Materials Horizons: From Nature to Nanomaterials

Sampa Saha
Chandrani Sarkar *Editors*

Biodegradable Polymers and Their Emerging Applications

Springer

Materials Horizons: From Nature to Nanomaterials

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Preface

The world is currently facing an urgent need for sustainable solutions to address the environmental challenges we are facing today. One of the major contributors to environmental pollution is the use of non-biodegradable materials, particularly plastics. Plastic waste has become a significant problem, with devastating effects on our planet and its ecosystems. Fortunately, the development of biodegradable polymers has emerged as a promising solution to address this issue. Biodegradable polymers have the potential to replace conventional plastics and reduce the amount of waste that ends up in landfills or pollutes our oceans and other natural habitats. This book is intended to provide an in-depth understanding of biodegradable polymers and their applications. It covers various aspects of biodegradable polymers, including their synthesis, properties, processing, and potential applications. The book also explores the challenges and opportunities associated with the development and adoption of biodegradable polymers.

The book is divided into 11 chapters. The introductory chapter, focusing on the classifications and synthesis of biodegradable polymers, sets the tone of the book. Chapter 2 "Processing of Biodegradable Polymers" provides knowledge about various processing techniques employed for biodegradable polymers and the effects of process conditions on the ultimate properties. Chapter 3 "Surface Modification of Biodegradable Polymers" provides critical insight into the methods of surface modification of biodegradable polymers and the application areas of such modified platforms. Chapter 4, titled "Carbohydrate-Based Biodegradable Polymers for Biomedical Applications," deals with various carbohydrate polymers and their applications. Cellulose, the most abundant polymer on the Earth, and its derivatives are discussed in the Chap. 5 with major focus on synthesis, properties, and applications. Chapter 6, "Biodegradable Polyurethanes and Their Biomedical Applications," provides valuable perception about utility of biodegradable polyurethane in various biomedical applications. Chapter 7 "Biodegradable Polymers—Carriers for Drug Delivery" discusses in brief about various natural and synthetic biodegradable polymers and their applications in drug delivery. Chapter 8 "Biodegradable Polymers for Food Packaging Applications" discusses the food packaging application

of various biodegradable polymers. Chapter 9 "Biodegradable Polymers for Agriculture" reviews the recent advancements in agricultural applications of biodegradable polymers. Chapter 10 "Bio-polymeric Green Composites for Thermal Energy Storage Applications" focuses on the uses of biodegradable polymers in thermal energy storage for green buildings. The final chapter "Biodegradable Anisotropic Polymeric Particles and Their Emerging Applications" showcases some of the trailblazing works with biodegradable polymeric anisotropic particles ranging from pickering emulsion stabilization to targeted drug delivery. The chapter also delivers critical insight into fabrication techniques of such anisotropic particles from recent scientific works.

The chapters in this book have been written by researchers in the field of polymer science and engineering. They provide a comprehensive overview of the latest research and development in biodegradable polymers, from both academic and industrial perspectives.

We hope that this book will serve as a valuable resource for researchers, students, and professionals interested in the field of biodegradable polymers. We also hope that it will inspire further research and development in this important area, and contribute to a more sustainable future for our planet.

New Delhi, India

Sampa Saha
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Historical Overview of Biodegradable Polymers

People started using biodegradable materials in biomedical field from very early age. For example, hair, wool thread, plant fiber, etc. were used as sutures by ancient Egyptians at the very early ages. The usage of natural latex and rubber was started by Olmecs, Aztecs people in 1500 BC [1]. The first documented suturing technique was provided in Samhita, by Indian surgeon Susruta in 500 BCE. He discovered catgut suture which is made from the intestine of sheep. Since then people started finding new bio-based materials. First man-made bioplastic, **Parkesine** was synthesized by Alexander Parkes in 1862. Parkesine was made from Cellulose [2]. 1n 1897, **Galalith** was synthesized from Casein by German chemists. It was used as a bioplastic at that time. Now this biomaterial is used as buttons [3]. After a few years, the first time scientist, Maurice Lemoigne developed bioplastic from bacteria in 1926. He had synthesized polyhydroxybutyrate (PHB) from Bacillus megaterium bacteria. The first man-made synthetic biodegradable polymer was Polyglycolic acid in 1954 [4]. By that time Hermann Staudinger (1881–1965) made an significant impact in the field of polymers. He was called "father of polymer chemistry." He exactly described the definition of polymers [5]. And finally, in 1953 he was awarded with Noble Prize for his pioneering contribution in polymer science.

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Contents

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Sampa Saha is currently working as an associate professor in the Department of Materials Science and Engineering at Indian Institute of Technology Delhi, New Delhi, India. She received her PhD from Michigan State University, USA. Sampa Saha is editorial advisory board member of Journal of Macromolecular Science. She has published more than sixty peer-reviewed articles, five book chapters on polymer science and holds eight Indian patents.

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Abbreviations

3D	Three-dimensional
3-HV	3-hydroxy valerate
6-MP	6-Mercaptopurin
AAC	Antioxidant activity coefficient
AAc	Acrylic acid
AADC	Amino acid decarboxylase enzyme
AAV	Adeno-associated virus
ABDO	2-Amino-1-butanol
ABS	Acrylonitrile Butadiene Styrene
ACNF	Acetylated cellulose nanofiber
APS	Ammonium persulfate
ASTM	American Society for Testing and Materials
ATBC	Acetyl-tri-n-butyl-citrate
ATRP	Atom transfer radical polymerization
AVL	α-propargyl-δ-valerolactone
BC	Bacterial cellulose
BCNCs	Bacterial cellulose nanocrystals
BDA	1,4-Butanediamine
BDI	1,4- butanediisocyanate
BDO	1,4-Butanediol
BEMA	2(2-bromopropionyloxy)ethyl methacrylate
Bio PMF	Biodegradable polymeric mulch film
BPSCs	Biodegradable polymeric seed coatings
BUR	Blow-up-Ratio
^{14}C	Carbon-14
CA	Cellulose acetate
Ca-alginate/PNIPAm@PDA	Ca-alginate/ poly(*N*-isopropylacrylamide)@polydopamine
CAB	Cellulose acetate butyrate
CAGR	Compound annual growth rate
CCA	Carrot carbon aerogels

CCM	Curcumin
CD	Carbidopa
CHDI	1,4-Cyclohexane diisocyanate
CHDM	1,4-Cyclohexanedimethanol
CMC	Carboxymethyl cellulose
CMCS	Carboxymethyl chitosan
CMCelPolyArg	Carboxymethylcellulose with poly-L-arginine
CMR	Cumulative measurement respirometric
CN	Cellulose nitrate
CNC	Cellulose nanocrystals
CNF	Cellulose nanofibers
CS	Cellulose Sulfate
Detroit 562	Human pharyngeal carcinoma cells
DHPC	*O*-(2,3-dihydroxy propyl) cellulose
DMR	Direct measurement respirometric
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOD	Degree of deacetylation
DPPH	Diphenylpicrylhydrazyl
DS	Degree of substitution
DSC	Differential scanning calorimeter
DTP	3,3′-dithiobis(propionohydrazide)
DVS	Divinyl sulfone
DX	Doxorubicin
EAP	Electro-active paper
EBM	Extrusion Blow Molding
EC	European Community
ECM	Extra-cellular matrix
ED	1,2-Ethanediamine
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
EG	Ethylene glycol
ELDI	Ethyl 2,6-diisocyanatohexanoate
FBPI	Faba bean protein isolate
FCM	Food contact materials
FDA	Food and drug administration
FDM	Fused Deposition Modeling
GA	Gum Arabic
GA_3	Gibberellic acid
GC-MS	Gas Chromatography-Mass Spectrometry
Gel	Gelatin
GlA	Glycolic acid
Glu	Glutaraldehyde
GNPs	Gold nanoparticles
GPC	Gel Permeation Chromatography
GSE	Grape seed extract

GSH	Glutathione
HA	Hyaluronic acid
HaP	Hydroxyapatite
HAZ	Heat affected zone
HCMC	Hydrophobic Carboxymethyl cellulose
HEC	Hydroxyethyl cellulose
HEMA	2-hydroxyethyl methacrylate
HDI	1,6-Hexamethylene diisocyanate
HPC	Hydroxypropyl cellulose
HPLC	High-Performance Liquid Chromatography
HPMA	N-(2-hydroxypropyl)methacrylamide
HPMC	Hydroxypropyl methylcellulose
IAA	Indole Acetic Acid
IBM	Injection Blow Molding
IPC	Interfacial polyelectrolyte complexation
IPDI	Isophorone diisocyanate
KB cells	Human epidermoid carcinoma cell
LA	Lactic acid
LbL	Layer by layer
LCST	Lower critical solution temperature
LD	Levodopa
LDI	L-lysine ester diisocyanate
LDPE	Low-density polyethylene
LHS	Latent heat storage
MAP	Modified Atmosphere Packaging
MC	Methylcellulose
MCC	Microcrystalline Cellulose
mcl PHA	Medium chain length Polyhydroxy alkanoate
MCSC	Maleylated Cotton Stalk Cellulose
MFI	Melt Flow Index
MLDI	Methyl 2,6-diisocyanatohexanoate
MMA	Methyl methacrylate
MMT	Montmorillonite
MO	Methyl orange
MOF	Metal-organic framework
MPS	Mononuclear phagocyte system
MW	Molecular weight
NAPL	Non-aqueous phase liquid
NASA	National Aeronautics and Space Administration
NC	Nanocellulose
NIAS	Non-intentionally added substances
NMP	Nitroxide-mediated polymerization
NMR	Nuclear Magnetic Resonance
NPK	Nitrogen Phosphorous Potassium
OH	Hydroxyl

OTR	Oxygen transmission rate
PA	Polyanhydrides
PA	Palmitic acid
PADCs	Poly(alkylene dicarboxylate)s
PAG	Photo acid generator
PAM	Polyacrylamide
PAMAM	Polyamido amine
PBA	Polybutylene adipate
PBAT	Polybutylene adipate-co-terephthalate
PBS	Polybutylene succinate
PBSA	Polybutylene succinate adipate
PC	Polycarbonate
PCA	Pumpkin carbon aerogels
PCL	Polycaprolactone
PCl	Palmitic Chloride
PCL-co-PEG-coPCL	Poly(lactic acid-ethylene glycol-co-lactic acid)
PCMs	Phase change materials
PCUU	Polycarbonate urethane urea
PD	Parkinson's disease
PDGF	Platelet-derived growth factor
PDMAPS	Poly(3-dimethyl-(methacryloyloxyethyl) ammonium propane sulfonate)
PDMS	Poly(dimethylsiloxane)
PE	Polyethylene
PEC	Polyelectrolyte complex
PECUU	Polyester carbonate urethane urea
PEG	Polyethylene glycol
PEG-b–PCL	Poly(ethylene glycol)-b-poly(caprolactone)
PEI	Polyethyleneimine
PEM	Polyelectrolyte multilayer
PEO	Poly(ethylene oxide)
PET	Poly (ethylene terephthalate)
PEUU	Polyester urethane urea
PFPE	Perfluoropolyether
PGA	Polyglycolic acid
PHA	Polyhydroxy alcanoate
PHB	Poly-3-hydroxybutyrate
PHBHx	Poly-3-hydroxybuterate-co-3-hydroxyhexanoate
PHBV	Poly-3-hydroxybuterate-co-3-hydroxyvalerate
PHEMA	Poly(2-hydroxyethyl methacrylate)
PK1	HPMA copolymer–doxorubicin conjugate targeting moiety
PK2	HPMA copolymer–doxorubicin conjugate having galactosamine
PLA	Poly(D,L-lactide)

PLGA	Poly(lactide-co-glycolic acid)
PLAGA-PEG-PLAGA	L-Lactide/glycolide/polyethylene glycol terpolymer
PLL	Poly-L-Lysine
PMETA	Poly(2-[(methacryloyloxy)ethyl]trimethylammonium chloride)
PNP	*p*-Nitrophenol
poly (MMA-co-HEMA)	poly (methyl methcrylate-co-2-hydroxyethyl methacrylate)
poly(NIPAM)	Poly(N-isopropylacrylamide)
POE	Poly(ortho ester)
PPC	Polypropylene carbonate
PPE	Poly(phosphoesters)
PPEGMA	Poly(poly(ethylene glycol) methacrylate)
PPF	Poly(propylene fumarate)
PPO	Poly(propylene oxide)
P-PUUs	Piperazine based polyurethane urea
PRINT	Particle Replication in Non-wetting Templets
PSR	Processing Speed Ratio
PTMO	Poly(tetramethylene oxide)
PU	Polyurethanes
PVA	Polyvinyl alcohol
PVC	Poly (vinyl chloride)
PVP	Poly(vinylpyrrolidone)
PS	Polystyrene
QDs	Quantum dots
RAFT	Reversible addition-fragmentation chain transfer
RBC	Red Blood Cells
rBMP	Recombinant human bone morphogenetic protein
RC	Regenerated chitin
RCA-1	Ricinus communis agglutinin
REX	Reactive Extrusion
RFID	Radio frequency identification
RMS	Root mean square
ROMP	Ring-opening metathesis polymerization
ROP	Ring-opening polymerization
SA	Salicylic Acid
SAM	Self-assembled monolayers
SAP	Super absorbent polymer
SAXS	Small-angle X-ray scattering
SCC-4	Squamous carcinoma cells
scl PHA	Short chain length Polyhydroxy alkanoate
SEM	Scanning electron microscopic
SHS	Sensible heat storage

SIATRP	Surface initiated atom transfer radical polymerization
Si-HPMC	Silicon impregnated Hydroxypropylmethyl cellulose
SMCC	Silicified microcrystalline cellulose
SPI	Soy protein isolate
SSE	Single Screw Extruder
SSPCMs	Shape-stabilized phase change materials
SNP	Sulfur nanoparticles
TCE	Trichloroethylene
TCNCs	Tunicate cellulose nanocrystals
TE	Thiol-ene
TEGDA	Triethylene Glycol Diacrylate
TES	Thermal energy storage
TMC	N,N,N-trimethyl chitosan
TMDI	2,2,4-Trimethyl hexamethylene diisocyanate
TORC	Tetramethylpiperidinyloxy mediated oxidation regenerated cellulose
TPP	Tripolyphosphate
TPS	Thermoplastic starch
TSE	Twin Screw Extruder
TTI	Time-Temperature Indicator
US-NIOSH	United State-National Institute for Occupational Safety and Health
UV	Ultraviolet
WAXD	Wide-angle X-ray diffraction
WVP	Water vapor permeability
XRD	X-ray Diffraction
ZNP	Zien nanoparticles
ZVI	Zero Valent Iron

Chapter 1
Introduction to Biodegradable Polymers

Mouli Sarkar, Anu Priya, Chandrani Sarkar, and Sampa Saha

1 Introduction

In our continuously ever-growing society, polymers play a vital role in our day-to-day applications. Some of them do not persist in our ecosystem for too long as they are degraded away by microorganisms and other natural factors. But many others tend to remain in our environment and get accumulated as waste. Most of them are reprocessable, whereas some are not. Economically, it is relatively easier to manufacture materials from petroleum-based sources. Majority of the non-biodegradable polymers that are used today are plastics made up of polyethylene, polypropylene, polystyrene, etc. lead to waste-disposal problems. These plastics tend to stay in our environment because there is hardly any microorganism that may feed them. Due to their adaptability in modeling, durability, and simplicity of use, across a range of manufacturing and production processes, plastics are widely used and since then rate of production of plastic products has increased since 1970s. The production of plastic waste was manageable in 1970s but in early 1990s the plastic waste production was more than tripled. Today the generation of plastic waste is more than 400 million tons [1]. The increase in plastic waste has become a serious problem for the environment. Most of this plastic waste includes single use plastic bottles, food wrappers, plastic grocery bags, cigarette filters, etc. Millions of tons of plastic waste are introduced to the environment; these plastics waste sometimes are shipped to thousand kilometers and dumped or burned which in turn affects our ecosystem. It has been studied that polyethylene may need 100–1000 years for its degradation in nature depending on

Mouli Sarkar and Anu Priya are equally contributed.

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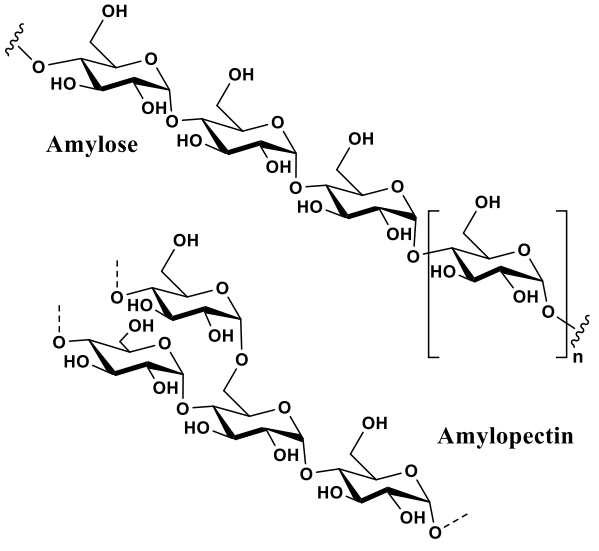
the product [2]. These non-biodegradable polymers on burning produce greenhouse gases which further cause global warming and severe respiratory problems. As these polymers are non-biodegradable, they stay in environment in form of microscopic plastic and contaminate our soil and water bodies. Despite the efforts being made to overcome these issues, 75–200 million tons of plastic wastes are found in our ocean. On the other side, plastics are causing the planet serious challenges by either clogging the water system or interrupting the food chain system. Almost 79% of the plastic waste are dumped in landfills [3]. Also, our petroleum source is limited, so it is highly expected those non-biodegradable polymeric materials should be replaced with recyclable and biodegradable alternatives.

Biodegradable polymers are either extracted from renewable sources or obtained via polymerization in laboratory and degrade easily in nature. On their own, their shelf life and service life both are less because they degrade more easily than non-biodegradable polymers, but with continuous advancement in polymer technology this can be improved. Common biodegradable polymers—starch, cellulose, gelatin, chitosan, Polyhydroxy alkanoate (PHA), Polyvinyl alcohol (PVA), Polybutylene succinate (PBS), Polylactic acid (PLA), Polyurethanes (PU), Polycaprolactone (PCL), and Poly(ortho ester) (POE) are being widely used in several sectors. The chemical structure and applications of these polymers are tabulated in Table 1. The reason for their appreciable biodegradability is the presence of heteroatom in the backbone of the polymer as C–X linkages (X=O, N, S, etc.). The bond energies [C–O(~67 kcal/mol) < C–N(~72 kcal/mol) < C–C (~85 kcal/mol)] prove C–X bonds can be easily cleaved by environmental factors [4–6]. These polymers possess unique properties of degradation in the environment either by the microbial action or by the effect of natural factors [7]. The polymer degradation can happen in multiple ways—(1) chemical degradation which includes hydrolysis and oxidation; (2) Physico-chemical degradation which occurs via photodegradation, thermal degradation, and mechanical degradation; and lastly (3) degradation via enzymatic pathway [5]. Besides these factors, molecular weight, morphology, crystallinity, tacticity, branching, and nature of side groups also affect the rate of degradation [8].

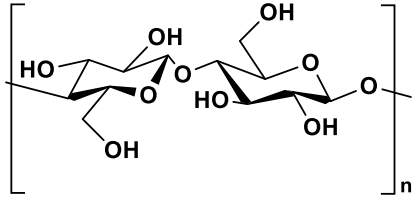
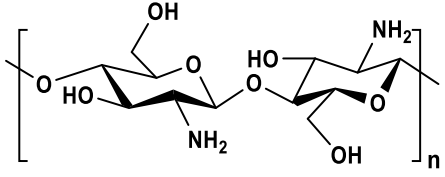
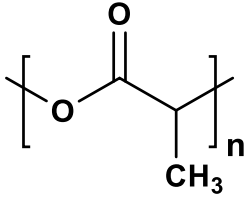
The easiest methods to evaluate the degradation of biodegradable polymers are—visual observation (formation of cracks or color changes with time), weight loss measurements by GPC (Gel Permeation Chromatography), HPLC (High Performance Liquid Chromatography), GC–MS (Gas Chromatography- Mass Spectrometry), clear-zone formation NMR (Nuclear Magnetic Resonance), and XRD (X-ray Diffraction) [6, 7]. Lastly, the most effective method is CMR (cumulative measurement respirometric) or DMR (Direct measurement respirometric) which measures the amount of CO_2 released with respect to certain reference materials [8].

Table 1 Different biodegradable polymers, their structures, and applications

Polymer	Chemical Structure	Applications	Refs.
Starch		Used in food and pharmaceutical packaging industries, water treatment, and emulsion stabilization	[9, 10]

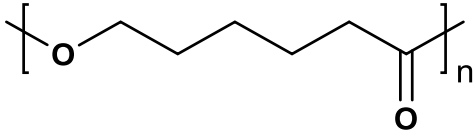
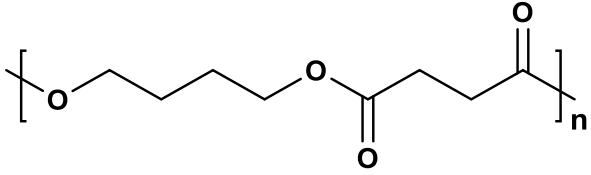
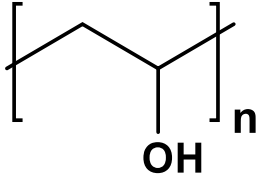
(continued)

Table 1 (continued)

Polymer	Chemical Structure	Applications	Refs.
Cellulose		Used in paper industry, metal industry, packaging industries. Also used in tissue engineering, and agricultural fields	[11–16]
Chitosan		Due to its exceptional biocompatibility, it is used in wound healing, blood hemostasis, and therapeutic delivery (drug/vaccine delivery)	[17–20]
PLA		Large applications in kitchen appliances (disposable bags, cutlery, microwaveable trays), in electronic gadgets (laptops, mobile devices), in feminine hygiene products and diapers. It is also used for upholstery and automotive parts (floor mats, panels, and coverings)). PLA is also used in biomedical field as implants (suture, anchors, screws, fixation pins) drug delivery carrier, and scaffold	[21–23]

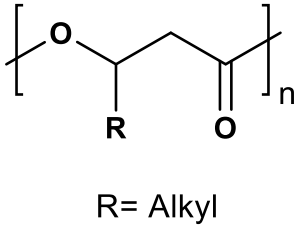
(continued)

Table 1 (continued)

Polymer	Chemical Structure	Applications	Refs.
PCL		PCL is used as orthopedic sutures, dermal fillers, and drug carriers	[24, 25]
PBS		PBS is used as food packaging material, mulch film, plant pots, fishing nets, and hygiene products	[26, 27]
PVA		It is used as adhesives, surfactants, and film-forming material	[28–30]

(continued)

Table 1 (continued)

Polymer	Chemical Structure	Applications	Refs.
PHA		It is used to make biomedical implants—scaffolds, screws, sutures, and pins	[31, 32]

2 Classification of Biodegradable Polymers

Biodegradable polymers can be classified with respect to many factors, i.e., sources, composition, synthesis procedure, processing method, applications, etc. Among all, the most important categorization is source and application based. Conventionally, biodegradable polymers are categorized into three major divisions—natural, semi-synthetic, and synthetic biodegradable polymers (Fig. 1). Natural polymers are those which are directly obtained from biomass, and when monomers are obtained from natural source and polymerized in laboratory is called semi-synthetic polymers. Synthetic polymers are purely synthesized in laboratory through chemical routes [33, 34]. Natural, semi-synthetic, and synthetic polymers are discussed in detail with proper examples in subsequent sections.

2.1 Natural Biodegradable Polymers

Natural biodegradable polymers are the materials originating directly from nature, i.e., extracted from plants and animals. These polymers play a vital role in our daily life as all living beings are based on them—proteins and nucleic acid that occur in human and animal body, and polysaccharides are found in cell walls of plants and bacteria. In nature, all organisms' growth cycles leads the formation of these

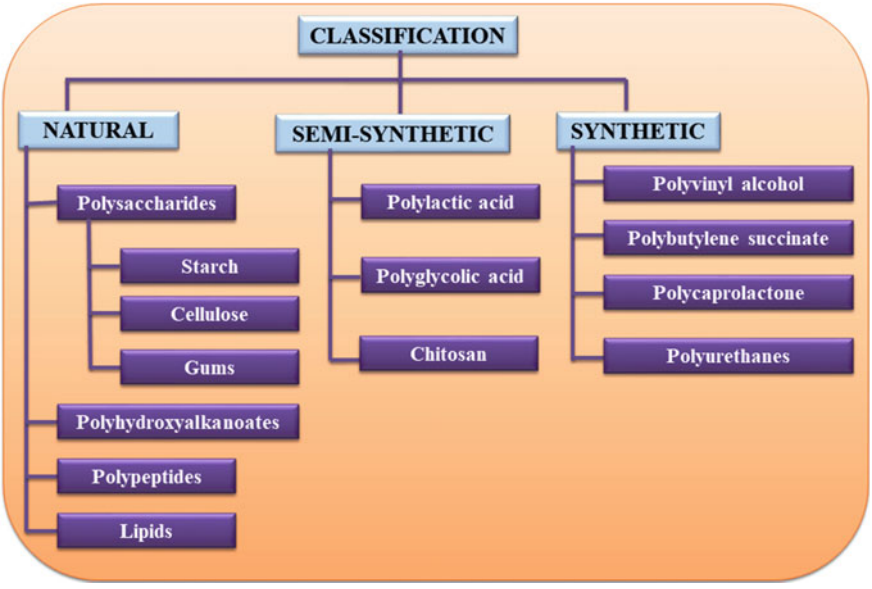


Fig. 1 Classification of biodegradable polymers. Redrawn from [35]

polymers—first, metabolic process generates different active monomers within cells, and those monomers get polymerized through enzyme catalyzed polymerization and produced natural polymers. The structure, properties, and applications of a few common natural biodegradable polymers are discussed below.

Polysaccharides

These are complex carbohydrate structures originating from bacteria or fungi. More than one unit of monosaccharides is connected via glycosidic linkages to form polysaccharides. Most of the polysaccharides are obtained from cell walls plants, crustaceans, and shrimp. Cellulose, starch, chitin, and gums are examples of polysaccharides [36].

Starch

The chemical formula of starch is $(C_6H_{10}O_5)_n$. Starch is the major component for storing sugar in plant cells during photosynthesis and hence, acts as a reservoir of food for plants [37]. Amylose and amylopectin are two units of starch which are connected via α-1,4-glycosidic linkages in branched form [chemical structure given in Table 1]. Starch contains alternating semi-crystalline growth rings which are made up of crystalline amylopectin and amorphous amylose moieties. Interestingly, the quality of starch depends on the ratio of amylose to Amylopectin. Most of the commercial starch is produced from corn, wheat, potato, and tapioca [13, 38, 39]. Because of their increased biodegradability, renewability, and superior oxygen barrier qualities, materials made from starch are the best solution for several commercial applications. However, the use of naturally occurring starch is restricted since it is highly hydrophilic in nature and presence of the intermolecular forces, and hydrogen bonds provide starch a significant impact on the polymer's processability as a thermoplastic polymer, leading to a high glass transition temperature (T_g) and low melting point (T_m). So, further processing is needed where plasticizers such as glycerol, urea, sorbitol, or glycerine are added to the starch matrix to create thermoplastic starch (TPS) which can be utilized in making compost bags, food packaging, and films for marine, meat, and vegetable sectors [40, 41]. Granular Starch [42], Gelatinized Starch [43], Thermoplastic starch [44] are some examples of modified starch that has various applications. On the other side, starch that has been blended with ester groups to provide thermal stability, control water vapor transmission rate, moisture absorption, and enhanced barrier qualities for various gases. Cassava starch, polyvinyl alcohol (which serves as an adhesive and thickening agent), glycerine (used as a plasticizer), talc powder (which acts as a lubricant), urea (which acts as a crossing link agent), and water were combined to create a biodegradable plastic packaging film [45]. The film was subsequently investigated for various physicochemical changes and their impact on the food inside during storage, and the findings revealed the comparative characteristics of the film with the traditional polymer.

Cellulose

Cellulose is also a plant-derived linear polysaccharide where monomer sugar units are connected via β-1,4-glycosidic linkage [structure given in Table 1]. Cellulose is the basic component of wood, leaves, and stalks. Other sources are algae, bacteria, and tunicates. The presence of large hydroxyl (OH) groups controls the chemical and mechanical properties of cellulose [46]. The intramolecular H-bonds between OH-groups of glucose units of the same cellulose units provide rigidity and thermo stability of the chains, whereas intermolecular H-bonds between two different cellulose chains are responsible for the development of the supramolecular structures [47]. This extensive H-bonding is responsible for poor solubility in both common organic and inorganic solvents. Cellulose is highly susceptible to acids but unreactive to strong alkalis. The human body cannot digest cellulose, so it is easy to apply cellulose material in food packaging applications. Apart from that, OH-groups can be easily modified by chemical treatment [15, 48, 49]. These cellulose derivatives (methylcellulose (MC), carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), cellulose acetate (CA), and hydroxypropyl methylcellulose (HPMC), etc. have much more utility in the application field rather than crude cellulose.

Gums

Gums are complex carbohydrates and are hydrocolloids which are extensively used in food industries as either ingredients or food additives [50]. It has several properties like gelling, water solubility, thickening, emulsification, and stabilization. Gums are extracted from shrubs (Karaya, cashew), plant exudates (tragacanth), seed endosperm of Guar gum, algae, etc. [51]. Typically, they can create extremely viscous aqueous solutions at low concentrations. An exception is there, Gum arabic and other "low viscosity grade" gum require high concentration to form a highly viscous solution. Gums are formed by numerous sugars where complexation in structure may form due to branching. One of the most well-known and widely used gums is gum arabic, which is produced by the species Acacia Senegal. Gum ghatti and Karaya gum are the other two types which are extracted from the trunk of *Anogeissus latifolia* and *Sterculia urens* trees, respectively [52, 53].

Polyhydroxy Alkanoate (PHA)

PHA is an optically active biodegradable polymer which is produced by fermentation of microbes and then by microbial cell lysis. The development of microorganisms using agricultural waste as a growth medium has been studied as a potential source for bioplastics and biopolymers (polysaccharides). One such microbiologically produced plastic is polyhydroxyalkanoate, also known as PHA. It is produced by several bacterial species using inexpensive renewable resources, and it is completely degraded aerobically by microorganisms in a stimulated control environment to CO_2

and H_2O. PHA is produced utilizing various natural isolates and recombinant bacteria strains. They are produced by the fermentation of sugar or lipids to store carbon and energy via bacteria. It is generally produced from saturated and unsaturated hydroxyalkanoic acids [54]. The monomer used can be unbranched or can be a homopolymer, copolymer, or terpolymer. PHA can be produced via bacteria under balanced and unbalanced growth conditions; this controls the kind and quantity of PHA in the cell [55].

PHA are polyesters derived from (R)-3-hydroxy alkanoic acids that are biocompatible, non-toxic, and have similar thermoplastic qualities to petrochemical plastics. The length of the monomer's carbon chain influences its categorization. The final characteristics of PHA, including T_m, T_g, and their degree of crystallinity, are greatly influenced by the chemical composition of the polymer, which is affected by the source growth environment, and the method of extraction of the polymer. As a result, they are suitable for a wide range of applications. Short chain length PHA (scl PHA) often exhibits characteristics that are most similar to those of traditional polymers like polypropylene, but medium chain length PHA (mcl PHA) exhibits more elastomeric characteristics. The most extensively researched PHA polymer is poly-3-hydroxybutyrate (PHB); it is brittle and highly crystalline. PHB is produced by certain steps—The first step involves combining two molecules of acetyl CoA to form acetoacetyl-CoA via 3-ketothiolase. Then the reductase Acetoacethyl-CoA reduces the acetoacetyl-CoA via NADH to form 3-hydroxybutyryl-CoA. Lastly, polymerization of PHB-CoA occurs to generate PHB (Fig. 2). The production of PHB by bacteria is increasing significantly every year. PHB possesses distinguishable physical characteristics such that it can be processed into a transparent film with $T_m >$ 130 °C and is degradable without residue [56–58].

The thermal and mechanical properties of PHA can also be tuned by co-polymerization with different monomers examples—Poly-3-hydroxybuterate-co-3-hydroxyvalerate (PHBV), Poly-3-hydroxybuterate-co-3-hydroxyhexanoate (PHBHx). With the increase in the side chain length, the degree of crystallinity decreases, hence Tm decreases and the copolymer becomes less brittle.

Polypeptides

Polypeptides are constituted of different amino acids through peptide bonds. Different proteins like—silk, wool, and collagen are all polypeptides. Collagen is an animal-based protein and consists mainly of glycine, proline, hydroxyproline, and lysine [59]. The flexibility and unique biological properties made collagen a perfect material to be used in biomedical fields. One of its denatured derivatives is gelatin which contains 19 amino acids. It is water soluble. Its physical and chemical properties highly depend on molecular weight distribution and amino acid composition. There are few plant-based polypeptides are also available—wheat gluten is one of the polypeptides derived from cereal grains. It contains two types of protein—gliadin, and glutenin [60]. Glutenin molecules are connected via disulfide bonds with gliadin chains to provide the gluten flexibility (Fig. 3). Wheat gluten is an extremely

biodegradable material and the products obtained are non-toxic. This biopolymer acts as a good film-forming agent but without a plasticizer, it became brittle. Soy protein is another type of plant-based protein which is beneficial for health [61].

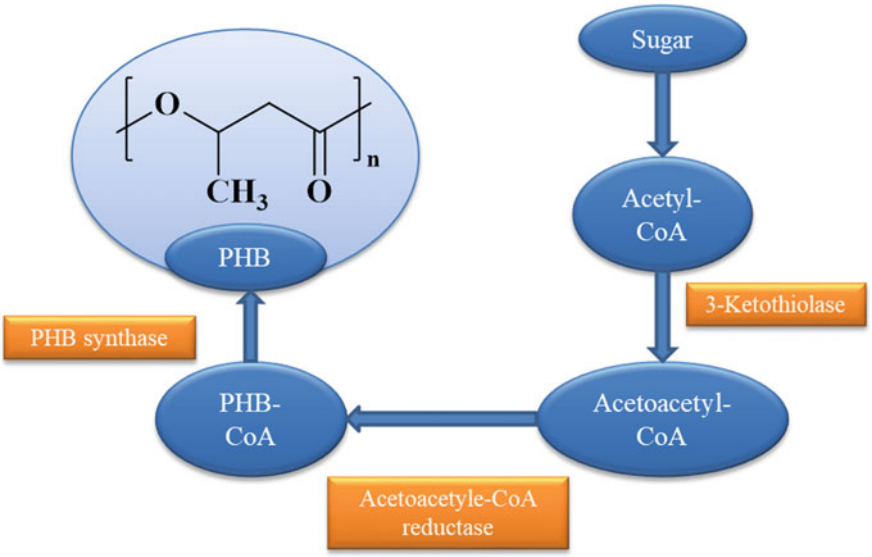


Fig. 2 Industrial production process of PHB. Redrawn from [59]

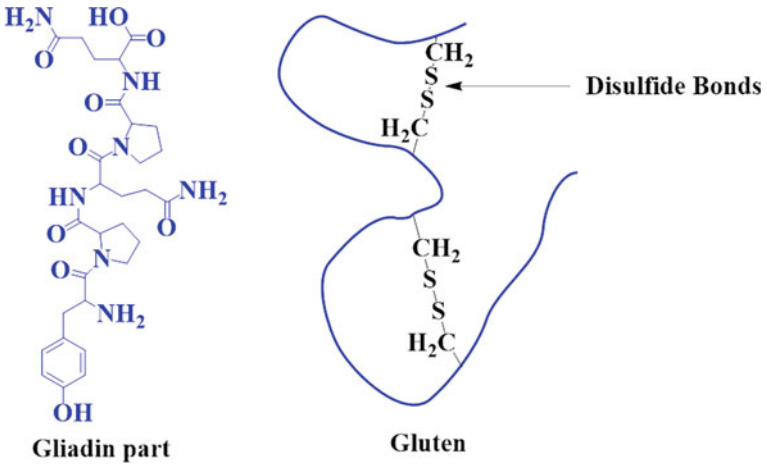


Fig. 3 Structure of gluten. Redrawn from [62]

Lipids

Lipids are hydrophobic and soluble in hydrocarbons. Phospholipids, sterols, wax, saccharolipids, sphingolipids, and polyketides fall under the class of lipids. Fatty acids are extracted from oils and fats in the form of triglycerides and depending on the functional groups present over the triglycerides, lipids can be synthesized using free radical or cationic polymerization [63]. Nowadays, lipids or fatty acids become a synthetic toolbox for an industrial chemist. The functional groups of lipids can be easily modified and produce different polymers from a single feedstock. Fatty acids mainly consist of poly anhydrides, polyester, and poly (ester-anhydrides) linkages. More prominently, the structure consists of an acid group and aliphatic carbon chain (length ranges from 4 to 22 carbons) with unsaturation, monounsaturation, or polyunsaturation in their backbone (Fig. 4) having varied properties [64].

2.2 Semi-synthetic Biopolymers

Semi-synthetic polymers are also derived from nature, but they undergo chemical modifications after extraction. Monomers are derived from biomass and the extraction process and polymerization is carried out via chemical synthesis in laboratory. Some of the examples are discussed below.

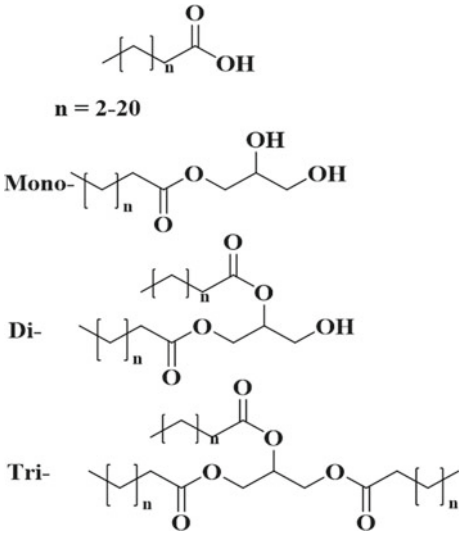


Fig. 4 Structure of lipids. Redrawn from [64]

Polylactic Acid (PLA)

PLA is an aliphatic biodegradable polyester that is frequently synthesized from hydroxyl acids. L and/or D-lactic acid (monomers) are microbial fermented and then chemically polymerized to make PLA [65]. Injection molding and extrusion are two common processing techniques that are used to transform polylactic acid (PLA). The concentration of lactic acid enantiomers within PLA chains has a significant impact on the ultimate properties of PLA, including the degree of crystallinity, T_m and T_g. PLA homopolymers (poly DL-lactic acid) containing optically pure L-lactic acid or D-lactic acid, and are semi-crystalline polyesters having T_m of about 175 °C and a Tg of around 55 °C, while PLA heteropolymers (poly DL-lactic acid) are amorphous since the polymer chains are disordered. Depending on the crystallinity, the biodegradability of PLA can be monitored. PLA shows slow degradation due to the presence of bulky CH_3 group in its polymer chain which creates a steric hindrance to resist hydrolysis.

The first approach produces PLA by using cyclic lactic acid dimer lactide, which is created during the lactic acid cycle also known as the Kori cycle [66]. The lactate is produced via an anaerobic reaction. The laboratory synthesis includes direct polymerization of lactic acid using condensation polymerization under a vacuum for the removal of a water molecule. This technique typically yields low-molecular-weight polymers with water as a by-product which leads to back biting. The alternative method includes fermentation of the lactic acid where the conversion of lactic acid into polylactic acid occurs via bacterial polyester fermentation. The bacteria such as *Bacillus megaterium* and *Alcanivoraxbor* are being employed for this process. These bacteria need sugar which is provided by corn to provide fuel for cellular activities, Alcanivoraxbor employed which needs sugar from plants, such as corn, to fuel their cellular functions, and the by-product of these cellular processes is the polymer, which is used to make polyesters.

The most used industrial procedure to produce PLA is represented in Fig. 5. The first step includes the fermentation of sugar sources such as corn, which provide energy for the cellular function of microorganisms, the microorganism then produces lactic acid which is further polymerized via condensation polymerization and ring opening polymerization (ROP) to produce polylactic acid. High molecular weight PLA is synthesized via ROP of lactide in the presence of catalysts is $Sn(Oct)_2$ [67].

Polyglycolic Acid (PGA)

PGA is a completely linear aliphatic polyester and highly crystalline (crystallinity 45–55%). The melting point of PGA is also higher (220–225 °C) than PLA as PGA has higher crystallinity (Tg ~35 °C). But its low solubility limits biomedical applications. Higher molecular weight PGA is more soluble in organic solvent than low molecular weight PGA which is comparatively soluble in water. The degradation rate is higher for PGA as water can easily attack the carbonyl moieties leading to the formation of acids. PGA is also synthesized as the same procedure as PLA.

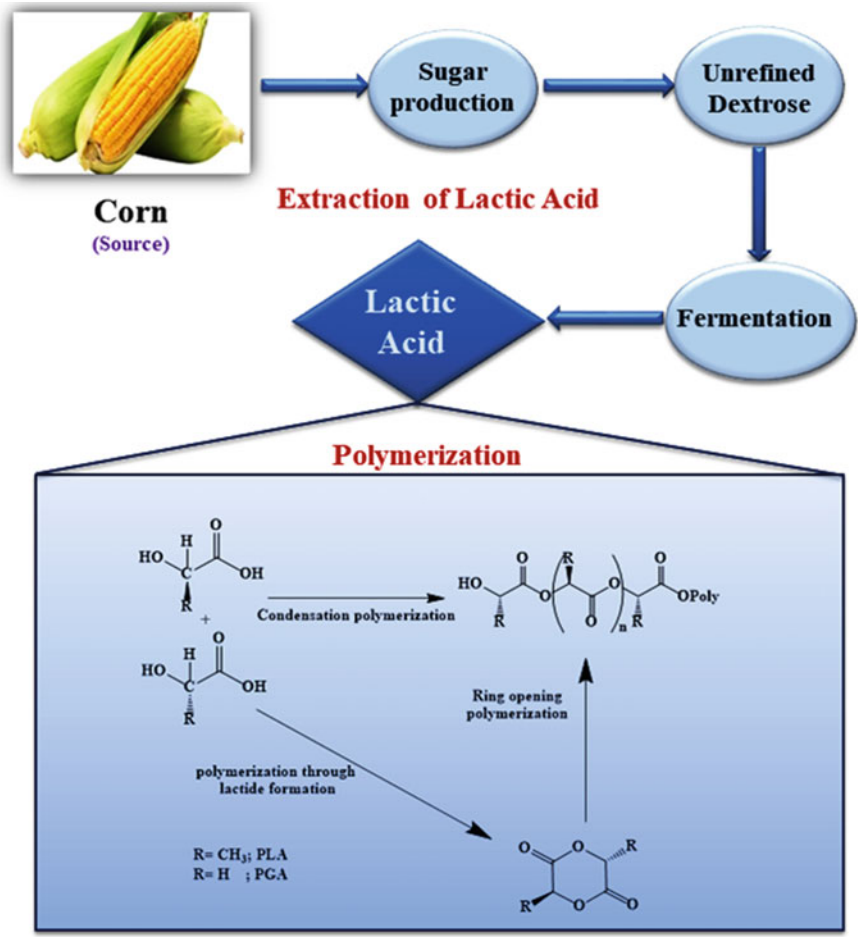


Fig. 5 Industrial process for PLA/ PGA synthesis. Redrawn from [35, 68]

Chitosan

Chitosan is an amino polysaccharide [structure given in Table 1]. It consists of copolymer N-glucosamine and N-acetyl-glucosamine units connected by β-(1,4) linkages produced by partial deacetylation of chitin [68]. Chitin is found in the exoskeleton of many crustacean animals, diatoms, algae, insects, etc. Crustacean shell waste majorly consists of protein (30–40%), calcium carbonate & calcium phosphate (30–50%), and chitin (20–30%). These ratios vary with species and with the season. Thus the preparation of chitin/chitosan also varies depending on the sources [69].

Chitin consists of polysaccharide groups connected by β-1,4-glycosidic linkages and has acetamide groups in C-2 position. It is an ordered fibrillar structure

having inter/intramolecular H-bonding, forming a highly crystalline structure which is responsible for insolubility in water, whereas chitosan with a higher degree of deacetylation contains one water molecule per polysaccharide unit and lesser crystalline part than chitin. Chitosan is soluble at acidic pH (~6.2–6.4) and less soluble above pH ~ 7.4 [69, 70].

Industrially, the shells obtained from the crustacean insects are processed through the following steps: **demineralization (DM)** [elimination of $CaCO_3$ in acidic treatment]**, deproteinization (DP)** [alkaline treatment], **decolorization (DC)** [by hydrogen peroxide, sodium hypochlorite, or acetone], **and deacetylation (DA)** (Fig. 6). The nature and quality of the chitosan depend on the degree of deacetylation as chitosan differs from chitin by means of solubility, viscosity, and other several biological activities [36, 37].

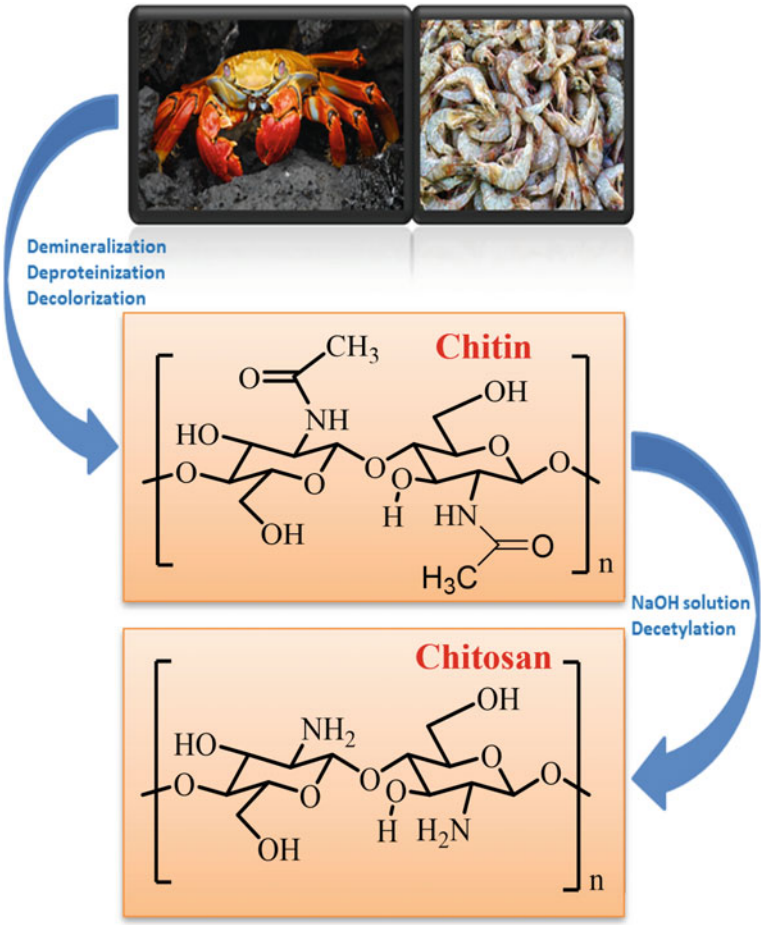


Fig. 6 Synthesis of chitosan. Redrawn from [35, 71]

2.3 Synthetic Biodegradable Polymers

These polymers are completely synthesized in laboratory, hence can be easily tuned their properties. A few common synthetic biodegradable polymers are discussed below.

Polyvinyl Alcohol (PVA)

PVA is the most common synthetic biodegradable polymer. It is highly hydrophilic, thus readily degrades in soil. It is not possible to directly synthesize PVA from vinyl alcohol due to the existence of its tautomeric form, i.e., acetaldehyde. PVA is generally synthesized from vinyl acetate through different routes. One of the most crucial methods is free radical polymerization of vinyl acetate (Fig. 7) which forms the intermediate polyvinyl acetate via emulsion polymerization in the presence of ammonium persulfate (APS) initiator at 70–80 °C [71]. PVA is obtained by hydrolysis of acetate via a strong base in the presence of methanol. Physical and chemical properties of PVA are determined by its molecular weight [72]. Generally, high molecular weight PVA shows high crystallinity and high tensile strength. PVA is an odorless, white-colored translucent granular powder. PVA is resistant to oil and grease and has flexibility that provides excellent film-forming as well as adhesive properties. PVA also possesses high moisture barrier film-forming capability as well as strong oxygen and aroma barrier properties [34, 72].

