interaction with biological membranes and tissues making them more susceptible to toxicity. The surface properties such as composition, charge, and porosity are important factors affecting

nanoparticle-associated toxicity [163]. Nanoparticle composition and surface charge, generally indicated by zeta potential, can affect tissue accumulation and toxicity. Zeta potential reflects the electrical potential of the nanosystems imparting physical stability to the system as well as the tissue affinity in the circulation. For example, cationic liposomes can result in dose-dependent toxicity and pulmonary inflammation in in vivo models. DOTAP, a monovalent cationic lipid and lipofectamine, a multivalent cationic liposome, accumulate in the vasculature and can be preferentially internalized by the liver and the spleen. Stearylamine, the first-generation monoalkyl cationic lipid, causes hemagglutination and hemolysis of human erythrocytes. Hence, their use in humans is not recommended for drug delivery [164, 165]. Nanoparticles tend to agglomerate via Brownian motion and van der Waals forces due to the increased surface area to volume ratio. Prevention of agglomeration is a key factor during clinical use of nanoparticles since this may alter the physicochemical properties such as size distribution, surface to volume ratio, surface activity, as well as concentration of nanoparticles. This in turn affects the potential toxicity of nanoparticles due to vascular or lymphatic blockage. Several preventive measures like sonication, detergents, lung surfactants, PEG, and serum can prevent agglomeration to decrease toxicity or deleterious side effects [166, 167].

Considering the risk associated with nanoparticles, detailed characterization of nanoparticles and validated procedures are necessary for the assessment of nanoparticles. Nanoparticle possesses special characteristics, which impose a higher challenge in assessing toxicity using classical assays. Furthermore, lack of standardized guidelines for nanoparticle toxicological characterization could impede movement of these agents to the clinic [168]. Characterization of physicochemical properties, cellular and noncellular in vitro toxicity assays, and animal-based toxicological assessment are the key elements needed to evaluate the potential toxicity. Chemical composition, particle size and distribution, agglomeration, density, shape, and surface properties such as area as well as charge are the physicochemical properties that may influence the toxic effects of nanomaterials [169, 170]. In addition, various in vitro assessments should be done for the safety and efficacy of nanoparticles like biocompatibility assays, hemolysis and platelet aggregation assay, immune system activation assay, reactive oxygen species and oxidative stress measurements, genotoxicity assay, mutagenicity assay, etc. [171].

12.8 Conclusion

Novel and improved therapeutic strategies evolve with the discovery of molecular basis of diseases, new intracellular targets, and the mechanisms to specifically target them. Though significant strides have been made in the direction of organelle-targeted drug delivery in the recent past, this field of research demands more competence. There have been few partially successful, yet promising, attempts at directing therapeutics to the cytoplasm or individual organelles. Most of them provide qualitative analysis of intracellular sequestration of drugs based on the cell line

or in vitro experiments. Sensible selection of materials and physical attributes of drug carriers, real-time molecular and functional study of the various uptake mechanisms, and the interaction of these carriers with cellular components are of paramount importance while designing organelle-targeted nanocarriers. Another important factor to be considered is the intracellular fate and subsequent disposition of these carriers warranting detailed nanotoxicological evaluations of the developed drug delivery systems. Although the goal of organelle-targeting seems challenging now, utilizing innovative nanomaterial and molecular biology advancements can help in the success of this new paradigm in nanomedicine to achieve a realistic clinical outcome. Further, innovative strategies like drug repurposing in combination with nanotechnology advancements can help in overcoming the high attrition rates, high costs, and slow pace of new drug discovery.

Acknowledgments We would like to acknowledge UGC for providing D.S. Kothari Postdoctoral Fellowship to Sreeranjini Pulakkat.

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