Poly (Alkylene Dicarboxylate)s (PADCs)

PADCs are the linear aliphatic polyesters. PBS is one of the family of PADCs. It is made up of 1,4-butanedial and succinic acid. PBS is synthesized by condensation process using succinic acid and 1,4 Butanediol under a vacuum. Figure 8a represents the production of PBS via the thermal polycondensation method. This produces by-products such as alcohol and water that leads to the formation of low molecular weight PBS (<30,000). This issue can be overcome by using transition metal catalysts such as Ti(IV) isopropoxide or isobutaoxide or scandium triflates. PBS obtained by ring opening polymerization of p-dioxanone (Fig. 8b) are highly degradable. PBS is thermoplastic polyester having melting temperature, T_m ~113 °C. Injection, extrusion, and blow molding are used to process this polymer for versatile

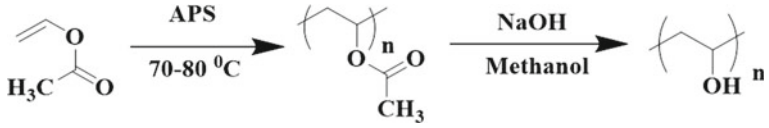


Fig. 7 Synthesis of PVA from vinyl acetate. Redrawn from [73]

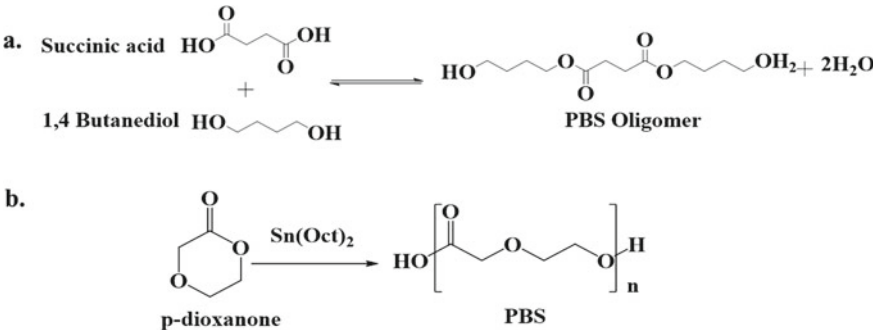


Fig. 8 Synthesis of PBS via **a** condensation reaction and **b** ring opening polymerization. Reprinted and redrawn from [82]

applications. PBS is extensively used in mulch films, containers, and plastic bags. PBS degrades slowly due to its high crystallinity. For this, different co-polymers are also synthesized. One of the superior co-polymers of PBS is polybutylene succinate adipate (PBSA) which is synthesized by butane diol, succinic acid, and adipic acid. Adipic acid is incorporated to enhance the biodegradability of PBS [26, 74, 75]. Blending and composite formation of PBS with other materials like—PLA, adipic acid, butylene terephthalic acid, butylene furandicarboxylic acid are also adopted for improving its degradability [76 –79].

Polybutylene adipate (PBA) is also a part of PADCs family. It contains 1,4-butanediol and adipic acid. PBA shows polymorphism in its melt crystallized form. Wide-angle X-ray diffraction (WAXD) and small-angle X-ray scattering(SAXS) prove that PBA has two crystalline forms α and β which grow at temperature above 32 °C and below 27 °C [80]. Since, aliphatic portion increases in PBA, crystallinity becomes poorer than PBS, and hence biodegradation rate increases for PBA [76]. Another copolymer example is Polybutylene adipate-co-terephthalate (PBAT) (Fig. 9). It is a random co-polyester of 1, 4-butanediol, terephthalic acid, and adipic acid and synthesized by polycondensation of these monomers in presence of zinc, tin, or titanium catalyst. This biodegradable polyester is manufactured by BASF in the commercial name of Ecoflex®. In presence of terephthalate groups, PBAT possesses high flexibility and toughness. However, this high flexibility is the drawback for the polymer that it cannot be used in synthesizing strong materials. The degradation of PBAT was studied in compost simulation test and it was found to occur at around 60 °C. PBAT is widely used in synthesizing mulch films and is considered to be the promising materials for bio-based products [81].

Polycaprolactone (PCL)

PCL is a biodegradable aliphatic polyester. It is prepared by ring opening polymerization of ε-caprolactone in presence of stannous octanoate [$Sn(Oct)_2$] as a catalyst

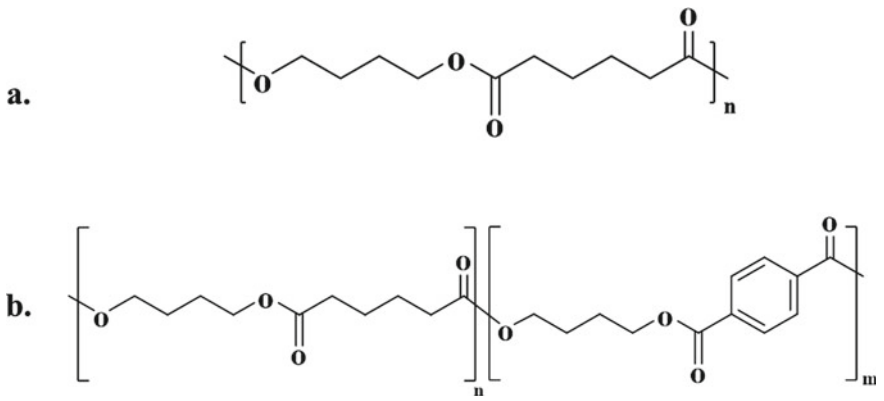


Fig. 9 **a** Structure of PBA and **b** its co-polymers PBAT . Redrawn from [82]

[82]. It is also formed as an intermediate product during the oxidation of cyclohexanol via microorganisms (Fig. 10). The by-products of this enzymatic oxidation are ε-caprolactone and 6-hydroxy hexanoic acid. The most effective enzyme for the production of polycaprolactone is lipase. Industrial production of ε-caprolactone includes oxidation of the cyclohexanone by peracetic acid. PCL is a semirigid material at room temperature. The ester bonds in PCL are easily degraded under physiological conditions. The degradation is also carried out by enzymes like lipases and esterases [83]. Its melting temperature is around 60–65 °C and Tg is about − 60 °C. The number average molecular weight of the PCL are in the range of 3000–80,000 g/mol [84]. PCL has good elastic properties that are suitable for implantable biomaterial, particularly as sutures and prosthetics.

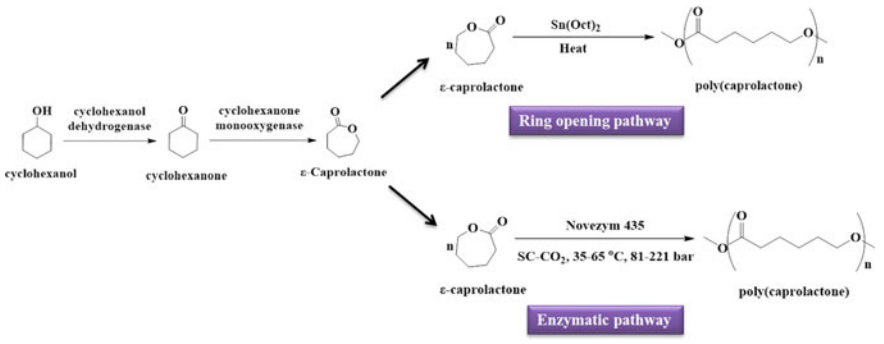


Fig. 10 Synthesis of caprolactone from cyclohexanol, and its polymerization via ring opening pathway and enzymatic pathway leads to the formation of PCL. Redrawn from [87]

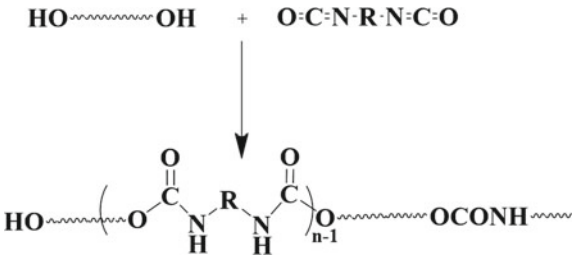


Fig. 11 Synthesis of PU via step polymerization. Redrawn from [88]

Polyurethane (PU)

As we have discussed in earlier section of this chapter biodegradable polymers and their crucial application, one such important biodegradable polymer is polyurethane. PU can degrade via both abiotic and biotic pathways. PU is commonly synthesized by the reaction between isocyanates and diols in stepwise method which yield polymer with urethane bond (Fig. 11). The physico-chemical, mechanical, and degradation properties of PU can be easily tuned by the changing of building materials, i.e., isocyanates and diols. Its tunable properties have made PU very attractive for surgeons and biomedical industries. PU's one of the advanced uses in biomedical field is prosthetics.

3 Applications of Biodegradable Polymers

The biodegradable polymers are compatible with physiological conditions such that they are efficiently employed in the biomedical area. The applications are highly reliable in the case of pharmaceutics, implants, sutures, drug delivery, tissue engineering, etc. [4]. The biomaterials are non-toxic and easily excreted or digested inside the body. Other than these, biodegradable polymers are now getting commercialized for application in the food, packaging, automobile manufacturing industries, and medical implants, etc. Details of some commercialized biodegradable products are given in next section. The constituent monomers and their ratios determine the properties of these products and their uses. Besides these, biodegradable polymers are utilized everywhere and in a wide range of products are available including kitchenware, packaging, wrapping materials, bottles, food containers, clothing, accessories, automotive parts, electronics, furniture, and many others (mentioned in Table 2). Figure 12 shows different products made up of biodegradable polymers [89].

Table 2 Commercially available biodegradable polymeric products. [85, 86]

Sl no.	Trade name	Manufacturer name	Polymer components	Applications
1.	Ecofoam®	American Excelsior Company (USA)	Starch	Wrapping materials
2.	Bio-D®	Cirad (France)	Proteins from cotton seed	Agricultural films
3.	Nodax®	Procter and Gamble Company (America)	Poly-3-hydroxybuterate-co-3-hydroxyhexanoate (PHBHx)	Making injection molded utensils, plastic bags, biodegradable agricultural films, etc.
4.	Bioceta®	Mazzucchelli (Italy)	Cellulose acetate	Making packaging films, toothbrushes, etc.
5.	Bioplast®	Biotech Company	Starch copolymer	Making food containers, cutlery, bags, etc.
6.	Ecoflex®	BASF (Germany)	Co-polyester	Making agricultural films
7.	Mater-Bi®	Novamont Company (Italy)	Starch and polyester	Making biodegradable trash bags, and disposable materials
8.	Biopol®		PHB/PHV	

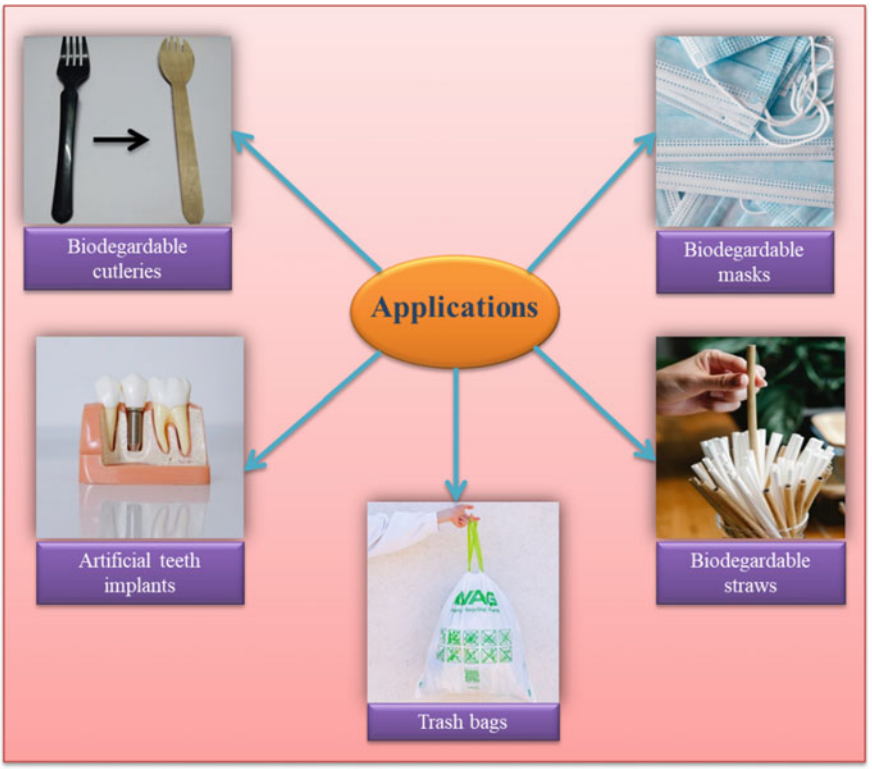


Fig. 12 Different products made up of biodegradable polymers. Reprinted with permission from [87–89]

3.1 Commercially Available Products Based on Biodegradable Polymers

4 Conclusions

Undoubtedly, biodegradable polymers have become promising materials that have potential to replace the non-degradable polymers synthesized from non-renewable sources. The petroleum-based plastics create a huge imbalance in the environment. With increase in population, people are getting habituated with the materials from cheaper sources at the expense of a compromised ecosystem. With the advancement of technology, and on growing global awareness to make a greener world, there is a dire need to commercialize the biodegradable polymers. They have introduced an appealing interest in the past few decades due to their excellent biocompatibility and biodegradability that ultimately facilitate the sustainable development of mankind. However, poor mechanical properties, molar mass, crystallinity, and toughness of

those biodegradable polymers limit their applications. Since these polymers are easily affected by natural factors, thus they are prone toward bacterial or fungal attacks, in addition to abiotic factors such as oxidation, hydrolysis, and UV light. Moreover, they face difficulty in processing them, without which no commercialized product can be made. A careful modification in processing parameters may mitigate the degradation problem, albeit with enhanced cost, thus making them not economically competitive with other commodity plastics such as polyethylene. In the present time, few groups of biodegradable polymers have market presence and their products are available for daily use. Commercialization of biodegradable products mainly relies on their price, so future work should focus on the development of industrially viable, cost-effective biodegradable products made from biodegradable polymers.

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Chapter 2
Processing of Biodegradable Polymers

Goutam Panda, Chandrani Sarkar, and Sampa Saha

1 Introduction

Famous American author and proponent of biomimicry, Janine Benyus once famously quoted, "What if, every time I started to invent something, I asked, 'How would nature solve this?'" [1]. The very crux of this conviction stems from the fact that nature has enough in her cradle to teach humans invaluable lessons of life. The rich treasure of knowledge on biodegradable polymers, from starch to cellulose, from proteins to chitosan are one amongst such lessons that humans should conceive sooner than later. Moreover, a knowledge on their processing, furthermore, is befitting, if the human civilization is keen on solving the burgeoning problem of plastic pollution and the question of non-biodegradability of conventional thermoplastics.

At this juncture, it is important to clarify that processing of biodegradable polymers is an evolving and complex discipline and must be dealt with caution. The difficulty and complexity of processing of biodegradable polymers primarily arises from the susceptibility of biodegradable polymers to degradation under the influence of high temperatures, moisture and acute shear conditions [2].

Therefore, due attention must be accorded while processing of biodegradable polymers through various techniques such as employing shallow cut screws with

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non-shearing conveying elements for reducing shear stresses inside the barrel [3], maintaining a favourable temperature profile to avoid temperature build-up [4] and using sophisticated drying systems to arrest hydrolytic degradation owing to moisture [5]. This chapter outlines general commentaries with regard to processing of biodegradable, as well as discussion on conventional and advanced/emerging processing techniques.

2 General Commentaries on Processing of Biodegradable Polymers

Most biodegradable polymers often tend to degrade through various pathways when exposed to high temperature, moisture and shear conditions.

2.1 Processing Window of Biodegradable Polymers

Biodegradable polymers differ from commonly used thermoplastics in their structure and properties. Hence, processing these polymers is also quite unique. The most critical aspect of processing biodegradable polymers is their narrow processing window as shown in Fig. 1 [6]. To overcome this problem of narrow processing window it is often required to make engineering interventions in the processing equipment. One way is to use a special screw wherein mixing elements are specially designed to incorporate non-shearing elements which only convey and facilitate pumping action of the screw but that do not contribute to the unwanted shear heating [7]. This is particularly true for starch or lignin based, or cellulosic polymers, to cite a few.

Additionally, a favourable temperature profile should be maintained in the barrel to avoid temperature build-up. This can prevent the thermal degradation of biodegradable polymers.

2.2 Effect of Moisture

Pre-drying, to expel moisture is almost compulsory for biodegradable polymers since majority of them are hygroscopic in nature. Presence of moisture can not only decrease molecular weight (MW) but also cause brittleness in parts [8]. Moreover, humidity should also be controlled even during processing of biodegradable polymers [9], otherwise moisture can cause plasticization of the polymer leading to deterioration of the final properties of the polymer. While pre-drying of commonly available thermoplastics like Nylon, Acrylonitrile Butadiene Styrene (ABS) or Polycarbonate (PC) is relatively simple, the pre-drying process for certain biodegradable

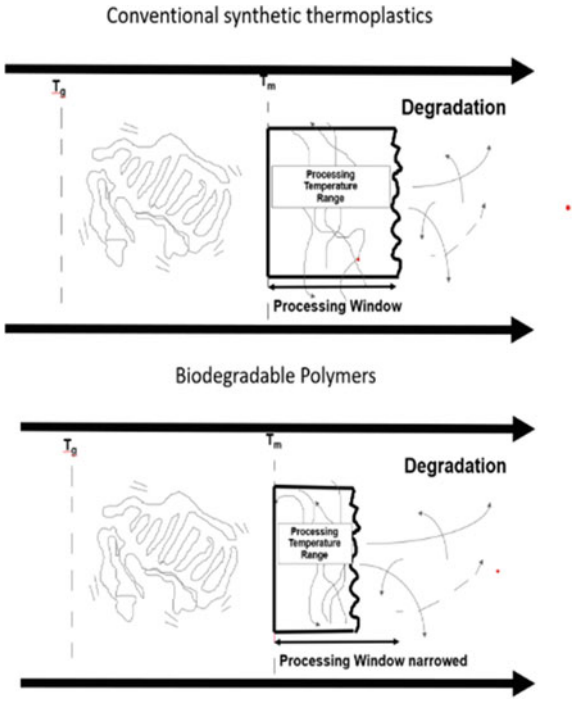

Fig. 1 Narrow processing window of biodegradable polymers as compared to wider processing window of conventional synthetic thermoplastics

polyesters like Poly (hydroxy alkanoate) (PHA) and Poly(lactic acid) (PLA) is quite complex. An extremely high pre-drying temperature would soften these biodegradable polyesters and cause agglomeration. Furthermore, inadequate temperature can lead to improper drying of these biodegradable polymers. Given the complexities of drying and the sensitivity of biodegradable polymers to moisture, the drying equipment must be carefully chosen. Sophisticated methods of pre-drying such as infrared crystallizing and drying units or rotating pulsed fluid-bed crystallizers may have to be retrofitted in processing equipment. Additionally, hopper agitators may be needed to prevent agglomeration accruing from high pre-drying temperature [10, 11].

2.3 Effect of Temperature

Processing biodegradable polymers at high temperature can cause thermal degradation resulting in the formation of monomers. This can cause plasticization of polymer adversely impacting the final mechanical properties. Thus, a favourable temperature profile should be maintained to arrest the unwanted thermal degradation of the biodegradable polymers [10].

The characteristic temperature profile required for melt processing of Ecovio IS1335, a commercially available injection grade PLA is shown in Fig. 2. Typically,

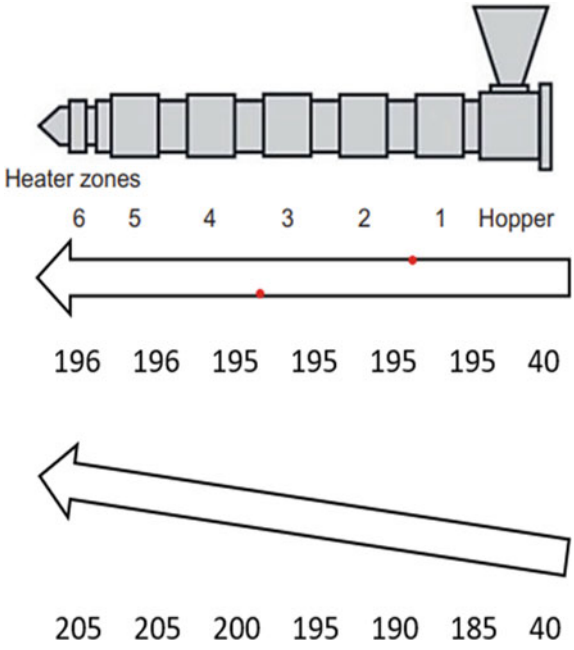

Fig. 2 Temperature profile in the processing of Ecovio IS 1335; adapted and modified from Ashter, Syed. (2016) [10]

an even distribution of temperature in the polymer melt can be ensured with the aid of shallow scut screws with non-shearing mixing elements [11]. Moreover, the temperature has to be cautiously maintained so as to ensure appropriate distribution of heat in the polymer melt while facilitating the pumping action of the screw [12, 13].

On the contrary, some other biodegradable polymers such as Metabolix Mirel P1003, a commercially available injection-grade PHB [poly (hydroxybutyrate)] may require a reverse temperature profile maintaining at 165°–170 °C at the nozzle, and 175°–180 °C at the rear to avoid temperature build-up and arrest thermal degradation [14–16].

The temperature control while processing biodegradable polymers is not just limited to barrel but also extends to the mould. For example, the recommended mould temperature for the processing of Ecovio IS 1335 (i.e. PLA-based biodegradable polymer) is typically around 25 °C. Additionally, the design of the runner system and the gates should be such that an even distribution of temperature can be ensured.

2.4 Effect of Shear

As the rate of shear increases, most biodegradable polymers, like the conventional thermoplastics exhibit a typical pseudoplastic behaviour, i.e. showing reduction in

apparent viscosity. This is largely attributed to the molecular alignments and disentanglements in the long polymer chains. However, the viscosity drop in biodegradable polymers can be tricky, and a variety of non-Newtonian flows may be expected, from pasty flows sticking to the barrel to highly shear thinning ones, more so, they may not be able to endure the shear rates that are relevant for conventional thermoplastics. For example, native starches are highly sensitive to high shearing during melt extrusion, which affects the integrity of the starch granules by increasing the amylose content and paste viscosity [17]. Processing parameters such as screw speed, screw configuration and residence time are interrelated and must be tailored to suit the needs of processing.

Typical compression ratios used for melt shearing in extruder are 2.2–2.8 or even lower, so as to arrest unnecessary pressurization and resulting heat build-up. Screw speed is recommended in the range of 50–150 rpm, or even lower can be expected. Furthermore, specially designed screw with lesser kneading blocks and predominance of non-shearing conveying elements may be recommended restricting high shear forces [18].

2.5 Other Peculiarities in Biodegradable Polymers

Certain biodegradable polymers display peculiarities during their processing. Starch, for example, in its processible and mouldable form is commonly referred as Thermoplastic Starch (TPS) or plasticized starch where raw starches are plasticized with water, glycerol, sorbitol, etc. However, starch granules pass through a peculiar order–disorder phase transition known as gelatinization. Starch granules, in presence of water, experience near solubilization along with an irreversible destruction in their crystalline structure [19]. In absence of shear forces, around 70% water content is required for gelatinization of starch granules. The requirement of water is much less under the influence of shear forces since these forces are sufficient to mechanically disrupt the molecular bonds in starch granules resulting in easier penetration of water into starch granules [20].

Another peculiarity is witnessed in cellulose. When native cellulose is hydrolyzed by a strong acid, disintegration of its structure leads to the formation of Microcrystalline Cellulose (MCC) [21].

Similarly, soy proteins exhibit peculiar irreversible changes and complex physicochemical interactions such as disulfide-disulfide interactions during melt extrusion. This often results in eccentric and unpredictable melt rheological properties. Use of plasticizers can improve processibility of protein-based polymers to some extent.

3 Conventional Processing Techniques

Biodegradable polymers, like any other petroleum-based thermoplastic polymer can be processed and moulded (with caution) by employing several processing techniques such as compression moulding, extrusion, injection moulding, blow moulding, blown film extrusion, etc. [22]. A brief discussion on each of them has been given below.

3.1 Compression Moulding

Compression moulding is a processing technique in which the moulding material, after being preheated, is placed in an open, heated mould cavity using a two-part mould system [23]. Since biodegradable polymers are susceptible to shear heating and likely to undergo thermal degradation, it is noteworthy that compression moulding being a low shear process offers a lot of flexibility, and is a lot simpler when it comes to processing of biodegradable polymers.

Compression moulding can be used to mould several biodegradable polymers such as Thermoplastic Starch (TPS), polyvinyl alcohol (PVA), Poly (lactic acid), soy-based plastics [24, 25]. For certain starch-based, soy-based proteinaceous polymers and cellulosic polymers, blending with plasticizer glycerol or sorbitol may be necessary prior to compression moulding. For example, audio speakers have been manufactured by Technare GmBH with the aid of compression moulding using Arboblend resins. Arboblend comprises lignin, bio-polyesters, cellulose, bio-polyamide and bio-olefins.

3.2 Melt Extrusion

Melt extrusion may be described as system consisting of a heated barrel, a rotating screw and a die in which the screw rotates inside the heated barrel, ‘plasticizes’ the polymer and an extrudate of consistent diameter is conveyed through the die under pressure [26]. The schematic of a typical extruder is shown in Fig. 3 [27]. Being a high shear process, melt extrusion poses a mammoth challenge for process engineers due to high shear sensitivity of the biodegradable polymers.

Melt extrusion of biodegradable polymers can be carried out either by a Single Screw Extruder (SSE) or a Twin Screw Extruder (TSE) [27, 28]. It is wiser to process biodegradable polymers like starch with TSE instead of SSE as processing starch with an SSE may cause clogging of starch powder at the feeding port. Also, relatively shorter residence time in the barrel for TSEs not only ensures high output but also helps to prevent temperature build-up [29].

The extrusion processing of starch is complex and difficult to control than that of many other polymers. The processing of starch involves the plasticization (granule

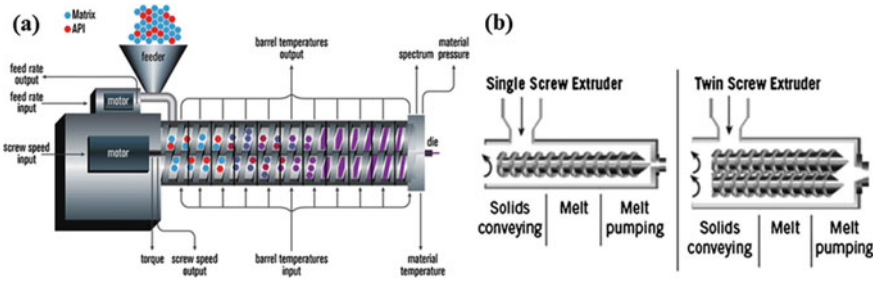

Fig. 3 **a** Schematic of a typical extruder used in pharmaceutical industry, **b** Schematic of single screw extruder (SSE) and Twin Screw Extruder (TSE). Reproduced with permission from [27]

transformation) of starch and macromolecular degradation of starch molecules. These in turn can affect the processability (rheology) and final product properties. To overcome this problem, water cooling may be necessary since enormous amount of viscous heat is dissipated during extrusion, that may increase the temperature of plasticized starch by up to 50 °C [30].

Similarly, the challenge of narrow processing window begins to plague melt processing of PLA. Thermal degradation of PLA begins at around 240 °C, close to its melting temperature (T_m). Substantial decrease in MW owing to thermal degradation occurs at 270 °C [31]. The residence times in the barrel thus should not be too long. Polyglycolic acid (PGA), like PLA, also has a very narrow processing window because the onset of thermal degradation begins only at $T_m + 30$ °C. However, since Polycaprolactone (PCL)-based polymers have a low T_m of 60 °C, they have relatively high thermal stability in the molten state. Due to this reason, PCL-based polymers have a broader processing window as compared to PLA and PGA [32, 33].

3.3 Injection Moulding

Injection moulding, like melt extrusion is a high shear process used for moulding products where the design is more complex and intricate with complex shapes, where high dimensional precision is required. It is one of the most popular processes commonly known for non-degradable thermoplastic polymers.

Although typical thermoplastics can be readily processed with a general-purpose screw as shown in Fig. 4 [34], most biodegradable polymers may require specialized screw configuration for injection moulding. As discussed in Sect. 2.4, most biodegradable polymers are susceptible to shear heating and the degradation associated therein. It is because of this reason that high shear screws like Nylon screws are best avoided for the injection moulding of biodegradable polymers. Special shallow-cut single-flighted screws with a constant-taper design are well suited for injection moulding of biodegradable polymers. These screws typically have a compression

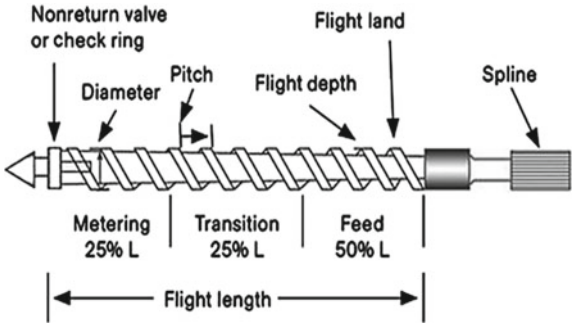

Fig. 4 A typical general-purpose screw Reproduced with permission from Syed Ali Ashter [34]

ratio of 2.2:1–2.5:1 compression and 20:1–25:1 L/D. The typical shot volume is around 30–70% of the barrel volume [35–37].

From a material stand point, nucleating agents may be needed for injection moulding of biodegradable polymers as they require longer cycle times due to slow crystallization. Another challenge encountered during the injection moulding of biodegradable polymers is the sticking of these polymers to the metal surfaces due to absorption of moisture. To overcome this problem, sophisticated pre-drying equipment that are often retrofitted with injection moulding machine include pulsed rotating fluidized bed crystallizing and drying units and infrared crystallizing and drying units [10].

During injection moulding of biodegradable polymers, injection moulded purging is absolutely necessary to prevent molten polymer from sticking to metal surfaces which can cause problems in further moulding cycles.

The mould temperature also plays a crucial role in injection moulding of biodegradable polymers. For example, the mould temperature for PLA should not be more than 25°–30 °C, otherwise surface finish and final weight of moulded products made from PLA can be impacted due to cold tooling surfaces owing to lactide condensation [38].

Novamont's Mater-Bi injection grade, a commercially available starch-based biodegradable polymer (Melt Flow Index (MFI) = 6–30 g per 10 min) can be processed with a single-flighted screw with a constant-taper design to keep the residence time under check [39]. Another commercially available starch-based biodegradable polymer such as Biomax TPS by DuPont can be processed with low-compression screws with a compression ratio of 2.2:1 to 2.8:1 and an L/D of 20:1 [40–42].

From a mould design aspect, processing of biodegradable polymers may require hot runner systems and heated nozzles due to homogeneity in melt temperature and a reliability in purging. Additionally, the gate point should have good thermal isolation to have a better control on moulding [42].

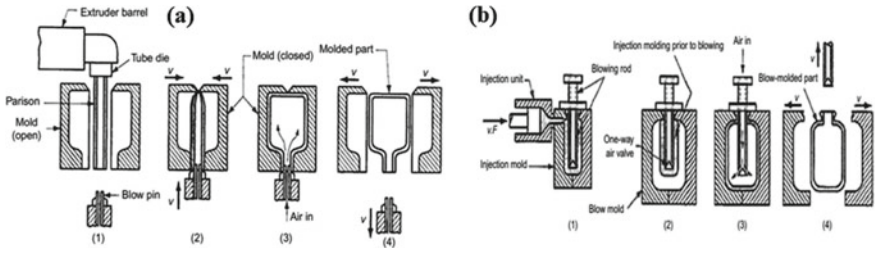

Fig. 5 Schematic diagram of **a** EBM, **b** IBM screw. Reproduced with permission from Syed Ali Ashter [34]

3.4 Blow Moulding

Blow Moulding is typically used for moulding of hollow parts such as plastic bottles. The two commercially acknowledged variants of blow moulding are Extrusion Blow Moulding (EBM) and Injection Blow Moulding (IBM) as shown in Fig. 5 [43–45].

EBM slightly differs from IBM in the machine arrangement and moulding stages. In EBM, polymer in the shape of a hollow tube section, called as 'parison', drools out through a die whereas in IBM, molten polymer is fed into a manifold. Furthermore, in EBM air is blown through blowing rod into the parison to inflate it inside the mould, whereas in IBM, the core rod is rotated and a hollow chilled blow mould clamps the core rod [46, 47].

FKUR, a global biodegradable manufacturer, has introduced a grade called BIO-FLEX which is a blend of co-polyester and PLA (no starch or starch derivatives). Due to its controlled branching and higher elongational viscosity and strain hardening parameter, it has been used for several blow moulding applications and manufactured daily used products as shown in Fig. 6 [48]. Husky has used a biodegradable polymer from Nature Works company (a corn-based PLA resin) and successfully stretch blown to a water bottle. It is world's first compostable water bottle [49].

3.5 Blown Film Extrusion

Blown film extrusion whose schematic is shown in Fig. 7, is a process equipped with an extruder which pumps polymer melts through the die, mandrel and finally air blown in the shape of a tube. This inflated 'balloon-like' tube is flattened using nip rolls and then finally wound as flat film on to the winder [49].

The Blow-up-Ratio (BUR) is defined by

$$\text{BUR} = \frac{\text{Bubble Diameter}}{\text{Die Diameter}}$$

Fig. 6 Examples of products made by **a** injection blow moulding, **b** extrusion blow moulding, **c** Husky's first compostable bottle made by Injection Stretch Blow Moulding Reproduced with permission from Syed Ali Ashter [34]

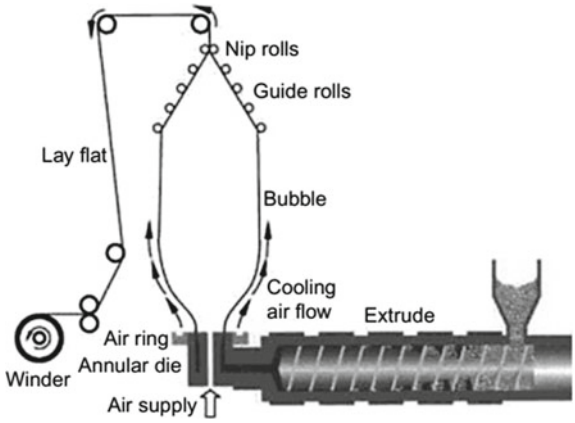

Fig. 7 A schematic set-up for Blown Film Extrusion Reproduced with permission from Syed Ali Ashter [34]

The problem with film blowing of biodegradable polymers is that most of them lack sufficient extensional viscosity and strain hardening parameter which are essential in the formation of a stable bubble during film blowing [50].

The poor visco-elastic properties and low melt strength of PLA cause difficulty in formation and stability of the inflatable bubble. Molten PLA often accumulates near the die resulting in melt sag. Film blowing process for PLA requires meticulous control of melt rheology. PLA films generally require low processing temperatures. Additionally, several processing parameters such as Processing Speed Ratio (PSR) and air pressure need to be tuned for film blowing of PLA [51]. Material modification strategies like blending of PLA with PCL or polybutylene succinate or modification

of PLA with chain extenders like maleic anhydride and chain branching agents, etc. These are primarily used as film blowing grades of PLA [52, 53]. Typical Blow-up ratio (BUR) for PLA films is around 2:1–4:1.

During the film blowing of TPS, the films become brittle and stiff beyond a critical limit of the shear viscosity [54]. Additionally, to obtain comparable mechanical properties in both transverse and longitudinal direction, TPS films are biaxially oriented [55].

3.6 Thermoforming

Thermoforming is of numerous types and varieties depending upon the machine arrangement. A typical thermoforming process, however, comprises of heating and softening a polymeric sheet and then drawing or pushing it against a mould to form a rigid or semi-rigid shape [56].

Mostly amorphous polymers exhibiting a distinct rubbery region glass transition temperature (Tg) have good thermoformability. Semi-crystalline polymers are difficult to thermoform as they have a narrow thermoforming window. This aspect of material characteristics is equally valid for biodegradable polymers [57].

Amongst several biodegradable polymers, only PLA has been successfully thermoformed so far. Since PLA has a very narrow thermoforming window, control of the forming temperature is the trickiest part while thermoforming of PLA [58]. Thermoforming of TPS is challenging as TPS is high heat and moisture sensitive. Due to favourable heat transfer properties, aluminium is generally used as mould material for thermoforming of biodegradable polymers. Thermoforming can be accomplished with the aid of compressed air, vacuum or even mechanical actuation. The depth of drawing and wall thickness optimization are critical parameters in thermoforming. For optimized thickness of parts, plug-assisted thermoforming can be beneficial depending on the part design [59].

3.7 Fibre Spinning

Spinning is a widespread technique used for formation of fibres. The two main variants are melt spinning and electrospinning. Melt spinning is deployed for polymers that can be readily converted into molten state. For polymers which are heat sensitive, solvent-based spinning or electrospinning is usually used [60].

Melt spinning of biodegradable polymers involves melt extrusion followed by expelling strands by means of a spinneret. Typically, a Single Screw Extruder (SSE) with 22:1–35:1 with the provision of cooling in the feed throat zone is well suited for processing of biodegradable polymers. In order to ensure temperature distribution, optimum dispersion of additives as well as melt polymer homogeneity, static mixers are used.

Lenzing AG an Austrian company manufactures make viscose (regenerated cellulose) fibres that can be used for multifarious applications in the biomedical field. Special PLA grades for fibre spinning, blended with cotton or viscose can be utilized for several applications such as carpets, geotextiles and agricultural textiles. A tea bag has been made from PLA fibre by a Finnish company [61].

Electrospinning involves leveraging electrostatic forces to manufacture fibre yarns from a polymer solution. A charged polymer drop at the tail-end of spinneret elongates under the influence of electrostatic forces. At a critical voltage, the electrostatic forces exceed the surface tension of the polymer solution, forming a continuous jet [62]. This causes rapid vaporization of solvent producing fibres. A typical electrospinning set-up is shown in Fig. 8.

A wide range of biodegradable polymers including gelatin, chitosan, silk, collagen, PLA and their copolymers including their blends [63] have been successfully electrospun into nanofibers for several biomedical and tissue engineering applications [64, 65].

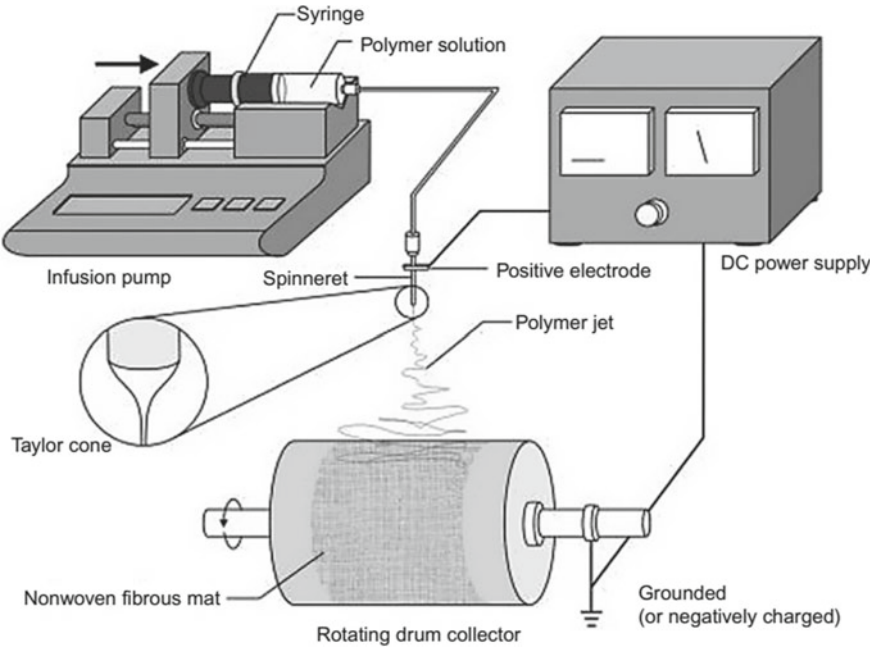

Fig. 8 A electrospinning set-up reproduced with permission from Syed Ali Ashter [34]

3.8 Emulsion

When immiscible droplets are dispersed between two liquid phases, it is called an emulsion. For example, dispersion of water in oil stabilized by a suitable surfactant. Aqueous biodegradable polymeric emulsion consists of a biodegradable polymer such as Poly (hydroxy-alkanoate) (PHA) or PLA, a surfactant, a plasticizer and water. The mixing is generally done in a high-pressure reactor, with high stirring, at a temperature beyond the melting point of the polymer. The surfactant helps to decrease the interfacial surface tension whereas the plasticizer aids in reducing intra-molecular cohesion. Rapid cooling of the reactor helps to arrest the recrystallization of the polymer. Aqueous biodegradable polymeric emulsions usually have a dry matter content of around 30–40%. The average particle size of the solid content is about 10–150 microns dispersed throughout the emulsion. Solvent based emulsion where instead of molten PLA, a solution of PLA in a good solvent was dispersed in water in presence of surfactant to make oil/water-based emulsion. Upon removal of solvent including water, PLA based polymeric particles were formed that can be used as active delivery vehicles for various applications such as drug delivery, active food packaging and agrochemical/plant nutrient delivery [66].

Emulsification of the biodegradable polymer is not only affected by concentration of the polymer, but also by the nature and concentration of the surfactants and plasticizers. An inappropriate choice of surfactant or plasticizer may result in the destabilization of the emulsion or failure of a polymer to emulsify in the first place.

4 Emerging Processing Techniques Related to Biodegradable Polymers

Apart from the conventional techniques, new advances and emerging techniques are also being employed for processing of biodegradable polymers. This includes additive manufacturing, reactive extrusion, micro-cellular foaming, femto-second laser processing and microfluidics, etc. to name a few. These are invaluable and novel techniques employed in pharmaceutical, packaging, aerospace and defense applications. However, it is worth emphasizing here that these techniques are at a nascent stage and their usage is not yet widespread. Moreover, a lot of researches are being undertaken on improving the effectiveness of these techniques. Nevertheless, brief introduction on these recent advances is certainly necessary to appreciate the nuances of contemporary developments.

4.1 Additive Manufacturing

Additive manufacturing, as opposed to conventional milling processes wherein a solid block is deducted and shaped by cutting, drilling, grinding and polishing, involves layer-by-layer deposition of materials as shown in Fig. 9 [67].

Additive manufacturing is numerous varieties such as three-dimensional (3D) printing, rapid prototyping, solid-freeform fabrication, Fused Deposition Modelling (FDM). Despite differences in their construct and working, all of them rely on the basic principle of layer-by-layer deposition and adhesion of materials to manufacture a product.

In recent times, as shown in Fig. 10, commercial polyvinyl alcohol (PVA) has been fabricated into tablets by using FDM [68–71].

A scaffold made of electrospun Poly(Ɛ-caprolactone) (PCL) is coated with a mixture of sirolimus and poly(lactide-co-glycolic acid) (PLGA) and 3D printed to

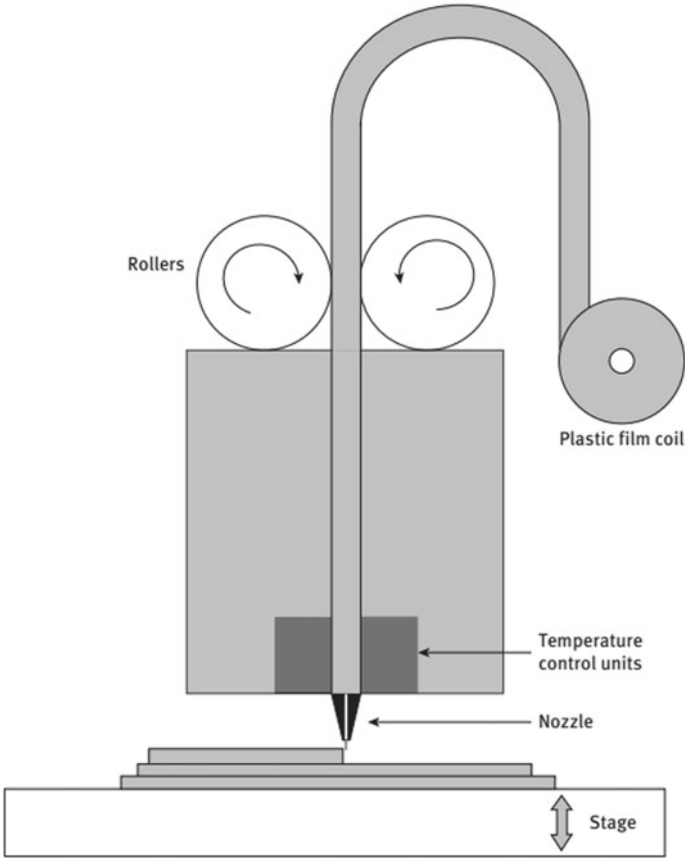

Fig. 9 A schematic of FDM 3D printer. Reproduced with permission from Gross et al. [68]

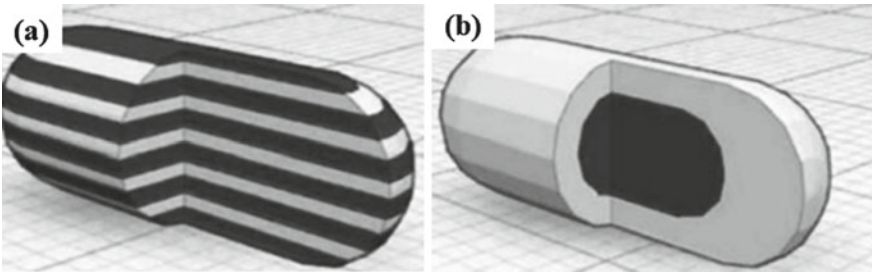

Fig. 10 3D representation of multilayer oral dosage forms: **a** sectioned multilayer device (alternating 1-mm layers) and **b** sectioned DuoCaplets (caplet within a caplet). Reproduced with permission from Goyanes et al. [71]

manufacture bioresorbable stents [72, 73]. Several in-vivo studies over the years have confirmed that coated stents perform better than uncoated stents. This provides a futuristic scope for drug-eluting polymeric stents fabricated by 3D printing and other techniques of additive manufacturing [73].

4.2 Reactive Extrusion

Reactive Extrusion (REX) is a dependable technique for processing of biodegradable polymers as it facilitates effective mixing and heat transfer, and thus helps to arrest uncontrolled increase in viscosity which is usually witnessed in a batch reactor. Apart from this, REX enables an appreciable control on the residence time through control of operational conditions and geometrical specifications of screw extruders. Thus, a substantially lower residence time may be expected for REX as compared to batch reactor. This is critical so far as processing of biodegradable polymers concerned as long residence times can cause long exposure to high temperatures leading to degradation of biodegradable polymers. The advantage of REX is that an extruder can be utilized as a reactor to handle high-viscosity polymers without solvents.

Biodegradable polymers such as aliphatic polyesters, e.g. PCL and PLA can be polymerized with controlled molecular weight and polydispersity using REX. For REX of PCL via Ring-Opening (Co)polymerization (ROP) of Ɛ-Caprolactone, a modular intermeshing co-rotating twin-screw extruder is preferable [74–76]. The screw configuration in this case is likely to consist of conveying elements only, so as to avoid undesirable thermal degradation caused otherwise due to kneading elements. Similarly, PLA can be manufactured via ROP of Lactic acid by employing $Sn(Oct)_2$ as catalyst through continuous one-stage reactive extrusion [77–81].

4.3 Micro-cellular Foaming

Micro-cellular foaming is a process where foam cells are formed within the material by dissolution of gas into solid or molten polymer [82, 83]. The formation of gas is facilitated by a blowing agent. Depending upon the blowing agents utilized, micro-cellular foaming can be classified as physical foaming and chemical foaming.

Foamability of biodegradable polymers is closely intertwined with extensional viscosity and strain-induced hardening behaviour, a measure of the ability of biodegradable polymers to withstand the stretching forces thus facilitating the bubble growth. Macromolecular designing incorporating some branching on linear molecules, increasing molecular weight or broadening the molecular weight distribution can improve strain hardening parameter of polymers [84, 85].

By employing a variety of such techniques, several foam systems such as PCL/N_2 system and PCL/CO_2 systems [86] have been successfully achieved. Similarly, PLA, a biodegradable polymer with poor visco-elastic properties can be chemically modified to introduce some degree of branching to make it foamable.

4.4 Femtosecond-Laser Processing

Femtosecond laser-based processing employs oscillating laser beams for fabrication. This processing technique has several advantages over conventional methods as it does not necessitate the use of a mould or chemical solvent. Moreover, customized fabrication is possible because of computer-aided scanning.

Femtosecond lasers allow precise fabrication of 3D structures with visible and near-infrared wavelengths. Since femto-second laser pulse interacts with the polymeric material for an extremely short period, it results in smaller heat affected zone (HAZ). This allows fabrication of 3D structures from several biodegradable polymers having low Tg.

Numerous attractive applications can be realized if the degradation rate of biodegradable polymers can be controlled such as controlled release in drug delivery systems and control degradation of scaffolds employed for tissue regeneration. Femtosecond laser processing provides tremendous flexibility and precision control in several sophisticated biomedical applications [87].

5 Summary

Processing of biodegradable polymers poses a unique challenge even for trained processing engineers owing to a distinctly narrow processing window. Almost all biodegradable polymers are likely to undergo thermal and hydrolytic degradation under the influence of high temperature, moisture and high shear conditions.

Some biodegradable polymers also exhibit peculiarities during their processing, for example, gelatinization in starch and disulphide-disulphide interactions in soy proteins. While low shear processes like compression moulding is relatively less challenging, high shear processes like melt extrusion and injection moulding pose greater challenge due to shear forces contributing to thermal build-up and aid in degradation of biodegradable polymers. Besides maintaining a cautious temperature profile, specially designed shallow-cut single-flighted screw with a constant-taper design, having a 2.2:1–2.8:1 compression ratio and 20:1–25:1 L/D help in reducing excessive shear and thermal degradation inside the barrel. The screw design should be such that there is a judicious balance of kneading and conveying elements. Longer residence time must be avoided. To overcome the problem of hydrolytic degradation due to moisture, sophisticated drying systems such as infrared crystallizing and drying units and rotating pulsed fluid-bed crystallizers may be retrofitted as per machine and process requirements. For processes like blow moulding, blown film extrusion, melt spinning and micro-cellular foaming, specially modified grades of biodegradable polymers with sufficient visco-elastic properties and strain hardening parameters are required. REX can be chosen over conventional melt extrusion where controlled MW and polydisperse are important considerations. Other advanced processing techniques like electrospinning, additive manufacturing and femtosecond laser processing are instrumental in advancing their applications in biomedical arena such as tissue engineering, coronary stents, tissue scaffolds and capsules.

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Chapter 3
Surface Modification of Biodegradable Polymers

Meenakshi Verma, Chandrani Sarkar, and Sampa Saha

1 Introduction

Biodegradable polymers are polymers that maintain good mechanical strength during their service life and degrade to form low molecular weight and non-toxic compounds such as water and carbon dioxide, when desired [1]. In the recent era, biodegradable polymers have shown promising role in biomedical science including the potential replacement of metallic implants [2]. For example, devices made out of biodegradable polymers could be implanted in the human body without the need of a second surgical procedure necessary to remove the implant (e.g., made of stainless steel) [3, 4]. Also, to fix a fractured bone, an implant made out of stainless steel has a tendency to cause refracture once the implant is removed. However, an implant based on biodegradable polymer degrades gradually to transfer the load slowly to the fractured bone, thus reducing the chance of refracturing the bone. Another impressive application shown by biodegradable polymers is their use in controlled delivery of drug [5]. A wide range of biodegradable polymers has been employed as carriers of drug useful for the treatment of diseases such that it kills only the infectious cells without harming the healthy ones [6, 7]. Biodegradable polymers also show significant applications in the domain of tissue engineering. They can be produced in the form of three-dimensional scaffolds to offer optimal support and environment for the growth of tissues [8].

Although biodegradable polymers have been shown as the promising candidates in the biomedical arena, their surface properties greatly influence their wide range of applications suggesting the need for its modification [9]. Surface modification of biodegradable polymers hase been widely utilized to achieve attractive long-term

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and short-term effects for their desirable functionality. Tunable bulk material properties of biodegradable polymers like tensile strength, elasticity, and density also aid in widening the scope of their application with further increase in their effectiveness after the surface treatment. For example, extensive studies of biodegradable aliphatic polyesters as scaffold materials for applications in tissue engineering have been carried out, due to their non-toxicity, good mechanical properties, adjustable degradation rates, and low immunogenicity [10, 11]. However, there is ineffective cell attachment, spreading of cells and their proliferation caused by backbone hydrophobicity of the polymers which reduces the surface energy of these polymers [11]. Consequently, surface modification of these polyesters is required to enhance their affinity towards healthy cells [12]. Exploration in controlling the behavior of cells while interacting with artificial surfaces is the way for many applications in the field of biotechnology [13].

Further, microbial infections and their contamination have been viewed as hazardous complications faced by the medical, healthcare, and sanitation industries [14, 15]. Biomaterial-based biomedical implants exhibit infections caused by bacteria while using them inside the human body and have been considered as a major threat to human health. Generally, the interactions of bacteria with any surface, including the biomedical device comprising of biodegradable polymers lead to the growth of planktonic cells on the substrates which flourish to form biofilm. Removal of the proliferated biofilm on the surface becomes a very difficult task. Without intervention, the biofilm rapidly spreads to cause deadly infections. Thus, surface modifications with anti-infective coatings, i.e., resisting the microbes, promise a great potential in mitigating the infections associated with biomaterials used inside the body. Understanding these aspects for designing the biomaterials, it is crucial to control and manipulate the surface properties of the biomaterial without compromising their bulk properties [16, 17]. Ultimately, surface treatment of polymers did exhibit excellent properties related to antibacterial and cytotoxicity permitting their use in biomedical applications [18].

Biodegradable polymers have also been extensively explored as drug delivery systems for carrying low-molecular-weight drugs [19]. Research additionally shows that there are failures in achieving favorable clinical outcomes in delivering the drug at the targeted site of action [20]. It has been found that a sufficient amount of drug is spread among the normal tissues or organs which are not included in the pathological process, frequently leading to harsh side effects. This envisions the need for the development of systems for targeted drug delivery involving the delivery of bioactive agents or drugs at the desired site of action [21, 22]. Thus, the biodegradable polymeric surface is modified chemically or with different substances to remain in systematic circulation for longer duration of time and reach the specific organ in order to release the drug [6, 23]. The improvement in biodistribution of drugs and pharmacokinetics could increase the compliance of patients and efficacy in therapy, thus enhancing the outcome of the treatment [6]. Moreover, biodegradable polymers have also been employed in the field of catalysis where they can be used as Pickering emulsion stabilizers and participate in interfacial catalysis to remediate the pollutants from water. In replacement of surfactants, surface-modified biodegradable polymers

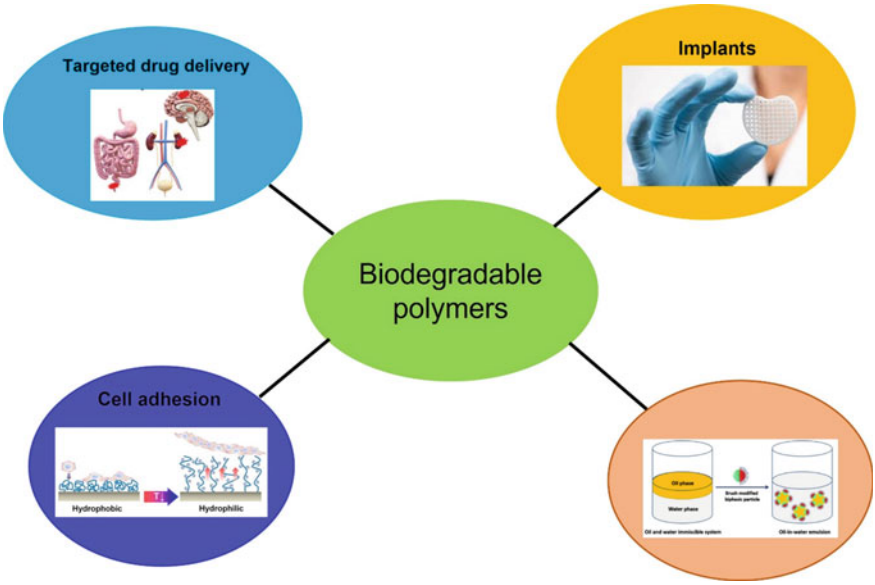

Fig. 1 Schematic representation of applications of surface-modified biodegradable polymers. Reproduced with permission from [26–28]

are used as emulsion stabilizers as they are converted into particles to modify their surface in such a way that they can be adsorbed at the interface of oil and water to produce a stable emulsion consisting of these two phases [24, 25].

The methods of surface modification such as plasma treatment, corona treatment, chemical modification, ultraviolet (UV) treatment, and their process parameters such as wavelength of UV, gas flow in plasma treatment, source in corona treatment, etc., greatly affect the performance and functionality of these biodegradable polymer-based systems or devices suggesting the need for focusing on these methods. The selection of the modification method perpetually destines the properties in the enhanced polymer. Hence, this particular chapter pursues to focus and stipulate a broad outlook on several methods for the treatment of surface of biodegradable polymers in addition to their use (Fig. 1). Emphasis has also been given on their durability, lifetime, and advantages/disadvantages of the particular method used for modifying the surface.

2 Methods to Modify Surfaces

There is a wide range of methods to achieve the surface treatment of biodegradable polymers. It is most commonly accomplished by modulating the surface energy of the material in order to manipulate its adhesiveness and other properties such

as wetting, releasing, or absorbing by subjecting the polymer to various treatment processes such as chemical, ionic, or light-induced techniques to introduce different functional groups on the surface of the material [29–31]. The surface roughness of the biodegradable polymer can also be altered by chemical or mechanical processes in order to modify the polymer top layer [32]. However, the various methods to modify the surface of biodegradable polymers are discussed below.

2.1 Physical Routes

The use of techniques like extrusion, injection molding, and lamination modifies the surface of polymer during the fabrication [33–35]. Physical method for polymer surface modification induces micro and nanoscale roughness changing its wettability while maintaining the existing polymer's chemical nature. The change in roughness of the surface helps in attaining properties such as superhydrophobicity to attain several applications. The surface changes from hydrophilic to hydrophobic as the roughness of the surface is altered [36]. Surface modification of the polymer performed by physical methods is comparatively cost-effective, scalable, and simple. These methods do not require any use of chemicals to make the method eco-friendlier. This also increases the robustness of the modified polymer surface for use in industrial applications [37]. In this method, the modification is different from other methods for surface treatment where the treatment is accomplished as part of surface treatment rather than the modification on the surface of the already formed polymer surface. For example, Wang et al. prepared blend films of PLA/epoxidized soy oil/zeolite in a melt blow mold by extrusion (Fig. 2). Zeolite was used as a nucleating agent and oil as the plastizer to produce a film with a higher tensile strength [38]. The main advantage of the modification performed by physical methods over other methods is that they do not involve the use of any fluorine-based chemicals which are unsafe for environment. These methods are always preferred unless otherwise required. Nonetheless, the approach of physical modification is constrained to thermoplastic polymers to process in their solid or molten states, and not manipulating bulk properties of them involving elasticity and mechanical strength.

2.2 Chemical Modification of Biodegradable Polymeric Surface

Specific chemical reactions are involved in the chemical modification of polymeric surface. Polymer brushes grafted on the surface of biodegradable polymers are an attractive class of surface modification of biodegradable polymers as they have controlled architectural features. These are the polymeric chains attached to a solid substrate via one end. The functional groups present on the surface are exposed to

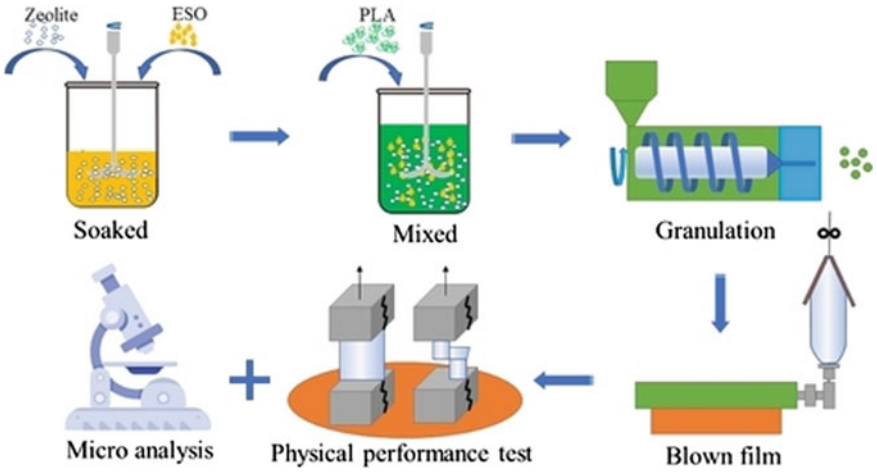

Fig. 2 Schematic representation of the preparation of blown film of PLA reinforced with zeolite and epoxy soybean oil as a plasticizer. Reprinted from Ref. [38] under a CC BY license

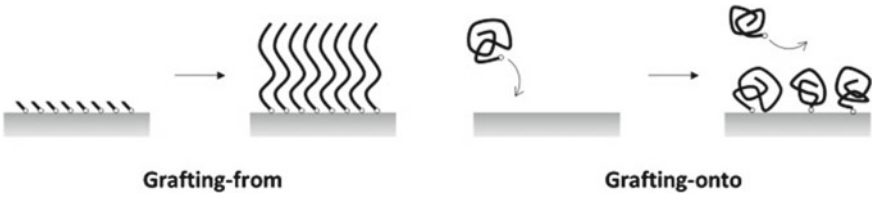

Fig. 3 Schematic representation of "grafting-from" and "grafting-onto" methods for surface modification. Reproduced with permission from Ref. [39]; Copyright 2020 Elsevier

react with the particular functional group present in the polymeric chains to graft the polymer brushes bound to the material surface. As compared to the physical method, chemical reactions are involved in the chemical method to chemically bind the polymer brush to the surface of the substrate. It is a well-known fact that chemical bonds are stronger than physical bonds and thus, a graft layer attached chemically binds more firmly to the surface. Polymer brushes can be attached via a "grafting-to" approach (chains of polymer are covalently bound to the surface) or via a "grafting-from" approach (initiator molecules present on the surface allows the growth of polymer chain from surface) [11] (Fig. 3).

Grafting-To

This approach involves the chemical reaction between the reactive groups present on the surface of the substrate and the functionalized polymers. The characterization of the grafted polymers and their structure in the grafting-to approach is more convenient

as compared to the other technique. However, the effect of steric hindrance includes the difficulty for grafting the polymer chains which generally reduces the grafting density of the attached polymer.

Grafting-From

An active site present on the surface of the substrate is used to initiate the polymerization in situ for the reaction of the monomer in this "grafting-from" approach. This approach involves the growth of polymeric chains from the surface of the substrate utilizing initiator moieties attached to the surface or self-assembled monolayers known as surface-initiated polymerization. As compared with the "grafting-to" approach, this approach can effectively control the grafting density and thickness of polymer brushes grafted on the surface with accurate precision. Moreover, densely grafted polymeric chains onto the polymeric surface can be achieved, since small initiator moieties and monomer molecules are interacting, thus devoid of crowding problem caused by steric congestion.

2.3 Plasma Treatment

Inert gases like hydrogen, oxygen, and nitrogen during the plasma treatment dissociate to react with surface of the substrate for changing the surface properties like adhesion, wettability, and printability [40, 41] (Fig. 4). The gaseous mixture composed of particles like free-ions, electrons, and radicals having no net electrical charge is used to create plasma while interacting with electric field or radiation. Photon emission takes place as the electron returns to the ground energy level causing the plasma luminosity. There are two subcategories in which plasma can be divided based on the temperature of the gas, i.e., thermal and cold (non-thermal) plasma [42–44]. Thermal plasma consists of electrons at a very high temperature and charged/neutral heavy particles which cannot be utilized in the modification of polymeric surface as they are heat sensitive. However, in non-thermal plasma, charged and neutral particles at low temperature are involved along with the electrons emitted at high temperature. He, Ar, $N_{2,}$ and O_2 are inert gases that do not induce a polymerized coating on the surface, rather they can induce or replace the functional groups present on the surface or generate free radicals contributing to the modification of the surface to create desired properties like improved hydrophilicity or adhesive properties [12]. Modification on the surface is achieved indirectly or directly. However, the methods involved directly induce the free radicals when treated with inert surface to manipulate them for applications which are targeted in nature, e.g. making them hydrophilic to repel bacteria and improve the anti-adhesion property of the surface. On the contrary, the methods involving the indirect methods comprised of grafting of polymer [45]. The methods used for plasma treatment of the surface of the sample decide its efficiency through the parameters such as type of gas used, frequency,

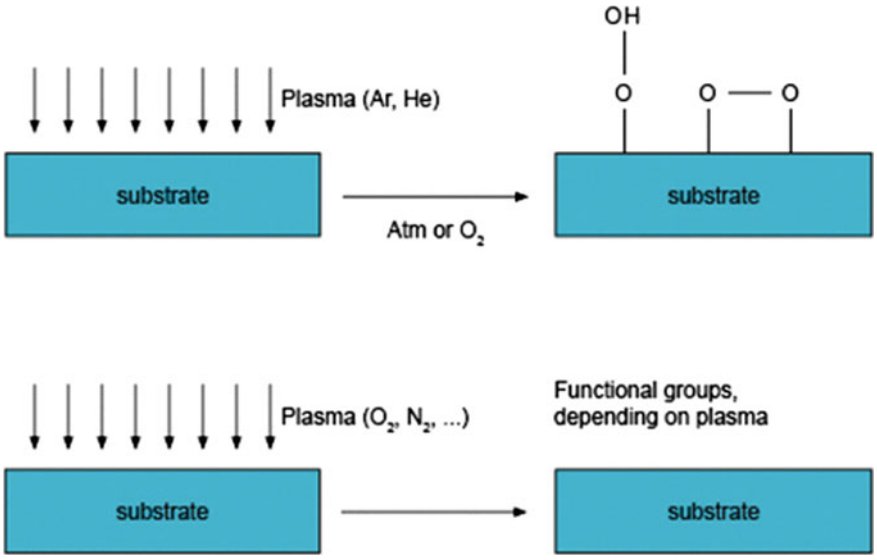

Fig. 4 A scheme representing different gases involved in the treatment of plasma on a substrate. Reproduced with permission from Ref. [48]; Copyright 2009 ACS

pressure, time, and power [46, 47]. However, the polymers face the recovery of their hydrophobicity due to their inherent nature in order to attain equilibrium by decreasing the surface energy. The reduction in surface energy takes place due to the several processes involved such as chemical rearranging on the surface treated with plasma, degradation and oxidation of the surface treated by plasma.

2.4 Corona Treatment

This treatment is associated with the non-local thermodynamic equilibrium of plasma being created in air or active or inert gas atmosphere [49]. The corona discharge helps in introducing the polar groups to improve the energy of the surface significantly to affect the surface properties such as roughness, adhesion, and wettability. The treatment of polymeric surface by the corona discharge has significantly undergone advancements in the last decade. In this treatment process, power devices with logic control have taken over the power supply being driven by the generator or manually providing the more consistent parameters for the process such as time of exposure, distance between the electrode and substrate, and the power (Fig. 5). Among these parameters, the most important is the density of the power facilitating the increase in surface energy by discharging ions in the presence of oxygen to create oxygenyl functional groups depending on the application such as printing, extrusion or coating, extrusion or printing of the material and variables involved in the process [50].

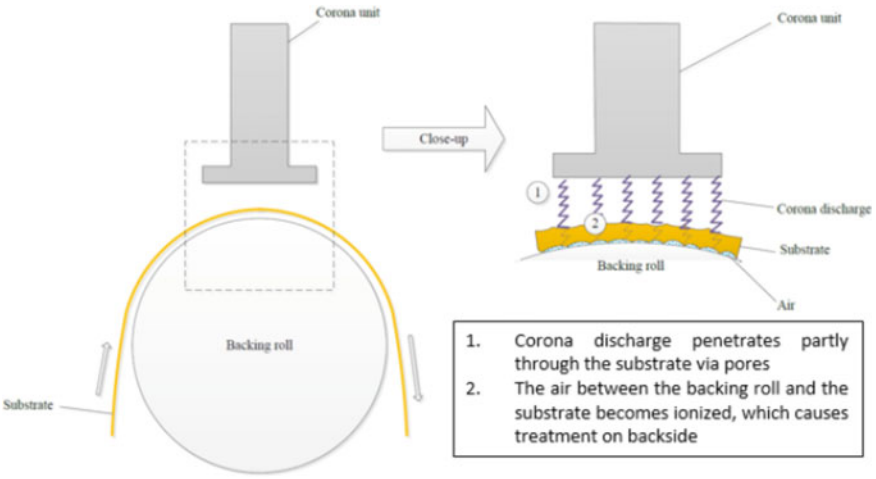

Fig. 5 The schematic representation of the mechanism for corona treatment on solid substrate. Reproduced with permission from Ref. [51] under CC BY license

2.5 Self-assembled Monolayers

In 1946, Zisman was the first scientist to report about Self-assembled monolayers also known as SAM [52, 53]. They are assemblies of molecules formed spontaneously on a solid substrate by the gas or solution phase adsorption. However, the molecules present in the gas or solution phase spontaneously adsorb to organize themselves in a singular layer on the surface to call them the self-assembled monolayer. The common examples of polymer samples mounted on the surface are protein, polyethylene glycol, and deoxyribonucleic acid (DNA) [54]. Gong et al. synthesized carboxymethyl chitosan grafted *Cis*-3-(9H-purin-6-ylthio)-acrylic acid polymeric prodrug which self assembles in presence of aqueous media into the spherical micelles. These micelles were successful in the storage and release of 6-Mercaptopurin (6-MP) in the presence of glutathione (GSH) [55] (Fig. 6).

2.6 Layer-by-Layer (LbL) Self-assembly

Twenty years ago, Moehwald, Decher, and Lvov first propped the method of deposition using LbL self-assembly [56]. In this method, self-organized polyelectrolytes are adsorbed alternately on the surface of the material and form the films in the form of polyelectrolyte multilayer (PEM) [47]. These PEM films are well known for providing a huge surface area to adsorb a large number of biomolecules and maintaining their biological activity. The process parameters are adjusted and controlled to manipulate the growth of their internal structure. Aqueous conditions are utilized

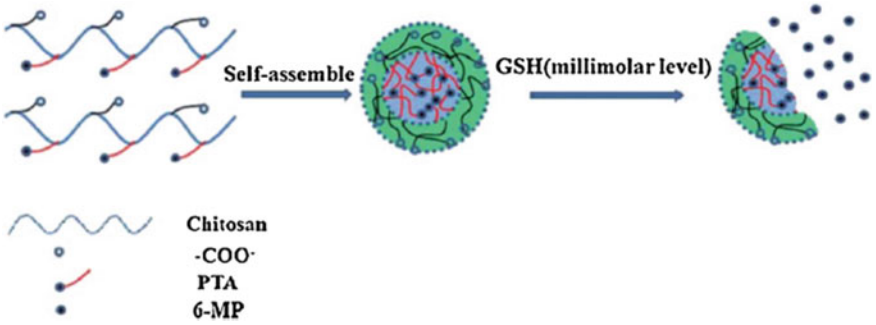

Fig. 6 Self-assembly of conjugates of chitosan–6-MP for self-assembly and the conjugates releasing 6-MP. Reproduced with permission from Ref. [55] under CC BY license

to prepare the PEM films under mild conditions leading to a great advantage for the use of bioactive agents and biopolymers. Therefore, wide use of the components involved in the LbL process regulates their parameters and controls the cell adhesion behaviour [45]. For example, Khademhosseini utilized micropatterns of hyaluronic acid (HA) for immobilizing proteins and cells on a glass substrate. The authors also utilized the HA surface for understanding the subsequent adsorption of poly-L-Lysine (PLL) [57] (Fig. 7).

2.7 Ultraviolet (UV) Treatment

The treatment of the surface by the UV has proved to be efficient, effective, and economical for non-contact purposes consisting of less number of processing steps. The treatment of surface by UV alters and modifies the adhesion and wettability of the polymeric surface. The surface modification is extended through the penetration into the surface of polymer by a magnitude of tens of microns and is analyzed utilizing the treatment conditions of UV involving intensity duration of treatment and wavelength. The poor adhesion of polymers is due to their decreased surface energy and thus, limits their applications. The adhesion or hydrophilicity of polymers can be enhanced by the oxidation process using UV–Ozone or UV [58, 59]. The oxidation of polymer with the breakage of polymeric chains into free radicals is caused by the irradiation by UV to react with the atmospheric ozone or oxygen and forms hydrophilic groups such as carbonyl or carboxyl. Time of irradiation, concentration of monomer, solvent, and photo initiator controlled the extent of the modification of the surface. Oxidation

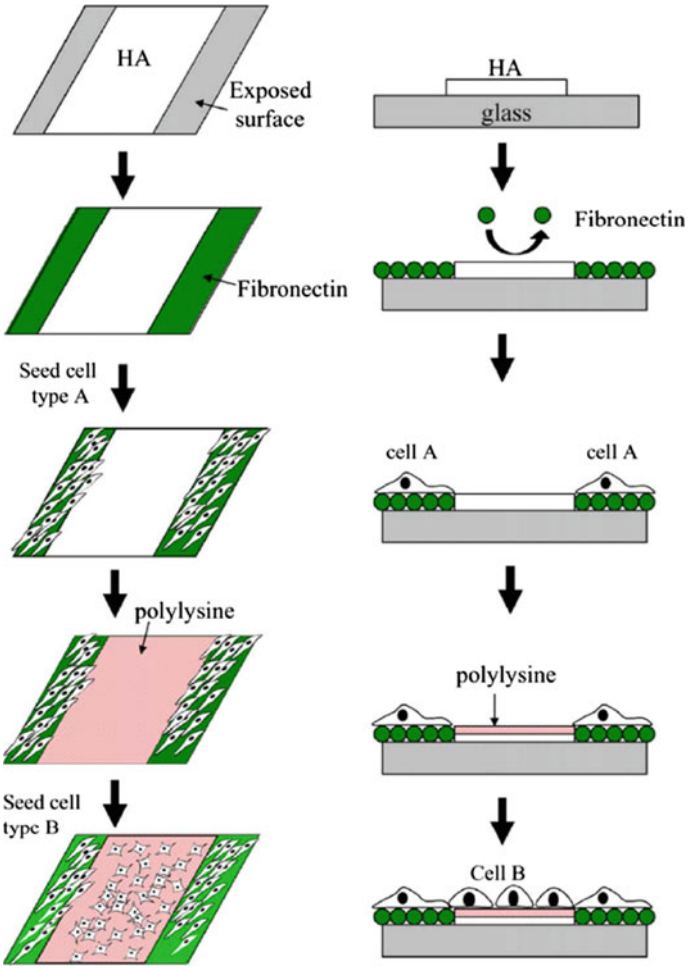

Fig. 7 Deposition of HA-PLL on solid substrate. Reproduced with permission from Ref. [57]; Copyright 2004 Elsevier

by UV also creates roughness at nanoscale on the surface having RMS (root mean square) value of 3–5 nm in addition to the formation of polar functional groups containing oxygen which also contributes to the increase in surface polarity and adhesion. For example, Gudko et al. explained the incorporation of nanoparticles prepared from cadmium sulfide (CdS) in the polymer polyvinyl alcohol (PVA) for enhancing the persistence to UV light. The defect formation was diminished due to the nanoparticle incorporation in the polymer [60] (Fig. 8).

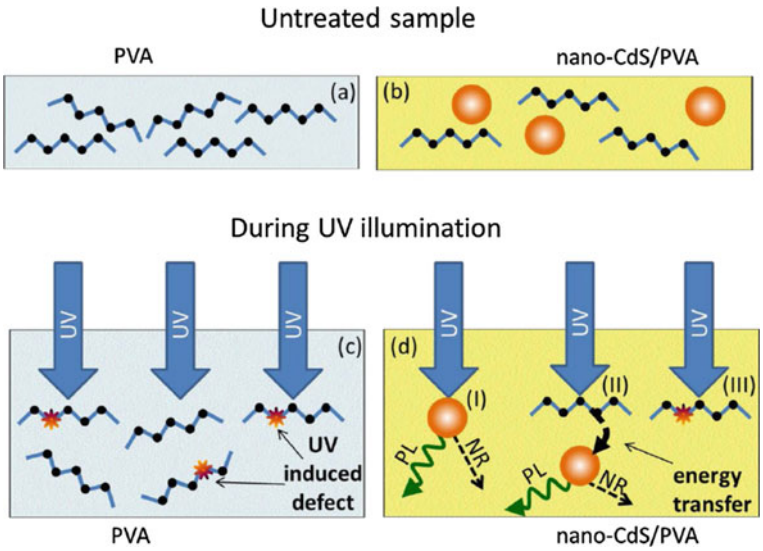

Fig. 8 **a, c** The schematic representation of control polymer sample and **b, d** nanocomposite of CdS/PVA in the process induced by UV. Reproduced with permission from Ref. [60] under a CC BY license

3 Applications

3.1 Targeted Drug Delivery

A variety of different materials are employed as carriers of drugs such as synthetic or natural polymers, surfactants, lipids, and dendrimers [61–64]. Among these, a natural polymer known as chitosan has gained enormous consideration due to their outstanding biological and physical properties. Due to the presence of various reactive functional groups, it has offered a pronounced opportunity for modification chemically to afford a varied range of derivatives like carboxyalkyl chitosan, N,N,N-trimethyl chitosan (quaternized in nature), sugar-bearing chitosan, thiolated chitosan, cyclodextrin-linked chitosan, bile acid-modified chitosan, etc. [65–68]. The derivatives of chitosan are fabricated to improve the properties specific to the chitosan native. The amphiphilicity is imparted in chitosan by the chemical modification of their surface to synthesize chitosan-based self-assembled nanoparticles for their potential applications in drug delivery. The nanoparticles contain a hydrophobic core acting as microcontatiner or reservoir for the different bioactive agents. Nanoparticles can be intravenously injected due to their small size for the application of drug delivery. The targeting moieties are conjugated to the surface of the nanoparticles loaded with the drug which improves the therapeutic efficiency of the drug. It has been extensively used as delivery system for the drugs such as low molecular

weight drugs, peptides, and genes. For example, the idea of polymer–drug conjugates for releasing small molecular hydrophobic drugs to the targeted site where the action is required [68]. The drug–polymer conjugates consist of a polymer which is soluble in water and is conjugated chemically through a biodegradable spacer to the drug. This biodegradable spacer can be present in the stream of blood stably and cleaved by degradation of enzyme or by hydrolysis at the site of target. In general, the drug-conjugated polymer particles whose surface was decorated with targeting moiety, can be selectively accumulated at the site of tumor to be followed by the delivery of drug due to the spacer cleavage (Fig. 9). Due to this concept, various conjugates of drug-polymer have recently been utilized in clinical trials at phase I/II level. One important example is N-(2-hydroxypropyl)methacrylamide (HPMA) drug conjugates based on copolymer like HPMA copolymer–doxorubicin conjugate (PK1) and a targeting moiety of HPMA copolymer–doxorubicin conjugate having galactosamine (PK2), employed for the primary or secondary liver cancer treatment.

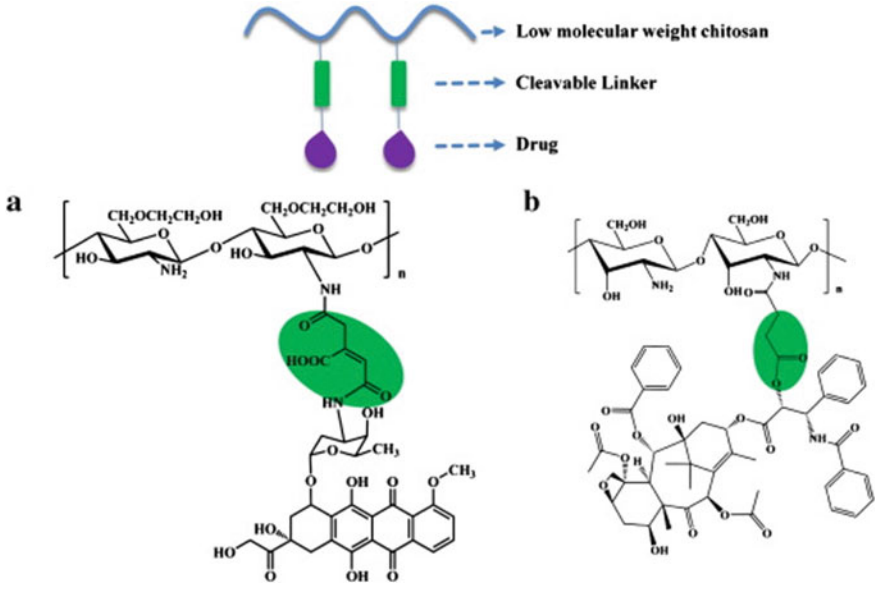

Fig. 9 Schematic representation of the conjugates of chitosan and drug having a cleavable linker. Chemical structure of **a** glycol chitosan–doxorubicin conjugate with the cis-aconityl linkage and **b** chitosan–paclitaxel conjugate with the succinate linkage. Reproduced with permission from Ref. [60]; Copyright 2010 Elsevier

3.2 Biomedical Implant

For different biomedical applications such as biosensing, antibacterial coatings and delivery of drugs, and modification of surface by polymeric brushes regardless of their geometry have been widely studied [69]. Most importantly, anti-infective polymer brushes tethered on biomedical implants are known to provide bacteria-free implant surface which generally serves as platform to proliferate bacteria causing infections when used inside the body. Therefore, polymer brushes are considered as the essential modifications in the applications of antibacterial coatings due to their good mechanical stability, thickness, roughness, and morphology. During their adhesion on the surface, these polymer brushes are utilized for the barrier in adhesion of bacteria or these coatings can kill the bacteria through the mechanism known as contact killing. For instance, biodegradable surfaces of polylactide (PLA) were covalently modified to immobilize polymers of three different types showing effective antibacterial property. Three different polymers, namely, poly(2-[(methacryloyloxy)ethyl]trimethylammonium chloride) (PMETA), poly(poly(ethylene glycol) methacrylate) (PPEGMA), and poly(2-hydroxyethyl methacrylate) (PHEMA) were grafted on the PLA surface via the technique known as surface-initiated atom transfer radical polymerization (ATRP). These brushes were tested against both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria. Verma et al. found that the PLA surface modified with PMETA exhibited the highest killing of bacteria. This work exhibited the creation of polymer brushes on the biodegradable PLA surface having excellent antibacterial property [70]. Dhingra et al. modified the biomaterials based on aliphatic polyester derived from tartaric acid through the growth of antibacterial (PMETA) polymer brushes and antifouling/antiadhesive (PPEGMA and PHEMA) polymer brushes using surface-initiated polymerization (specifically ATRP). The authors explained the process of synthesis for preparing the polyester based on tartaric acid in which the protected hydroxyl groups can be unmasked and conjugated to the initiating moiety of ATRP to grow the polymer brushes as mentioned above. The conditions used are mild to prevent the degradation of backbone of the biodegradable polymer. PMETA brushes contain cationic ammonium groups that exhibited the highest antibacterial property. The authors have further expanded the work by blending the polyester based on tartaric acid with PLA to form the 3D scaffold fabricated from 3D printing. These scaffolds were used to grow PMETA polymer brushes for evaluating the antibacterial study against Gram-negative and Gram-positive bacteria and the test of cytocompatibility against the mammalian osteoblast cells (Fig. 10). The authors reported a balanced antibacterial and cytocompatibility by the growth of PMETA brushes onto the surface. Therefore, a cytocompatible coating which is anti-infective, stable, and non-leaching can be used to address the infections originated from biomedical implants [71].

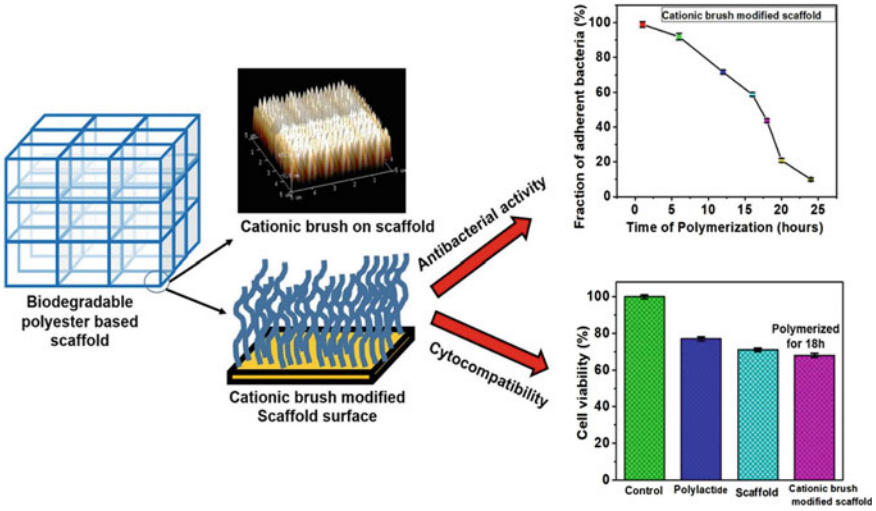

Fig. 10 3D scaffold of aliphatic polyester based on tartaric acid and their antibacterial and cell compatibility study. Reproduced with permission from Ref. [63]; Copyright 2021 Elsevier

3.3 Cell Adhesion

Extracellular matrix (ECM) is a natural 3D structure that surrounds the cell when present in vivo. To maximize the environmental simulation in vivo around the cells, vast development in 3D scaffolds for meeting biological needs has been made. Behavior of cells is affected by these developed 3D biological scaffolds offering the most suitable tool for providing the real environment for growing cells. In this regard, Dhingra et al. developed a brush system consisting of a copolymer of poly(3-dimethyl-(methacryloyloxyethyl) ammonium propane sulfonate) (PDMAPS) and poly((oligo ethylene glycol) methyl ether methacrylate) (PPEGMA) grown on the aliphatic polyester as mentioned above. In a similar manner, a blend of PLA and polyester was used to prepare 3D scaffold to attach the mixed copolymer brush on its surface through SIATRP. Authors found 100% suppression of bacteria on the mixed brush system as mentioned above. In addition, 100% cytocompatibility was also found for mixed brush system comprising of PDMAPS and PPEGMA. These results show a promising and innovative mixed brush coating revealing the high potential in a durable implant used inside the body being anti-infective with preservation of healthy cells [72]. Further, treatment by hydrolysis technique is simple that it can be utilized for increasing the roughness of the surface in addition to the hydrophilicity through the NaOH treatment. This method was used by Yuan et al. for functionalizing the porous microspheres of PLGA using PLL (poly-L-lysine) shown in Fig. 11. Briefly, the PLGA microspheres were hydrolyzed to form PLGA-OH to soak in PLL solution kept overnight. Treatment by hydrolysis results in the creation of a homogeneous and interconnected porous structure due to the dissolution of a thin polymer

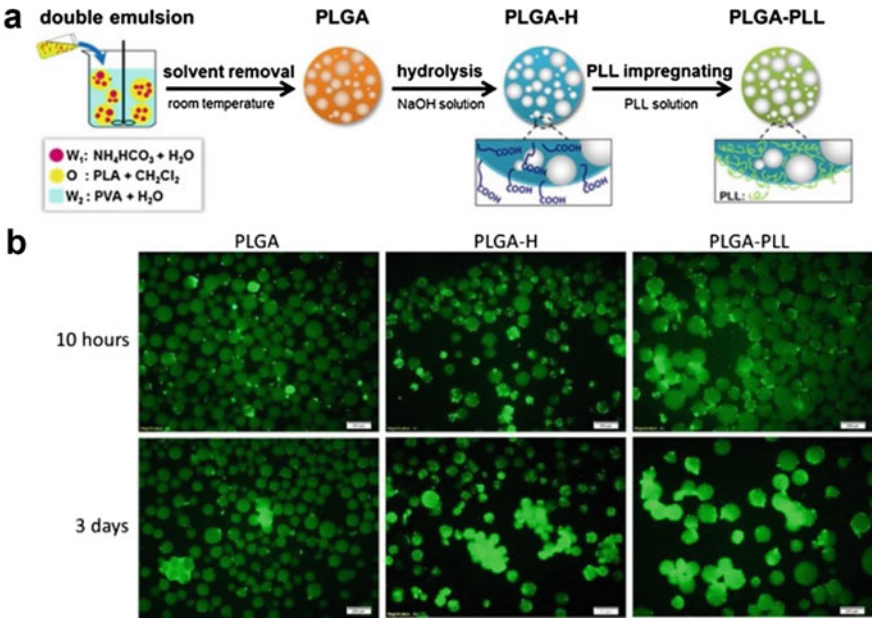

Fig. 11 **a** An illustration for the process involved in the formation of microspheres of PLL modified porous PLGA. **b** Fluorescence images of microspheres stained with FDA after culturing by MG63 at different time. The scale bar is 200 μm. Reproduced with permission from Ref. [65]; Copyright 2018 Elsevier

around the pores. Finally, the authors found that the surface modification via the PLL treatment promoted the initial attachment of cell and also found the improvement in the interactions of cell matrix [73].

3.4 Interfacial Catalysis

Biodegradable polymers can be converted into solid particles whose surfaces are modified to use them as an emulsion stabilizer. The anisotropically modified solid particles having polymer brushes in hemisphere which are hydrophilic in nature can employ a balance between hydrophilic and hydrophobic parts to use them as an ideal surfactant, commonly known as pickering emulsion stabilizer [25]. Zoppe et al. proposed an interesting work based on stabilization by pickering emulsion stabilizers using polymer brush-modified anisotropic particles (PBMAP) [74]. The authors have shown a system based on oil-in-water with heptane and water, respectively. They utilized the thermosensitive polymer poly (NIPAM) to modify the surface of anisotropic nanocrystals of cellulose for emulsion stabilization to form poly(NIPAM)-g-CNCs. This system having brush-modified anisotropic particles was

able to stabilize the emulsion in oil–water for up to 4 months as compared to unmodified naked anisotropic solid particles of cellulose nanocrystals (CNC). Poly(NIPAM) plays the role of reducing the interfacial tension among oil and water due to its hydrophilic nature after the emulsification at the oil–water interface. Apart from this, Ifra et al. experimented to form PLA based microparticles which are spherical and anisotropic Janus type. These particles were fabricated through a technique known as electrohydrodynamic co-jetting where two compartments consisting of macroinitiator containing polymers blended with PLA were co-jetted in side by side manner so that macroinitiator (used to grow polymer brushes later) is present on one side of the particle. The surface of these microparticles was utilized to graft pH-responsive poly(DMAEMA) polymer brushes on one compartment selectively through SIATRP. This modification of the surface of these microparticles imparted the amphiphilicity in them. Further, this system was used and applied in stabilizing emulsion comprised of octanol/water to form a pickering emulsion (Fig. 12). The authors found that the amphiphilic Janus particles as a pickering emulsion stabilizer by tuning the pH of the brush-modified particles was stable for more than 4 months [75]. They are considered to contribute towards the green chemistry and sustainability with the promise to work as an interfacial catalyst in various chemical reactions and cleaning of contaminated water by degrading the waste via iron nanoparticles embedded in Janus particles. Due to the amphiphilic nature, the particles were located at oil/water interface to facilitate interfacial catalysis for remediating water.

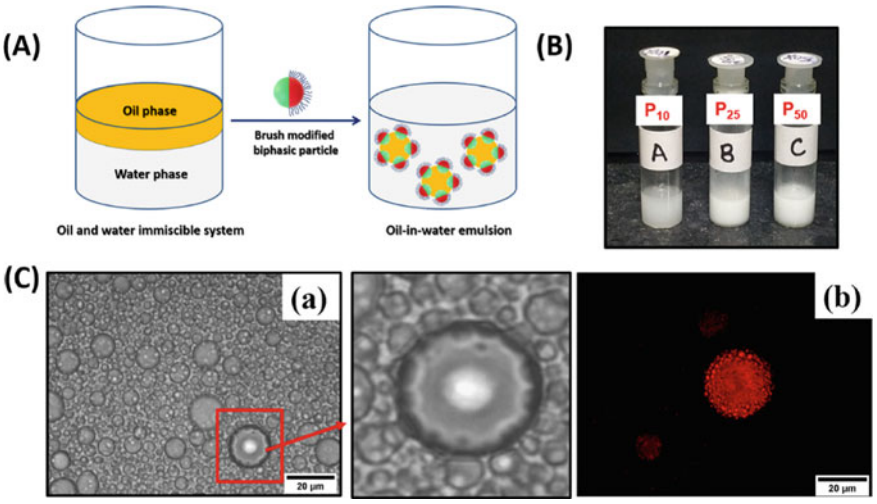

Fig. 12 **A** Scheme showing the pickering emulsion being stabilized by brush-modified Janus particles. **B** Digital images of pickering emulsion stabilized by Janus microparticles modified with brush. **C (a)** Brightfield micrograph of pickering emulsion stabilized by Janus particles modified with brush. **(b)** Fluorescence micrograph of droplet of pickering emulsion stabilized by dye-loaded Janus particles and modified by brushes. Reproduced with permission from Ref. [67]; Copyright 2021 ACS

4 Conclusion

In recent years, a novelty in research related to biomedical field has aimed at developing new methods for modifying the surface of biodegradable polymers to achieve stable, infection-free, biomaterials. These modified biomaterials are widely applied in the area of targeted drug delivery, tissue engineering, wound healing, and infection-resistant coating. Therefore, the novel surface modification methods for biodegradable polymers have emerged with developed traditional technologies, thus facilitating the manufacturing of durable functional surfaces of polymers. In this chapter, the most common methods for polymer surface modification (physical, chemical, SAMs, plasma, corona, UV) have been described with a focus on the methods to alter the surface morphology and their properties in addition to their use in specific areas for biomedical field. An attempt has been made to compare the surface modification methods with the prospective area of applications. However, alternative surface treatment routes for the modification of biomaterials are also emerging to achieve similar surface properties to meet the needs of future for biomedical field. A wide range of biodegradable polymers with their unexplored functionalities and properties are being investigated to improve their surface-property relationship for broadening their use in different applications in the real world.

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Chapter 4
Carbohydrate-Based Biodegradable Polymers for Biomedical Applications

Aiswarya Thattaru Thodikayil, Chandrani Sarkar, and Sampa Saha

1 Introduction

Carbohydrates are the third major class of biopolymers derived from various natural sources like plants, algae, animals, and microbes. They are commonly known as "hydrates of carbon" having an empirical formula of $C_nH_{2n}O_n$, n representing carbon atoms combined with water [1]. Carbohydrates are widely classified as mono, di, and polysaccharides based on the saccharide repeating units of the backbone chain. The term saccharide was derived from the Greek *sakcharon* (sugar). The saccharide units are connected through covalently linked O-glycosidic bonds.

Monosaccharides are termed as simple sugars, composed of single sugar unit that cannot be broken into smaller units by hydrolysis. Galactose, mannose, glucose, and fructose belong to this category. Monosaccharides when combined through the *glycosidic bonds* formed from dehydration reactions result in larger carbohydrates namely *disaccharides* and polysaccharides (Table 1) [2]. *Disaccharides* are made up of two monosaccharide units chemically linked to each other through glycosidic bonds. Sucrose and lactose are some of the most common examples of disaccharides. Hydrolysis of disaccharides with acids/enzymes results in two similar or dissimilar monosaccharide molecules. For example, hydrolysis of sucrose gives glucose and fructose, whereas maltose gives two molecules of glucose. When more than 20 units of monosaccharides combine, long polysaccharide chains are formed. These chains can be branched (cellulose) or unbranched (chitin). Polysaccharides are majorly obtained from algae (alginate), microbes (dextran), plant (cellulose), and animal (chitosan) [3].

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Table 1 Properties and applications of various carbohydrates

Carbohydrate	Repeating units	Properties	Applications
Polysaccharides			
Chitosan	β-1-4 glycosidic bonds link D-glucosamine and N-acetyl-D-glucosamine units	• Enhanced stability • Solubility in acidic aqueous • Hemostatic and mucoadhesive properties	Wound [4–6], drug delivery [7–9]
Cellulose	β-1,4-glucosidic bond link glucose units	Large specific surface area, excellent mechanical stability, and tunable chemical properties	Artificial [10, 11], drug delivery [12, 13], Bioimaging [14] and biosensors [15, 16], Tissue engineering [17, 18]
Starch	Amylose and amylopectin	Total degradability without toxic residues, thermoplastic behavior	Protein and drug delivery [19, 20]
Dextran	α-linked d-glucopyranosyl	Great water solubility	Drug [21, 22]
Hyaluronic acid	Glucosamine linked D-glucuronic acid and N-acetyl-D-through β-1,4 and β-1,3 glycosidic bonds	• Higher transfection efficiency and reduced cytotoxicity • Interact with CD44 tumor receptor	Drug delivery [23, 24], wound healing [25, 26], tissue engineering [27, 28]
Monosaccharides			
D-Glucose		Increased binding affinity	Targeted drug delivery [29]
D-Mannose		Target C-type lectin receptors present on alveolar macrophages	Targeted drug delivery [30, 31], Bioimaging [32]
Disaccharides			
Sucrose		Can act as excipients with excellent emulsification and solubilization behavior	Dermal drug delivery [33, 34]
Lactose		Enhance flowability of drugs	Used as a carrier for dry powder inhalers (DPIs) [35, 36]

Along with proteins and nucleotides, carbohydrates are crucial for the distinct biological functions. They play a pivotal role in energy storage, adhesion, stimuli responsiveness, molecular recognition, and cell–cell communication/response [37, 38]. In addition to this, they are crucial for different physiological and biological activities like cell proliferation, cell growth, and immune regulation activities.

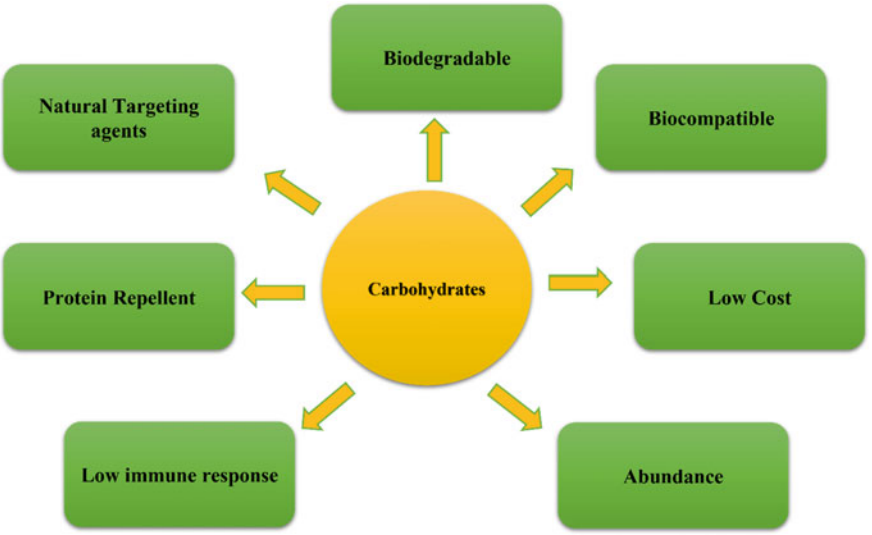

Fig. 1 Features of carbohydrates

Their abundance, low cost, solubility, stability, biodegradability, and biocompatibility promote them as a powerful and feasible biomaterial for a wide spectrum of biomedical applications like as delivery of therapeutic entities, imaging, biosensing, etc. (Fig. 1) [39]. Their potential to carry out multiple biological and physiological activities makes them an exceptional choice for various biomaterials, ranging from drug carriers to implants.

Often, they are used as an alternative solution to overcome poor biological activity of synthetic polymers. Monosaccharides and disaccharides are extensively functionalized or immobilized over the surface of organic/inorganic biomaterials, to make them biologically active. However, one of the main reasons to use polysaccharides as matrix for biomaterials is their in vivo degradation behaviur. They undergo timely and controlled degradation in biological conditions releasing nontoxic, harmless products that can be easily metabolized and absorbed in the human body. Predominantly, human body absorbs polysaccharides as nutrients, coverts them to their smaller saccharide units, and eliminates through metabolic pathways [40].

2 Mono- and Disaccharide Based Biomaterials

Mono- and disaccharides are being modified extensively over the years to give a wide range of glycoderivatives and fabricate different kinds of morphologies such as vesicles, fiber, micelle, etc. Difficulty in monitoring the biological activity as well large

chain length of mono/disaccharides prompted the development of carbohydrate technologies and fabrication of diverse saccharide-based morphologies (particle, tube, fiber, etc.) [41]. These morphologies enhance the detection limit of saccharides by increasing the multiple valence sites. Carbohydrates are crucial for diverse biological events and life processes; however, their interaction with proteins plays a key role in these activities. Carbohydrate-binding proteins (Lectins) on the cell surface initiate and mediate certain biological responses by specifically interacting and binding with their complementary carbohydrate structures. For example, monosaccharides like D-mannose, D-galactose, shows high affinity towards lectins.

Among various morphologies, nanoparticles are dominating various biomedical disciplines owing to their stability, effectiveness, and fabrication methods. Besides, carbohydrate-based nanoparticles are comparable in size with most biological molecules and capable of mimicking sugar molecules, hence can be utilized as a probe for analyzing glycan–glycan/glycan–protein interactions. Carbohydrate-based nanoparticles are widely used as biomarkers and carrier molecules of bioactive compounds antimicrobials, anticancer drugs [40].

3 Polysaccharide-Based Biomaterials

The building block of polysaccharides determines their chemical structure. Based on the nature of monosaccharide unit, they form linear or branched structures. Polysaccharides possess enhanced mechanical properties and different hydrophilic derivable groups such as hydroxyl, carboxyl, and amino groups that are amenable to physical and chemical modifications [42]. They can be easily tailored for the desired applications [43]. Polysaccharides are further classified based on their charge, examples are chitosan (positive charge) and alginate (negative charge). These charges help in fabricating polysaccharide-based nanoparticles via methods like covalent/ionic crosslinking, polyelectrolyte complexion, as well as self-assembly. Moreover, the availability of hydroxyl groups promotes non-covalent bioadhesion with several biological tissues (epithelia, mucous) ensuring effective drug targeting. A wide range of biomaterials like nanocarriers, membranes hydrogels/microgel/nanogels, scaffolds, nanocomposites, etc., are being derived from polysaccharides for various biomedical applications. For example, polysaccharides derived from algae have been significantly used for several biomedical applications like wound care, tissue engineering, and drug delivery. In addition to this, the potential of polysaccharides-based biomaterials to store, preserve the conformation and bioactivity of biomolecules ensures their candidature as carrier for several bioactive molecules, especially for proteins that require its activity and conformation to be maintained till final delivery. Polysaccharides can provide adequate mechanical properties as a substrate/matrix, thus can be used as an alternative to many synthetic polymers to overcome their inadequate biological performance.

4 Carbohydrate-Based Nanoparticles

As discussed earlier, carbohydrates are predominant cellular molecules that help in multiple biological processes. Their hydrophilicity, cell specificity, large-scale production and ease of modifying the binding affinity make them an ideal choice as carriers. Carbohydrate-based nanoparticles have been effectively used to deliver various therapeutics. It has been reported that carbohydrate polymers can boost up the brain's potentiality in absorbing drugs and can cross the blood–brain barrier, a crucial characteristic to target brain diseases [44]. Nanoparticles are one of the potential drug delivery tools by virtue of their ability to deliver drug at the targeted site, improved drug uptake, reduced toxicity, and stability, and to control drug release properties at various physicochemical conditions and metabolic responses like pH, temperature, and ionic strength. For the effective drug delivery, two methods have been adopted, namely passive and active targeting. Delivering of drugs to macrophages/organ/cells through specific targeting ligands (active targeting) or based on the size of drug carrier or target organ/cell and their physicochemical properties (passive targeting). Administration of free forms of drug to cure macrophage-mediated diseases results in side effects due to their low bioavailability at the desired site and availability at undesired sites. An ideal drug carrier will delay the drug clearance process; reduce drug loss and dose frequency, especially for the one having a short life and narrow therapeutic window.

Carbohydrate-based nanoparticles fall broadly into two categories, oligo/mono/di/polysaccharides used as a matrix for nanoparticle fabrication and surface functionalization of organic/inorganic nanoparticles with various carbohydrate moieties. These nanoparticles have gained enormous attention by virtue of their carbohydrate–carbohydrate/carbohydrate–protein interactions, and ability to imitate sugar molecules on the cell surface as they fall under similar size range of different biomolecules.

4.1 Glycopolymer-Based Nanoparticles

Nanoparticles with carbohydrate moieties on their surface are highly efficient bioactive molecules, whereas pendent carbohydrate moieties from the synthetic glycopolymers act as a multivalent ligand that can interact with the lectins, similar to natural glycoproteins. Self-assembly is one of the main strategies used for the fabrication of glycopolymer-based nanoparticles. This technique relies on the ability of amphiphilic copolymers to self-assemble into distinct morphologies with a size ranging from 10 to 100 nm. Kataoka and his co-workers had synthesized galactose and glucose bearing Poly(ethylene glycol)–Poly(D,L-lactide) (PEG-PLA) micelle via self-assembly. PEG-PLA block copolymers having protected sugar groups at PEG end chains were synthesized via ring-opening polymerization of ethylene oxide and D,L-lactide using a metalated protected sugar (initiator). Further, the deprotection of sugar group was done at room temperature using trifluoroacetic acid to remove

the protective groups from the sugar moiety. Preparation of micelle of diameter less than 40 nm was done by dialyzing a solution of sugar-bearing block copolymer in N,N-dimethylacetamide against water. Binding efficiency of these micelles having sugar groups on the exterior to Ricinus communis agglutinin (RCA-1)lectin, that can recognize β-D-galactose residue proved that this micelle is apt for drug delivery applications [45]. Similarly, a series of mixed shell glycomicelles were prepared by Chen et al. using galactose and/or mannose-functionalized aliphatic polyesters. Here, the first step involved the synthesis of block (PCL-*b*-PAVL) and random (PCL-*co*-PAVL) copolymers. Sequential ring-opening polymerization of α-propargyl-δ-valerolactone (AVL) and ε-caprolactone (ε-CL) using stannous trifluoromethanesulfonate (catalyst) and ethanol(initiator)yielded block copolymer whereas, simultaneous addition of polymers obtained random copolymer formation. Furthermore, these alkyne-containing copolymers undergo click reaction with azido ethyl-functionalized galactose and/or mannose groups. PCL-*b*-PAVL (BP) react with 2′-azidoethyl-*O*-D-mannopyranoside/2′-azidoethyl-*O*-D-galacopyranoside to form P-BP-Man and P-BP-Gal (block glycopolymers). Also, the simultaneous reaction of azido functionalized mannoside and galactoside with copolymers obtained P-BP-MG, where Man and Gal pendants are distributed randomly along the sugar block. Likewise, the click reaction between random glycopolymer PCL-*co*-PAVL and azido sugars yielded P-CP-Man, P-CP-Gal, and P-CP-MG. Eight different glycol micelles having different architectures were prepared via self-assembly of glycopolymer solution in dimethyl sulfoxide (DMSO) upon the addition of water. Self-assembly of glycoblock (hydrophilic) and polyester backbone (hydrophobic)of block copolymer formed micelle having a polyester core and glycoblock shell. Single (BP-Man and BP-Gal) and blended (BP-M/G) sugar micelles were prepared from P-BP-Man and P-BP-Gal glycopolyesters. Random glycopolymers, P-CP-Man and P-CP-Gal, were used in same manner to yield glycomicelles, CP-Man and CP-Gal. Glycomicelle CP-M/G was made by blending these two random glycopolymers at a 7:10 Man/Gal unit ratio (Fig. 2). Further investigation confirmed that the mixed shell (M/G) architecture showed higher lectin binding and cell uptake than single sugar component (MG), this can be attributed to the higher sugar receptor interaction of M/G in the contact region compared to MG due to the phase separation resulting from the simultaneous interactions of two sugar units with the receptors on the cell surface [46].

4.2 Polysaccharide-Based Nanoparticles

Polysaccharides have been contributing immensely to various biomedical applications due to their stability, hydrophilicity, ease of functionalization, and adhesivity. It's a challenge to copy these naturally occurring carbohydrates in laboratory, so they are often modified chemically and tailored to achieve desirable properties. The presence of functional groups on their backbone provides facile chemical modification for the development of nanoparticles [47]. Also, hydrophilic groups such as

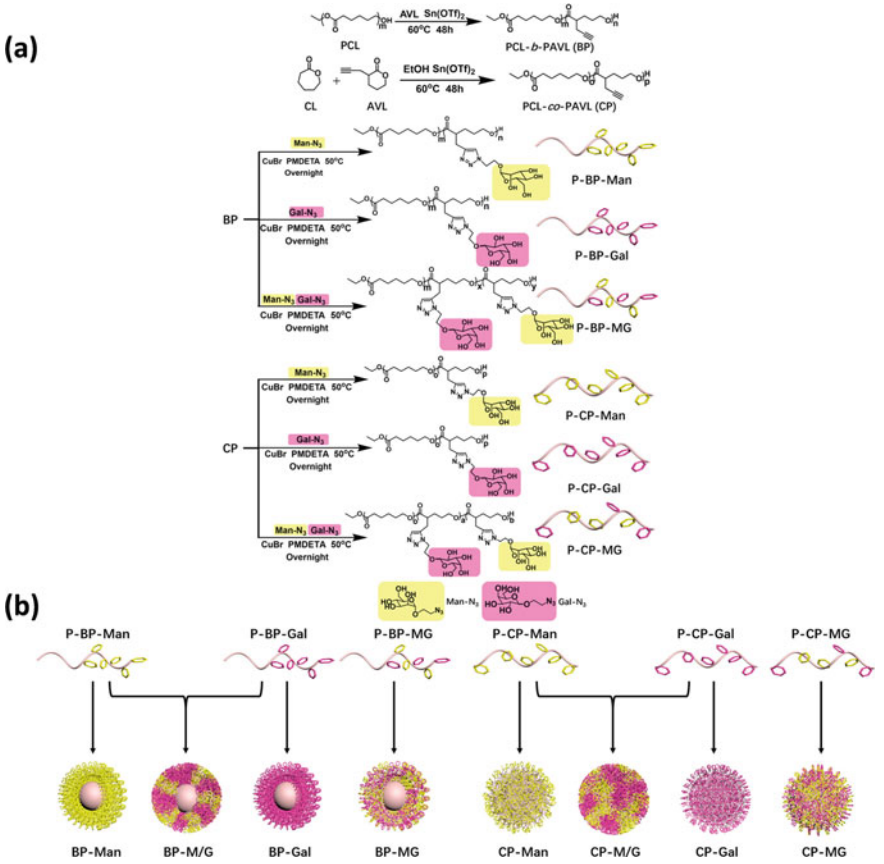

Fig. 2 **a** Schematic representation of the synthesis of glycopolyesters, **b** self-assembly of glyconanoparticles [Reproduced with permission from Ref. [42] under a CC BY license]

hydroxyl, amino, and carboxyl groups enhance their bioadhesion to various biological tissues through noncovalent interactions. Their intrinsic ability to recognize specific cells promotes their application for targeted-drug applications via receptor-mediated endocytosis. Techniques like ionic and covalent crosslinking, nanoprecipitation, gelation of emulsion droplets, polyelectrolyte complexation self-assembling, etc., or combination between them are majorly used to fabricate polysaccharide-based nanoparticles (Fig. 3) [48].

Covalent Crosslinking

Crosslinking phenomenon involves covalent binding between two macromolecular chains forming a three-dimensional network connecting the macromolecular chains. The covalent crosslinking is mainly introduced between the polysaccharide chains

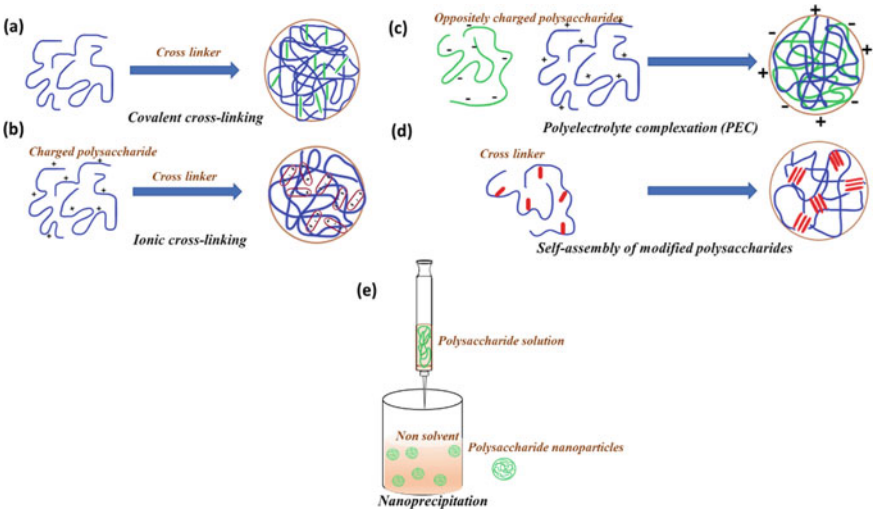

Fig. 3 Illustration of fabrication of polysaccharide-based nanoparticles via **a** Covalent crosslinking, **b** Ionic crosslinking, **c** Polyelectrolyte complexation, **d** Self-assembly of polysaccharides, **e** Nanoprecipitation method. [Reproduced with permission from Ref. [49]; Copyright 2018 Elsevier]

through a proper crosslinker (Fig. 3a). Molecules having at least two reactive functional groups can act as covalent crosslinkers, e.g., dialdehydes (glutaraldehyde), and natural di- and tricarboxylic acids. Polysaccharide-based structures generated through covalently crosslinking method form a permanent stable network structure, these networks can absorb and permit biomolecule adsorption even if the pH conditions have been changed. Depending on the crosslinker used during reaction, the properties of these networks vary. They can be responsive to various stimuli like pH, temperature, and light. These characteristics make them attractive for macrophage-promoted drug release where intracellular pH is similar to the bloodstream. Nanoparticle systems based on linear polysaccharide, chitosan, are mainly prepared using covalent crosslinking method using agents such as glutaraldehyde, dopamine, and acids such as citric acid, malic acid, etc. [50]. Likewise, hyaluronic acid (HA)-based nanoparticles are prepared by the covalent crosslinking of HA via carbodiimide chemistry for targeting macrophages. Pandit et al. designed nanohybrid nanoparticle using polyethyleneimine–hyaluronic acid (bPEI-HA) copolymer using carbodiimide chemistry. Nanoparticles were prepared by conjugating HA and branched polyethyleneimine (bPEI) through carbodiimide chemistry, where the copolymer was capped by mannose at the terminal chains [51].

Ionic Crosslinking

Ionic crosslinking is a nontoxic, organic solvent-free method where the nanoparticles are entirely prepared in water at mild conditions. Nanoparticles are obtained

from the reaction between a charged polysaccharide chain and an oppositely charged crosslinker (Fig. 3b) [52]. Commonly used crosslinkers are salts of calcium, potassium, and barium (cationic) and sodium tripolyphosphate (TPP), magnesium sulfate, and sodium sulfate (anionic).To prepare chitosan nanoparticles TPP is commonly used as a crosslinker. Addition of TPP to aqueous solution chitosan in acetic acid, results in the formation of inter- and intra-crosslinking between cationic amino groups of chitosan and anionic phosphate groups of TPP [53]. Among anionic polysaccharides, alginate gets crosslinked with small cations such as bivalent calcium, zinc, or barium ions to form nanoparticles [54].

Polyelectrolyte Complexation and Self-assembling

This technique involves the construction of polyelectrolyte complex using intermolecular electrostatic interactions between oppositely charged polymers. Formation of a spontaneous interpolymeric aggregation or nano/micro-sized polyelectrolyte complex (PEC) occurs due to noncovalent electrostatic interactions between different polycations and polyanions chains when mixed in an aqueous solution (Fig. 3c) [55]. Factors such as intrinsic variables (molecular weight of polymers, chemical nature, and concentration of polymers, mixing ratio and fraction charge of polymer), extrinsic variables (ionic strength and distribution, temperature, pH), and process parameters (mixing speed, volume, order of addition) have a significant role in the preparation of nanoparticles through this method. James et al. prepared self-assembled polyelectrolyte complex (PEC) nanoparticles from sodium alginate (anionic) and ethylenediamine-modified gelatin (cationic). Addition of aqueous solution of anionic sodium alginate to cationic gelatin under vigorous vortexing at room temperature formed nanoparticles. This hybrid PEC nanoparticle was utilized for the delivery of curcumin to carcinoma cells [56]. Self-assembled micelles/vesicles can also be generated from amphiphilic polymers obtained by grafting hydrophobic fragments onto hydrophilic polymers or adding hydrophobic molecules onto the hydroxycarboxylic or amino groups of the polysaccharide backbone (Fig. 3d) [57]. Intra- or/and inter-molecular interactions between segments results in the formation of micelles or vesicles. For example, Sun and his co-workers synthesized anionic poly(ethylene glycol) (PEG)-carboxymethyl chitosan (CMCS) and calcium phosphate hybrid nanoparticles to deliver siRNA using pH-sensitive PEG grafted CMCS [58].

Nanoprecipitation

This method is also called solvent displacement or interfacial deposition, solvent-shifting process, or ouzo effect. For this phenomenon to occur, two miscible phases in aqueous and organic/oil phases are needed. The process mainly involves dissolution of hydrophobic solutes in water-miscible solvents (acetone, tetrahydrofuran) followed by the addition of this mixture to an excess of anti-solvent (water, buffer

solutions). This generates droplets or particles in a stable dispersion or emulsion (Fig. 3e). Excess solvent can be removed by evaporation, dialysis, or by lyophilization. Monal et al. prepared chitosan nanoparticles through nanoprecipitation method by adding polyelectrolyte *N*-(methylsulfonic acid) chitosan dissolved in water and chitosan dissolved in acetic acid to methanol (nonsolvent diffusing phase). Water-insoluble chitosan was converted to water-soluble polyelectrolyte *N*-(methylsulfonic acid) chitosan when reacted with sodium formaldehyde bisulfite. It was observed that upon decreasing polymer concentration and increasing nonsolvent to solvent ratio, particle size decreased [59]. Kaewprapan and his co-workers investigated the dependence of polymer concentration on the nanoparticle size. Dextran fatty ester was synthesized using lipase catalyzed grafting of aliphatic hydrocarbon chains onto dextran. Nanoparticles were obtained by adding different concentrations of modified dextran having various degrees of substitution to aqueous solution under vigorous magnetic stirring. It was observed that higher polymer concentration in organic phase improves the collision and aggregation probability, thus reducing the particle size [60].

5 Carbohydrate-Derived Hydrogels and Microgels

Hydrogels are three-dimensional crosslinked network structures capable of absorbing a large amount of water as well as biological fluids. They are prepared by self-assembly of polar monomer units and macromolecular polymers through covalent, non-covalent interactions and/or by crosslinking between macromolecular chains. Under physiological conditions, they are insoluble in water; however, they can expand in aqueous or biological fluids. The swelling and absorption behavior of the hydrogel can be attributed to the availability of a large number of hydrophilic groups like carboxyl, hydroxyl, amino, etc., in their backbone that can form covalent/noncovalent bonds. Carbohydrate-based hydrogels are highly in demand by virtue of their intrinsic biodegradability, biocompatibility, good mechanical properties, adhesion, and abundance in nature. These hydrogels are engineered to meet the desired applications, majorly to encapsulate diverse therapeutic molecules like proteins, genes, drugs, etc., prevent degradation of encapsulated biomolecules, wound management, and tissue engineering. Polysaccharides like alginate, cellulose, and chitosan are majorly utilized for preparing hydrogels. These hydrogels can promote cell division, cell growth, and healing. Besides, they are widely explored for tissue engineering and drug carrier as they can mimic in vitro tissues and control the drug release pattern. Hydrogels encapsulated with various bioactive molecules, deliver them in a sustained manner and can maintain their local concentration for a prolonged period through diffusion and expansion processes.

5.1 Synthesis of Carbohydrate-Based Hydrogel

Hydrogels are broadly classified into physically crosslinked and chemically crosslinked systems. Physical crosslinking involves noncovalent interactions like hydrogen bonding, ionic interactions, hydrophilic–hydrophobic interactions, or multivalent ion-supported ionic crosslinking. Multivalent ion-supported crosslinking works on the principle of gelation of polyelectrolyte solution upon adding oppositely charged multivalent ions or charged structures (micro/nanowires, tubes, and particles). Physically crosslinked hydrogels can encapsulate bioactive molecules by weak interactions and cleavable bonds. For example, anionic alginates can combine with divalent cations (Cd^{2+}, Ni^{2+}, Zn^{2+}, and Ca^{2+}) through coordination and electrostatic interactions. Transition metals bind with carboxyl groups of alginate with unidentate binding, but cations of alkaline earth groups form ionic bonds with alginates [61].

Chemically crosslinked hydrogels are formed by covalently binding multifunctional molecules through strong irreversible linkages. Crosslinking agents such as glutaraldehyde, epichlorohydrin, tripolyphosphate, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) are used for chemical crosslinking. Polysaccharides are modified by grafting reactive functional groups in their chains to take part in crosslinking. Incorporation of reactive groups like thiols, alkene, and acrylates assists easy functionalization of polysaccharides because of the availability of hydroxyl, amine, and carboxyl groups in their chains.

6 Carbohydrate-Based Nanocomposite

Polysaccharides like chitin, chitosan, cellulose, starch, hyaluronic acid, heparin, alginate, dextran, cyclodextrin, etc., are considered as green alternatives to various synthetic polymers. A wide range of polysaccharides are being utilized as matrix for bionanocomposites due to hydrophilicity, molecular weight range, nontoxicity, non-immunogenicity, and can imitate the heterogenicity of native extracellular matrix. They are generally used in combination with nanofiller, nanoparticles, and nanosheets to improve their properties. Polysaccharide-based nanocomposites incorporated with bionanomaterials like silver, gold, or titanium oxide as nanofibers/nanowires or nanocrystals are being utilized as scaffolds having higher specific area and Young's modulus. Polysaccharides with micro- and nanoscale fibrous structures are mainly developed using gelation, dry, wet, melt, or electrospinning processes. These bionanocomposites are employed as bio platforms by a two-stage approach. Initially, blending of nanomaterials in polysaccharides (as matrix) with proper distribution and dispersion, followed by electrospinning of this nanocomposite to fabricate desired shape (Fig. 4). Electrospinning process has been used for the fabrication process as it can imitate the fibrous structure of natural ECM and is one of the convenient cost-effective techniques.

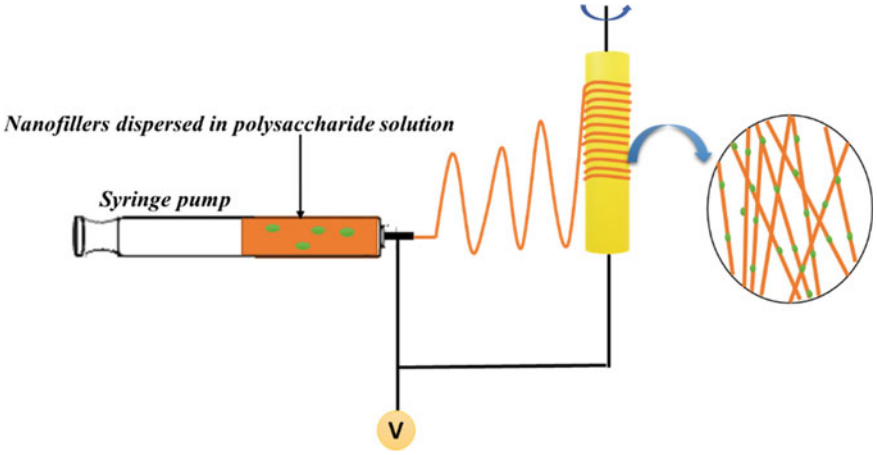

Fig. 4 Fabrication of polysaccharide-based bionanocomposite via electrospinning technique

7 Applications

7.1 Theranostics and Bioimaging

Theranostics includes treatment methods that involve simultaneous or sequential diagnostic imaging and molecular radiotherapy to cure diseases like cancer. The main aim is to target the receptors present in the cancerous cells followed by radiation treatment targeting these receptors. An ideal material to be chosen as a theranostic material should be capable of effectively delivering therapeutic components as well as imaging agents to targeted site with minimal side effects.

Among various biomaterials, carbohydrates are considered as the apt choice due to their stability, prolonged half-life, low toxicity, target specificity, and stimuli response. Mansur and his coworkers had developed a green, fluorescent polysaccharide—$AgInS_2$ quantum dots nanobioconjugates of 3.3–3.7 nm for in vitro bioimaging of brain cancer cells. The system was prepared by chemically modifying carboxymethylcellulose with poly-L-arginine (CMCelPolyArg) and using it as capping ligands for the synthesis of fluorescent $AgInS_2$ quantum dots in an aqueous colloidal media. Cytotoxicity and cell internalization of this core–shell nanostructures are composed of semiconductor core stabilized by CMCelPolyArg shell. This system showed no cytotoxicity and was internalized by cell lines HEK 293 T and U-87 MG thus can be a good candidate for bioimaging and biolabeling [62]. Tan et al. fabricated a core–shell nanomaterial using chitosan encapsulated photoluminescent Ag_2S QDs entrapped with anticancer drug doxorubicin (DX) for both drug release and NIR imaging purpose. The synthesized oleic acid-capped Ag_2S QDs were reacted with *N*-hydroxysuccinimide, followed by conjugating chitosan at its amino

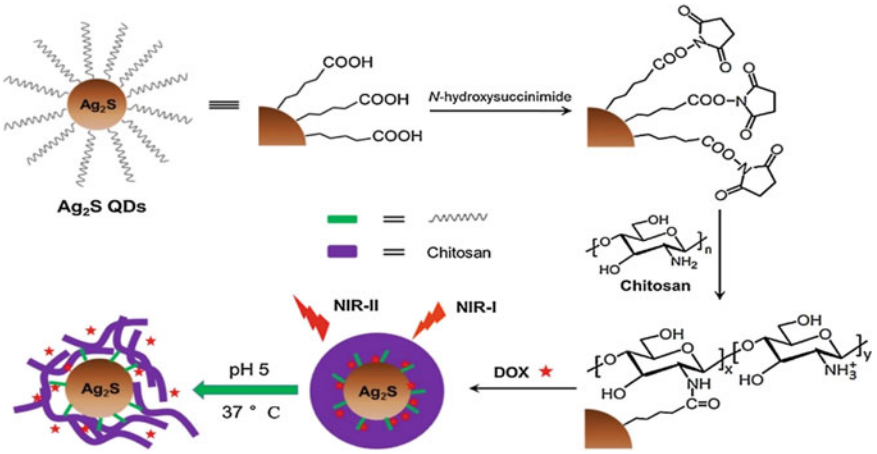

Fig. 5 Schematic synthesis and mechanism of Ag_2S(DX)@CS nanospheres [Reproduced with permission from Ref. [59]; Copyright 2018 Elsevier]

sites. The oleoyl groups are hydrophobic and are susceptible to form local aggregates. These hydrophobic aggregates efficiently entrap doxorubicin via hydrophobic interaction generating nanospheres. The pH-dependent oleoyl-CS chains accelerate the drug release under different pH conditions (Fig. 5). Strong hydrophobic interaction between oleyl chains at pH $\geq$ 7.0 helps in the entrapment of DX in nanospheres, whereas, at lower pH, protonation of amines groups results in the expansion and repulsion of charged oleoyl-CS chains leading to the drug release. These core–shell nanospheres serve as both drug delivery as well as a bioimaging system [63].

7.2 Sutures

Sutures or stitches are natural or synthetic threads that are used to repair wounds, body tissues, or close cuts. Suture materials can be non-absorbable or absorbable. Currently, degradable absorbable materials are preferred as nonabsorbable materials are required to be removed once the wound is healed. Even though synthetic biocompatible polymers like polyglycolic acid (PGA), poly(lactic-co-glycolic acid (PLGA) have been widely used as sutures, they can induce mild inflammatory reactions. However, inexpensive polysaccharides such as chitin, cellulose, alginate, and their derivatives provide inherent antibacterial activity, resemblances to the extracellular matrix (ECM), and their capability to support cell proliferation apart from biocompatibility and biodegradability. Li and his coworkers prepared braided sutures made of tetramethylpiperidinyloxy-mediated oxidation regenerated cellulose (TORC) that possess suitable mechanical like knot-pull tensile strength and clinical properties.

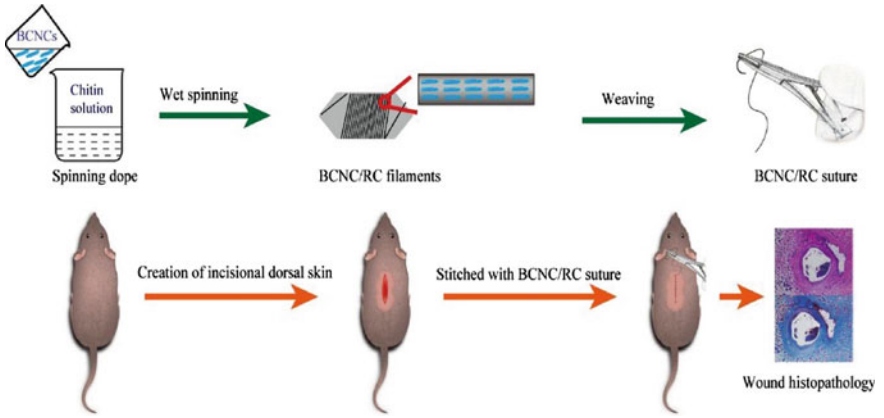

Fig. 6 Schematic representation of suture preparation [Reproduced with permission from Ref. [61]; Copyright 2019 Elsevier]

The knot-pull tensile strength was observed to be decreased with increased oxidation times [64]. Similarly, Wu et al. and his group developed ideal suture material using bacterial cellulose nanocrystals (BCNCs)/regenerated chitin (RC) fibers by wet spinning technology. Cellulose nanocrystals enhanced the mechanical properties of the matrix as it prevents slippage of chitin molecules (Fig. 6). Further, in vivo murine skin wound closure experiments and enzymatic degradation studies were conducted to analyze in vivo biocompatibility and in vitro enzymatic degradation, the investigation ensured that the developed suture material developed can promote wound healing and can degrade successfully in model enzyme lysozyme-containing solutions [65].

Incorporation of bioactive molecules like pharmaceutical ingredients into the suture enhances its activity by providing adequate support and active molecule release to the desired site. For example, an ideal gene delivery system was developed by interfacial polyelectrolyte complexation (IPC) technique using functional chitosan/heparin fiber generated from at interface. This technique involves spinning of intrinsically stiff chitosan (cationic) and heparin (anionic). These oppositely charged polymers come in close contact with each other and bind to each other at the interface to form a microscale polymeric complex. Heparin can act as a molecular reservoir as it can store and release proteins and peptides in a controlled manner. The presence of heparin at the fiber surface promotes the immobilization of adeno-associated virus (AAV), a vector for gene therapy. This chitosan/heparin fiber demonstrated outstanding strength low immunogenicity, degradability over three-month time, flexibility, and AAV binding at the surface ensured sustained gene expression at local incision sites for a longer period, thus this fiber can serve as a therapeutic suture [66].

7.3 Tissue Engineering

The main aim of tissue engineering is assembling functional constructs that rebuilt, improve, preserve, or replace biological activities of injured tissues and organs. In this regard, the biomaterial used for tissue engineering purpose must provide suitable physicochemical and biological characteristics that can mimic the native extracellular matrix (ECM) as it delivers various biological signals that assist cell migration, adhesion, and differentiation, during the time of its action (degradation and reconstruction). Polysaccharides inherently possess similar structures and activities of ECM components such, as proteoglycans, glycosaminoglycans glycoproteins, and glycolipids [67]. In addition to this, use of these glycan moieties as biomolecular signals establish polysaccharides worthy in fabricating biomaterials for applications like tissue engineering [68, 69]. Cellulose, alginate, hyaluranon, chitin, and chitosan are mostly used for tissue engineering applications. Cellulose possesses abundant hydroxyl groups that provide platform for easy functionalization, chemical interactions, and grafting. Goudarzi et al. fabricated poly (ε-caprolactone) (PCL)/gelatin (Gel)/CNF-modified acetylated CNF (ACNF) based bionanocomposite using electrospinning technique for soft tissue engineering. Incorporation of ACNF enhanced the thermal, mechanical, and biological properties. ACNF nanocomposite showed higher biocompatibility and promoted cell proliferation as compared to PCL/Gel composite [70]. Cellulose nanofiber/polylactic acid (PLA)-based fibrous membrane was fabricated through electrospinning process and was used for bone tissue engineering. Here, the CNF incorporation improved the thermal properties, Young's modulus, tensile strength, crystallinity, and hydrophilicity of the membrane [71]. Chitin is a lightweight material possessing higher surface-to-volume ratio and lower thermal expansion compared to metals like steel, aluminum, and commonly used synthetic polymers. After cellulose, chitin has the highest stiffness among polysaccharides. Duan et al. functionalized nanofibrous chitin microspheres using hydroxyapatite (HA) for bone scaffolding applications (Fig. 7). The noncovalent between HA and chitin fibers boosts up the adhesion at their interface. This biomaterial mimics the ECM promoting healing process, in vitro cell adhesion and in vivo bone regeneration [72].

8 Future Scope and Conclusion

Over decades, carbohydrate-based biomaterials are being used as a substitute for synthetic polymers for potential biomedical applications. Their exceptional reputation, inherent biocompatibility, biodegradability, low cost, ease of chemical modification to attain desirable properties, promote them as an efficient substitute for synthetic biopolymers that have flaws like toxicity, inadequate biocompatibility, and complicated synthetic approaches. Their resemblance to biological macromolecules such as natural extracellular matrix (ECM), and glycoproteins further encourages their

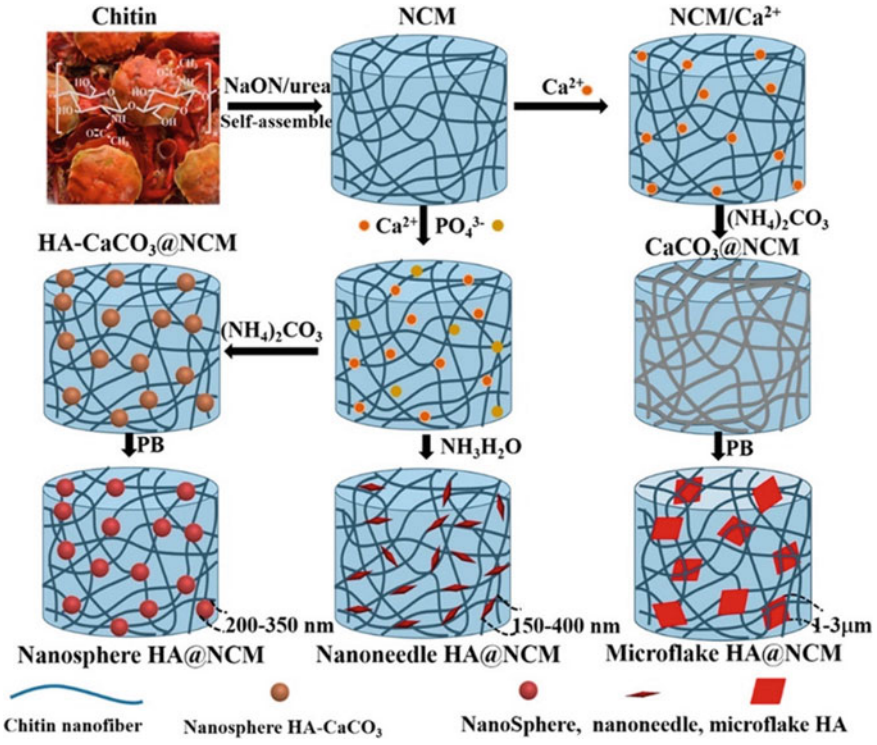

Fig. 7 Schematic representation of Microflake (NCMH1), Submicron-Needle (NCMH2), and Submicron-Sphere (NCMH3) [Reproduced with permission from Ref. [68]; Copyright 2017 ACS]

use in applications like drug delivery, wound management, and tissue engineering. The presence of amenable functional groups such as hydroxyl, amino and carboxyl groups located on the structures assist in tailoring their properties, thus serving as a distinct biological tool for several biomedical fields. Natural polysaccharides like chitosan, crellulose, alginates, cellulose, starch, etc., are being widely engineered onto various biologically biologically superior molecules through different techniques like chemical modification, grafting, as well as atom transfer radical polymerization (ATRP), etc., to promote its candidature in biopharmaceutics. Carbohydrates can be modified to form amphiphilic polymers and distinct architectures that can conjugate a wide range of bioactive molecules. Besides, since polysaccharides are conventionally derived from natural resources, there exist limitations and challenges like batch-to-batch variations by virtue of their source differences, chance of microbial contamination, thickening, and viscosity reduction in the course of storage, as well as increased rate of hydration etc restricting their widespread applications. Fortunately, these flaws could be eliminated by modifying these polysaccharides through grafting, crosslinking, or blending them with natural or synthetic polymers. Extensive research is being carried out worldwide to further understand their several

biological functions. Moreover, materials scientists in collaboration with biologists are attempting to develop new carbohydrate-based nano/microparticles that may selectively carry a set of drugs/proteins/enzymes to target a diseased organ and cure a complex disease. Also, there are many biomedical areas where the use of carbohydrates is limited; hence, an effective usage of these naturally occurring materials is a dire need of this era.

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Chapter 5
Cellulose-Based Biodegradable Polymers: Synthesis, Properties, and Their Applications

Mouli Sarkar, Ashank Upadhyay, Dharmendra Pandey, Chandrani Sarkar, and Sampa Saha

1 Introduction

Biopolymers have significantly drawn attention for creating numerous biodegradable products. These biopolymers are synthesized within the biological cells through enzymatic pathways. Among several polysaccharides such as starch, cellulose, xanthan, pullulan, hyaluronic acid, chitosan, etc., cellulose gains popularity as it contains large numbers of OH groups that can be modified according to the requirements. It shields plants, and fungi from external chemical, biological, and mechanical disturbances. The large supramolecular structure containing large amounts of OH moieties makes cellulose hydrophilic as they are susceptible to water attack. About 40–50 weight percent of the woody biomass in plants is made up of cellulose, the most common polymer, and a considerable amount of this biomass is found in crystalline forms [1]. Chemically, cellulose is a long linear chain of anhydro-D-glucopyranosyl units joined by β-(1,4)-glycosidic linkages (Fig. 1a) [2]. The cyclic hemiacetal groups contain equatorial OH groups (in the C_1 position) which defines that the cellulose structure exists in β-form (or β isomer), whereas, in the case of α isomer, the OH group remains in the axial position. The different isomers differentiate cellulose from other polysaccharides in terms of its biodegradation through hydrolysis reaction [3].

X-ray diffraction, ^{13}C CP/MAS, and solid-state NMR reveal two crystalline forms of cellulose structure, viz. I_α and I_β. These varieties completely depend upon sources.

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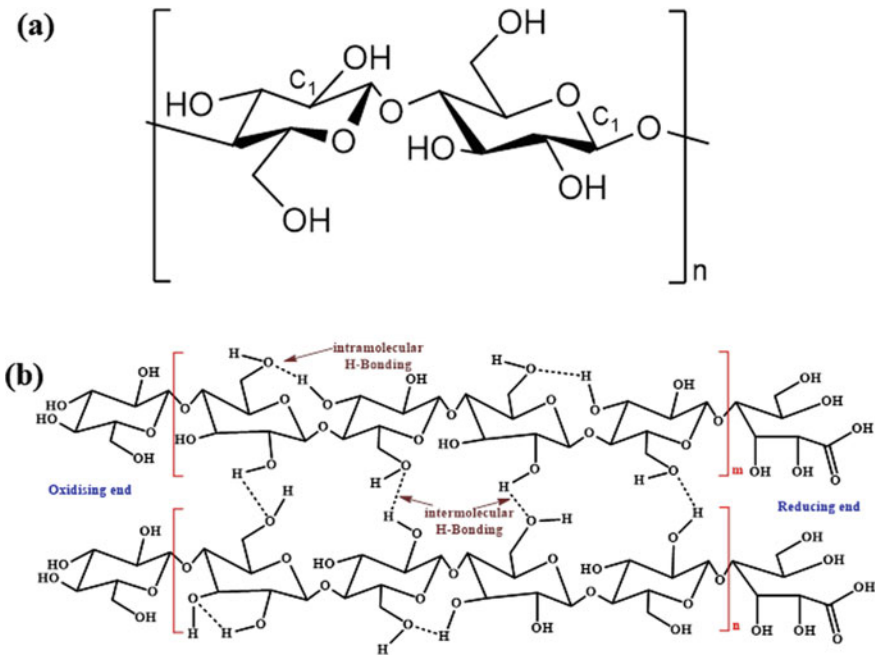

Fig. 1 **a** Structure of cellulose; **b** Cellulose structure featuring inter and intramolecular H-bonding in the repeating unit and reducing (right) and non-reducing (left) end groups. Redrawn from the Ref. [4]

Valonia, bacterial cellulose, and the cell wall of *Glaucocystis* are rich in I_α, whereas tunicate (*Halocynthia roretzi*) or animal cellulose are rich in I_β [5, 6]. The OH groups in the cellulose network control the chemical and physical characteristics of the cellulose chains. The intramolecular H-bonds between OH-groups of glucose units of the same cellulose units provide rigidity and thermostability of the chains, whereas, intermolecular H-bonds between two different cellulose chains are responsible for the development of the supramolecular structures as shown in Fig. 1b [4].

In addition to controlling their chemical reactivity, these OH groups can be modified by a variety of chemical reactions like esterification, acetylation, and nitration. Although cellulose is recognized to be the most plentiful and cost-effective biopolymer, its poor water solubility limits its commercial applications [7].

To address this problem, researchers have developed a variety of derivatives, including methylcellulose (MC), hydroxyethyl cellulose (HEC), carboxymethylcellulose (CMC), as well as cellulose acetate (CA) and hydroxypropyl methylcellulose (HPMC). The advantage of functionalization is to make a significant impact on the properties of cellulose by breaking H-bonding [2, 8]. Due to their simplicity of processing, these cellulose derivatives are also employed extensively in the

cosmetic and pharmaceutical industries. Mostly, industries employ them commercially in a variety of forms, including tablet and capsule coating materials, stabilizers, thickening agents, bioadhesives, mucoadhesives, pressure-sensitive adhesives, binders, gelling agents, flavor maskers, fillers, free-flowing agents, and hemostatic compounds [9, 10].

2 Sources

French scientist Anselme Payen first extracted cellulose from the cell walls of the plant in 1938 and, later, the chemical structure was determined by Hermann Staudinger in 1920. Finally, synthetic cellulose was first chemically synthesized in the laboratory by Kobayashi and Shoda in 1992 [11].

Wood is the primary resource of cellulose. Others are bacterial cellulose, algal cellulose, and tunicate cellulose [2, 12, 13]. Bacterial cellulose is very pure, highly crystalline, and contains a high DP (degree of polymerization). It has been investigated that, annually a tree can produce 10^{11}–10^{12} tonnes of cellulose during photosynthesis [14]. Figure 2a illustrates the different sources of cellulose.

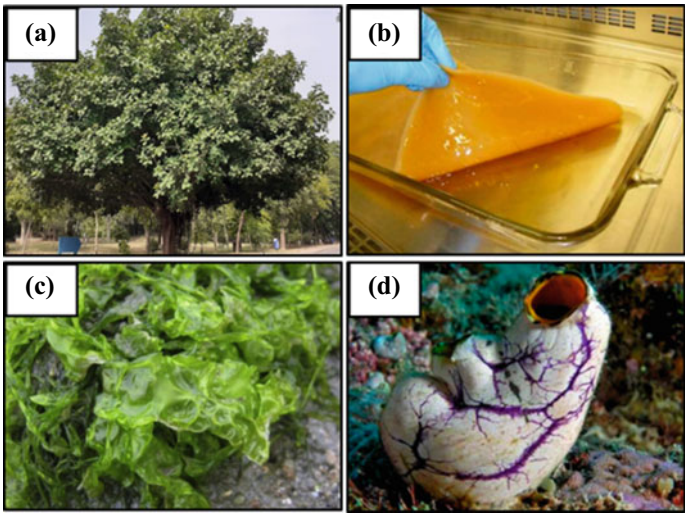

Fig. 2 Different sources of cellulose **a** tree, **b** bacterial culture, **c** algae, and **d** tunicate. Reproduced with permission from Courtenay et al. [13] and Hardouin et al. [15]

2.1 Wood and Plant Cellulose

The primary source of cellulose is wood and plants. The sources vary as corn, cotton, jute, pineapple leaves, flax, hemp, potato peel waste, cereal straws, oil palm biomass, cotton, etc. [2, 16]. The cellulose content in the plant varies with the location. In the soft woody part, it ranges from 30 to 75%, while, in the case of the hard woody part, it is around 40 to 50%. Fibers extracted from both these parts exhibit similarities in composition and structure. They are made of carbohydrates, (such as cellulose, hemicellulose, and lignin) having a complex structure. Hemicelluloses are found in terrestrial plants and algae. Xylan-type polysaccharides are mostly characterized by hemicellulose, whereas lignin is the highly branched 3D complex network having several functional groups. The nature of cellulose highly varies with the amount of lignin, hemicellulose, and fibers.

2.2 Bacterial Cellulose (BC)

Bacterial cellulose (BC) is often very pure (no lignin or hemicelluloses). It is highly crystalline having a high degree of polymerization. It becomes more significant that numerous bacteria belonging to the genera Acetobacter, Agrobacterium, Sarcina, and Rhizobium produce cellulose [17]. Agro-industrial wastes are commonly used as carbon sources to manufacture BC, and the yield of bacterial culture can reach 40%. Most often, BC is acquired in pure form having a purity of more than 90%. BC is capable of being transformed into a variety of morphological forms, including spheres, films, fleeces, and hollow particles. Pure cellulose face masks also frequently have a higher biodegradability than commercial counterparts, which is an additional benefit. A fibrous network of cellulose chains gives them a porous structure, and they are typically wide ribbon-shaped fibrils (diameter ~100 nm), which contain numerous nanofibrils (diameter ~8 nm). As a result, distinctive nanomorphology has a wide surface area, high water holding capacity (~99% water), high wet strength, strong elasticity, and conformability.

2.3 Algal Cellulose

Another source of cellulose is algae. It is highly crystalline. Algae cellulose is specifically produced from brown species, red species (Gelidium elegans), and green species (Cladophora). Algal cellulose grows more quickly than plant cellulose, giving it a competitive edge in industrial applications. Oceans, lakes, ponds, and wastewaters are just a few of the environments where algae can develop, and they can produce cellulose [15]. Algal cellulose is not produced in its purest form because hemicellulose, protein, and lignin are highly associated with them. Red algae and green algae

are good sources of cellulose. The main types of carbohydrates found in red algae, or Gelidium elegans, are cellulose and agar. Green algal cellulosic cellulose exhibits outstanding qualities such as large specific surface area, high porosity (mesopores), and high crystallinity (~70%) among others.

2.4 Tunicate Cellulose

The only known animal source of cellulose is tunicates. They are marine invertebrate animals, and cellulose is extracted from the outer tissue of these animals. It contains a large amount of cellulose (~60%) and a small amount of nitrogenous compound (~27%). In tunicates, cellulose is also present as a nano fibrillar form arranged in a multi-layered structure at the surface of its epidermis. The shape and size of these nanofibril bundles vary with different species. Commonly, the length and width of nanofibrils are in the range of 100 nm–2 μm and 10 nm–30 nm, respectively. It also has a high specific surface area (150–170 m^2 g^{-1}). The extraction of cellulose from various sources is one of the important processes and most of the commercially used cellulose is primarily extracted from plant-based sources. In the following section, we are going to discuss the extraction process of cellulose from plant-based sources (Table 1).

Table 1 Various sources of cellulose, cellulose content, properties, and their applications

Various sources	Cellulose content	Properties	Applications	References
Wood and plant	30–95%	Strength and properties of cellulose fibers vary with different varieties of wood and plants	The application also varies with the source, but the major application areas are paper, textile, and pharmaceutical industries	[2]
Bacterial	Approx. 90%	High degree of crystallinity (80–90%), high degree of polymerization, high mechanical strength, and degradation rate of BC is slightly higher than that of wood and plant cellulose	Biomedical applications, tissue engineering, pharmaceutical industry, emulsion and hydrogel stabilizers, drug-delivery systems, and smart artificial skin	[18–20]
Tunicate	Approx. 60%	Highly crystalline, high aspect ratio fibrils, high specific surface area	The excellent properties of tunicate cellulose is a good choice for various chemical and mechanical applications	[21, 22]

(continued)

Table 1 (continued)

Various sources	Cellulose content	Properties	Applications	References
Algae	Approx. 70%	High crystallinity (90%), low moisture adsorption capacity, and high porosity in the mesoporous range	Algal nanocellulose has excellent potential for biomedical applications such as tissue engineering because of its nontoxicity, and facile chemical modification	[23–25]

3 Extraction of Cellulose

Different types of structural polymers like polysaccharides and polyphenolic compounds make up the constituent of a typical plant. The cell wall of a plant comprises of cellulose, pectin, and hemicellulose. Cellulose is present in the form of fibrillar and is the major part of the biomass [16]. Conventionally, cellulose is isolated from plants starting with the pulping process. This process removes the extractable materials like lignin, and hemicellulose without degrading the fibrillar structure of cellulose. Bleaching is carried out as the next process which utilizes oxygen, ozone, and hydrogen peroxide. The final product after bleaching mainly contains alpha-cellulose and hemicelluloses in residual amounts. This process extracts 40% cellulose, 10–11% as secondary products like furfural, xylose, and acetic acid, and the remaining as waste material [26]. Salimi et al. elaborate on the stepwise extraction of cellulose [27]. In addition to fibrillated cellulose, cellulose nanoparticles can also be produced and a scheme to obtain the same is shown in Fig. 3, a detailed discussion of which is provided in the next section [28,29]

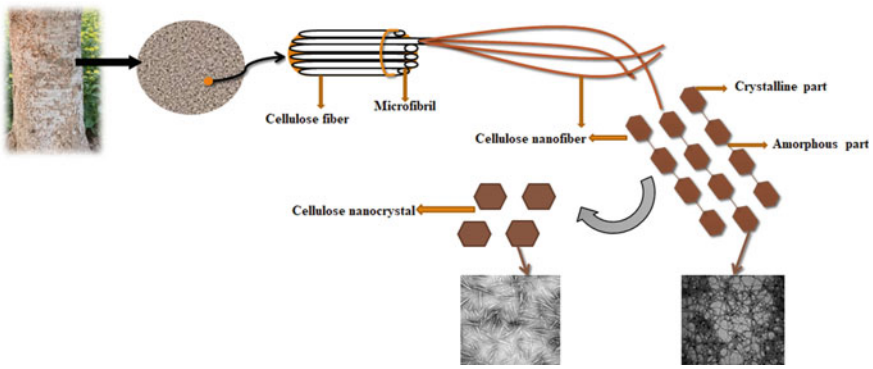

Fig. 3 Scheme of extraction process of cellulose. Modified from Gopakumar et al. [28]

3.1 Cellulose Particles

Based on the size and morphology, the cellulose particles have been broadly characterized into cellulose crystals and cellulose fibers. These differ in size, shape, crystallinity, aspect ratio, and physiochemical properties [2, 15, 20].

3.2 Cellulose Fibers

Naturally found cellulose is present in the form of microfibrils which assemble and organize themselves in the form of cellulosic fibers. Three types of cellulose fibers are known viz. pulp fibers whose length is found in the range of 1–10 mm, staple fibers with a length of approximately 60 mm, and strand fibers with a length range of 20–100 cm. Strand fibers contain multiple cells, whereas staple fibers contain a single cell. Cotton fibers are an example of staple fibers with a length range of 25–45 mm. These two types of fibers are obtained from wild plants and crops via a pulping process. The fibers obtained are further disintegrated into micro and nanofibrils by a mechanical process that includes homogenization and microfluidization. The length of cellulose nanofibrils obtained is generally 1 μm and the width ranges from 2 to 100 nm. The fiber size is mainly depending on the pretreatment, fibrillation process, and source. Cellulose nanofibrils have superior mechanical strength with a tensile strength of ~1 GPa and an elastic modulus range of ~14–36 GPa [30].

3.3 Cellulose Crystals

Enzymatic, mechanical, and chemical treatments of cellulose microfibrils lead to the formation of cellulose crystals. During treatment, the cellulose microfibrils get fragmented into microcrystalline cellulose and cellulose nanocrystals. Microcrystals have a high degree of crystallinity and form rod-like stiff particles. Microcrystalline cellulose (MCC) was first introduced as an ingredient for direct tableting. The common source for pharmaceutical MCC is wood cellulose. Cellulose nanocrystals (CNCs) particles are harnessed from the cellulose microfibrils' crystalline regions. CNCs are synthesized via sulfuric hydrolysis of cellulose, which leads to the disintegration of highly crystalline CNCs particles which are eventually extracted. The final characteristic of CNCs depends on the cellulose source and extraction parameters like temperature of hydrolysis, controlled time, and further modification like dialysis and neutralization. CNCs display exceptional mechanical and thermal properties like high TS, modulus, low density, and high thermal properties [31]. Due to the superior properties of CNCs, various potential applications have been explored [32].

4 Properties of Cellulose

4.1 Solubility

As we have seen that plants contain hemicellulose and cellulose known as holocellulose, lignin, and inorganic materials (such as ash). Cellulose can be simply hydrolyzed by acids to form water-soluble sugars and is resistant to strong alkalis. Cellulose is proportionally resistant to oxidizing agents. Hemicellulose forms a supportive matrix for the cellulose microfibrils which are hydrophilic in nature. This hydrophilicity helps its easy dissolution in alkali and easy hydrolysis in acids. The harder part (lignin) does not get hydrolyzed in acids but is soluble in hot alkali, gets condensed in the presence of phenol, and quickly oxidized. A mixture of dimethyl sulfoxide (DMSO) and 10–20% (w/v) tetra butyl ammonium fluoride trihydrate can dissolve cellulose without any pretreatment at room temperature. Cellulose is insoluble in water and other organic solvents which limits its applications. The OH groups present in the cellulose form H bonding restricting the entry of solvent molecules [33]. This is the main reason for the insolubility of cellulose. It can only be dissolved when this interaction is broken. This can be induced by the addition of functional groups in the cellulose backbone which break the intermolecular H-bonding and in turn solvate the chains. Due to the compact structure of cellulose, a complex solvent system that required minimum energy of dissolution is used in dissolving cellulose, Initially, Copper complexes (Cuoxam) were used to dissolve the cellulose [34]. However, other metal complexes based on Co, Ni, Cd, and Zn are also being used for dissolving cellulose. Thus cellulose can be easily dissolved in phosphoric acid and trifluoroacetic acids by disrupting the Hydrogen bonds. Various ionic liquids are found to be suitable agents for dissolving cellulose since the solvents are eco-friendly, less toxic, having good thermal stability and recyclability. However, the high cost and energy-intensive nature of ionic liquids limit their usage.

4.2 Mechanical Property

Cellulose shows high crystallinity and high intermolecular interaction which manifests itself in the form of superior mechanical properties, viz. tensile strength and modulus. The rigid cellulose nanocomposites have a modulus similar to that of Kevlar and Steel. Bacterial cellulose (BC) is softer and finds application in the replacement of collagen networks. Looking at the impressive mechanical properties of cellulose leads to potential applications in wound healing, tissue engineering, and drug delivery where a strong and stable building block is required [35].

4.3 Hygroscopic Property

Cellulose is highly hygroscopic and attracts water, this is by the virtue of hydrogen bonds present in the structure. Cellulose absorbs water almost 30% of its biomass and gets swollen, the water permeates into the structure via the amorphous region (disordered domains) [36, 37]. This swelling of cellulose assists in the aqueous processing of cellulose and its composites. The hygroscopic nature of cellulose leads to lower wet strength and which might pose limiting parameters for various applications.

4.4 Structure and Degradability

The backbone of cellulose is structured on β-1,4-glycoside-linked glucose units. The rigid structure of cellulose can be attributed to the intermolecular hydrogen bonds leading it to good mechanical properties making it useful as a building material in plants. These superstructures produced are stable till significantly a higher temperature. The degradation of cellulose happens below the theoretical melting point of 260–270 °C. The melting point can be reduced by breaking the H-bonding in the structure, this can be effectively done by derivatizing the hydroxyl group of cellulose. Some of the most commonly used cellulose derivatives which are used industrially are cellulose acetate, cellulose acetobutyrate, ethyl cellulose, and benzyl cellulose. Thermoplasticity in these derivatives is achieved by complete derivatization of hydroxyl group. The average degree of substitution (DS) value is the number of substituted OH groups per anhydroglucose unit. The substitution level is inversely proportional to the biodegradability of cellulose derivatives as enzyme attack requires a free glucose unit [38].

4.5 Mechanism of Degradation

One of the well-recognized degradation routes for cellulose is by the brown rot fungi which produce H_2O_2, which in turn assists in the production of hydroxyl radical (·OH). The attack by ·OH leads to the cleavage of the cellulose chains generating lactone as shown in Fig. 4. The ·OH radical is produced via the Fenton reaction ($H_2O_2 + Fe^{2+} \rightarrow H_2O + Fe^{3+} + OH$) in which iron is used from the wood itself. The hydrogen abstraction by ·OH is a fast reaction that leaves behind a carbon-centered radical which rapidly reacts with oxygen from the environment, which subsequently eliminates ·OOH [39].

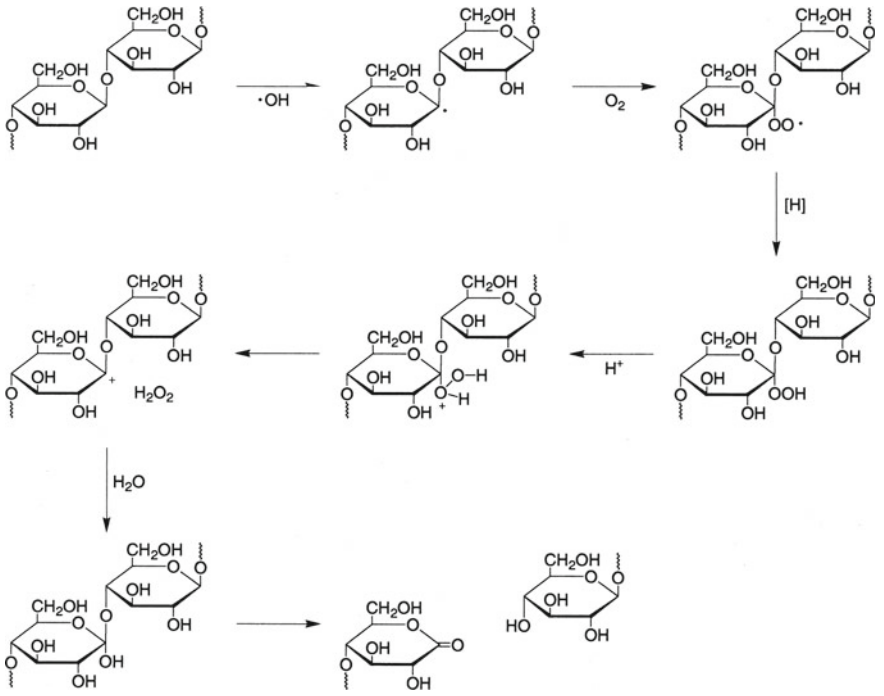

Fig. 4 Plausible mechanism of degradation of cellulose by Brown rot fungi, reproduced with permission from Hammel et al. [39]

5 Functional Derivatives of Cellulose—Synthesis, and Biodegradability

As we have depicted in the previous section that crystallinity and hydrogen bonding in the cellulose structure leads to difficulty in the processability of cellulose; hence, it is essential to functionalize the cellulose. Esterification, etherification, nucleophilic substitution, oxidation, and copolymerization are the most common routes to achieve functionalization in cellulose. Functionalization has a two-fold advantage, viz. feasible processibility, and better plastic properties. The functionalization helps in breaking the crystalline structure and assists in solubilization which further assists in processing. The amount of substitution has an impact on biodegradability. As the size and degree of substituent groups increase, the biodegradability of the cellulose decreases [40].

The OH groups in cellulose being susceptible to reactions, is utilized for the functionalization to undergo various kinds of reactions. Figure 5 shows the chemical structure of cellulose after functionalization. The degree of substitution affects the final properties of the polymer obtained. To design a new functionalized cellulose-based polymer, it is essential to understand the changes in properties achieved with

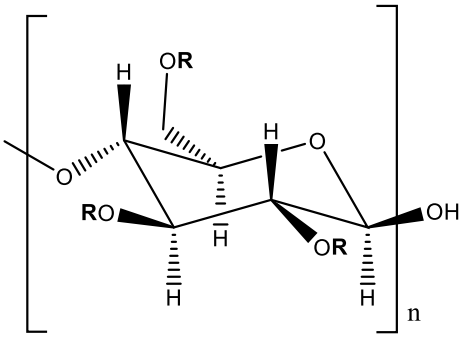

Fig. 5 Cellulose derivatives, redrawn from [2]

the substitution. The various cellulose derivatives are discussed in detail below (Table 2).

5.1 Cellulose Ethers

When OH in the anhydroglucose unit of cellulose is substituted with the alkyl group, cellulose ethers are obtained. Cellulose ethers are synthesized by the reaction of cellulose with NaOH and subsequently reacting with alkyl chloride as shown in the scheme below (Fig. 6). Cellulose ethers consist of methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and carboxymethylcellulose and their derivatives.

Methylcellulose (MC)

Methylcellulose is the simplest functionalized biodegradable cellulose ether. It has a vast application in the food industry, tissue engineering, coating, and preparation of mulch films. It comes with the advantage of easy processability, large availability, and low cost. The biodegradability however limits its application in high-end products. Hence, two methods which helps to modulate the biodegradability of the polymers with required properties are the incorporation of fillers with a high aspect ratio to increase the tortuous path, and secondly by incorporation of crosslinks such as glutaraldehyde (Glu) between the polymer chains. This will delay the hydrolysis and provide an enhanced property with the loss in biodegradability [41].

Methylcellulose is synthesized in an alkaline medium in the presence of methylating agents like methyl chloride or dimethyl sulfate [42]. Degree of substitution depends on the synthesis conditions such as reaction time and methylating agent. As the degree of substitution is increased from the range 1.4–2.0 to 2.4–2.8, the solubility of methylcellulose is enhanced in water as well as in some organic solvents [43].

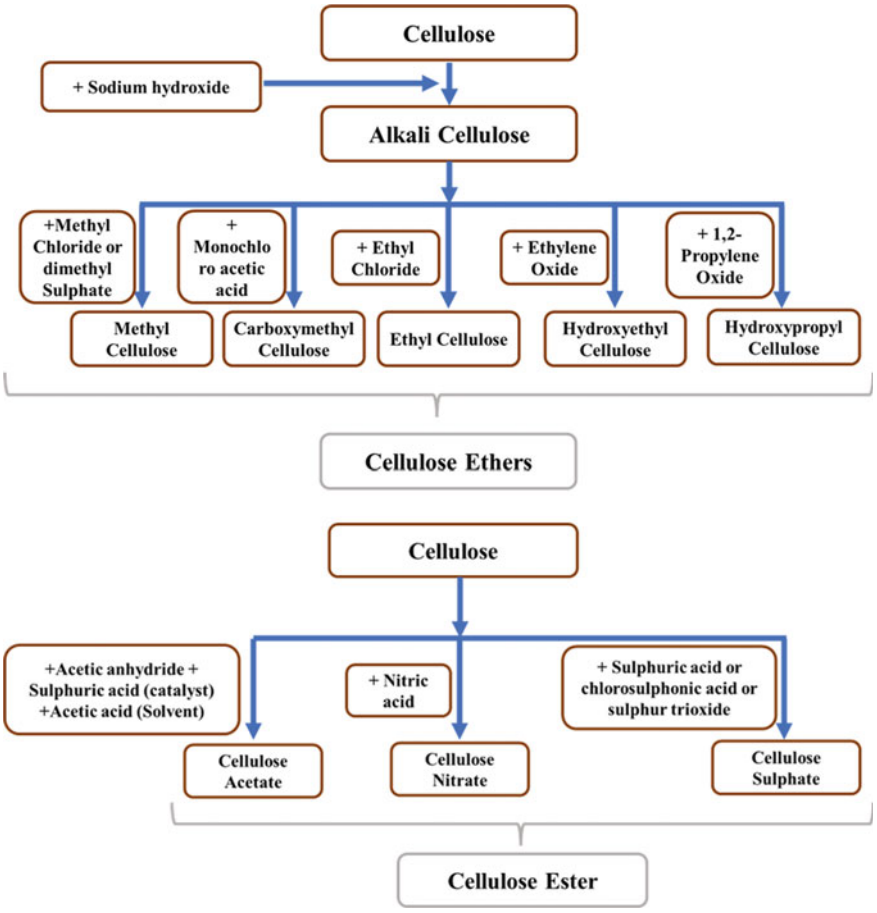

Fig. 6 The above scheme represents the summary of the synthesis of cellulose derivatives viz. esters and ether, redrawn from [2]

Carboxymethylcellulose (CMC)

CMC is one of the most popular and commercially available cellulose ethers. It is biodegradable, non-toxic, water-soluble, and has better chemical stability. CMC has myriad applications by the virtue of its properties in the food industry, textile industry, paper industry, drugs and cosmetics, leather, films, filaments, paints, and lacquers [44]. CMC is an efficacious thickening agent, binder, and emulsion stabilizer, and has film formability. CMC is synthesized by a reaction of cellulose with monochloroacetic acid in which the hydroxyl group (predominantly C_2) is substituted by carboxymethyl groups ($–CH_2–COOH$).

The degree of substitution is typically between 0.6 and 1.25. The properties are dependent on the large molecular structure, degree of substitution, and molecular

Table 2 Derivatives of cellulose

Functionalization	Derivatives	R
Cellulose ethers	Methylcellulose	H or CH_3
	Carboxymethylcellulose	H or CH_2COOH
	Ethyl cellulose	H or CH_2CH_3
	Hydroxyethyl cellulose	H or CH_2CH_2OH
	Hydroxypropyl cellulose	H or $CH_2CH(OH)CH_3$
Cellulose esters	Cellulose acetate	H or $(C=O)CH_3$
	Cellulose sulfate	H or SO_3H
	Cellulose nitrate	H or NO_2

weight [45]. The sodium salt is soluble in water and hence CMC is usually used as its sodium salt.

Ethyl Cellulose (EC)

Ethyl cellulose is another commercial biodegradable cellulose ether that is formed when the hydroxyl group is substituted by the ethyl group. Ethyl cellulose is synthesized by the reaction of cellulose alkali with ethyl chloride at 60 °C for several hours [46]. For commercial products, normally the degree of substitution lies in the range of 2–2.6 [47]. The properties of ethyl cellulose depend on the molecular weight, degree of etherification, and molecular uniformity.

EC has an excellent film-forming capacity with superior barrier properties and hydrophobicity making it a suitable candidate for biomedical applications, majorly in drug delivery. Ethyl cellulose is generally brittle and hence plasticizers are added in order to enhance its flexibility, thermal stability, and processability [48].

Hydroxyethyl Cellulose (HEC)

Hydroxyethyl cellulose is synthesized by reacting alkali cellulose with ethylene dioxide to achieve hydroxy ethyl group ($–CH_2–CH_2–OH$) at 2, 4 and 6 positions of glycosyl unit of cellulose. This OH group acts as a reactive center which can be utilized for further modification. Hydroxyethyl cellulose is highly soluble in water and other organic solvents. Mixing cellulose with HEC allows easy processing of it, and diversifies its biomedical application [49].

Hydroxypropyl Cellulose (HPC)

Hydroxypropyl cellulose is a biodegradable polymer in which the OH group is substituted by 2-hydroxypropyl. Like HEC, HPC also has a secondary alcohol group that can be utilized for further functionalization of the cellulose chains for biomedical applications such as tissue engineering. HPC forms a liquid crystal when dissolved in water depicting an interesting property of mechanochromism meaning it shows a change in color on the application of pressure. This property makes it a suitable candidate for application in sensing applications [50].

5.2 Cellulose Esters

Cellulose esters offer the advantage of solubility in a common solvent and easy melt processability over cellulose. It also affords cellulose to be molded into 3D shapes, drawn into thin wires, and solution cast into films, sheets, or coating applications [51]. The modification can also be done over the surface of the cellulose substrate keeping the crystallinity intact to avail high mechanical properties [52]. Common cellulose esters are discussed below.

Cellulose Acetate (CA)

Cellulose acetate is synthesized from the acetylation of cellulose. The DS defines the properties of the CA. DS of 2.5 is the most common level that provides optimum molecular weight and rheological/solution properties. These properties help CA to be used in various applications like textiles, thermoplastic, films, and cigarette filters [53].

The key mechanism of biodegradation of CA is chemical hydrolysis and acetyl esterases as the first step which subsequently leads to the degradation of backbone which mainly contains cellulose. Various studies have confirmed that CA is indeed biodegradable in natural environment. One interesting study is done by Komarek et al. in which acetyl carbon was labeled with ^{14}C and CO_2 evolution was monitored. The study compared CA with DS of 1.85, 2.07, and 2.57, and found a reduction in degradation rate by increasing the level of acetylation [54].

Cellulose Nitrate (CN)

Cellulose nitrate also known as nitrocellulose, is synthesized by the substitution of an OH group with a nitrate group by treating cellulose with concentrated nitric acid. The typical DS is 2.2–2.8 which eventually decides its properties and application. A major application of CN is in explosives, plastics, coating, and ink industries [55].

CN is found to be 40% biodegradable only due to inhibition by various products formed during the degradation of main degrading enzymes [56].

Cellulose Sulfate (CS)

Sulfonation of cellulose is carried out using sulfuric acid, sulfur trioxide, and chlorosulfonic acid. It is water soluble, antiviral, antibacterial, and has anticoagulant properties due to the presence of a sulfate group. CS shows excellent biocompatibility, film-forming ability, and biodegradability. These properties make it highly viable for application in tissue engineering and drug delivery [57]. In vitro studies showed favorable biodegradable properties of sodium cellulose sulfate (NaCS) and chitosan-based films. The DS also has an inverse effect on the biodegradability of CS [58].

6 Applications

6.1 Packaging Industry

Plastics are commercial materials derived mainly from synthetic polymers. These materials are cheap and remain intact throughout their packaging life. But synthetic polymer leads to some side effects on human beings, animals, and the environment. The usage of plastic bags cannot be reduced as they are easy to handle. That's why to get rid of the sustainability issues, it is important to introduce biodegradable polymers to reduce the solid waste in the environment. Among the well-known biopolymers, cellulose has been extensively used in the food packaging industry [59].

In order to convert cellulose into a polymeric substance, first cellulose has to be extracted from natural resources. The best methods to extract cellulose were described by Han and Rowell and later by Borella et al. [52, 53, 60]. Recently, partially biodegradable biocomposites and green biocomposites gained much attention in synthesizing biobased products, which can be degraded easily by microorganisms [3, 52, 53]. Biocomposites consist of biofiber and matrix polymer. Partially biodegradable biocomposites contain biodegradable biofiber and non-biodegradable polymer matrix whereas, biodegradable biocomposites consist of both biodegradable fiber and polymer. Also, there exist hybrid biocomposites which contain two or more biofiber in combination with a polymer [61]. In recent days, biodegradable polymers blended with inert polymer matrices are becoming more attractive. In this case, upon disposal of the plastic in the environment, the biodegradable part can be degraded by microorganisms and the residual polymer component loses its integrity and fades away. A cellulose ester known as cellulose acetate butyrate (CAB) can be added to other cellulose ester-based film formers as well as employed as a reactive polyol during curing of the coating. The regenerated cellulose fiber, i.e., cellophane is used as breathable packaging material for baked food. Apart from that, cellulose

esters and cellulose ethers are being used in the processing of film coatings, edible films, etc. [62].

6.2 Pharmaceutical Industry

Cellulose-based polymers are gaining much importance in the field of pharmaceuticals. Especially, cellulose ethers and cellulose esters are having unique physicochemical and mechanochemical properties by which they can be used broadly as healthcare products in the form of tablets, gelling agents, bioadhesives, mucoadhesives, etc. Another well-known derivative of cellulose MCC is a multifunctional excipient such as silicified MCC (SMCC) which is being extensively used instead of only MCC. Recently, cellulose is converted to nanocomposites which are also used as drug-delivery agents and as ion-sensing materials [63–65].

6.3 Electronic Industry

In order to meet the sustainability issues, it is necessary to utilize renewable energy sources. Thus biodegradable materials such as cellulose derivatives are highly used in the field of the electro-technological field for their lightweight, low cost, transparency, portability, and flexibility in electronic and solar energy conversion [66, 67]. Cellulose fibers having a diameter of ~20 μm, would have been suitable for usage in solar cells, but their high surface roughness and porous structure render their effectiveness in coatings. Also, the fiber diameter is much larger than the wavelength of visible light. So, traditional papers made of cellulose are opaque which is difficult for using the materials for transparent devices. Chang et al. showed that *O*-(2,3-dihydroxypropyl) cellulose (DHPC) produces a smooth surface with excellent ductility and transparency and can be effectively used in a flexible solar cell. However, due to poor mechanical strength, this derivative of cellulose is further reinforced by rigid tunicate cellulose nanocrystals (TCNCs) [68].

6.4 Metal Industry

Water bodies are playing a major role as a carrier of heavy metals, non-metals, and organic dyes. Cellulose backbone contains a huge amount of OH groups which can interact with metal ions through electrostatic force and hydrogen bonding. Besides, these OH groups can be converted into several other functional groups (phosphonate, sulfonate, amine, carboxyl, ether, ester, etc.) which change the surface charge over the cellulose matrix. These modifications provide excellent interaction with metal ions. Hajeeth et al. employed cellulose extracted from sisal fiber in the form of a

cellulose-g-acrylic acid copolymer to adsorb Ni(II) and Cu(II) from aqueous solutions [69]. Cellulose was also successfully modified to produce cellulose-amine and cellulose-thio adsorbents. The obtained sample showed strong adsorption potential towards Hg(II) in aqueous solutions [59]. Cellulose can also be used as an adsorbent when combined with montmorillonite (NaMMT). It was applied to eliminate Cr(VI) from the aqueous solutions. Other modified cellulose were listed in Table 3.

6.5 Biomedical Industry

Cellulose contains abundant OH groups over its backbone. Hence, cellulose hydrogel can be easily produced by physical crosslinking [91]. There are some water-soluble cellulose derivatives, such as Methylcellulose, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, and Carboxymethylcellulose that are often used for the fabrication of cellulose-hydrogels. It was shown that, when OH moieties are partially substituted by methyl or hydroxypropyl groups, both hydrogen bonding and hydrophobic interaction play a key role in determining the gelation ability of the hydrogels [92]. In the case of chemically crosslinking structures, some di-functional reagents are employed to provide a three-dimensional shape to the cellulose hydrogel structure. Sannino et al. prepared super-hydro porous hydrogels based on crosslinking of CMC and HEC with a crosslinker such as DVS (divinyl sulfone) (Fig. 7). The main feature of these hydrogels is that they can change their sorption capability depending on the ionic strength and pH of the excipient. The super-adsorbent hydrogel has been efficiently applied for the treatment of edemas [93–95]. Apart from medication, cellulose-based hydrogels are often used in tissue engineering, sensors, agriculture, water purification, and chromatographic support which are discussed below [96–99].

In the biomedical field, hydrogels have never-ending applications. It has the ability to remove excess water from the body and is highly effective in the treatment of edema. Polyelectrolyte-based cellulosic hydrogels, such as sodium salt of carboxymethylcellulose and hydroxyethyl Cellulose are highly pH-dependent and get removed from the body with feces without affecting the function of other body parts. The water uptake capability varies with the changing ratio of NaCMC/HEC [101]. Besides, superabsorbent cellulose-based hydrogels are being extensively used in personal care products like diapers as these hydrogels absorb liquid and keep that

Table 3 Several cellulose derivatives and their applications

Purpose	Cellulose components	Applications	References
Metal adsorption	Phosphorylated cellulose (nano paper)	Copper ions adsorption	[70]
	Tetraethoxysilane-cellulose acetate composite material	Cr(VI) adsorption	[71]

(continued)

Table 3 (continued)

Purpose	Cellulose components	Applications	References
	Fe(III) metal based aminofunctionalized poly(glycidylmethacrylate)-grafted TiO_2-densified cellulose	As(V) adsorption	[72]
	Sulfonated wheat pulp nanocellulose	Pb(II) adsorption	[73]
	Amino-propyl-triethoxy silane modified micro fibrillated cellulose	Cu(II), Ni(II), Cd(II) adsorption	[74]
	Cellulose functionalized methyl-iodide and triethylenetetramine	Cr(VI) adsorption	[75]
	Cellulose nanofiber	Ag+ adsorption	[76]
Packaging	Cellulose esters	Laminates, optical films, and laminates	[77]
	Cellulose acetate butyrate, and methylcellulose	Coatings and additives in film former	[78]
	Carboxymethylcellulose	Thickener, stabilizer, and suspension agents	[79]
	Cellophane	Breathable packaging for baked goods and textiles	[80]
	Methylcellulose with polyethylene glycol, and PEG400 plasticizers	Edible film	[62]
	Nanocellulose	Food packaging	[81]
Hydrogels	Si impregnated hydroxypropyl methylcellulose (Si-HPMC)	Biomedical applications	[82]
	Chitosan/methylcellulose/Na_3PO_4 hydrogels	Tissue engineering	[83]
	Poly(N,N-dimethyl acrylamide)/ cellulose hydrogels	Optical applications	[84]
Smart material	Cellulose electro-active paper (EAP)	Biosensors	[85]
	O-(2, 3-dihydroxypropyl) cellulose (DHPC) with tunicate (TCNCs) cellulose nanocrystals as reinforcing agents	Flexible solar cells	[68]
	Sodium cellulose sulfate	Biomaterials for microcarriers' designing	[58]

(continued)

Table 3 (continued)

Purpose	Cellulose components	Applications	References
	Nitrocellulose	Explosives	[86]
Biofuel	Cellulose	Energy production	[87]
Others	Oxycellulose	Bioadhesives and cosmetics	[88]
	Hydroxyethyl cellulose	Agriculture, textile, and paper industries	[89]
	Hydroxypropyl cellulose	Lubricant in artificial eyes and food additives	[90]

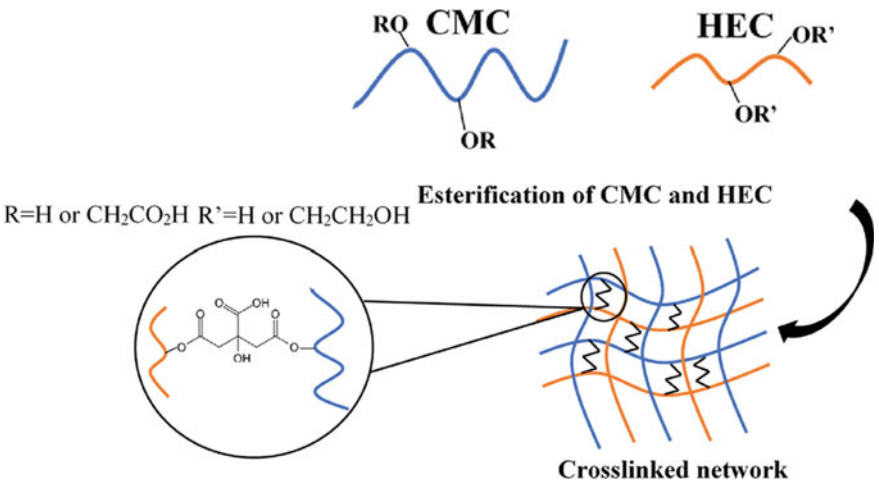

Fig. 7 Scheme of formation of HEC and CMC crosslinked network, redrawn with permission from Ayouch et al. [100]

place dry, and also prevent diaper rash and any other fungal attack. These products are also cheap and safe to use. Furthermore, these superabsorbents prevent leakage and reduce the risk of fecal contamination, and gastrointestinal problems [102, 103]. In 1966, Harmon and Herper separately patented superabsorbent materials [104].

The superabsorbent cellulosic system contains three main parts (1) an envelope of non-oven tissue, (2) a plastic cover material, and (3) an absorbent made of wood pulp cellulose mixed with some hydroporous superabsorbent polymer (SAP). The latter two components were usually non-biodegradable. Hence, for the recovery of cellulose materials and recycling of the absorbent, usage of cellulose-based hydrogels was suggested. Among them, NaCMC and HEC crosslinked with DVS show similar properties to SAP and produce higher retention ability and swelling ratio [105].

6.6 Agricultural Industry

In order to optimize the water resources in the agricultural field, especially for the cultivation in the desert area, a constant water supply is highly needed. So, the super-absorbent provides the required quantity of water throughout the time by releasing the water slowly through a diffusion-drive mechanism [106]. Cellulose-based hydrogels perform as an alternative to acrylate-based hydrogel which is not biodegradable. Some cellulose-based SAP hydrogels were suggested which have the absorption ability of almost one liter of water per gram of hydrogel [107, 108].

6.7 Biofuel Industry

In recent days biofuel supplies 86% of the energy of the world. With the increment in population, energy usage is also expected to surge in the coming days. High usage of petroleum-based fuels leads to an impact on environmental changes like global warming and the reduction of biomass. In that case, cellulose is the most active renewable resource used in the production of energy in the world (chemical energy stored in biomass is approximately 6–7 times that of total human energy consumption per year) [109]. Moreover, a human can not digest cellulose, so it is advantageous to use this polymer as it does not compete with food resources. Production of biofuel from cellulosic materials is generally carried out by the processes of gasification, pyrolysis, and hydrolysis. First, the woody biomass is disintegrated to produce isolated cellulose from other constituents of lignocellulosic materials. Next, cellulose is depolymerized (basically converted to glucose units), followed by conversion of glucose into biofuels via biological treatment, and finally purification of the biofuel. In the meantime, it is necessary to deoxygenate the biomass as it reduces the heat content thereby lessening the chance of blending with other fossil fuels [110]. The detailed procedure for the formation of biofuel was studied by Fatehi [87].

6.8 Paper Industry

The major ingredient of paper is cellulose fibers. The quality of paper highly depends on the size and quality of cellulose fiber. Higher the cellulose content in the paper pulp, the better the quality of the paper. In earlier times, the paper used to be made up of bamboo fiber, and silk. Nowadays, it has been replaced by cellulose-based, plant fiber, which has excellent writable properties and is also cheap. Cellulose-based papers are highly porous, rough, and hydrophilic. Three kinds of pulp were studied such as chemical pulp, semi-chemical pulp, and mechanical pulp during paper production. Industrially, the chemical pulp is being extensively used as paper produced from this becomes strong, stable, and easy to bleach, as compared to other pulps [111].

Recently, nano-fibrillated cellulose has become an industrially promising material for the formation of papers. It acts as a reinforcing material on the fiber surface. Also, the nano-fibrillated cellulose plays the role of filler and is incorporated in the voids and pores between the fibers [112].

7 Conclusion

Cellulose being a ubiquitous and easily biodegradable polymer has an immense potential to replace petroleum-based non-degradable polymers. Cellulose possesses fascinating mechanical and thermal properties making it comparable with that of conventional polymers. Cellulose is majorly extracted from the plant via multiple stages of chemical treatment. Other sources include bacteria and marine invertebrate animals called tunicates. Hydrogen bonding present in the Cellulose makes them crystalline, thereby enhancing their mechanical property, but reducing solubility in various solvents, thus affects its solution processability. To enhance the processability of cellulose and to provide better plastic properties, it has been functionalized via various routes viz. etherification and esterification. The free OH group in cellulose assists in their functionalization to produce cellulose derivatives. For example, CMC and EC are some of the commercially available Cellulose ether derivatives used in myriads of application. Cellulose acetate, cellulose nitrate and cellulose sulfate are some of the common cellulose esters discussed in this chapter. By a virtue of their property, cellulose has a great potential to be used in various areas, viz. packaging, pharmaceutical, electronic, biomedical, biofuel, and paper industry. With the development of nanotechnology, cellulose–inorganic hybrid hydrogels are found to have multifunctional applications. Besides, microbial cellulose has become popular in the generation of biomedical devices such as in wound healing, organ replacement etc. Cellulose has become the most studied biopolymer that can be easily processed and industrialized . Therefore, the development of cellulose derivatives along with other polymers as well as inorganic fillers has the potential to show extensive application in our daily life. Nonetheless, they suffer from challenges such as source variation, availability, lack of economically attractive extraction procedures, etc., which require to be overcome in the near future for their widespread applications.

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Chapter 6
Biodegradable Polyurethanes and Their Biomedical Applications

Chandrani Sarkar and Sampa Saha

1 Introduction

Nowadays, synthetic polymers with defined structures and good processability are attracting the attention of researchers. One of the interesting classes of synthetic polymers is Polyurethanes (PUs). PUs are available in a broad range of segmented block structures. They are generally fabricated by the reaction of isocyanates, polyols (diols or triols), and chain extenders; those are the building materials of PUs (Fig. 1) [1–3]. Various types of isocyanates, diols, and chain extenders are commercially available. A few of them are given in Table 1; particularly used for the fabrication of biocompatible PUs. The physicochemical properties of PUs can be tailored with the selection of appropriate types and molar ratios of building materials. The tuning of the physical properties and biodegradability are associated with the quality and percentage of the soft segment (ester bonds), while the hard segment (urethane bonds) is the main factor affecting the structural strength and mechanical properties [4–6]. Due to this versatility, PU became an attractive biomaterial for engineered structures. The investigation of PUs in the biomedical field has been started since the 1960s. The first generation implantable PU is commercially available in 1967 [5, 7–9]. Traditionally, PU is used as a bio-stable implant like vascular grafts, heart valves, catheters, and prostheses. Some commercially available medical grades PUs are given in Table 2. Since 1990, a major drive in the development of biodegradable PUs has been initiated because the next generation medical implants require excellent biocompatibility with controlled degradation to address the materials need for modern medical utility. A deep understanding of the relationship between the molecular structure of PUs on

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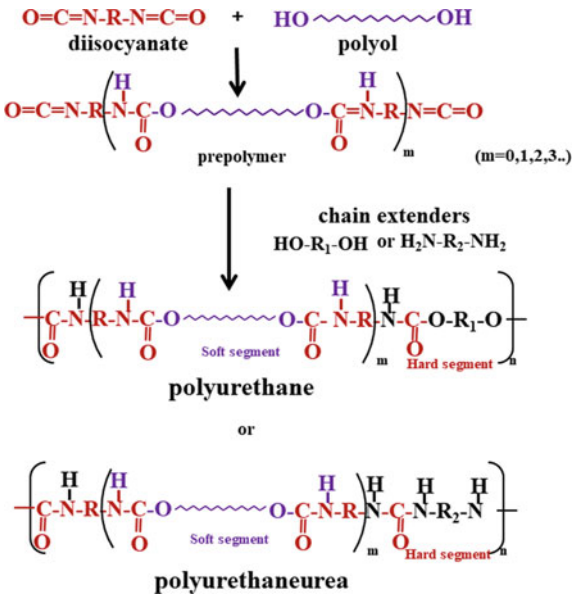


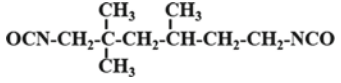
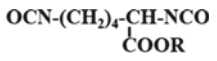
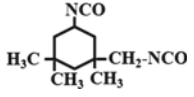
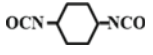
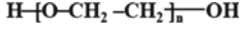
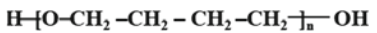
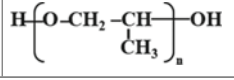
Fig. 1 Formation schemes of PU and PU-urea. Redrawn from [7]

mechanical properties and degradation in in vivo environments plays a key role in designing biodegradable PUs for biomedical applications. In this chapter, we cover the biodegradation and biocompatibility of PUs and their biomedical applications, particularly in tissue engineering and pharmaceutical fields.

2 Biodegradability and Biocompatibility of Polyurethanes

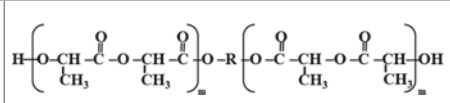
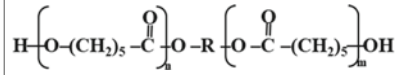
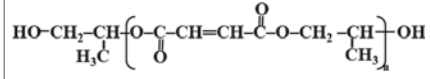
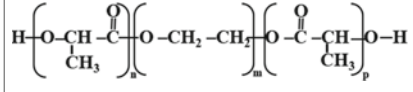
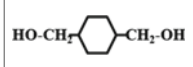
In PUs, degradation mainly relies on the chemical behaviour of its segmented block structure. Each segment link with each other through the urethane or carbamate [−RNHCOOR'−] group in their backbones [2, 4, 5]. As can be seen from Fig. 1, PUs are made up of three constituents: diisocyanate (aromatic or aliphatic), polyol (diols or triols), and chain extender (diols and diamines). They react and form segmented polymer chains with alternating soft and hard segments in their backbones. The soft segments are normally polyester or poly alkyl diol and the hard segments are usually an aliphatic or aromatic diisocyanate [8, 10, 11]. The degradation of PUs is generally tuned with the incorporation of hydrolysable segments into their backbones. In most cases, the degradation rate is governed by soft segments (ester bonds) of PUs; because hard segments (urethane bonds) are not easily hydrolysed. However, incorporating a hydrolysable chain extender made the hard segment of PUs to be degradable [4, 7, 12]. Studies show that the biological degradation of PUs is due to the cleavage of hydrolytic sensitive bonds present in their backbone. The kinetics of the hydrolysis depends on their structural compositions [4, 13]. It is noticed that aliphatic

Table 1 Diisocyanates, polyols, and chain extenders are commonly used in formulating biodegradable PUs

Components	Chemical name	Molecular structure
Diisocyanate	1,4-butanediisocyanate **BDI**	$OCN–(CH_2)_4–NCO$
	1,6-Hexamethylene diisocyanate **HDI**	$OCN–(CH_2)_6–NCO$
	2,2,4-Trimethyl hexamethylene diisocyanate **TMDI**	
	Ethyl 2,6-diisocyanatohexanoate (R=Ethyl) **ELDI** Methyl 2,6-diisocyanatohexanoate (R=methyl) **MLDI**	
	Isophorone diisocyanate **IPDI**	
	1,4-Cyclohexane diisocyanate **CHDI**	
Polyol	Poly(ethylene oxide) **PEO**	
	Poly(tetramethylene oxide) **PTMO**	
	Poly(propylene oxide) **PPO**	

(continued)

Table 1 (continued)

Components	Chemical name	Molecular structure
	Poly(D,L-lactide) **PLA**	
	Poly(ε -caprolactone) **ε-PCL**	
	Poly(glycolide) **PGA**	
	Poly(propylene fumarate) **PPF**	
	Poly(lactic acid-ethylene glycol-co-lactic acid) (PCL-co-PEG-coPCL)	
Chain extender	Ethylene glycol **EG**	$HO–CH_2–CH_2–OH$
	1,4-Butanediol **BDO**	$HO–(CH_2)_4–OH$
	1,4-Cyclohexanedimethanol **CHDM**	
	1,2-Ethanediamine **ED**	$H_2N–CH_2–CH_2–NH_2$
	1,4-Butanediamine **BDA**	$H_2N–(CH_2)_4–NH_2$

(continued)

Table 1 (continued)

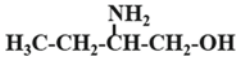
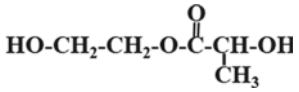
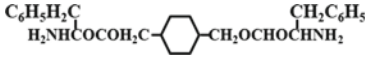
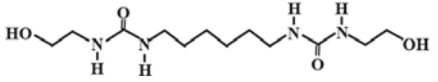
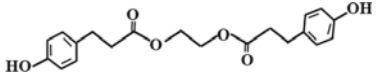
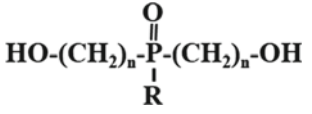
Components	Chemical name	Molecular structure
	2-Amino-1-butanol **ABDO**	
	2-Hydroxyethyl-2-hydroxypropanoate	
	4-((1-(1-amino-2-phenylethoxy)ethoxy)methylcyclohexyl)methyl-2-amino-3-phenylpropanoate	
	1,1-(Hexane-1,6-diyl)bis(3-(2-hydroxyethylurea	
	Ethane-1,2-diyl bis(3-(4-hydroxyphenyl)propanoate	
	Bis(2 hydroxyethyl)phosphate [R=H, n=2] BEP Bis(2-hydroxyhexyl)phosphate [R=H, n=2] BHP	

Table 2 Commercially available medical grade PUs

Comercial name	Manufacturers
Texin®, Texin®4210, Desmopan® DP 2590A, Desmopan® DP 9370A,	Bayer material science
Tecoflex®, Carbothane®, Pellethane®	Lubrizol
Elastollan® SP806	BASF
ChronoFlex®	AdvanSource biomaterials
Bionate®	DSM biomedical
Elast-Eon®	RUA biomaterials
Artelon®	Lavender medical
Lacthane®	Polyganics
NovoSorb BTM	PolyNovo

ester bonds are more susceptible to hydrolytic cleavage than aromatic ester linkages [2, 4, 14]. Moreover, the degradation rate depends on the composition of polyesteric soft segments of PUs. PUs with hydrophilic soft segments [e.g., polyethylene glycol (PEG)] degrade more rapidly than PUs with hydrophobic soft segments [e.g., PCL] [2, 12, 15]. If soft segments are aliphatic polyesters like PCL, PLA, and PGA, then PUs are readily biodegradable. The crystallinity of soft segments also affects the degradation rate of PUs, amorphous segments degrade more rapidly than semicrystalline segments. Because the high content of crystallinity reduces water absorption capacity and restricts polymer chain mobility, thereby reducing the degradation rate of PUs [2, 12, 16, 17]. Tang et al. observed that the degradation rate also depends on the hydrogen bonding of the segmented structure. The hydrogen-bonded urethane degrades slower than the non or less hydrogen-bonded urethanes [18, 19].

Understanding the rates of degradation and bioresorbable mechanisms in biological environments is essential for clinical applications of PUs. The main functional groups susceptible to hydrolytic or enzymatic degradation are ester and urethane in biodegradable PUs [2, 7]. The degradation rate of the ester group is considerably higher than urethane which results high concentration of oligomeric products of PUs during the early stage of the degradation. These oligomeric molecules are excreted from the body via filtration through the kidneys. The safety of these oligomeric molecules is crucial to assess because of the difficulties in their isolation steps [7, 12]. Various studies on in vitro degradation of PUs have been conducted in PBS (phosphate buffer solution) medium at pH 7.4 and 37 °C for mimicking hydrolytic environment. The change in mass of PUs and pH of the medium are generally measured as a function of degradation [7]. Few studies showed that PUs made with aromatic isocyanates are less biocompatible due to the release of aromatic amines after degradation [2]. However, in vitro degradation tests are only applicable for the initial screening of materials. A well-designed in vivo study is essential for site-specific applications of PUs. Numerous in vitro and in vivo studies have evidenced the biocompatibility of aliphatic PUs, which is favourable in biological environments. Standard cytotoxicity assays and in vitro cell studies with different cell lines

like chondrocytes [20–27], fibroblasts [27–32], osteoblasts [15, 33–39], endothelial [15, 40–43], and stem cells [40, 44–47] on biodegradable PUs with a broad range of chemical composition have been reported. Studies demonstrated that biodegradable PUs have acceptable cytocompatibility. Researchers extensively studied the biomedical application of biodegradable PUs both in tissue engineering and drug delivery field which are critically reviewed in subsequent sections.

3 Polyurethanes in Tissue Engineering Applications

In tissue engineering, biological substitutes should facilitate the regeneration of tissue and help in the restoration of its function. For this, the material should mimic the microstructure, physicochemical and mechanical properties of natural tissue [48, 49]. In our body, different tissues possess different structures and properties. Most studied tissues and adequate material properties are concise in Table 3. In the tissue engineering process, biodegradable materials play a critical role to support and accelerate the new tissue formation. They should be biocompatible and have tunable degradation rates with nontoxic degradation products [50]. Biodegradable PUs are promising materials used in the synthesis of scaffolds to regenerate tissues. Numerous studies on the design and fabrication of PUs for tissue engineering applications have been reported [7, 51–53]. Biodegradable PUs have been studied for both soft tissue and hard tissue, details of which are given below.

Table 3 Most studied tissues and adequate material properties

Tissues	Adequate modulus	Adequate porosity and pore sizes	References
Cardiac tissues	5–50 kPa	75–96%, $\leq$300 μm	[53–55]
Skeletal muscle	5–170 kPa	90%, 50–200 μm	[53, 56, 57]
Cartilage	2.8–18.6 MPa	75–87%, 75–175 μm	[58, 59]
Nerve guide	0.30–30 MPa	60–80%, 30–50 μm	[60]
Vein	34 kPa (circumferential) 102 kPa (longitudinal)	6.5–7.6 nm	[61, 62]
Aorta	128 kPa	1–20 μm	[62, 63]
Bone	1.28–1.97 GPa, (cancellous) 10.4–20.7 GPa (cortical)	75–90%, 140–600 μm (cancellous) 5–10%, 10–50 μm (cortical)	[53, 64]

3.1 Polyurethanes in Soft Tissue Engineering Applications

Soft tissues are found throughout the human body. They support, connect and protect all the organs of the body, and give shape/structure to the body. There are different types of soft tissues—muscle, fibrous tissue, vessels, and nerves. Extreme activities lead to soft-tissue damage which causes pain, swelling, and bruising. Sometimes, it needs autografting. Due to certain limitations of autografting, biodegradable synthetic materials are used as alternatives [65, 66]. In this chapter, various biodegradable PUs for soft tissue engineering applications have been discussed.

Cardiovascular Applications

Cardiac tissues are found in the wall of the heart which allows the heart to pump blood. Biodegradable materials with high tensile strength and elasticity are generally required for cardiovascular tissue engineering. For this, biodegradable PUs comprised of polyols like PCL, PEG, and their copolymers along with diisocyanates such as ELDI (Ethyl 2,6-diisocyanatohexanoate), HDI(1,6-Hexamethylene diisocyanate), and BDI (1,4-butanediisocyanate) have been designed. PCL generally improves the elastomeric properties of PU whereas PEG makes it hydrophilic and affects the degradation rate [24, 67, 68]. Structural modification of PUs by chain extender is one of the prominent strategies used by researchers to develop biodegradable PUs for soft tissue engineering. The incorporation of chain extenders based on amino acids has been explored by several groups to develop PUs for soft tissue engineering [69–71]. Rechichi et al. designed chain extenders by reacting phenylalanine with 1,4-cyclohexanedimethanol and synthesized a series of PUs using MLDI, PCL or PCL-PEG-PCL [28]. Fromstein et al. showed the effect of blending amino-acid-based PUs with other components like MLDI/PCL or MLDI/PEG on properties and degradation rate to assess their suitability for soft tissue engineering. The mechanical properties of the blends varied from 6 to 20 MPa, while elongation at break varied in the range of 512–690% [44, 72]. Gorna et al. designed a series of PUs using PCL, PEG, HDI, IPDI, and chain extenders BDO and 2-amino-1-butanol in different ratios. They showed a wide range of tensile strength from 4 to 60 MPa, whereas the elongation varied from 100 to 950% [66]. Earlier studies were mainly focused on the development of materials that possess elastomeric properties which provide sufficient mechanical support to the cardiac system. Nowadays, biocompatible and bioactive materials having good mechanical properties are in demand. Many biocompatible cardiac materials made up of PCL-based PUs having urethane and/or urea groups in their backbone have been studied. Guan et al. fabricated a series of PU-urea elastomers using PCL-PEG-PCL, BDI, and 1,4-butanediamine. These showed good endothelial cell adhesion due to the immobilization of Arg-Gly-Asp on its surface. Moreover, these PUs have good mechanical properties (tensile strengths ~8–20 MPa, strains ~325–560%) [15]. Sometimes, researchers incorporated gold nanotubes/nanowires in PUs in order to improve the electroactivity of

material, and stimulate cardiomyocyte cells for accelerating cardiac tissue regeneration [73]. Researchers also fabricated highly porous PUs for soft tissue engineering applications. Guan et al. fabricated a highly porous PUs scaffold (porosity ~80–97%) by a thermally induced phase separation process. Porous scaffold supported good cell adhesion and proliferation. However, the tensile strength of the scaffold was 1 MPa, which is sufficient for soft tissue engineering applications [67]. Researchers prepared an elastomeric porous cardiac patch from biodegradable PU based on butyl diisocyanate, PCL, and putrescine, and showed degradation in the rat model. At 4 weeks, ingrowth of fibroblast into PU patch was found and cellular infiltration of the implant enhanced. At 12 weeks, the PUU patch was completely degraded [74]. The same authors investigated PU cardiac patch for its effectiveness to promote vascular remodelling and improve function by implanting the patch onto sub-acute infarcts in Lewis rats. It was observed that the left ventricular wall was thickened and the patch was mostly remodelled [75]. PU patch accelerated the formation of new contractile phenotype smooth muscle tissue and enhanced contractile function. Researchers also synthesized myoblast seeded PUs scaffolds from MDI, 1,3-diaminopropane and ε-PCL-diol (530 Da) for direct intramyocardial cell transplantation [76, 77]. Hashizume et al. designed porous biodegradable PU and applied in a rat model of ischaemic cardiomyopathy for 16 week and found degradable cardiac patch benefit in treating ischaemic cardiomyopathy [78] (Fig. 2).

Musculoskeletal Applications

Since 1990s, biodegradable PUs scaffolds have been evaluated for the knee-joint meniscus. In the early years, MDI-based PUs were investigated for the healing of meniscal lesions. However, its toxic degraded product, i.e., MDA limits its applications. So, PUs scaffolds based on aliphatic diisocyanate BDI, poly(ε-caprolactone-co-l-lactic acid) diol, and 1,4-BDA or 1,4-BDO have been studied for cartilage tissue regeneration and found suitable for regeneration of fibrocartilage [79]. Spaans et al. fabricated microporous PUs-based scaffold for replacement of knee-joint meniscus. They used 50/50 l-lactide/PCL polyol for soft segment and BDI/adipic acid/water for hard segment formation. The reaction between water and BDI forms CO_2 gas which creates micropores (porosity ~70–80%). This microporous PUs scaffold facilitated fibrocartilage formation in the lateral meniscus of dogs after 18 weeks of implantation [80, 81]. Similarly, Grad et al. demonstrated porous PU fabricated from HDI, ε-PCL, and isosorbide diol favoured chondrocyte attachment, proliferation and provide mechanical support to grow functional cartilage-like extracellular matrix [23]. Field et al. formulated an in situ curable biodegradable PU based on dl-LA/GA and ELDI to repair meniscal cartilage tissue [82]. Researchers fabricated PU-based nanofibers using the wet-spinning process for anterior cruciate ligament reconstruction. PU-based fibres showed high strength and stiffness and retained almost 50% of their tensile strength for 9 months at physiological temperature [83]. In vivo studies

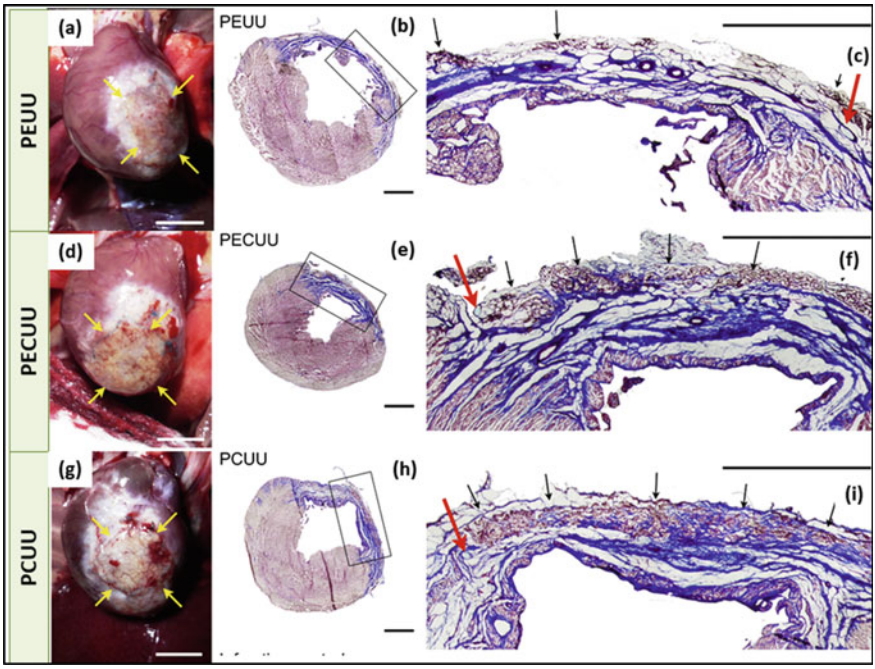


Fig. 2 Representative macroscopic images **a**, **d**, **g** of using different polyurethane [polyester urethane urea (PEUU), polyester carbonate urethane urea (PECUU), polycarbonate urethane urea (PCUU)] cardiac patches after 16-week study in a rat model of ischaemic cardiomyopathy [scale bar ~5 mm]. The corresponding images **b**, **e**, **h** of Masson's trichrome stained cross-sections of the heart after 16-week implantation of PEUU, PECUU, and PCUU [**c**, **f**, and **i** are magnified images] [scale bar ~2 mm]. Yellow and black arrows indicate the edge and regions of the implanted PU. Red arrows indicate the suture lines. Reprinted with copyright permission from Elsevier [78]

supported its biocompatibility and safety issues. The trade name of this material is Artelon® commercialized by Artimplant® AB, Goteborg, Sweden. This material has also been developed as a spacer for the trapeziometacarpal joint for the treatment of osteoarthritis [84].

Neural Applications

Nerves are soft tissues of the human body that control the movement and functions of the whole body. Nerve tissue collectively in the brain and spinal cord creates the central nervous system of the body, and nerves outside the brain and spinal cord create the peripheral nervous system. Peripherical nerve injury is the most common clinical problem. Researchers focus on the development of tubular structures that guide nerve regeneration [52, 85]. Biodegradable PUs offer attractive properties like tunable mechanical strength, flexibility, and high

biocompatibility in fabricating tubular grafts for nerve regeneration. Borkenhagen et al. designed PU-based tubular structures made up of poly[glycolide-co-(ε-caprolactone)]-diol, poly[(R)-3-hydroxybutyric acid-co-(R)-3-hydroxyvaleric acid]-diol and 2,2,4-trimethylhexamethylene diisocyanate. This nerve conduit (10 mm long) was implanted in rats for 4, 12, and 24 weeks. They found regeneration of nerve tissue in the implanted site with no inflammatory reaction with degraded product [86]. Dezhznz et al. fabricated nerve conduits from biodegradable PU based on ε-PCL-diol, HDI, and PEO-diol. In in vivo study, myelinated axon regeneration and PU degradation were observed after 4 weeks and 12 weeks of implantation in rabbits, respectively [87]. Nowadays, researchers mainly focus on the development of fully functional nerve reconstruction in the minimum time span. The porous PU scaffold exhibited good nerve regeneration potential due to high interconnectivity and varied pore sizes in the outer (42 μm), inner surfaces (9 μm), and cross-sectional (23 μm) area. Asymmetrical pores facilitate good wound inflammation waste drainage and better permeability for growth factor that leads quick nerve regeneration [88]. Researchers demonstrated new electroactive nerve conduits made up with PU based on poly (glycerol sebacate) and aniline pentamer. Its higher electroactivity accelerated neuronal Schwann cells for high release of nerve growth factor that induced neurite growth and fast nerve regeneration [89].

Vascular Applications

Blood vessels (veins, arteries, and capillaries) are functionally dynamic tissue with minimal regeneration potential. These vessels are long, elastic hollow tubes with varying thicknesses and architecture. Blood passes through these vessels and transports oxygen, nutrients, and waste products around the body. Various polymeric materials have been developed for blood vessel replacement. Clinical use of synthetic vascular grafts is limited mainly due to thrombosis and intimal hyperplasia. Thrombus formation is occurred by platelet adhesion and slow endothelialization that leads to abnormal accumulation of vascular tissue in the graft lumen [90–93]. In order to solve these problems, a strategic approach like surface modification of synthetic vascular grafts has been adopted which enhanced the hemocompatibility and long stability of vascular grafts [91, 94]. PU is the most common polymer used for the production of blood-containing devices like blood bags and artificial hearts valve due to its good hemocompatibility and mechanical properties [90, 94]. Researchers modify the surface of PU with PEG and peptides in order to compliance with natural blood vessels [95–97]. Modified PU showed good mechanical stability and less thrombogenicity. Researchers have designed PU film based on PCL, MDI, and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). PHBV incorporation increased the mechanical properties and surface hydrophilicity of the film. Moreover, PU film showed exceptional cytocompatibility and hemocompatibility with poor platelet adhesion and haemolysis, suitable for vascular grafts [98].

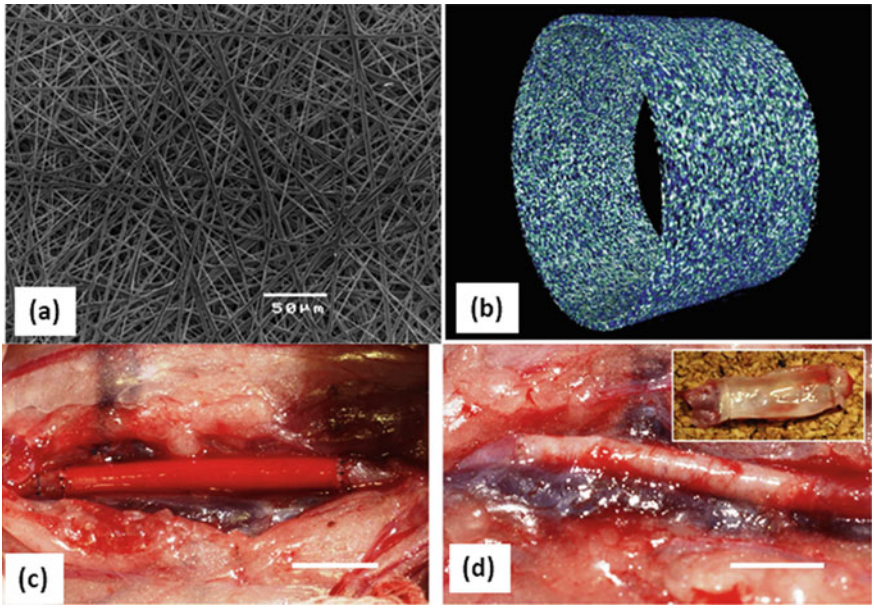


Fig. 3 **a** Scanning electron microscopic image and **b** 3D μCT image of electrospun PU vascular graft. Images of PU grafts just after implantation (no blood leakage observed) (**c**) and after 12 months implantation (well integrated with adjacent tissue with no inflammation and no thrombus formation) (**d**) [scale bars ~6 mm]. Reproduced with permission from Elsevier [100]

Long-term mechanical stability of vascular graft is needed for complete regeneration and restoration of the vascular wall structure. Researchers developed mechanically robust, long-lasting PU-based elastomeric scaffolds for vascular grafts [99]. Bergmeister et al. fabricated vascular grafts from biodegradable PU and these grafts showed good performance at the implant site of Sprague Dawley rat for one-year study [100] (Fig. 3).

3.2 Polyurethanes in Hard Tissue Engineering Applications

Calcified tissue like bone is categorized as hard tissue of the body. It has good healing ability under specific biological environments. Throughout our life, it undergoes a continuous process of remodelling. However, severely damaged bones need immediate replacement with functional bone substitutes. The suitability of bone substitutes depends on their mechanical and structural properties such as strength, modulus, porosity, and size of pores that support cell mobility, vascular ingrowth, and bone tissue formation [48, 49, 101]. In the next section, we have discussed various biodegradable PUs scaffolds for bone tissue engineering.

Polyurethane Scaffolds

Since last decade, the development of biodegradable PU scaffolds has increased dramatically due to their tailorable physicochemical and mechanical properties. These biodegradable PU scaffolds have certain limitations like poor cell adhesion, differentiation, and biomineralization properties that may be due to pH changes around the scaffold after degradation. Although it is known that osteoblasts proliferate and differentiate at physiological pH 7.4 [102], researchers have attempted to control pH changes in the microenvironment by designing a 3D printed PU-urea scaffold based on poly (D, L-lactic acid) diol with piperazine moieties and isosorbide-HDI/HDI. In the in vivo study, the scaffold exhibited excellent cytocompatibility and bone tissue formation ability after 8 weeks of implantation. This is due to the stable neutral pH maintained by piperazine after the degradation of the scaffold [103–107]. In another study, researchers designed chondroitin sulfate sodium (bone extracellular matrix component) grafted PU-based scaffolds to promote osteoblast adhesion and bone tissue regeneration [108, 109]. Inorganic fillers were incorporated to gain mechanical properties as compared to bare polymers. Researchers have incorporated bioactive particles like hydroxyapatite (Hap, an inorganic component of bone) into the PU matrix and enhanced the mechanical properties as well as the bioactivity (e.g., osteoconductivity, supports bone tissue formation) of scaffolds [110–112]. Liu et al. incorporated Hap in PU during the PU formation step and designed a highly porous (pororsity ~83%) scaffold with good mechanical properties (compressive strength ~554 kPa) [112]. Similarly, Nasrollah et al. prepared PU-Hap scaffolds via in situ polymerization and described the role of Hap in pore creation as well as cell attachment and proliferation on the scaffold [113]. In another study, researchers showed that Hap-incorporated PU scaffolds significantly enhanced cell adhesion and proliferation both in cell study and animal study. Researchers demonstrated the suitability of highly porous (porosity ~78–81% and pore size ~300–1000 μm) Hap-incorporated PU foam in the biomineralization and bone tissue regeneration process. They found the formation of bone matrix and trabecular regeneration in their study that showed excellent biocompatibility and osteogenic differentiation of cells in presence of Hap incorporated PU foam [114]. Scientists implanted citric acid (calcium-complexing agent) incorporated PU scaffolds in oestrogen-deficient sheep and found high bone regeneration after 18–25 months [115]. All these studies showed that PU composite scaffolds can be potentially used in bone tissue engineering applications (Fig. 4).

Injectable Polyurethane Prepolymer Systems

The injectable bone void fillers loaded with/without growth factors are commonly used for the treatment of bone defects. The formulation of two-component prepolymer systems that react upon mixing under mild conditions has the advantage of such delivery to the defect site through minimally invasive procedures. Researchers extensively investigated the potential of liquid two-part urethane formulation in such biomedical applications. The injectable prepolymer systems are formulated to form

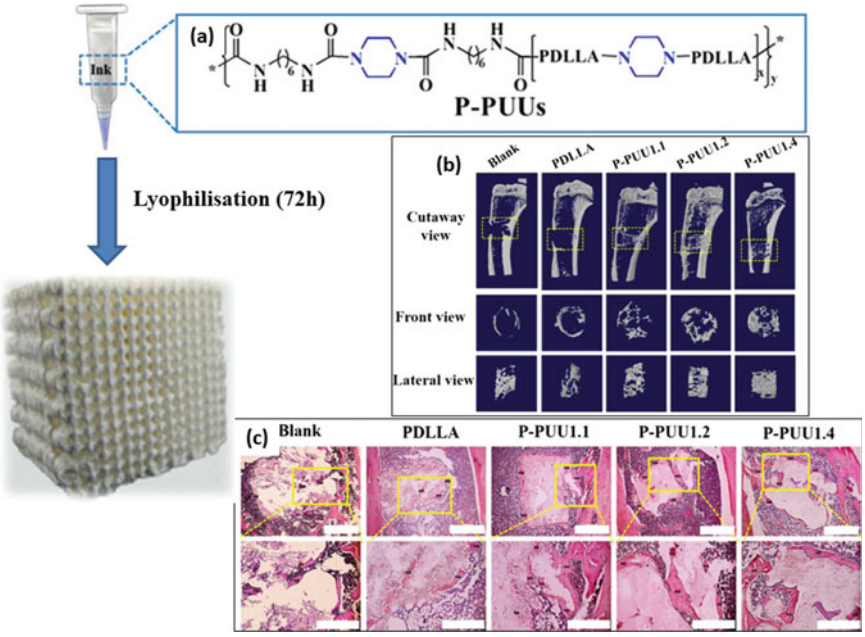


Fig. 4 Schematic presentation of piperazine-based PU-urea (P-PUUs) **a** Chemical formula of P-PUUs, **b** 3D μCT images, and **c** H&E staining images [Scale bar ~1 mm (top image) and 500 μm (bottom images)] after 8 weeks implantation of scaffolds (different content of piperazine) in rat model. Reproduced with permission from the American Chemical Society [103]

cross-linked polymer networks upon completion of the urethane formation once the components are mixed together. These liquid two-part urethane systems should be formulated in such a way that no by-products (low molecular weight) are released during curing, and they cure with a low reaction exotherm (not exceeding body temperature) [7]. Gunatillake et al. developed multiple PU prepolymers systems for varied applications in the biomedical field including tissue engineering [116]. They mixed diisocyanates ELDI or MLDI (liquids at and above ambient temperature) with multifunctional core molecules (pentaerythritol, glucose or glycerol) and produced isocyanate end functional prepolymers (Prepolymer A) which were viscous liquids at ambient temperature. Polyester polyol like PCL /PLA /PGA /PLGA polyols was used as the second component (Prepolymer B). The reaction of the two prepolymers (Prepolymer A and Prepolymer B) produced a cross-linked polymer network at ambient temperature. With the appropriate choice of polyols and diisocyanates, they produced a cross-linked PU network with a wide range of mechanical properties (Compressive strength ~260 MPa, compressive modulus ~2 GPa) [25, 35, 116, 117]. PU prepared by this approach showed good compatibility with osteoblasts. It is found that highly viscous liquids create some miscibility and injectability issues. To eradicate these issues, Guelcher et al. have employed a quasi-prepolymer approach and end-capped all the polyol hydroxyls with excess use of polyisocyanate (NCO:OH

equivalent ratio >5:1). The excess diisocyanate kept the viscosity low of the quasi prepolymer, and formed PU networks by the reaction of the available isocyanate groups with a polyester polyol. The compressive strength and modulus of PU films were in the range of 82–111 MPa and 1200–1430 MPa, respectively. PU films were found to release nontoxic degraded products and supported the attachment and proliferation of MC3T3 cells [118]. The degradation, safety, and suitability of injectable prepolymer systems were also evaluated in an animal model (in sheep). PE and ELDI were used as Prepolymer A, and PE and DL-lactic acid (molecular weight 456) or PE and glycolic acid (molecular weight 453) were used as Prepolymer B. The cured polymers in this study exhibited compressive strength and modulus in the range of 100–190 MPa and 1600–2300 MPa, respectively. So, researchers had used both precured scaffolds and prepolymer liquid mixture for in vivo study. Precured cylindrical scaffolds (diameter ~10 mm) were implanted in sheep femurs, and prepolymer mixture in liquid form was injected to fill the voids and allowed to set for 8–10 min before closing the surgical site. This study demonstrated that PU in both forms (injectable and precured) did not show any surgical issues, even new bone tissue formed and PU degraded gradually [117] (Fig. 5).

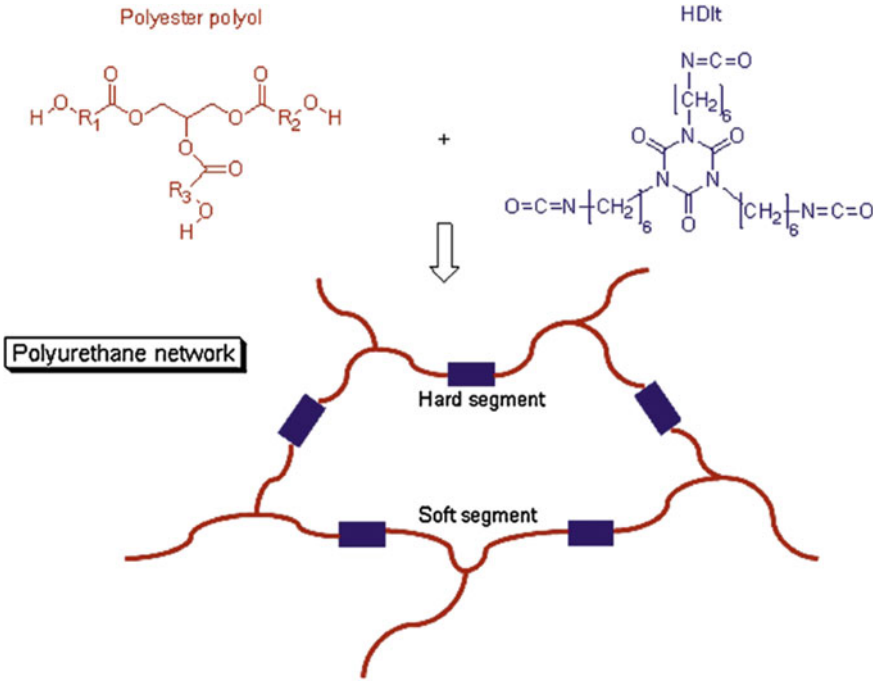


Fig. 5 Formation of PU network [119]. Adapted with permission from Elsevier [2]

4 Polyurethanes in Drug Delivery Applications

PUs are a common choice for the synthesis of drug delivery vehicles due to their tunable composition and tailor-made properties. Several drug delivery systems in different forms like micro/nanosystems (micelles, micro/nanoparticles), membrane/film systems, and matrix systems such as gels or scaffolds based on degradable PUs have been reported [2–6, 119–121]. Various forms of PU-based drug delivery systems are tabulated in Table 4. In numerous reports, the release behaviour of PU systems is generally correlated with the composition, swelling, and degradation rate at different pH. The drug release from PU matrices relies on the loading content and solubility of the drug as well as the degradation rate and swelling of the matrices [2, 122]. Water swollen PU system showed a linear relationship between cumulative drug release of a hydrophilic drug such as tenofovir with time [123]. Moreover, a more linear release of dapivirine (another anti-retroviral agent) was observed from water-absorbed PU matrices than from non-water-absorbed PU matrices due to controlled dapivirine diffusion [123].

The stimuli-responsive structure of PU facilitated the modulation of the drug release profile by tuning the degradation and/or adjusting the glass transition temperature of PU. Temperature increases the mobility of the PU chains, weakening the interactions between PUs and drugs; thereby leading to enhanced drug diffusivity [4, 122]. Fast degradation of PU matrix shows a more rapid drug release compared to non-degrading or slowly degrading PU matrix. Drug delivery vehicles based on PUs with quick degradation have been developed by introducing highly degradable PLA or PLGA into PU chains; tuning the degradation rates by changing their molar ratio in the final PU [124–127] (Fig. 6).

Multiresponsive such as temperature, pH, redox, or enzyme-sensitive PU drug delivery systems have been also reported. The first stimulus, i.e., the temperature normally permits drug carriers to enter into cancer cells, and the second stimulus (for example enzyme attack) initiates the disassembly of polymers leading to final drug release [52]. Redox-responsive PU (PLA-dithiodiethanol-PLA diol) based self-assembled micelles were stable at physiological pH, whereas drug release occurred in the microenvironment of the cancer cells (acidic pH) [128]. Another stimuli assisted degradation is currently being explored and a major focus is on the development of enzymatic intracellular responsive PU systems for anticancer drug release [129]. A summary of several drug delivery systems based on PUs has been tabulated below.

5 Tissue Adhesives Applications of Polyurethanes

In most of the surgical procedures in the world, stapling/suturing is used for the purpose of tissue binding that keeps the tissues attached for healing and lessens bleeding. Uncontrolled bleeding and air/gas leaking are the few complications of these techniques. There is an emergence to develop an advanced tissue closure

Table 4 Polyurethane-based drug delivery systems

Delivery system	Drug incorporated	Outcome
PU nanoparticles	Adriamycin	– Temperature-responsive PU nanoparticles were created by using PEG and LDI (L-lysine ester diisocyanate) – Drug release behaviour depends on the transition temperature of LDI-PEG600 [130]
PU nanoparticle	Doxorubicin (DX)	pH and temperature-responsive PU nanoparticles were synthesized using HDI and MDI [131]
PU nanoparticles	DX	pH sensitive PU nanoparticles showed high cellular internalization and high anti-proliferative effects on MCF-7 cells (human breast cancer) [132]
PU nanoparticles	paclitaxel	Paclitaxel-loaded PU nanoparticles showed good distribution in healthy mice [133]
PU microparticles	Epigallocatechin gallate	Epigallocatechin gallate-loaded PU showed a toxic effect on Detroit 562 cells (human pharyngeal carcinoma) and SCC-4 cells (squamous carcinoma) [134]
PU microparticles	DX	PU microparticles showed effective transportation of DX into cells and high anti-tumour activity towards cancer cells and 3D multi-cellular tumour spheroids [135]
PU conjugates	DX	DX-loaded PU conjugates showed a high release of the drug under acidic conditions. It showed pH and ultrasound triggered drug release and inhibit tumour growth [136, 137]
PU nano micelles	Paclitaxel	PU nano micelles are easily internalized into the cells and released paclitaxel within tumour cells under an acidic environment [138]
PU nano micelles	DX	– Showed sustained release of DX at different pH. DX-loaded PU micelles exhibited high toxicity against RAW 264.7 and MCF-7/ADR cancer cells [139–143] – They also showed high anti-tumour efficacy in in vivo studies – Folic acid-conjugated DX-loaded PU micelles easily internalized into KB cells (human epidermoid carcinoma cell), and showed high toxicity with the release of DX – Thermoresponsive PU nano micelles have a lower critical solution temperature at 41–43 °C comparable to cancer tissue temperature. DX-loaded PU nano micelles exhibited high toxicity (almost 90%) towards MCF 7 cells

(continued)

Table 4 (continued)

Delivery system	Drug incorporated	Outcome
PU micelles	DX	– Redox-sensitive PU micelles showed controlled release of DX in the presence of glutathione (a reducing agent) and high cytotoxicity towards cancer cells [144–150] – DX-loaded PU micelles showed high anticancer activity and toxicity against C6 cells (rat glioma cells), Saos–2 cells, MCF-7 cells, and HeLa cells due to the quick release of DX under an intracellular reducing environment – Redox and pH-responsive PU micelles also showed toxicity to C6 cells due to the controlled release of DX – At low pH, DX was rapidly released and effectively transported into the cell nuclei and showed cytotoxic effects to cancer cells – The enzymatic degradation of PU micelles chiefly occurred at the ester linkage under the physiological condition for 8 weeks
PU micelles	Paclitaxel	Showed pH-responsive release of paclitaxel from PU micelles into H460 cancer cells [151]
PU micelles	DX and paclitaxel	Redox-responsive PU micelles exhibited high cytotoxicity towards tumour cells (HepG2) [128]
PU microcapsules	DX	– pH-sensitive PU microcapsules showed a controlled drug release profile – Those microcapsules are easily internalized into Hela cells and BGC 823 [152]
PU matrix	Cefamandole nafate	– Showed controlled release of drug and prolonged antimicrobial activity upto day 9 [153, 154]
PU matrix	Metoprolol tartrate	– Drug loading efficiency ~65% – Can be administered through the oral route [155]
PU pellet	Model drugs	– Double-coated PU pellets fabricated by using (carboxymethyl)(ethyl)-cellulose and azo polymer for controlled release of drug – Colon-specific delivery [156]
PU thermogel	DX	– Showed sustained release of DX and an anti-melanoma effect on tumours [157]
PU core–shell nanogel	DX	– Redox-responsive PU gels were designed with hydrophilic PEG [158] – Reducing agent, Glutathione triggered the drug release at pH = 7.4
PU film	Chlorhexidine diacetate	– Showed antibacterial activity against *Staphylococcus species* [159]

(continued)

Table 4 (continued)

Delivery system	Drug incorporated	Outcome
PU film	Gemcitabine	– Initial burst release [160] – Local drug delivery applications
PU films	Methotrexate	– Methotrexate was released with almost zero-order kinetics for 96–144 h [161]
PU core–shell nanofiber	5-fluorouracil and paclitaxel	Drugs were released in a controlled manner at both acidic and physiological pH [162]
Gold-coated PU nanofibers	Temozolomide	Sustained release of temozolomide was observed for 30 days which inhibit the growth of U-87 MG human glioblastoma cells [163]
Amphiphilic block segmented PU nanofiber	Curcumin	Curcumin-loaded triblock (PEG-PCL-PEG) segmented PU nanofibers were fabricated. These nanofibers showed a steady release of curcumin for 18 days and good antibacterial activity against Escherichia coli and *Staphylococcus aureus* [119]
PU membranes	Paclitaxel	Temperature responsive PU membranes were fabricated with a lower critical solution temperature of 44 °C. Below this point, the PU matrix prevented the diffusion of paclitaxel; upon heating above this temperature, the matrix suddenly switched on and diffusion of the drug occurred [164]
Waterborne PU membrane	DX	Waterborne PU membranes showed fine biodegradability, favourable cytocompatibility, hemocompatibility and sustained release of DX caused high toxicity to tumour cells [121]
Waterborne PU	5-fluorouracil	The release rate of 5-fluorouracil was tuned with the length of the chain extender and molecular weight of PEG [165]
PU foam	Gefitinib	Gefitinib was released in a controlled manner for nine months. This can be used for the treatment of broncho tracheal cancer [166]
PU foam	Anticancer compounds DB-67 and DX	– Drugs were covalently attached to PU foam – Differential release of drugs depends on the chemical structure of the drug and temperature [167]
PUs scaffold	Platelet-derived growth factor (PDGF)	– Biphasic release of growth factor – PDGF-loaded PU showed wound healing potential in in vivo study [168]
PU scaffold	Recombinant human bone morphogenetic protein (rBMP)	– Sustained release of rBMP enhanced new bone tissue formation [169]

(continued)

Table 4 (continued)

Delivery system	Drug incorporated	Outcome
PU adhesive	Thiamazole diclofenac and ibuprofen	– Pressure-sensitive PU adhesive showed excellent stabilization of the drugs without any irritation in the skin [170]
Modified PU	Ibuprofen	– Ibuprofen was incorporated in the polymeric backbone via ester linkages, and release was based on the degradation of ester bonds [171]
PU dual delivery system	Dapivirine, tenofovir	– Sustained release of drugs over time [123]
PU implant	Cyclophosphamide	– Controlled release of the cyclophosphamide [172]

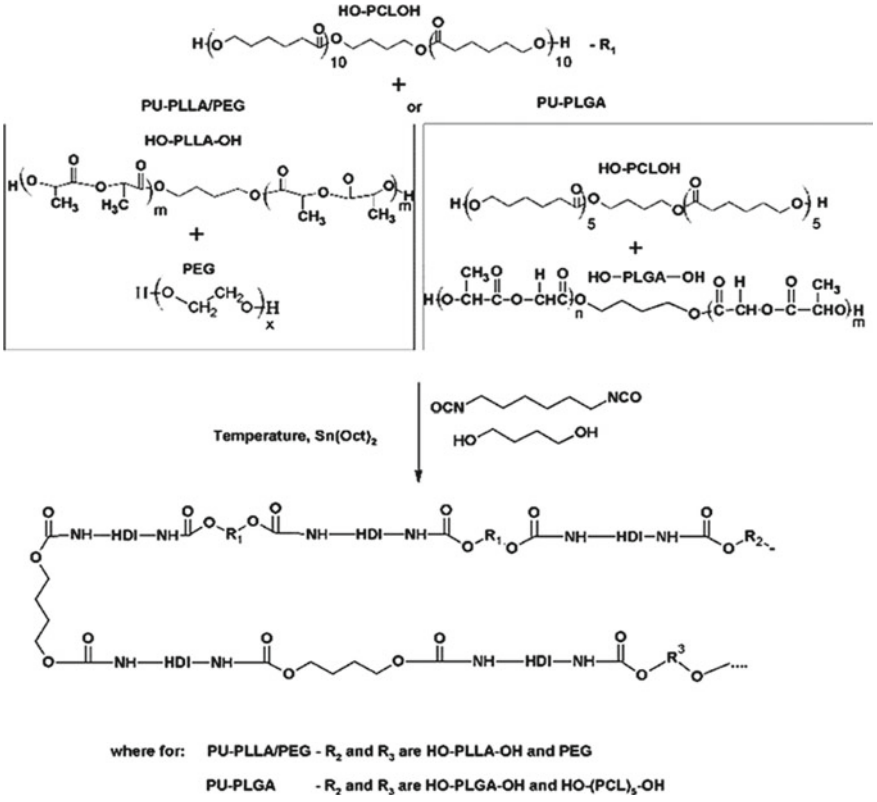


Fig. 6 Formation scheme of PU-PLGA and PU-PLLA-PEG. Reproduced with permission from Elsevier [127]

that replaces sutures. Therefore, tissue adhesive materials have been developed and are available in the market in different forms [52]. Based on the purpose, tissue adhesives are categorized in three different forms: (a) Haemostats are commonly used when blood loss occurs due to tissue damage, this material stops bleeding by involvement in the clotting process; (b) Sealants are commonly applied as a physical barrier during blood leaking. They act as a mid-range adhesive to tissues; (c) glues strongly adhere to tissues [173–175]. The performance of these materials is usually better in a dry environment; however, it is required to perform well in wet conditions also [176]. Besides this, a few other properties like fast curing time, no or low swelling, mechanical stability, and biocompatibility are the key requirements for tissue adhesive [177]. Polymeric tissue adhesives, chiefly PUs-based adhesives, have been extensively studied due to the reactivity of –NCO group in the PU backbone. The –NCO group reacts with water and –OH groups and accelerates tissue adherence in wet conditions. Thus, –NCO terminated PU adhesives can be easily cured in aqueous environment. However, the exothermic reaction water with –NCO group and toxic effects of these materials limit their applications [173, 178–182]. So, researchers developed saccharide based PU solutions for tissue adhesives applications. Numerous –OH groups from saccharide facilitated the adhesion process via hydrogen bonding because no free –NCO groups were available in the material [183] (Fig. 7). Researchers also improved curing time (cured with minutes) by designing biobased photo-crosslinkable networks based on oxidized urethane-modified dextran [184] or methacrylate end-capped PLA [185]. A few systems on biobased PU tissue adhesives have been developed so far. Still, research needs to be carried out to develop biobased PU adhesives for surgical adhesive applications. TissuGlu® is the PU-based (Lysine-derived Urethane) tissue adhesive which is commercially available in the market [52, 176]. Recently, Zou et al. designed a multifunctional wound adhesive using L-Arginine-based degradable polyurethane and gelatin-methacryloyl. It showed shape-adaptive adhesion and haemostatic effect of the damaged organ on rat liver haemorrhage model [186].

6 Conclusion and Future Prospective

Over the last two decades, many research groups have widely explored the potential of biodegradable PUs for biomedical applications, especially in tissue engineering and drug delivery field. In this chapter, we have discussed the tailor-made properties of biodegradable PUs with varied soft and hard segments; their biocompatibility both in vitro and vivo environments. The biomedical applications of biodegradable PUs have been discussed in detail covering tissue engineering, drug delivery, and tissue adhesive applications. With many supporting studies to confirm biocompatibility, the ability to tailor mechanical properties, and degradation kinetics coupled with numerous processing options, biodegradable PUs offer attractive future opportunities to fulfil needs for next generation biomaterials. For translation research, studies should be more emphasized on preclinical evaluation because of the limited number

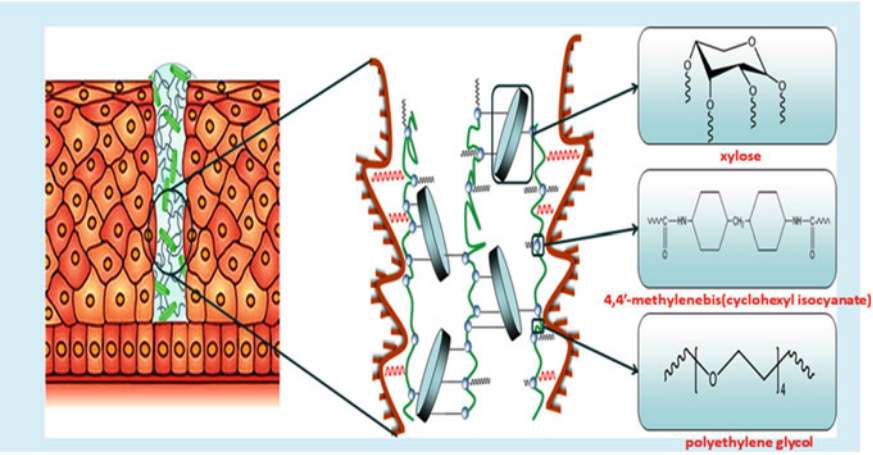


Fig. 7 Xylose-based PU for tissue adhesives applications. Reproduced with permission by Balcioglu et al. [183]

of in vivo studies available on biodegradable PU. The efficacy and safety of PU system should be demonstrated. The clearance of degraded products by metabolizing organs should also be thoroughly assessed.

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Chapter 7
Biodegradable Polymers—Carriers for Drug Delivery

Nidhi Gupta, Chandrani Sarkar, and Sampa Saha

1 Introduction

Drug delivery carriers are pharmaceutical formulations that can incorporate therapeutics and deliver them as efficiently as possible into the body's systemic circulation. They are intended to regulate the amount and duration of therapeutics in blood plasma, as most therapeutics have a short half-life, enzymatic hydrolysis, low stability, and first-pass metabolism on their way to the target [1, 2]. Carriers serve as a protective barrier during administration, enhancing pharmacological activity, stability, and site-specificity. Additionally, lowering the cost of multiple-dose, extended therapies, and avoiding side effects to improve patient compliance [3]. These therapeutic carriers are pharmaceutical reformulations that are engineered based on the need and location of administration in the body. They are capable of carrying both hydrophilic and hydrophobic drugs and can be in the form of nano/micro particulates, hydrogel, or implantable devices [4–6].

Biodegradable polymers have gained insight into the drug delivery system because of their inherent advantage of the controllable degradation rate, mechanical property, specificity, and ease of forming into different shapes [7]. The degradation rate

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permits the release of active ingredients sustained over days to months, thereby maintaining the therapeutic plasma concentration over a prolonged interval. Moreover, their degradants are naturally excreted from the body and are not immunogenic or harmful, which reduces the need for secondary surgical intervention, saving cost and time [8, 9]. Nevertheless, it has broadened the administration method for treatments from intravenous to oral, subcutaneous, and pulmonary and targeted, tailored each with the required need. These biopolymers encapsulate the payloads either by embedding them into the matrix or conjugating them with the polymers to transport them into the body. Moreover, the therapeutics are delivered from these carriers, either by surface erosion that accompanies the release of an entrapped drug; cleavage of a covalent bond between the conjugated therapeutics and polymer; from the bulk or surface of the polymer, followed by diffusion of active molecules or by diffusion-controlled of therapeutic with bioabsorption of the polymer [10].

Biodegradable polymers can be natural or synthetic, according to their origin. Natural polymers (polypeptides, polysaccharides, etc.) are susceptible to chemical or enzymatic attack, making them feasible to implant in the body [11]. At the same time, synthetic polymers (polyamides, polyesters, polyorthoesters, etc.) undergo cleavage under hydrolytic conditions.

This chapter aims to introduce a different kind of biodegradable polymer, the mechanism of drug release, and the commercially available drug delivery devices in drug delivery applications (Fig. 1).

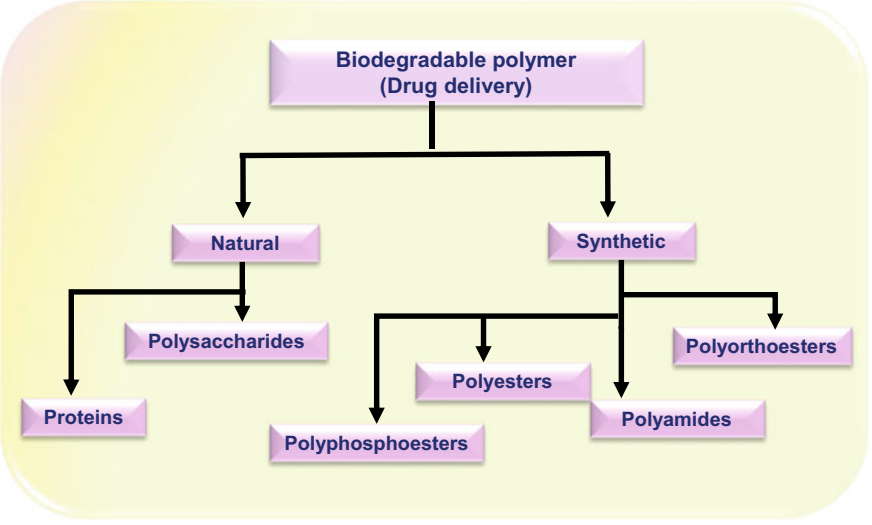


Fig. 1 Classifying biodegradable polymers for drug delivery applications

2 Natural Biodegradable Polymers for Drug Delivery

Natural polymers used for the development of pharmaceutical formulations are animal or plant-based proteins (collagen, albumin, and gelatin), polysaccharides (chitosan, dextran, and hyaluronic acid), and others—cellulose, starch, soy protein, zein, as well as proteins obtained from a microbial source. They are abundant in nature and have distinguished characteristics of biocompatibility, cell-activated proteolytic degradation, and low toxicity. However, they could be immunogenic and frequently need chemical alteration before being employed to create drug delivery carriers.

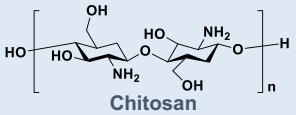
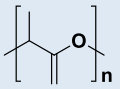
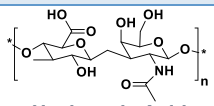
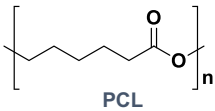
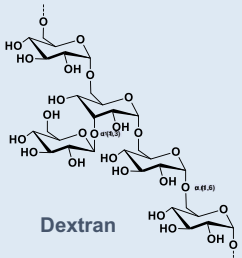
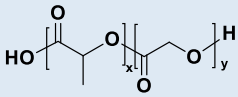
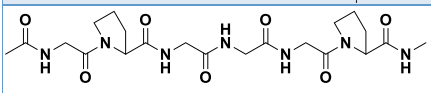
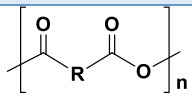
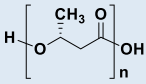
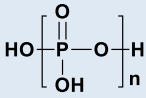
2.1 Chitosan

Chitosan, commonly referred to as soluble chitin, is the only cationic polysaccharide FDA-approved for use in medicinal delivery (Table 1) [12]. It is extracted from the exoskeleton of crustacean shells, insects, and fungal cell walls. It results from the deacetylation of chitin, which consists of random units of glucosamine and N-acetyl-glucosamine in its main chain, which regulates the pace of its breakdown [13]. It is the perfect choice as a gene carrier since the positive charge helps build a stable combination with the negative chemicals. Additionally, the polymer's inclusion of –OH and $–NH_2$ enables the development of a hydrogen bond, giving it the bio-adhesion property that enables it to pass through the tight junctions of epithelial cells and improve drug delivery [14]. The mucoadhesive characteristic also contributes to a more prolonged therapeutic residence duration for a more steady and controlled medication release. It has strong hydrophilicity and thus can be used for preparing carriers of various sizes. These carriers can be degraded by various enzymes such as pepsin, lysozymes, cellulases, chitosanase, pectinases, and lipases; and are nontoxic and bioresorbable [15]. The therapeutics' can be released from the carrier by surface erosion, bulk degradation, drug diffusion, drug adsorption, or a combination of erosion and degradation. The high physiochemical stability, easy functionality, mucoadhesive property, and non-toxicity make it an excellent choice for drug carriers, tablet coating, tablet excipients, wound dressing and healing, gene delivery, and diagnostics [16].

2.2 Hyaluronic Acid

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan with high molecular weight formed by linear repeating disaccharides units of β-1,3-N-acetylglucosamine and α-1,4-D glucuronic acid connected by alternating α-(1,4) and β-(1,3), respectively (Table 1). HA is a mucopolysaccharide found in the extracellular matrix of connective tissues, the eye's vitreous humor, umbilical cords, joint fluid, mucus, and

Table 1 Chemical structure of biodegradable polymers used in drug delivery

Natural Polymer	Synthetic Polymer
 Chitosan	 PLA
 Hyaluronic Acid	 PCL
 Dextran	 PLGA
 Collagen	 Polyanhydrides
 Polyhydroxyalkonates	 Poly(phosphoesters)

skin. It is mainly derived from rooster comb, umbilical cord or synovial fluid (animal source), and vertebrates from microorganisms (Strptoccous bacteria) for commercial use [17]. However, isolating end-stage products is problematic because of animal heterogeneity and the presence of endotoxins in microorganisms. However, due to its unique physiochemical features, it is being extensively investigated in drug delivery. It is an anionic polymer in physiological conditions due to the carboxylic groups in every disaccharide unit, which ionize at pH 7.4. It has a high water-binding capacity and interesting viscoelastic behavior due to the interchain interaction of hydrogen bonds [18]. It has poor mechanical properties but can be chemically modified by crosslinking or conjugation due to its backbone's functional groups (carboxyl and hydroxyl). Thus, functionalized HA can be used for fabricating carriers like hydrogels or gel particulates. Moreover, HA receptors in the body (CD44 cells) aid in the targeted delivery of antitumor drugs. The HA degrades naturally in the body by enzymes such as hyaluronidase. Thus, HA and its derivatives can be used for developing sustainable and controlled-release carriers for various drugs such as antitumors, proteins, peptides, and nucleic acids [19, 20].

2.3 Dextran

Dextran is a branched, neutral polysaccharide with high molecular weight derived from bacteria or by chemical synthesis. It consists of α-1, 6 linked D-glucopyranosyl linear chains of varying length and some branches of α-1, 2/ 3/ 4 linkages that vary depending on the bacterial strain (Table 1). It is naturally synthesized extracellularly by lactic acid bacteria using dextransucrase, a catalytic enzyme that aids in converting D-glucopyranose of sucrose to dextran. However, mass production is produced from both a batch-wise fermentation of Leuconostoc mesenteroides NRRL B512 F strain in the presence of sucrose, and chemically produced from cationic ring-opening polymerization of levoglucosan. Dextran is biocompatible, hydrophilic, non-immunogenic, and stable in moderate acids and bases. In vivo dextran is degraded enzymatically, allowing the development of carriers with controlled and sustained delivery of therapeutics [21]. Furthermore, the presence of the hydroxyl group enables easy chemical alteration of dextran's physiological properties to yield acetal, ester, dialdehyde, and ether [22, 23]. Dextran's esterification improves its flocculation efficiency in an acidic environment. Etherification changes the hydrophilic–lipophilic balance and ionic strength of the compound while decreasing enzymatic breakdown. A double bond in the side chains enables the photo-crosslinking of dextran, allowing the creation of hydrogels. Conjugation of drugs by covalent bonds prevents immune clearance and metabolism of drugs. Furthermore, the functionalization of dextran assists in tailoring stimuli responsiveness for the controlled delivery of drugs. Thus, it is a widely investigated carrier for proteins, plasmid DNA, and vaccines in the form of microspheres, hydrogels, or drug excipients [24].

2.4 Collagen

Collagen is a natural protein, fibrous in nature, obtained from animal or human sources. It is present in connecting tissues and constitutes about 25–35% of the body's protein. Up until this point, 28 different types of collagen have been reported. Atelocollagen is one of those that are utilized in drug delivery applications. It has low antigenicity because telopeptides are removed to obtain it. Collagen has been used as a drug delivery carrier due to its biodegradability, biocompatibility, adaptability, easy modification, hemostatic property, good absorption, and moldability (Fig. 2). They are developed as sponges for burns/wounds, shields in ophthalmology, injectable hydrogels for loading growth factor, pellets/tablets for protein delivery, and nanoparticle formulations for antibiotics dressing and gene delivery [25–27]. The presence of –OH, –NH, and –COOH groups on collagen molecules aids in easy chemical modification (Table 1). The mechanical, thermal, pH, and enzymatic stability is not provided alone by collagen, but in combination with other natural polymers such as chitosan, alginate, etc. Recombinant collagens and collagen-like peptides are being investigated as potential substitutes for extracted animal collagens. The inability of these

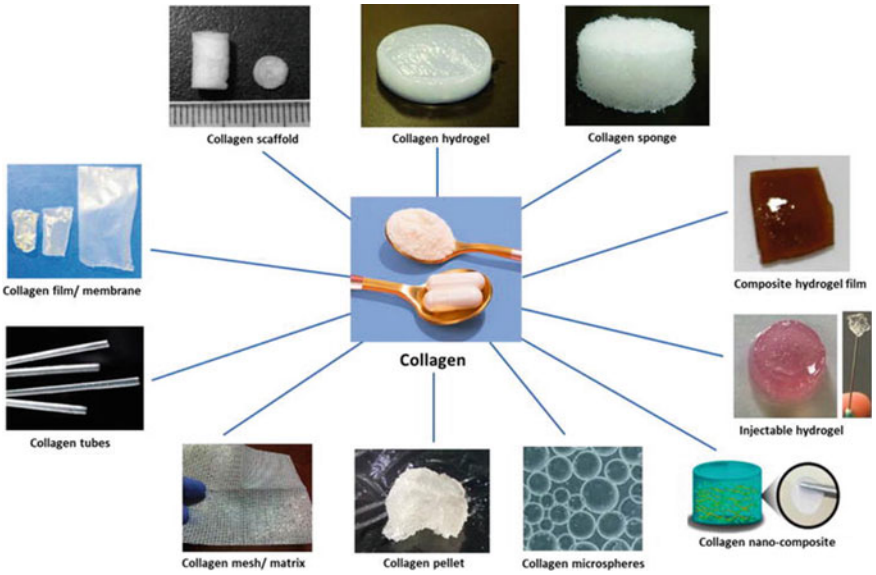


Fig. 2 Drug delivery devices of collagen [27]. Adapted with permission from Refs. [23, 27]. Copyright 2022 The Author(s). Licensee IntechOpen

substitutes to assemble into common D-periodic fibrils, which frequently perform biologically significant activities, poses a significant obstacle to their usefulness. However, the recombinant bacterial collagen can be functionalized and crosslinked to give the material properties [28, 29].

2.5 Albumin

Albumin is nature's drug delivery carrier. It is the most common plasma protein, accounting for approximately 40% of protein mass at a serum concentration of 35–50 mg/mL. It is created in the hepatocytes of the liver, where 10–15 g of albumin are produced and released into the vascular space each day [30, 31]. Because of this, albumin has fewer adverse effects than other carriers if it extravasates into tissues and then returns to the vascular space via the lymphatic system. It helps maintain 80% osmotic pressure, maintains plasma pH, and has a 19-day circulatory half-life. Three homologous α-helical domains, I, II, and III, make up its structure (Fig. 3). Two helical sub-domains (A and B, respectively) comprise each domain. Due to unpaired cysteine and Sudlow's sites I and II, it has seven fatty acid binding sites, seventeen disulfide binding sites, and one free thiol binding site [32]. As a consequence, it acts as a carrier for both endogenous and exogenous compounds. It has a binding affinity for hydrophobic molecules such as steroid hormones, fatty acids, folate, biliary acids, Vitamin D and C, and many other drugs. This bond between albumin and

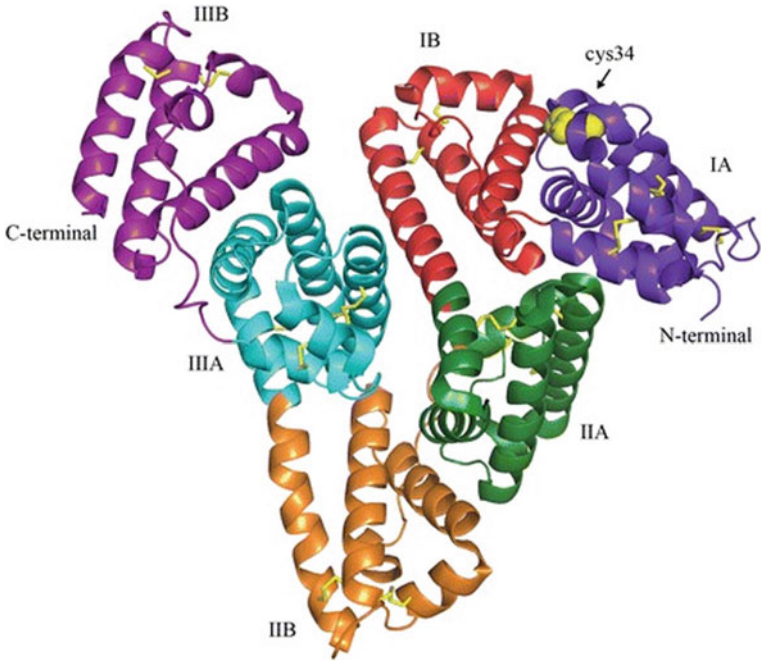


Fig. 3 Crystal structure of human albumin [32]. Adapted with permission from Refs. [28, 32]. Copyright © 2016 Larsen et al.

hydrophobic substances is reversible, thus facilitating easy transport and release of molecules onto the cell surface [33]. Moreover, the presence of a high level of amino acids on its surface, imparting it the negative charge, thus helps to conjugate drugs on the surface of nanoparticles by an electrostatic mechanism with charged drugs (positive/negative (Ganciclovir)) or amphipathic drug (Doxorubicin). Commercially available albumin-based formulations include Albuferon (hepatitis C), Levemir® and Victoza® (diabetes), Tc-Nanocoll 99 m (nuclear medicine), and Ozoralizumab® (arteritis treatment) [31, 34].

2.6 Polyhydroxyalkanoates (PHA)

Polyhydroxyalkanoates (PHA) (Table 1) is the biopolyesters obtained from microorganisms (*Alcaligenes latus*, *Cupriavidus necator*, and *Pseudomonas aeruginosa*) under the condition of limited nutrients (nitrogen, oxygen, sulphur, magnesium, or phosphorus) and excessive renewable carbon (fatty acids, carbohydrates, lipids organic acids, etc.). The PHA particles consist of a polyester core inside a phospholipid and protein shell, providing hydrophobic properties. PHAs are naturally metabolized during physiological processes into substances like 3-hydroxybutyrate

and hydroxyacyl-coenzyme-A [35, 36]. This contributes significantly to PHAs' non-immunogenicity, biocompatibility, and excellent bioresorbability; making them attractive as drug delivery carriers. Moreover, the hydrolysis of PHA is very slow; it depends on the porosity of the surface and molecular structure of the monomer, thus allowing to the tune of the release of therapeutics over the desired period of weeks or months [37]. Among all PHAs, Poly-3-hydroxybutyrate (PHB) and copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (PHBV) have been extensively used in drug delivery applications [38]. They are formed into biodegradable implants for local delivery of antibiotics for the prevention of postoperative and implant-related infection, microdevices (microspheres, microcapsules) for the controlled delivery of drugs like steroids, anesthetics, antibiotics, and vaccines; drug-releasing coating on stents to prevent arterial blockage [39].

Ionic polymers make up the majority of all-natural polymers. They can release therapeutics in response to changes in the environment's pH. For example, cationic polymers like dextran, chitosan, and gelatin can release drugs in the acidic conditions of tumors, i.e., in the endocytosollic cellular compartment. However, hyaluronic acid and gelatin-based anionic polymers can shield therapeutics from an acidic environment. In addition, natural polymers are highly biodegradable, but it has certain limitations such as (1) difficulty to purify, (2) batch-to-batch variability, (3) difficulty in identifying chemical structure, (4) lack of reproducible degradation rate (5) broad molecular weight distribution, and (6) most of the natural polymers are water-soluble and need some crosslinker to use them as a drug delivery carrier, thus making them less attractive then synthetic polymers as they are biologically inert, reproducible, versatile, and their chemical properties can be precisely controlled.

3 Synthetic Biodegradable Polymers for Drug Delivery

Synthetic polymers are man-made materials with well-defined chemical structures and degradation rates whose properties can be tailored according to the therapeutic need. They generally degrade by hydrolysis with a reproducible degradation rate without having any immunological concerns associated with naturally derived polymers. The most extensively used synthetic biodegradable polymers in drug delivery include polyesters, polyanhydrides, polyphosphazenes, polyorthoesters, polyanhydrides, and polyamides.

3.1 Polyesters

The polyester-based biodegradable polymers most explored for the drug delivery carriers are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), and polycaprolactone (PCL). They are biocompatible,

reproducible, and cost-affordable. They degrade in the physiological environment by hydrolysis, oxidation, or by enzymatic reaction of the ester bond.

3.2 Polylactic Acid (PLA)

PLA (Table 1) is an FDA-approved linear aliphatic biopolymer from renewable resources like sugarcane and corn. Ring-opening polymerization or the polycondensation method is used to create it commercially. PLA comes in two optical forms: D-lactide (amorphous) and L-lactide (semicrystalline). The D- and L-isomer racemization process or a hydroxyl acid comonomer component can be used to modify PLA's physical properties and biodegradability [40]. Due to its biocompatibility and biodegradability, PLA nanomaterial has found widespread use in drug delivery devices. There are approximately 15 formulations for direct human contact with PLA. FDA has approved PLA as a drug delivery device for the regulated release of antibiotics, antidiabetic, antitumor, antipsychotic, antidiarrheal therapeutics, and opioid antagonists [41]. They appeal because their hydrolysis product, L-lactic acid, is not bioaccumulative in organs and is excreted via the renal route. Moreover, their degradation rate can be tailored by various methods such as using a hydroxyl acid comonomer; racemization of the D- and L-isomer; grafting with a hydrophilic polymer like PEG, or tuning the molecular weight of the polymer. Thus, it aids in controlling the pharmacokinetics properties of therapeutics [41, 42].

3.3 Poly(ε-caprolactone) (PCL)

PCL is a semicrystalline, biocompatible, and biodegradable aliphatic polyester produced by ring-opening polymerization of Ɛ-caprolactone (Table 1). It is an FDA-approved, non-mutagenic, and innocuous polymer and has been utilized in wound dressing, contraceptive devices, and drug carriers [43]. In vivo, the degradation of PCL happens in two stages; it starts with the hydrolytic degradation of the ester bond first, as there is no enzyme present in the body to degrade it. Moreover, it takes about (4–6 months) for the weight loss process to start. The intercellular degradation of PCL happens when its molecular weight reaches below 5000. This leads to bulk degradation of PCL accompanied by enzymatic surface erosion. This process takes place very slowly and takes about 2–3 years to form 6-hydroxy caproic acid (end product), which further metabolizes into adipate [44]. Thus, it has both bioresorbable and biodegradable properties [28]. Moreover, the degradation rate of PCL can be tailored by blending or co-polymerizing it with hydrophilic polymers such as starch, chitosan, polyethylene glycol (PEG), and polyvinyl alcohol (PVA). Another essential feature of PCL is that it is rubbery at room temperature due to low glass transition temperature (−60 °C) and melting point (60 °C), thus providing high permeability to therapeutics. Thus, PCL has been explored for encapsulating bioactives, peptides,

proteins, DNA, siRNA, and oligonucleotides. As a result, many drug delivery devices are approved. Capronor [45], for example, is a contraceptive implant for prolonged delivery of levonorgestrel.

3.4 Poly(Lactic-co-Glycolide) (PLGA)

PLGA is an amorphous polyester, a copolymer of polylactic acid and polyglycolide (Table 1). It is produced from direct polycondensation of lactic acid (LA) and glycolic acid (GA) or by polyaddition of lactides and glycolides (ring-opening polymerization) [46]. Here, the physiochemical property of the polymer rests on the Lactide to Glycolide (LA: GA) ratio, as it influences the degradation rate. The higher the GA content, the faster the degradation. In vivo, PLGA undergoes hydrolytic degradation of ester linkage to hydroxyl and carboxylic acid as the end product. This ester cleavage from the backbone reduces the polymer to lower molecular weight chains by enhancing the hydrophilicity and reducing them to water-soluble fragments. That subsequently reduces to lactic acid and glycolic acids, which further metabolize to form carbon dioxide, water, and energy. PLGA carriers inside the body can also go through auto-catalytic degradation, where acid-by-product remains entrapped in the bulk of the polymer, acting as a catalyst to degrade the polymer to glycolic acid and lactic acid [47, 48]. This degradation mechanism sometimes is not beneficial for sensitive therapeutic proteins, which may degrade them. However, this issue can be solved by incorporating non-aqueous bases into the system. Thus, PLGA has prepared carriers of various geometry and sizes to incorporate proteins, antitumor therapeutic, hydrophobic/hydrophilic therapeutics, and growth factors. PLGA is used to prepare Eligard, which contains Leuprolide Acetate, a hormonal drug for treating prostate cancer. Nano/microcarriers, linked with targeting ligands for the targeted release of antitumor drugs and vaccines. PLGA-based carriers are also developed for the triggered release of therapeutics, i.e., in response to changes in pH, temperature, light, or chemical. For example, PLGA-PEG-PLGA copolymer is created to create thermoresponsive micelles, where PEG acts as a thermoresponsive component. In addition, pH-responsive polymers like chitosan and polypeptides are also added to PLGA-based carriers to trigger the release of therapeutics in the tumor microenvironment. For improved affinity, specificity, and delineation of the diseased area, efforts have been made to develop carriers with both therapeutic and diagnostic capabilities [49, 50].

3.5 Polyanhydrides

Polyanhydrides (PA) are distinguished by the anhydride bond in their backbone, connecting the repeating unit of the polymer backbone (Table 1). Their structure can be modified according to the need; thereby they can be classified as aromatic,

aliphatic, unsaturated, or crosslinked PA. They are hydrolytically unstable polymers believed to split into two carboxylic acids in the presence of water. However, the hydrolysis of anhydride bond happens in the presence of a base, thus its degradation is pH depend and degrades faster in basic media. Moreover, the degradation mechanism of the matrix follows surface erosion, as the hydrophobicity of the polymer chain restricts the water diffusion into the matrix. Thus, the therapeutic release would be directly proportional to the rate of surface erosion, also known as a surface-eroding polymer [51]. However, its degradation rate can be tailored by modifying the monomer. Hence, it can vary from a few days (aliphatic PA) to several years (aromatic PA). Moreover, its degradation products are nontoxic and non-mutagenic, thus it does not irritate in vivo. The sterilization by γ-irradiation does not affect the mechanical and physical properties of the polymer [52]. Hence, it is widely used in drug delivery applications, such as injectable formulations, implants for localized release, microcarriers, nanodevices, and so on for delivering vaccines, proteins, peptides, and gene delivery, e.g., Polysebaccic acid used to deliver Tetracaine and lidocaine (ophthalmic anesthetic) [53, 54].

Table 2 Biodegradable polymers in drug delivery

	Natural polymer	Synthetic polymer
Advantage	• Hydrophilic • Cell/tissue specific binding affinity • Safe • Easily available	• Design desired physicochemical features (copolymer) • Enhancing polymer functionality in delivery: crosslinking and surface modification through easy addition of functional groups • Controlled release profile for optimal therapeutic efficacy • Non-immunogenic • Can control mechanical and physical property by inducing branching
Disadvantage	• Possible immunogenicity • Require purification • Batch-to-batch variation • No controlled over the specification of raw material • Uncontrolled degradation • Short release profile	• Require binding moieties to attain site-specificity in cells or tissues • Require synthesis • Scale up challenge • Hydrophobic

3.6 Poly(phosphoesters) (PPE)

Similar to aliphatic polyesters, poly(phosphoesters) have the phosphoesters linkage as the repeat unit in its main chain (Table 1), where pentavalency of phosphorus allows modification in its side group, thereby altering its physical and chemical properties. They can be synthesized by various routes, such as polycondensation, polyaddition, transesterification, ring-opening polymerization (ROP), and enzymatic polymerization [55]. Depending on their side chain (alkyl or alkoxy) and phosphorus oxidation state, they are classified as polyphosphates (polyphosphodiester, polyphosphotriester), and polyphosphonate, polyphosphate, and polyphosphoramidate [56]. PPE follows hydrolytic or enzymatic degradation, much like polyesters. The presence of five-membered rings and oxygen in its backbone makes it more hydrophilic than polyesters. Moreover, the pendant chain's functional reactivity and length allow for fine-tuning of PPE's solubility, for instance, with methyl functionality, it is water-soluble and ethyl insoluble, making it an excellent option for controlled drug delivery devices [57]. Further, the advantages and disadvantages of biodegradable polymers in drug delivery application is summarized in Table 2.

4 Mechanism of Drug Release

Polymeric drug delivery carriers can be implantable devices, hydrogels, or colloidal carriers (micelles, liposomes, or micro/nanoparticles). The drug delivery systems are selected based on the length of therapeutic release and the path of administration into the body. Based on this, the drug release can occur through diffusion, matrix degradation, or a combination of both [48, 58, 59]. In carriers made of hydrophilic polymers, erosion-based degradation typically occurs. In these cases, the carriers take water from the environment and deteriorate the matrix due to hydrolysis of the polymer chain, swelling, disentangling, and ultimately dissolving from the carriers. On the other hand, the polymer may experience chemical modifications that cause cleavage of covalent bonds, chain protonation, or ionization. Thus, the erosion of the polymeric carriers happens with both chemical and physical processes.

4.1 Chemical Erosion

It refers to the decomposition of polymer chains into oligomers through hydrolytic cleavage or by enzymes. However, the involvement of enzymes is difficult for high molecular weight polymers, as it is difficult for enzymes (bulky group) to enter the carriers. Thus, in vivo enzymes act in the later stage, after the fragmentation of the chain, and degrade only the surface of the carrier.

Type I erosion: This kind of erosion is primarily seen in crosslinked polymers that form a three-dimensional network, for example, hydrogels. The crosslinking makes the polymer insoluble in water. It can only swell in an aqueous environment to the extent that is allowed by its crosslink density. It is used for sparingly water-soluble drugs.

Type II erosion happens in the polymer matrix, which becomes hydrophilic by the cleavage of the side chain or the pendant group by ionization or protonation, thereby making them water-soluble without any change in molecular weight—for example, cellulose acetate-derived polymers which become water-soluble by ionization of carboxylic group.

Type III erosion: The hydrophobic polymer matrix follows this kind of erosion in which the polymer backbone is broken into small fragments, forming low molecular weight chains that further metabolize by enzymes or hydrolysis to water-soluble molecules, e.g., PLA, PLGA, poly (ortho esters).

The three mechanisms described can be combined; they are not mutually exclusive.

4.2 Physical Erosion

The physical erosion of carriers happens in two ways: Surface erosion or Bulk erosion (Fig. 4). Surface erosion is a heterogeneous process; water diffusion through the matrix is slower than the rate of polymer degradation. Here, erosion happens from the surface and works downward layer by layer, maintaining the physical integrity as it degrades. Thus, the rate of erosion is directly proportional to the surface area of the matrix. It happens in the crystalline polymer. When it comes to bulk erosion, water penetrates the carrier at a faster rate than matrix degradation. Hence, it is a homogeneous process; degradation happens in the entire matrix. Additionally, the matrix's volume affects the erosion rate. It happens in hydrophilic polymer, as hydrolysis happens at a uniform rate.

Surface or Bulk erosion is not exclusive; many materials undergo a combination of both.

4.3 Release Kinetics Model

There are mathematical models that can be used to predict the in vivo bio performance and the release mechanism of therapeutics from the polymeric carriers. The widely used kinetics model was linearly fitted to the concentration of therapeutics released over time [61, 62].

$$\text{Zero order: } \frac{M_t}{M_\infty} = k_0 \cdot t \tag{1}$$

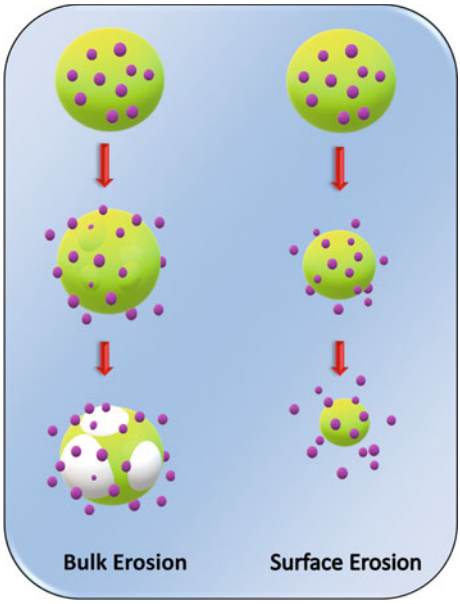


Fig. 4 Schematic representation of bulk and surface erosion of polymer as modified from Verde et al.[60]

$$\text{First order: } \frac{M_t}{M_\infty} = e^{k_1 \cdot t} \tag{2}$$

$$\text{Higuchi Model: } \frac{M_t}{M_\infty} = k_H \cdot t^{1/2} \tag{3}$$

$$\text{Hixson-Crowell: } M_0^{1/3} - M_t^{1/3} = k_s \cdot t \tag{4}$$

$$\text{Korsmeyer-Peppas Model: } \frac{M_t}{M_\infty} = k \cdot t^n \tag{5}$$

where,

M_t: cumulative drug release at a specific time *t,*

M_∞: cumulative drug release at infinite time,

M_0: Initial amount of drug,

k_0, k_1, k_H and k_s, k are the release constant.

The zero-order model is employed in slow and prolonged drug delivery systems such as in tablets with hydrophobic drugs, or in ophthalmic or transdermal systems.

The First Order is applicable for porous matrix containing water-soluble drugs.

The Higuchi Model applies to saturated systems with various modified-release of pharmaceutical dosages, such as hydrophilic drugs from matrix carriers. Also, it is applicable for carriers with different geometries, such as spherical, cylindrical, etc.

In the Hixon–Crowell model for cylindrical tablets, n characterizes the release mechanism.

$0.45 \leq n$: follows Fickian diffusion,
$0.45 < n = 0.89$ non-Fickian transport,
$n = 0.89$ zero order release,
$n > 0.89$ Super Case II transport.

5 Commercially Available Biodegradable Polymer-Based Formulations

Some of the commercially available biodegradable polymer-based drug delivery carriers are:

GLIADEL®: This drug delivery device is a wafer loaded with the chemotherapy drug Carmustine for treating brain tumors (glioblastoma multiforme). It is an implant developed from poly[bis(p-carboxyphenoxy)propane–sebacic acid] in a 20:80 molar ratio (Fig. 5) [63, 64].

Alburx®: This intravenously administered drug delivery carrier raises the blood's albumin level by containing 5–25% of human albumin (a natural polymer). Therefore, used for treating trauma patients such as accidental blood loss, burns, etc. [65].

Lupron®: PLGA and PLA microspheres are used to carry luteinizing hormone-releasing leuprolide acetate to treat endometriosis [66].

Decapeptyl SR®: It is a PLGA-based drug delivery carrier that delivers Triptorelin acetate to treat prostate cancer [67].

Triptodur®: It comes in the form of an extended-release injectable suspension developed from PLGA to treat advanced prostate cancer or precocious puberty in children [68].

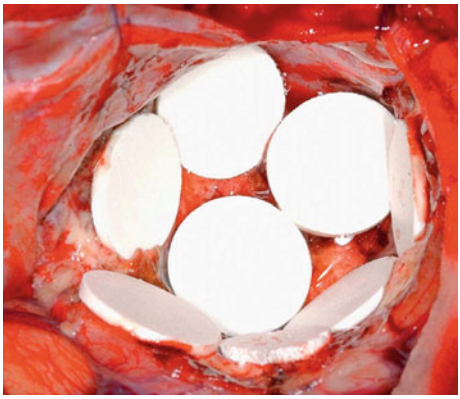


Fig. 5 Gliadel wafers with BCNU implanted into a brain tumor [64, 65]. Adapted with permission from Refs. [59, 65]. Copyright © 2011 Elsevier B.V. All rights reserved

INFUSE Bone Graft: In the form of an absorbable sponge made from collagen, it is created for the delivery of bone morphogenetic protein-2 in spinal-fusion procedures [69].

Nutropin Depot®: It is an injectable suspension of PLGA micronized particles for delivering recombinant growth hormone in pediatric patients [70].

Abraxane®: It is used for the first-line treatment of breast cancer. It is 130 nm size albumin-bound nanoparticles loaded with Paclitaxel, an antitumor drug [71].

Eligard®: It is a PLGA-based formulation used for extended-release of Leuprolide acetate for subcutaneous injections. It is used in advanced prostate cancer for palliative treatment, i.e., to relieve pain and other symptoms [72].

Trelstar®: It is a PLGA-based suspension used to treat prostate cancer in men [73].

Zoladex®: It is an injectable implant of lactide/glycolide copolymer developed by AstraZeneca used to continuously deliver goserelin over 12 weeks to treat breast and prostate cancer [73].

OncoGel™: It is a formulation of tri-block copolymer(PLGA-PEG-PLGA) for delivering paclitaxel locally for the management of tumor [74].

Furthermore, several biodegradable polymer-based drug delivery carriers have been undergoing clinical trials or have been recently concluded [75].

6 Conclusion

In the delivery of drugs, polymers are very helpful in improving the pharmacokinetics of therapeutic. As these natural and synthetic polymers are biocompatible, their degradation products are non-mutagenic, not toxic, and get biosorped into the system. Moreover, these polymeric carriers' easy modification with wide side chain functionality aids in the site-specificity of therapeutic. Also, their pH/temp responsiveness allows the triggered release of therapeutics, thereby improving drug delivery efficiency and making it more patient-compliant.

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Chapter 8
Biodegradable Polymers for Food Packaging Applications

Vikramsingh Thakur, Bhabani K. Satapathy, Chandrani Sarkar, and Sampa Saha

1 Introduction

Food packaging is a crucial step in the food supply chain, fulfilling critical tasks such as containing and transporting food, mitigating damage, and safeguarding against tampering and theft. Moreover, it plays a pivotal role in safeguarding food quality by acting as a barrier against external factors that can cause contamination or unintended alterations to the package. Polyolefins, poly (vinyl chloride) (PVC), polystyrene (PS), and poly (ethylene terephthalate) (PET) are frequently utilized plastics that can cause pollution, leading to negative impacts on the environment, including land, waterways, oceans, and living organisms, ultimately disrupting the ecosystem's delicate balance. This situation can adversely affect nutrient cycles, habitat changes, aquatic ecosystems, the loss of keystone species, and severe health risks for people. Despite the presence of regulations prohibiting non-biodegradable plastics, researchers are still actively seeking new eco-friendly alternatives. The Asia Pacific, market of biodegradable food packaging is projected to enhance at a compound annual growth rate (CAGR) of 6.35% from 2021 to 2027, driven by a growing awareness of environmental conservation, particularly in the aftermath of the pandemic. In 2021, Europe produced around 436,000 metric tons of biocomposite/bionanocomposites of polymers like Polylactic acid (PLA), Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), Polycaprolactone (PCL), and Polyhydroxybutyrate (PHB). The most promising application of biodegradable materials is in edible packaging, mainly protein-based films. The purpose of packaging is to protect, contain, and communicate to the customer, it can be served with biodegradable polymer in

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the form of bionanocomposites and blends. The inclusion of plasticizers, nanofillers, and polymer/oligomers can improve the functional properties (barrier and flexibility), which are prerequisites for food packaging materials. Smart biodegradable packaging can be either/both as active and/or intelligent and can provide a sustainable system. The various commercial products of biodegradable polymers were successfully prepared based on approaches like polymer blends and biocomposite/bionanocomposites. The addition of active and/or intelligent agents in biodegradable polymers is emerging and continuously growing as a smart solution for packaging. Though biodegradable polymers are sustainable, the inclusion of compounds and their release in the food can be perilous and cause toxicity concerns. So, the usage of the aforementioned constituents in a biodegradable matrix needs to be studied for the release of small molecules in food. This book chapter comprises the biodegradable polymers' classification, biodegradable blends, bionanocomposites, various applications, commercial products, and toxicological concerns in food packaging areas (Fig. 1).

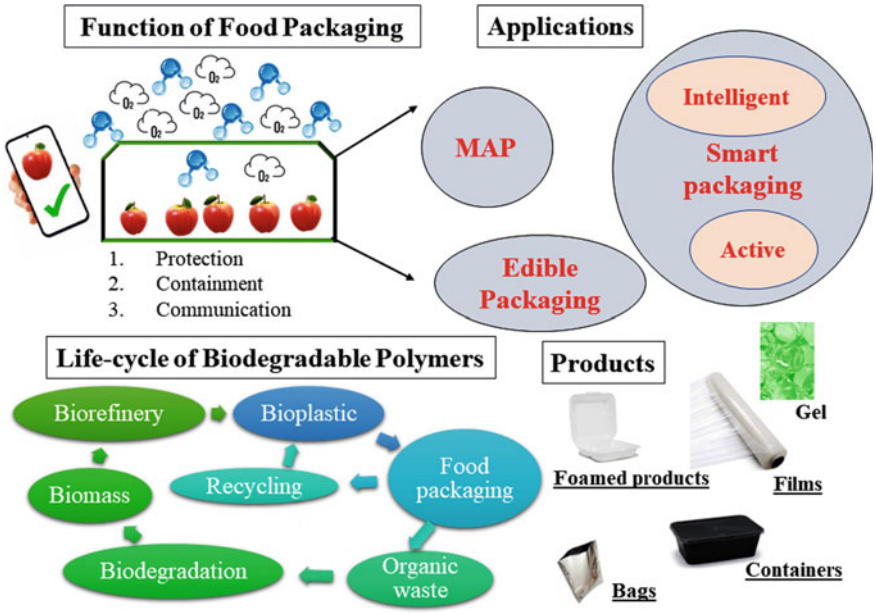

Fig. 1 Biodegradable polymers in food packaging: types and applications

2 Classification of Biodegradable Polymers in Food Packaging

Biopolymer-based food packaging made from polysaccharides, proteins, and aliphatic polyesters has been studied as a green alternative to conventional plastics. These materials can be cast into stiff, brittle films that are biocompatible, safe, and biodegradable. The classification of biodegradable polymers depends on the source and application used in food packaging applications (Fig. 2) that are discussed below.

2.1 Polysaccharides-Based Packaging Material

Polysaccharides are popular in food packaging due to their biodegradability, renewability, and excellent barrier properties. Starch, cellulose, chitosan, alginate, and pectin are a few examples of frequently used polysaccharides. Starch is a natural polysaccharide with strong mechanical qualities derived from a variety of plants like corn, cereals, wheat, barley, potatoes, and cassava. Whereas the Cellulose is a by product of plant cell walls and is a strong water and oil barrier. Unlike plant-based source, Chitosan, made from the shells of shellfish, possesses resistant to oxygen and water and has strong mechanical qualities. Seaweed-derived alginate is straightforward to prepare and has strong barrier qualities. Fruit and vegetable pectins have good mechanical qualities and are simple to prepare. Overall, polysaccharides are a promising replacement for traditional plastic packaging and are appropriate for use in sustainable packaging.

Chitosan has a charge density that influences its chain conformation and, as a result, it possesses barrier and mechanical properties of the resulting films. Therefore, the degree of deacetylation (DOD) and solubility are crucial components in determining film morphology. The investigation shows that higher DOD can significantly enhance the barrier and rheological characteristics of food packaging films [1]. The usage of chitosan as a polysaccharide in food packaging, whether in the

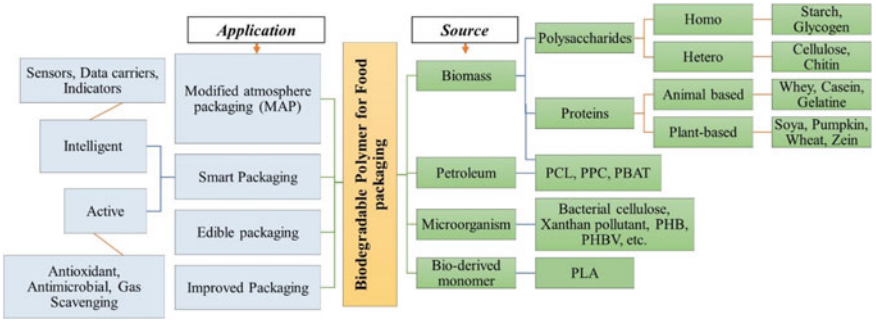

Fig. 2 Biodegradable polymers depending on source and application

form of packing films or coatings directly on food materials, has been extensively researched. Chitosan in the form of films or coating has been used as both neat chitosan films and chitosan films combined with other polymers/biopolymers such as proteins (Whey, Soya), polysaccharides (Starch), and other biopolymers [2, 3].

Starch in food packaging as a biodegradable polymer is used due to its film formability and digestability. Starch-based films are beneficial as they release glucose at a controlled rate, allowing the glycemic index to be expected. The decreased digestion of starch-based films may be helpful in diabetes patients' dietary planning [4]. However, the safety and health consequences of these films should be carefully considered during their development and use.

2.2 Proteins-Based Packaging Material

Proteins, which are made up of 20 amino acids with varying energies at different places, can be improved by physical and chemical means such as heat, pressure, and metal ions. Edible protein-based films can minimize moisture and flavor loss while also carrying active ingredients. Although protein-based biopolymers have excellent gas barrier capabilities, their mechanical properties are poor due to their high cohesive energy density, brittleness, and moisture sensitivity. Natural or biodegradable plasticizers can increase the viscoelasticity and extensibility of protein-based biopolymers, hence alleviating the abovementioned issues [1, 5]. Soy protein has a considerable film-forming ability and a diversity of functional qualities, including water and fat absorption, fiber formation, and emulsification. Soy protein isolate (SPI) is frequently utilized to make soy protein films with varying characteristics. The Young modulus and elongation at the break of soy protein films increase as molecular weight increases, and alkaline solutions generate better films than acidic solutions. Irradiation and heat curing are two post-treatments that can improve the performance of soy protein films [6]. Despite modest mechanical qualities, Soy protein-based films have strong oxygen barrier properties but poor water vapor barrier properties, most likely due to their hydrophilicity [7]. Another important protein-based possible biodegradable polymer for the food sector is Zein due to its hydrophobic nature, which is produced from corn kernels. In contrast to commodity polymers, it has a high-water vapor permeability (WVP) and poor mechanical properties. Plasticizers can be added to increase brittleness, but doing so also reduces the material's ability to act as a gas and water barrier, which further need to enhance by nanofillers [8]. Zien nanoparticles (ZNP) can also be used along with protein-based polymer, which is safe and can be employed as edible food packaging [9]. Oymaci and Altinkaya prepared a bionanocomposite film of 150 μm of whey protein/ZNP, which shows improved moisture barriers (WVP of ∼0.052 g mm/m^2 h kPa) with a slight increase in mechanical properties [10].

2.3 Polylactic Acid-Based Packaging Material

Polylactic acid (PLA) is a commonly utilized biodegradable biopolymer attributed to its biocompatibility, transparency, and capacity to degrade. However, PLA applications are constrained by their brittleness, poor heat resistance, and low barrier qualities. Numerous studies have concentrated on altering PLA to improve its inferior properties [11]. PLA can be utilized as blends, nanocomposites, and micro/nanofibers for food packaging applications [12]. The source of PLA is Lactic acid, where several enantiomers alter the crystallinity and physical characteristics of the final product. The distribution and amount of LA enantiomers inside the polymer chains determine the characteristics of the PLA. PLA with a high L-isomer content is crystalline, whereas meso-form (PDLLA) with a high d-isomer percentage (>15%) is amorphous [13]. The mechanical and barrier performance is influenced by the crystallinity, radius of gyration, spherulite size, long period (L_p), and morphology, which are all influenced by the orientation and packing of polymer chains [14]. However, PLA has outstanding thermomechanical stability, though its usage in food packaging applications is constrained by its poor extensibility and high permeability to low molecular weight gases and vapors. It has been observed that the ability of PLA to block out oxygen and water vapor might degrade the quality of packaged foods [15]. The PLA-based system can be used as blended and/or bionanocomposites which were discussed in Sects. 2.6 and 2.7, respectively.

2.4 Polyhydroxy Alcanoates Based Packaging Material

The polyhydroxy alcanoates (PHAs) family of polymers is emerging as the popular biodegradable polymers in the commercial market attributed to its beneficial properties, such as high biodegradability under various conditions and ease of processing. These bio-produced polyesters can potentially replace thermoplastics made from petroleum as a sustainable alternative. Bacterial cells grown on renewable raw materials such as waste can produce PHAs and can be used in packaging, adhesives, films, and additives. Focusing on food packaging, this section briefly introduces PHAs, covering their properties, processing methods, readily available biopolymers, and potential applications. Poly-3-hydroxybutyrate (PHB) is a biopolymer made up of D (-)-3-hydroxybutyrate, which is generated by several bacteria under constrained environments. However, its application is restricted due to its brittleness and constrained processing window [16]. Another strategy is to combine PHB with 3-hydroxy valerate (3-HV) monomer to produce poly (3-hydroxybutyrate-co-3-hydroxy valerate) (PHBV), which has a lower melting point, better brittleness, and a wider processing window. The 3-HV content influences the copolymer's flexibility and melting characteristics. PHAs have some advantages for food packaging, but their brittleness and manufacturing limitations still constrain their use. Combining

PHA with other polymers or plasticizers, which can lower the processing temperature and lessen brittleness, is one way to enhance its performance. For example, polybutylene succinate (PBS) blended with PHBV has been shown to have advantageous thermal and mechanical characteristics. The molecular insertion of PBS (ductile) chains to the stiff PHBV matrix postponed degradation and improved heat stability. It was found that the addition of PBS to the blend matrix to a critical level prevented crystallization and preserved lamellar size, potentially improving barrier characteristics when compared to pure PHBV [17].

2.5 Synthetic Biodegradable Polymer-Based Packaging Material

Poly(ε-caprolactone) (PCL) is a biodegradable thermoplastic polymer which has gained a significant amount of attention lately owing to its thermal processability, low melting point, and melt flow index (MFI). It is made by polymerizing caprolactone and can be commonly blended with other classes of biopolymers, for example, with PLA, to improve qualities like adhesion, dyeability, and stress crack resistance. PCL is also compatible with and can improve the characteristics of various other polymers, including PVC, polystyrene, and polycarbonate. Blending PCL with PLA reduces brittleness while enhancing thermal stability significantly. Poly (butylene adipate-co-terephthalate) (PBAT) is a co-polyester created by condensing 1,4-butanediol with terephthalic and adipic acid. It has outstanding qualities when the terephthalic acid concentration exceeds 35%, but the degradation rate reduces when the concentration exceeds 55%. PBAT is a soft and flexible material that is used to make films, bottles, and molded items. PBAT can be combined with other biodegradable polymers, such as cellulose, to improve hydrophilicity and mechanical and thermal properties. PBAT is made from both petroleum-derived and bio-derived ingredients, the latter of which being adipic acid and 1,4-butanediol [18, 19]. Polypropylene carbonate (PPC) is the most common food packaging material used as aliphatic polycarbonate, formed via the process of copolymerization of propylene carbonate and CO_2.

In comparison with PBAT, polyolefins, starch, and their blends, PPC films have higher yield strength and barrier characteristics for oxygen and water vapor. However, they have lesser tear resistance than PBAT and have several drawbacks, such as poor thermal stability, low mechanical characteristics, and performance variability depending on the catalyst employed in the manufacture. Even though PPC is amorphous, due to its shrinkage and low glass transition temperature (T_g) of 25–45 °C, it further needs modification by nanofillers and processing aids [20].

2.6 Blends of Biodegradable Polymers in Food Packaging

Available polymer blending techniques have been used in many industrial fields to improve the thermomechanical properties of biopolymers. By using the unique properties of each component, such as the high stiffness of PLA, PHBV, and the extra stiffness of PBAT or PCL, combined with special compatibilizers, biodegradable polymer blends can be made into products with a balance of stiffness and strength. Although biodegradable ingredients must be included or less than 1% untested ingredients required to ensure the biodegradability of the final mixture according to ASTM (American Society for Testing and Materials) D6400-2, the inclusion of ingredients with high barrier properties can result in high oxygen/water vapor barrier fusion [21]. Therefore, even though they can effectively improve the barrier qualities, non-biodegradable polymers with excellent barrier performance such as polypropylene (PP) or ethylene vinyl alcohol copolymer (EVOH) should not be considered for blending with biodegradable plastics [22]. The barrier performance of PLA, PBAT, and PBS can be improved by blending with biopolymers having barrier performance, such as PPC and polyhydroxyalkanoates family. Although these polymers possess low interfacial interaction with brittleness, blending eventually does not improve the barrier properties desired for food packaging. Some recently studied biopolymer blends are PLA/PPC [23], PLA/PHB [24, 25], PLA/PHBV [26], and PBAT/PPC [27, 28] indicating the improvement in the water vapor barrier properties but compromising on the mechanical properties of blends due to the higher loading of brittle biopolymers. The PHB gives nucleation effect in PLA, leading to lower chain flexibility and a lower oxygen transmission rate (OTR). However, the nanofillers were incorporated into the bio blends to improve the mechanical properties. Arrieta et al. immobilized cellulose nanocrystals (CNC) in the PLA/PHB blend, and the resultant ternary system are flexible and have UV stability. The CNC acts as a reinforcement for the PHB and leads to increased elongation at break and tear strength, which are the functional characteristics of food packaging [29]. The nanofiller incorporation was discussed in detail in Sect. 5. Numerous studies have investigated ways to increase PLA's ductility without sacrificing other desirable qualities in order to address the problem of low elongation at break. Although plasticization has been a typical strategy, it can result in plasticizers migrating to the surface, which may not be ideal for all applications.

The brittle blends can also be plasticized using non-toxic plasticizers which are approved for the food packaging application, such as acetyl-tri-n-butyl-citrate (ATBC), glycerol, and Poly(ethylene glycol) (PEG) [30, 31]. In PLA/PHB, the plasticizer can also enhance the disintegration of PLA, that may be slowed down due to PHB [32]. Biopolymer performance can be enhanced by mixing flexible polymers in the PLA. This frequently uses PCL, a thermoplastic biodegradable polyester with good mechanical properties. In the PLA /PCL immiscible blends, the thermal and mechanical properties of PLA are enhanced with the addition of PCL deepening of composition. Ivan et al. prepared PLA/PCL of 70/30 that shows intact shape-memory behavior with improved mechanical properties [33]. The PLA/PCL (70/30)

nanofibers mat prepared via electrospinning shows similar trends to conventional blends. Further addition of nano filler/active agents can improve the targeted property; for example, in a recent study, the inclusion of curcumin in PLA/PCL nanofibers led to enhance antimicrobial properties [34]. In conclusion, the incorporation of PCL increased PLA's heat stability and crystallization while lowering its hardness.

The oxygen gas barrier is also a concern regarding the biopolymer blends, which can be improved by blending with starch and PVA. Incorporating PVA in PLA/PVA blends can also improve the biodegradability of the resulting material since PLA is typically hydrophobic and has a low hydrolytic degradation rate due to its inability to absorb water [35, 36]. On the other hand, blending PVA with starch can decrease the mobility of the polymer molecules due to the presence of many H-bonds. This can be addressed by using plasticizers such [37] as water, polyols, glycerol, or urea, which can reduce brittleness, increase flexibility and processability, and lower the glass transition temperature of the blend [38, 39]. Suitable compatibilizers, plasticizers, and nanofillers are created to balance the mechanical toughness and oxygen/water vapor barrier of biodegradable polymer blends. The barrier characteristics of polymer blends are greatly influenced by their shape. Extending the oxygen diffusion path by stretching a phase (PBS) into micro or nanofibrils under a strong flow field, this in situ micro/nano fibrillation proved to be an effective way to enhance the oxygen barrier of these blends, as shown in Fig. 3 [40].

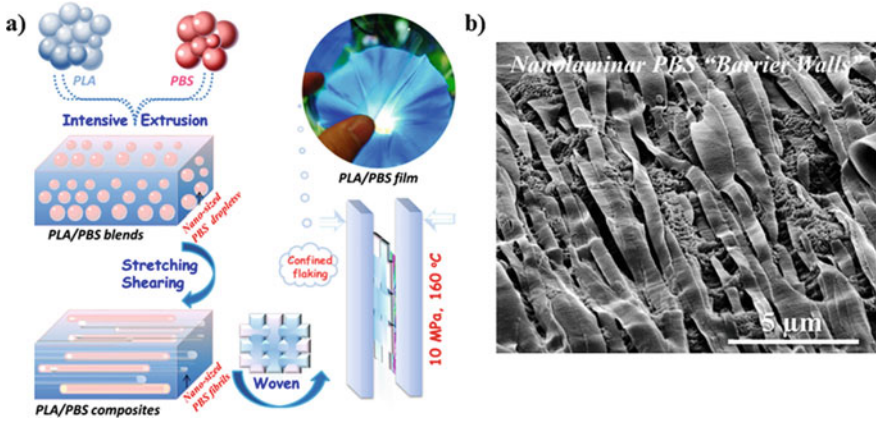

Fig. 3 **a** PLA/PBS blends prepared by Slit die extrusion followed by quenching containing PBS nanosheets and **b** Cryofracture SEM (scanning electron microscope) image of PLA/PBS (80/20) blend after etching of PLA phase (adopted with permission [40] Copyright © 2015, American Chemical Society)

2.7 Bionanocomposites in Food Packaging

The notion of bionanocomposites, which have improved functions and are biodegradable and environmentally benign, has been introduced by advancements in biopolymer nanotechnology. Bionanocomposites, also referred to as green nanocomposites, improve the barrier, mechanical, and thermal properties of biopolymers. The desired properties may be attributed due to a strong interfacial adhesion of the biopolymer and the nanofillers, which improves molecular mobility and relaxation behavior. The shapes of nanofillers, which can be either organic or inorganic, comprise of nanoparticles, nanorods, nanotubes, nanowhiskers, and nanofibers. Nanofillers have a substantially higher surface-to-volume ratio due to their tiny size. With active or intelligent packaging techniques, bionanocomposites can provide superior mechanical and barrier qualities. Another strategy to overcome the shortcoming of biodegradable films is Layer by layer assemblies (bilayer/multilayer). In the recent study, the bilayer film of chitosan/PCL containing nanocellulose (NC) and grape seed extract (GSE) was prepared by coating as well as by compression. The purpose of such bilayer structure is to improve the stability of the inner layer as in the aforementioned study is to improve the sustainability of NC and GSE [41]. The bilayer assemblies prepared by coating show improved barrier and mechanical strength as compared to compression. In a similar system of Chitosan /PCl, Zinc oxide (ZnO) was incorporated, which shows improved UV stability and barrier properties [42].

The gas and vapor barrier qualities of PVA blends are effectively reinforced by cloisite 30B nanoclays, raising initiation degradation temperature (T_i) while decreasing weight loss. The PVA/Cloisite 30B nanoclay blends' tensile characteristics were mainly improved with a loading of 5 wt% [43]. A higher concentration of Cloisite 30B nanoclays was added to starch/PVA (20/80) blends, improving the tear strength by ~80% of the food packaging film. Additionally, applying organically modified montmorillonite decreased water absorption for PLA, PPC, PBS, and PHBV [37]. Ilsouk et al. prepared PBS/5 wt% beidellite clay nanocomposites that increased the amounts of exfoliation and nanofiller dispersion and reduced the water vapor permeability by 37% as compared to pristine polymer [44, 45]. Chomachayi et al. added silk fibroin nanoparticles to the PLA/PCL binary blend of a 70/30 mixture to improve interfacial adhesion and reduce PCL droplet diameter in the PLA matrix. However, the increased intermolecular interactions slowed the crystallization process. Because of the effective dispersion of the nanoparticles in the polymer matrix, the inclusion of nanoparticles resulted in a considerable improvement in the blend's microhardness and barrier characteristics [46]. Ma et al. prepared PBAT/PPC/nano-silica with melt mixing; the ternary system shows improved storage modulus of the nanocomposite due to an increase in the crystallization of PBAT in the blend due to nano-silica acting as nucleating sites. It was evident that the double percolation network formed for the blends at 5% nano-silica for PBAT: PPC of 70:30 [28]. The advancement in bionanocomposites and their

applications were shown in Table 1. Active and intelligent/smart packaging are two types of bionanocomposite-based food packaging, as outlined in Sect. 2.7.

A group of researchers from the University of Tabriz Iron recently studied the silver, copper oxide, and zinc oxide nanoparticles incorporated in the starch matrix by solution casting [54]. The bionanocomposites containing 0.67 weight percent of each nanoparticle led to a synergistic enhancement in the water vapor barrier, and antimicrobial properties were observed as compared to neat starch film. Among other nanoparticles, Zn nanoparticles show better interaction with the matrix due to electrostatic interaction and hydrogen bonding [55]. The zinc oxide nanoparticles were also incorporated into the PBAT matrix, and it was observed that 10-weight percentage loading achieved a tensile strength of 45 MPa as compared to the PBAT neat film of 37.9 MPa [19].

Table 1 Advancement in biodegradable bionanocomposites and their properties

Bionanocomposites	Functionality	Observations	References
Cellulose nanofibers (CNF) functionalized star ZnO	*Active packaging*: Antimicrobial properties	ZnO with 3 wt% shows a reduction in the population of bacterial by ~50%	[47]
Gelatin/CNF/ mushroom-mediated sulfur nanoparticles (SNP)	*Active packaging*: Antibacterial, UV protection	SNPs show decisive action of antibacterial against the foodborne bacteria	[48]
Methyl cellulose/ chitosan nanofibers/ ZnO	*Active packaging*: Antibacterial, Antioxidant	The film gives ~84% antioxidant capacity	[49]
Electrospun nanofibrous sheet of PCL/zien with halloysite nanotubes	*Active packaging*: Improvement in Tensile strength with a slight improvement in barrier properties (WVP), Antioxidant, Antibacterial	Shows good DPPH (diphenylpicrylhydrazyl) antioxidant capacity with antimicrobial properties against gram-negative (*E. coli*) and gram-positive (*B. subtilis*)	[50]
Starch/zein nanoparticles (ZNP)	*Edible packaging*: Improved barrier, mechanical	The 9 wt% ZNP shows an improvement in the tensile strength and barrier performance in comparison with starch film	[51]
Faba bean protein isolate (FBPI)/ cellulose nanocrystals (CNC)	*Edible packaging*: Improved barrier, mechanical	The enhancement in the Young modulus of ~77% at ~7 wt% loading of CNC	[52]
Chitosan/gum Arabic/blood orange anthocyanins	*Smart packaging*: Antioxidant, Freshness indicator, antibacterial	Anthocyanins worked as plasticizers lead to improve the elongation at a break of ~76%	[53]

3 Applications

3.1 Biodegradable Polymer in Smart Food Packaging

Biodegradable smart packaging is an emerging concept that employs intelligent and active substances to enhance the quality of packaged products. Researchers are exploring the use of biodegradable materials as alternatives to electronic components in smart packaging systems. Smart packaging is broadly classified as active and intelligent packaging. Active packaging refers to packaging which is designed to actively engage in order to enhance shelf life and food quality, e.g., release active ingredients such as antibacterial and antioxidant. Whereas intelligent packaging provides information about the food quality. Various active and intelligent packaging materials derived from natural sources have been developed for direct and indirect food applications. For instance, as studied by Andrade et al., green tea and rosemary extract was incorporated in PLA films for the packaging of beef and almond. The research revealed that dried leaf rosemary extract and green tea at both concentrations of 2% had antioxidant activity, showing an inhibition percentage of blocking ~10% of 2,2-diphenylpicrylhydrazyl (DPPH) radicals. The antioxidant activity coefficient (AAC) which is a measure of antioxidant capacity is calculated by dividing the antioxidant capacity of a substance (expressed in units of antioxidant activity) by the concentration of the substance (expressed in units of weight or volume). The obtained values reflect the antioxidant activity per substance unit. In a recent study, AAC was calculated for PLA-based films using the Beta-carotene bleaching assay and shows a value of ~177, indicating the synergistic effect of using green tea extract and rosemary extract [56]. As a sustainable and biodegradable film for smart food packaging applications, a PLA/PPC blend containing curcumin (CCM) was also designed (Fig. 4a). CCM-loaded blends demonstrated high antioxidant activity, limited migration, and color changes in response to NH_3 vapor, indicating food freshness [57]. Compared to conventional petroleum-based packaging, active and smart packaging offers more remarkable preservation and has a lower impact on the environment and human health.

Active Food Packaging

Food packaging can use active materials to release or absorb gases and other ingredients, extending the shelf life of food goods. Depending on whether the active ingredients are continuously dispersed into the food package or are contained on the package itself, active packaging can be categorized as either migratory or non-migratory. The use of active function in biodegradable films is described in more detail below and is included in Table 2. The naturally sourced antioxidants found in commercial packaging help to prevent enzymatic browning and oxidative rancidity to prolong the food shelf life. These antioxidants promote health by preventing oxidative stress and lowering the risk of numerous diseases. Leaf extract, oils, acids, and

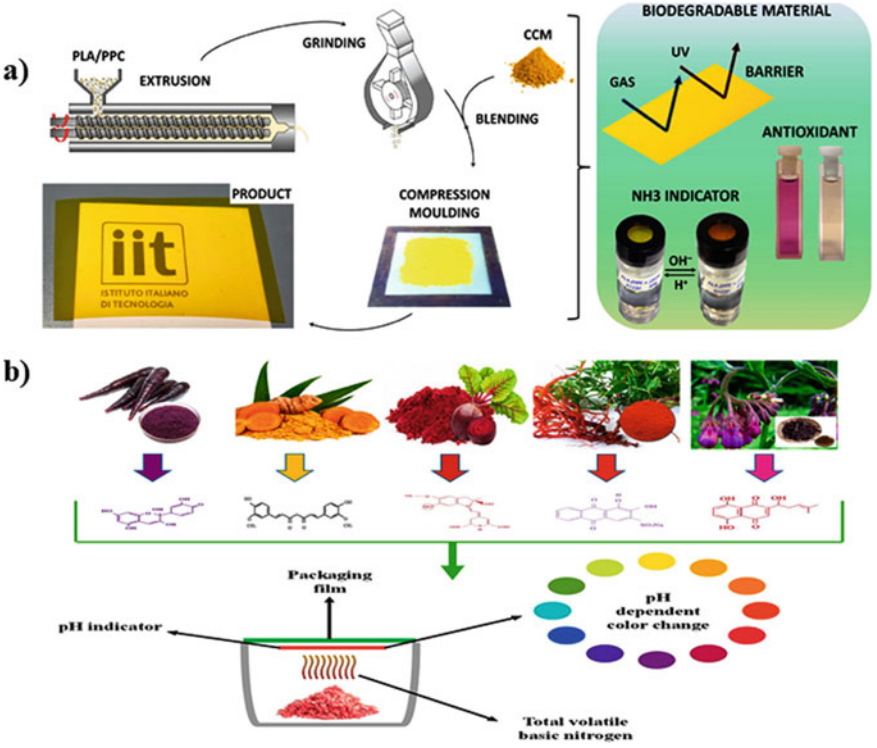

Fig. 4 **a** Manufacturing of PLA/PPC/curcumin for active packaging CC-BY [57] Copyright © 2022, **b** Natural halochromic substance for Intelligent packaging (adopted with permission Copyright © 2021, American Chemical Society)

other substances are used to create a biodegradable film or coating containing antimicrobial compounds to prevent the growth of bacteria, yeast, and mold that can cause foodborne illness. Essential oils and plant extracts are particularly rich in organic acids and phenolic compounds.

Table 2 Various active agents for active food packaging

Active agents	Types of foods	Examples	Benefits	References
Ethylene scavenger	Climatic food and vegetable	Potassium permanganate, halloysite, zeolite, palladium chloride, ZnO, and TiO_2	Reduce browning, mold growth, and retain vitamins (Vit. C)	[58, 59]

(continued)

Table 2 (continued)

Active agents	Types of foods	Examples	Benefits	References
Oxygen scavenger	Cheese, cooked meat products, fruits, and vegetables	Photosensitive dyes, iron, palladium (Pd), ascorbic acid, and laccase	Improve shelf life and slow the ripening process	[60]
Antioxidant	Meat, fish, powdered food, seed, oils, and fried food	Catechin, quercetin, citric acid, resveratrol, green tea extract, essential oil, etc.	Reduce oxidation and enhance oxidative stability	[60, 61]
Antimicrobial agents	Nuts, seafood, meat, processed fruits, instant meals, and milk	Essential oil, thymol, nanosilver, nisin, vanillin, sorbic acid, chitosan, potassium sorbate, etc.	Reduces bacterial growth and improves shelf life	[59, 62]
CO_2 emitters	Seafood and meat	Sodium bicarbonate, ferrous carbonate, and citric acid	Improve shelf life and cut down the MAP cost	[63]

Intelligent Food Packaging

By offering mechanical and barrier qualities, preventing or retaining specific substances, detecting and avoiding microbial damage, etc., all of these can be served by the active packaging. They can interact with food items to increase the freshness and shelf life of the package. On the other hand, intelligent packaging provides improved functionality through real-time quality monitoring, communication and marketing, and the integration of numerous sensors and indications. Intelligent packaging can be classified as direct and indirect. The gas sensor, Radio frequency identification (RFID) tags, and thermochromic sensor are indirect intelligent packaging, whereas other classifications contain freshness indicators, microwave doneness indicators, shock indicators, and biosensors. Physical and/or chemical changes can be communicated through intelligent packaging. For example, natural pH-sensitive dyes are used to observe the chemical changes obtained inside the food headspace. The natural pH-sensitive colorants extracted from the source, like beat root, carrot, cabbage, etc., have been studied for freshness indicators (Fig. 4b). Among other natural colorants, Anthocyanins are the most common halochromic substances obtained naturally and used in intelligent packaging; attributed to their non-toxic, antioxidant, biodegradable, and ecologically friendly characteristics, anthocyanins, bioactive chemicals with phenolic groups, are being researched for their potential as additives for smart packaging films. These films can potentially be employed as pH-sensitive bionanocomposites that can detect color changes brought on by food spoilage. Black carrot anthocyanins, chitosan/polyvinyl alcohol, and bentonite nanoclay (3 wt%) show enhanced mechanical, thermal, and antibacterial capabilities, according to the study [64].

Enzymatic or microbiological activity that conventional packaging materials are devoid of may induce clam rotting. By casting, photochromic smart films with the ability to detect the freshness of seafood have been created from chitosan, oxidized chitin, and purple cabbage anthocyanins. Chitosan/PVA nanocomposites containing ZnO oxide nanoparticles combined with anthocyanins from purple sweet potatoes and roselle flowers showed pH sensitivity and antibacterial activity [65]. Additionally, these nanocomposites have also improved in terms of water contact angle and mechanical properties. Compared to roselle-based films, the purple potato anthocyanin films demonstrated excellent antioxidant and antibacterial properties, making them promising materials for intelligent and active food packaging that can recognize color changes brought on by enzymatic or microbial changes in nanocomposites [58].

Temperature monitoring is crucial to guarantee food quality and safety during storage and transit. Temperature abuse can result in quality degradation and reduce the shelf life of the package. It is crucial to keep an eye on the temperature during the storage time in order to infer the product's quality status and true shelf life. A Time–Temperature Indicator (TTI) can show variations in temperature over time and provide information on a food's temperature history. These modifications can be detected by a temperature-dependent change in the polymer coating's color or by a color change in the thermochromic indicator that results in depreciating the pH arising from a temperature-induced reaction.

3.2 Modified Atmosphere Packaging (MAP)

MAP is a popular approach for packaging and preserving perishable items like fruits and vegetables. This necessitates altering the gas composition at the package's headspace, which slows respiration, delays ripening, and prevents moisture loss. Biodegradable packaging materials for fresh food are tested alternatives to ordinary plastic. According to research, the oxygen-absorbent wrapping biologically extends the shelf life of strawberries. The biodegradable disintegration of the biodegradable layers is ideal for fresh items such as sweet potatoes, cabbage, tomato, berries, and lettuce. Chitosan coatings containing anti-browning compounds and MAP were also evaluated for their ability to minimize browning and extend the shelf life of freshly cut lotus roots. In this regard, a typical eco-friendly packaging material is PLA. PLA is a conventional sustainable material used for packaging animal products and seafood [66].

3.3 Edible Films

Cellulose nanofibers have been added to fruit and vegetable puree-based biopolymer nanocomposites to enhance their characteristics. TiO_2, being FDA (Food and Drug

Administration) approved nanoparticle, has been vastly investigated to improve the antibacterial properties of whey protein, which has been investigated for its potential as an edible film with oxygen barrier capabilities. Although soy protein has been investigated as a biodegradable, edible material, its effectiveness has been constrained by its high stiffness and moisture resistance. Soy protein has been combined with plasticizers like starch to enhance the flexibility of the film without compromising the barrier properties. However, the fillers, like montmorillonite (MMT) clay, increase their barrier and mechanical properties. The mechanical strength of the nanocomposite has been observed to be increased due to the interaction between the soy protein and MMT clay [67]. Adding MMT clay (negative charge), in particular, ~320% and ~175%, increased Young's modulus and tensile strength, respectively, were observed for the soy protein nanocomposite with 20% loading. This is attributed to the surface electrostatic interaction due to the charge difference [68].

4 Types of Food Packaging Products

The packaging sector frequently uses biodegradable films, which were developed initially to replace non-biodegradable plastic. Regulated breathing, effective barrier properties, and sturdiness are crucial characteristics of packaging films. PLA-based blown films have proven successful because of their mechanical and transparent features. However, the degree of crystallinity affects the sealability, necessitating the employment of a co-extrusion technique when laminating the polyesters [69]. The food packaging film grade PLA available in markets are Ingeo (Nature works), Futerro, Hisun, and Biofront (Teijin). Since a single biodegradable polymer has a low melting point and sluggish crystallizations, it is unsuitable for creating blown films. Hydrogels and other biodegradable gels are excellent in preventing microbial contamination. Complex hydrogels, which provide an alternative to the manufacturing of biological polymers, can be created by combining hydrogels made of several polymeric components. Due to their flexibility, toughness, and resistance to rips, humidity, and temperature changes, biodegradable bags are primarily utilized in the food business, including PBAT (Ecoflex®) and Ecovio®. Loose fill is made of starch-based foams, and trays and shells of starch-based foam need to be coated when they encounter food. In the market, Green cell™, Biofoam (Synbra), and Novamont foam are the replacement for PP foam as a biodegradable alternative. Fruits and vegetables that require a regulated environment to retain their quality might be packaged in thermoformed trays or containers made of biodegradable polymers [70]. Tropical fruits, including mangoes and melons, have been stored in biodegradable trays and cups constructed of oriented PLA or with bionanocomposites of PLA/wood (Jeluplast®). Commercially available smart packaging sensors/indicators include Fresh Tag Sensor Q™, Tell-Tab™ (gas sensor), Cook-Chec (3M), and Ripesense™.

5 Toxicity Concerns

The negative effects on the environment and health risks associated with the use of biopolymer/bionanocomposites have made it possible to use biodegradable polymers in food packaging. Biopolymers, such as PLA, starch, and PHAs, have poorer barrier characteristics than conventional polymers and must be enhanced with additives. Nevertheless, their practical usage as packaging materials has been limited due to drawbacks such as lower barrier qualities to small molecules such as water and oxygen. Plastic materials must not leak more than a set number of components per food contact surface to ensure the safety of food products. Food simulants are used to analyze and quantify nanoparticle transfer from packaging materials to food products. Nanofillers such as nanosilver, nanoclay, CNC, ZnO, and TiO_2 are utilized to decrease migration risk due to their thermodynamic features of polarity and solubility in biodegradable polymers. For example, according to US-NIOSH (United States-National Institute for Occupational Safety and Health), silver nanoparticles are employed as antibacterial agents in food packaging, with an allowed limit of 0.01 mg/m^3 for all kinds of silver. Concerns have also been raised about the safety of metal nanocomposite film materials used for food packaging, as metal nanoparticle migration into food could pose health hazards. Fan et al. used food simulation fluid to evaluate nano-Ag migration in PLA/nano-Ag composite sheets under simulated food packaging circumstances. However, the migration of nano-Ag is under an acceptable limit, but there is a rise in WVP in the initial migration [71].

Apart from nanofillers, the degradation products such as oligomers and side reaction products are the principal source of non-intentionally added substances (NIAS) in biopolymer-based food contact materials (FCM). PLA oligomers include cyclic lactide, and linear or cyclic oligomers are not on the Directive 10/2011/European Community list, where the concentration must be less than 0.01 mg/kg of food, except for LA. According to studies, PHB and PBAT leaching solutions decrease Daphnia survival within 48 h of exposure. Thirty-seven non-volatile compounds, including significant amounts of cyclic oligomers such as butanediol, adipic acid, and phthalic acid, are present in PLA/Bio-PE blend films and granules.

6 Future Challenges and Opportunity

Biodegradable polymers have relatively low mechanical and barrier qualities and their hydrophilic character, which prevents the development of moisture barrier capabilities; biopolymer-based packaging materials confront difficulties. These drawbacks have been identified, and nanocomposite technology has been suggested as a potential remedy. Ongoing research looks into bionanocomposites to meet consumer needs for safe, natural, and minimally processed foods with a long shelf life. Additionally, bionanocomposites can outperform the limitations of biopolymers and can offer more advanced functionality and barrier characteristics. There hasn't been much

research on the nanotoxicology and nanoecotoxicology of biodegradable polymers, even though nanoparticles are used to enhance the qualities of polymers for food packaging. The multilayer structure consisting of biopolymer is a growing area of research with the use of techniques like co-extrusion, heat sealing, spin coating, and electrospinning. Rapa et al. in a recent study, deposited electrospun PHBV and Fe-doped ZnO nanoparticles having beaded morphology on the PLA films to enhance the antimicrobial properties. However, the migration of nanoparticles is still a challenge for biopolymers which need to be studied for different food stimulants. Another challenge of biodegradable polymers is the migration of oligomers, additives, plasticizers, and monomers that need to be studied thoroughly for food packaging applications.

Moreover, utilizing food simulants for migration studies does not properly imitate real-world conditions. When diffusion occurs from only one side of the material, the actual release of migrants is slower. Also, the release of nanofiller can hamper filler functionality on the migration. The usage of nanofibers for smart packaging applications majorly involves electrospun biodegradable nanofibers, and most research focuses on pH indicators and thermal control. The multilayered assemblies of biopolymer in the layer-by-layer structure open the research diversely. The continuous fueling of innovation in the field of smart packaging materials by adding active agents, substances, and fillers needs to be evaluated to possess no toxicology concern on the environment and health.

7 Conclusion

This book chapter discusses the food packaging application of various biodegradable polymers. In this regard, the physical, mechanical, barrier, and thermal properties of biodegradable polymers must be improved by using techniques like plasticization, blending, and/or processing them into bionanocomposites to fulfill the purpose of packaging. The morphology of filler nanoplates is being extensively researched to improve the mechanical and barrier characteristics of biopolymers. For example, adding PVA in the blend of biodegradable polymer and/or as a multilayered structure can enhance the mechanical properties, thermoplasticity, and oxygen barrier properties of the blend, making it a promising material for eco-friendly packaging. Such approaches have produced active and intelligent packaging solutions that improve customer/consumer friendliness and transparency while raising the bar for food safety and quality. Using nanotechnology in barrier packaging materials such as by the adoption of the approach of nanocomposites, nanoparticle-based antimicrobials, and sensors to detect changes in food may potentially transform current packaging methods and technologies. Bionanocomposites and polymers that offer better performance while lowering environmental impact are the key to the future of food packaging. The lower molecular weight of nanoparticles makes them more quickly absorbed and distributed throughout the body, possibly resulting in harmful cellular interactions. In addition to toxicity, it is essential to consider the sustainability of bioplastics, such as land use, greenhouse gas emissions, and social impact.

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Chapter 9
Biodegradable Polymers for Agriculture

Kunal Verma, Chandrani Sarkar, and Sampa Saha

1 Introduction

Agriculture plays a critical role in sustaining human life by providing food, fiber, and fuel. However, conventional agricultural methods can have significant environmental consequences, including land erosion, water contamination, and greenhouse gas emissions [1]. In agricultural applications, polymers are extensively used for intelligent agrochemicals and ultra-absorbents. Unfortunately, most of these polymers are non-biodegradable, causing severe pollution in the soil. Biodegradable polymers are needed to address these ecological issues. Unlike conventional polymers, which can take hundreds of years to decompose, biodegradable polymers typically degrade within months or years, depending on the polymer structure and environmental conditions. These characteristics make them a sustainable option that can help to reduce non-degradable waste in the ecosystem and preserve the health of our planet. The demand for biodegradable products is increasing due to public awareness of the harmful effects of conventional polymers and government regulations banning non-degradable synthetic polymers. This demand is expected to grow across various industries, including agriculture. According to a market research report, the global market for biodegradable polymers in the agricultural sector is projected to reach $6.48 billion by 2027, with a growth rate of 10% from 2022 to 2030 [2].

Biodegradable polymers generally decompose into water, carbon dioxide, or biogas under specific conditions, making them an environmentally-friendly option as compared to traditional polymers and other materials. The choice of a biodegradable polymer for different applications is based on the physical properties of the

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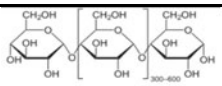
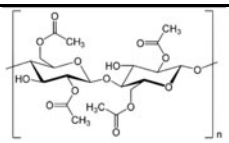
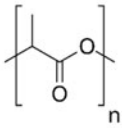
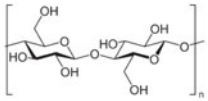
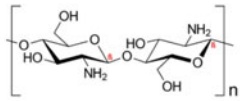
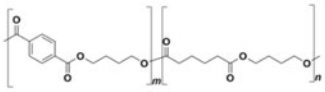
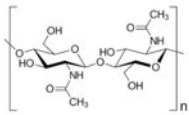
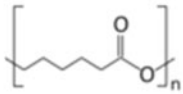
Natural polymers	Semi-synthetic	Synthetic polymers
 Starch	 Cellulose acetate	 Polylactic acid
 Cellulose	 Chitosan	 Poly(butylene adipate terephthalate (PBAT)
 Chitin		 Polycaprolactone (PCL)

Fig. 1 Chemical structures of some commonly used biodegradable polymers in agriculture

polymer. Natural polymers like cellulose, starch, alginate, chitosan, pectin, gelatin, and zein are commonly used for agricultural applications. Synthetic polymers like poly(lactic acid) (PLA), poly(vinyl alcohol) (PVA), poly(butylene adipate terephthalate) (PBAT), polyhydroxyalkanoates (PHAs), and poly(butylene succinate) (PBS) are also commonly used in agricultural sector. The structures of these polymers are shown in Fig. 1 [3–8]. A scheme is given in Fig. 2. shows the uses of these biodegradable polymers in different agriculture sectors, including mulch films, seed coatings, superabsorbent polymers, and agrochemical delivery systems.

2 Biodegradable Polymers in Agriculture Sectors

Recent studies have focused on using biodegradable polymers and their compounds as materials to manage soil health, water quality and food quality for improving production in agriculture sector [9–14]. Table 1 summarizes the different polymers

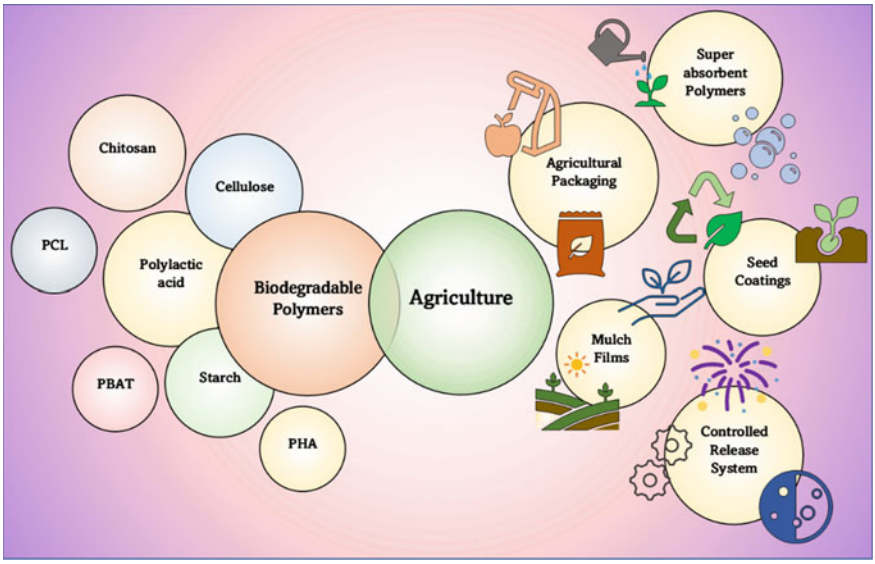


Fig. 2 Biodegradable polymers used in different agriculture sectors inspired from [9–14]

Table 1 Different agro-products, their functions and polymers used in their manufacturing

Agro-product	Function	Polymer used	References
Mulch film	Soil moisture conservation, soil temperature management, weed control, nutrient conservation, pest control, improved yield	PLA, cellulose, PBS, starch, PCL, PBAT	[15–20]
Seed coating	Soil moisture conservation, soil temperature management, weed control, nutrient conservation, pest control, improved yield	Chitosan, PLA, PHAs, starch, cellulose, gelatin	[8, 21–23]
Agrochemical delivery	Slow release of agrochemicals, low pollution, improved efficiency of agrochemicals, improve soil quality, increased yield	PLA, PHAs, chitosan, starch, alginate, poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG)	[3, 12, 19, 24–31]
Soil improvement	Water retaining agent Nutrient carrier	Chitosan Ethyl cellulose Sodium alginate	[32–35]

based agro-product, their functions, and polymers used in their manufacturing. A brief overview of each agricultural product has been provided below.

2.1 Mulch Films

Soil mulching is one of the most important uses of biodegradable polymers in cultivation. Mulch films are thin sheets of material used in agriculture to cover the soil surface in order to alter the microclimate of the soil, preserve moisture, reduce weeds, and safeguard crops. Mulching is a method used to coat soil with a covering of crop in order to keep moisture and control soil temperature [20, 36]. Mulch films are utilized in numerous farming practises, including the cultivation of vegetables, fruits, and decorative plants. Mulch films can increase crop harvesting and quality in veggie production by suppressing weeds, preserving soil hydration, and controlling soil temperature. By stopping the leaching of pesticides and fertilizers into the earth, they can also help to decrease their use. Biodegradable polymeric mulches have several benefits over conventional mulches (generally non-degradable), such as increased water absorption, decreased weed development, and increased agricultural output [18–20, 23, 36, 37], most importantly, no consumption of land-filling sites as they degrade on the soil without leaving any toxic residue in them. Figure 3 shows the biodegradation of mulch film by environmental conditions and microbial enzymes.

In a comparative study, the effects of LDPE (low density polyethylene) and Bio PMF (biodegradable polymeric mulch film) debris in either macro- or micro-sizes

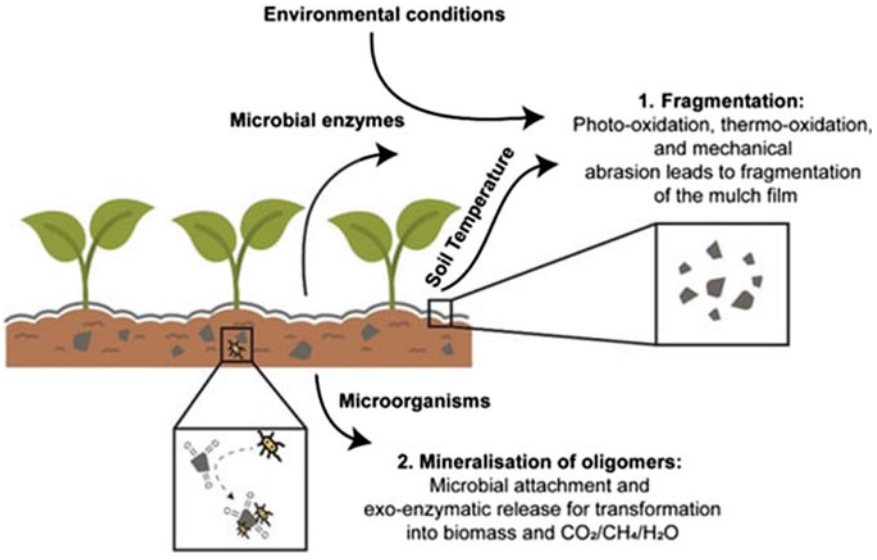


Fig. 3 Biodegradation of a mulch film. Reproduced with permission from Mansoor et al. [20]

on soil's hydrological and physiochemical parameters were evident, and these properties of tested sandy soil changed slightly due to residual amounts of PMFs. For example, the existence of LDPE debris reduced field capacity while the presence of Bioplastic debris increased it. When compared to micro-sized plastic detritus, macro-sized plastic debris showed more differences between the control. As a result, the detrimental impacts on plant development may be explained in part by the effects of plastic debris on soil properties [38].

According to a study which compared the effects of (polybutylene adipate terephthalate) PBAT-based mulch films and polyethylene (PE) mulch films on rice plants, microplastics affected nitrogen biosynthesis and photosynthesis. Microplastics inhibited rice root growth by inhibiting the phenylpropanoid biosynthesis pathway, decreasing lignin content, and inducing oxidative stress in rice roots during the vegetative stage, which ultimately led to the downregulation of nitrogen transporter genes and interference with nitrogen metabolism. Repression of nitrogen transporter genes reduced nitrogen transport from rice roots to shoots, leading to nitrogen deficiency, oxidative stress, and a decrease in chlorophyll content in shoots [39].

A study conducted in 2021 found that many polysaccharide-based mulch films on the market work as well as PE-based mulch films. But they have some problems, like being expensive, hard for farmers to use, and not good at keeping water out [36].

2.2 Seed Coatings

Seed coatings are another utilization of biodegradable polymers in horticulture. The purpose of seed coatings is to shield seedlings from insects, diseases, and weather stressors (Fig. 4).

To increase agricultural output and decrease environmental effects, seed coatings can be customized to the particular requirements of various crops [21, 22]. Traditional coverings, which contain hazardous, non-degradable polymers, need to be replaced with biodegradable polymers. Biodegradable seed coatings are a viable option to non-biodegradable coatings. During the germination and the initial development phases, biodegradable polymeric seed coverings shield seedlings from biotic and abiotic stressors [22]. These coatings can provide a regulated discharge of nutrients, provide protection against bugs and diseases, and enhance the soil's physical qualities. Additionally, seed coatings can increase seed handling and planting accuracy, resulting in higher agricultural outputs. Hydroxyethylcellulose, chitosan (CS), gelatin-gum arabi, PLA, PHAs, and starch-based polymers are the most prevalent compostable polymers utilized for seed coverings. These materials are safe, biodegradable, and versatile to the seed and crop's particular requirements [40, 41]. More recently, a biopolymer mixture of starch, gelatin and poly(vinyl alcohol) have been used due to its good adherence to seeds [42]. Biodegradable polymeric seed coatings (BPSCs) are applied to grains, veggies, fruits, and oilseeds, among other products. They are typically applied by seed-treating devices like rotating drum, rotary coating, fluidized

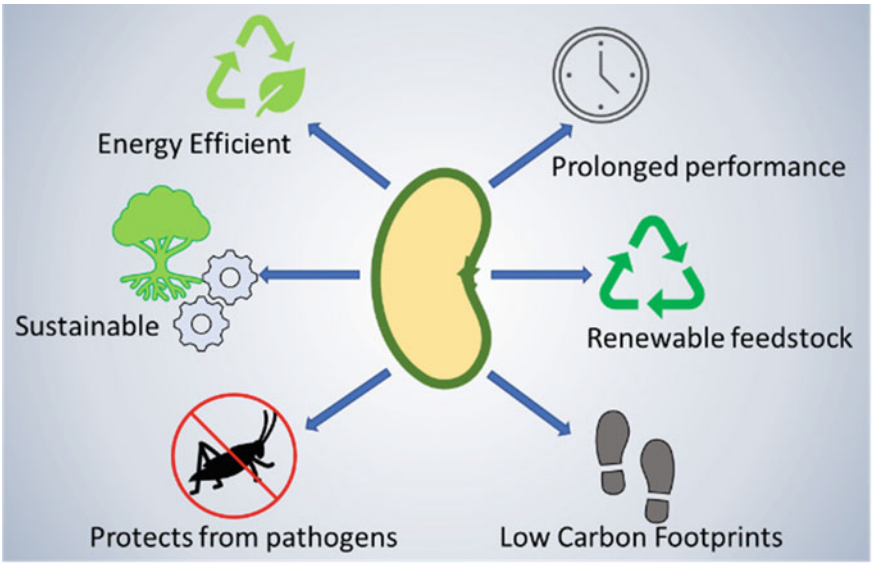


Fig. 4 Benefits of seed coatings [21]

bed and electrospinning (Fig. 5) that evenly cover the seeds. The coated seeds can then be buried with standard sowing tools.

Electrospinning technique is an advanced method to design scalable and sustainable seed coating using biodegradable polymers. This technique is also used to

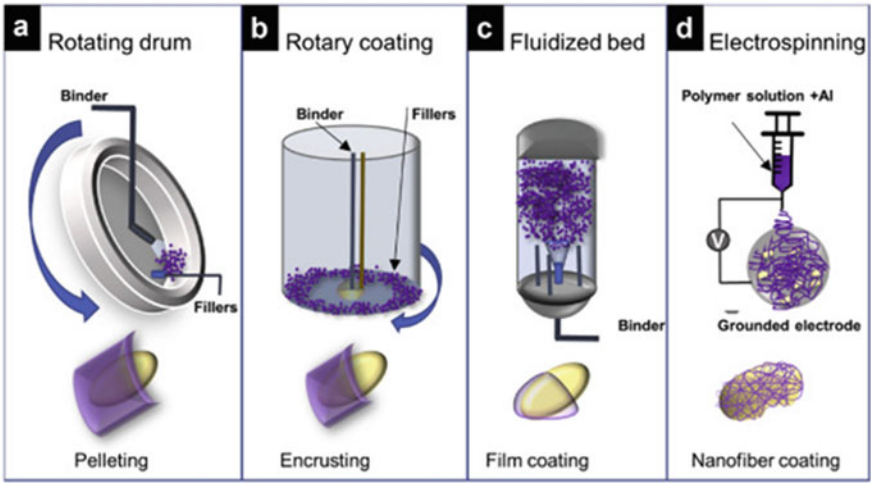


Fig. 5 Schematic of different seed coating methods. Reproduced with permission from Pirzada et al. [42]

develop biostimulants and insecticides incorporated with polymeric seed coverings [21, 22]. Because, these additives provide extra advantages, such as increased plant development, better plant resilience to pests and diseases, and decreased environmental effects. A study demonstrated a novel seed rejuvenation way by infusing hormones gibberellic acid (GA_3) and indole acetic acid (IAA) in electrospun nanofiber. In this investigation, groundnut and black gram seeds coated with GA3 and IAA-loaded nanofiber delivered hormones at the appropriate time, location, and concentration to enhance seed quality. GA3-loaded nanofiber and IAA-loaded nanofiber-coated seeds increased germination (78 and 88%) and seedling vigor (2987 and 3458), respectively, by 10 and 20% over uncoated seeds. In black gram, seeds invigorated with GA3 and IAA-loaded nanofiber recorded 78 (8% increase over control) and 86 (16% increase over control) percentages of germination and seedling vigor, respectively [43].

In another study, researchers designed copper loaded nanofibers using electrospinning and precisely distributed agrichemical (Cu^{2+}) around the seed at low dose. These model seeds coated with nanofiber seed coating were found to enhance germination and plant growth regardless of fungal disease present (Fusarium species) [44] (Fig. 6).

Despite the many advantages of compostable polymeric seed coverings, there are still some obstacles to overcome. The expense of the coatings, which is presently higher than non-biodegradable coatings, is one of the greatest challenges. Additionally, the compatibility of the coatings with various seed sizes and forms, as well as their ability to endure a variety of environmental circumstances, must be investigated further.

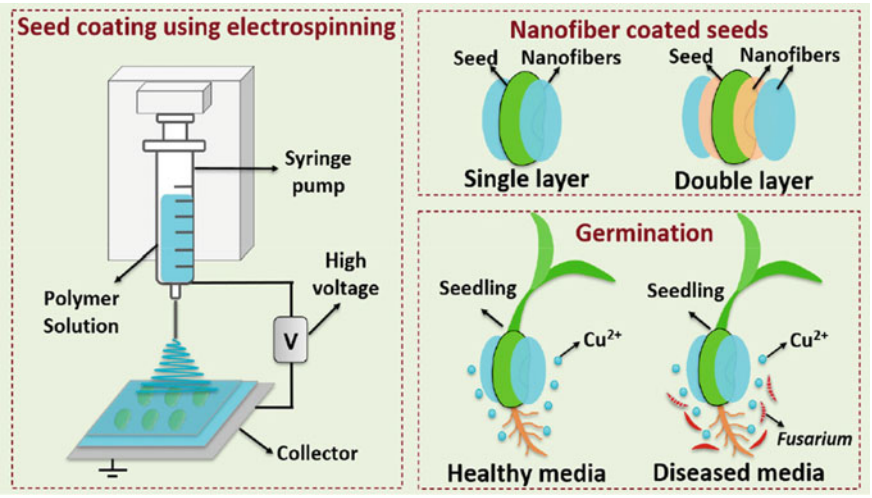


Fig. 6 Seed coating process using electrospun Cu^{2+} loaded nanofibers, and nanofiber-coated seeds. Germination of nanofiber-coated seed in the presence or absence of a fungal pathogen. Reproduced with permission from Xu et al. [44]

Biodegradable polymeric seed coatings (BPSCs) have the ability to increase food production, reduce environmental effects, and promote healthy agricultural practises. Additional study and development in this field could lead to the production of more efficient and cost-effective seed coatings for a variety of crops [8, 11, 17, 21, 37].

2.3 Agrochemical Delivery

As agriculture continues to play an important part in satisfying the world's food demand, there is an increasing demand for more efficient and sustainable agricultural methods. This can be accomplished by utilizing polymeric materials for agrochemical delivery. Modern agricultural methods frequently employ agrochemicals such as fertilizers, pesticides, herbicides, and growth regulators to increase crop output and safeguard harvests from bugs and diseases [9, 12, 28, 45]. However, the indiscriminate use of these substances can harm the ecosystem and human health as well. Biodegradable polymeric materials are a potential option to conventional chemical delivery methods. Several biodegradable polymers, like polylactic acid (PLA), polyhydroxyalkanoates (PHAs), starch-based polymers, and cellulose-based polymers, can be used to control the distribution of pesticides, herbicides, and plant nutrients, depending on their biocompatibility, biodegradability, and controlled release characteristics [28, 46]. The most common way to get agrochemicals to where they need to go is to load the desired herbicide, pesticide, insecticide, or nutrient into a suitable polymeric matrix [11, 12, 30, 47]. This can be either done by preparing hydrogel, films, microparticles, nanoparticles, emulsions and electrospun mats (Fig. 7).

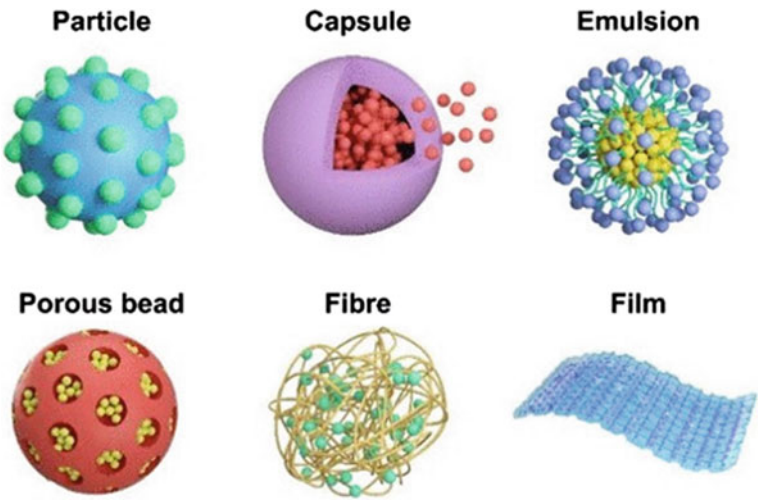


Fig. 7 Different carriers for agrochemical delivery. Reproduced with permission from Li et al. [48]

The selection of an agrochemical relies on the intended purpose and the targeted produce. They can be used as a coating to seedlings to regulate the release of agrochemicals during the germination and development phases of the produce. Additionally, they can be utilized as sheets for soil mulching and hydrogels for the regulated release of agrochemicals in the soil [49, 50].

One interesting example in this regard is cellulosic nanogel. A new cellulose-based nanogel was produced by cross-linking glyoxal-modified carboxymethyl cellulose (CMC) and 3,3′-dithiobis(propionylhydrazide) (DTP). Palmitic chloride (PCl) was used to splice hydrophobic branches onto cellulose strands in order to increase the loading efficiency of typical agrochemicals such as salicylic acid (SA) (Fig. 8). When subjected to pH and redox changes, the acylhydrazone and disulfide bonds give the nanogel with reversible sol–gel transitions. PCl-grafted nanogels have a maximal loading capacity of 40.6%, which is 31% greater than the original nanogels. A controlled release experiment revealed that HCl and Glutathione (GSH) solutions greatly hastened the release of SA, and nanogels with abundant carboxyl and thiol groups can complex with heavy metal ions; for example, around 89% of copper (II) ions can be removed from synthetic soil leachate [51].

Another study examined the controlled release of fertilizers using two types of polyhydroxybutyrate (PHB) systems. PHB is preferred because of its biodegradability and water-insoluble which allows large-scale pesticide encapsulation. One system used free NPK (Nitrogen phosphorous potassium) (PHB/NPK) while the other incorporated NPK into bentonite nanoparticles (PHB/m-Bent with NPK). The properties of the systems were found to influence the release rate of the active compounds and their biodegradation rates. The latter system (PHB/m-Bent with NPK) with better thermal and thermo-mechanical properties exhibited a more controlled release rate of compounds than those with lower properties due to better structural configuration. Controlled release assays showed that the PHB/NPK systems released 19–33% of their components in the first 24 h, and 37–53% during the entire testing period. In contrast, the release of NPK from the PHB/m-Bent systems was only 4–11% during the entire test. The PHB matrix underwent biodegradation regardless of the presence of NPK, and the PHB/NPK and PHB/m-Bent systems exhibited greater structural fragility, which may have facilitated the biotic process of degradation and the release of active compounds. The study suggests that the PHB systems have the potential for positive environmental and economic impacts due to their ease of processing and reduced release of active compounds into the environment, thereby decreasing the ecotoxicity [52].

In another example, Ca-alginate/poly(*N*-isopropylacrylamide)@polydopamine (Ca-alginate/PNIPAm@PDA) microspheres with a core–shell structure that are pH, temperature, and sunlight responsive have been created (Fig. 9). They can be used to control the release of water and chemicals in agriculture [53]. Similarly, L-Lactide/glycolide/polyethylene glycol terpolymer (PLAGA-PEG-PLAGA), PLAGA-PEG/dextrin-g-PCL (TER/dextrin), and PLAGA-PEG/maltodextrin-g-PCL (polycaprolactone) (TER/maltodextrin) were used to create herbicide-loaded microspheres with a low size distribution. The controlled degradation rate of particles, combined with the gradual release of both soil-applied pesticides (metazachlor and pendimethalin),

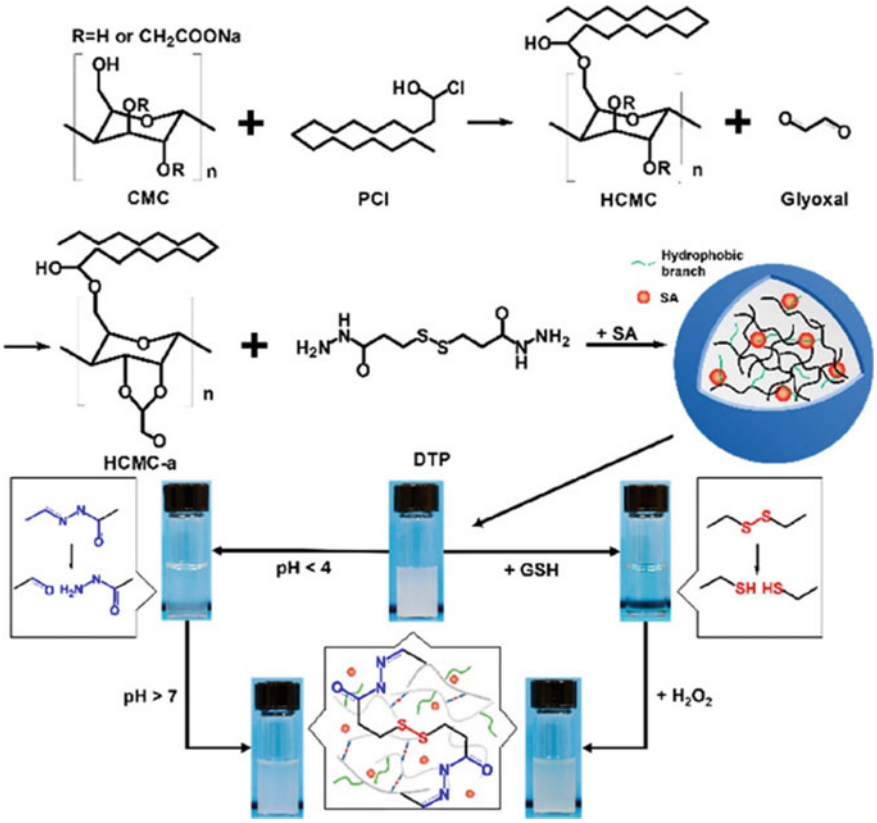


Fig. 8 Synthesis of salicylic acid loaded cellulose nanogel process using hydrophobic carboxymethyl cellulose (HCMC) and its pH responsive behavior. Reproduced with permission from Hou et al. [51]

gave agricultural plants with efficient weed protection for two to three months after entry into the soil. When compared to the PLAGA-PEG-PLAGA terpolymer, oligosaccharide-based polymers had the quickest degradation and release rate among the evaluated microspheres [54].

Numerous benefits are associated with the use of compostable polymeric materials for agrochemical distribution. First, it lowers the quantity of chemicals needed, thereby reducing environmental contamination and human exposure to hazardous substances. In addition, it offers a more controlled discharge of agrochemicals, thus reducing the risk of groundwater contamination. Biodegradable polymers can also increase the efficacy of agrochemical distribution by lowering the necessary quantity of active components and prolonging the period of release. A table (Table 2) is given on various types of biodegradable polymeric agrochemical carriers for different plants.

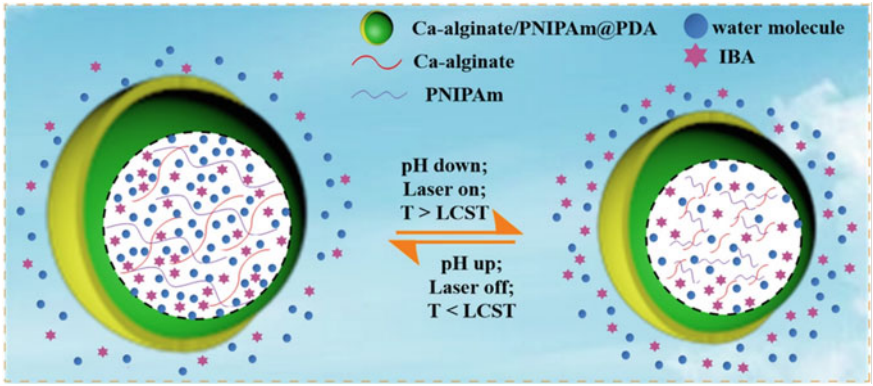


Fig. 9 Stimuli–responsive release behaviors of Ca-alginate/PNIPAm@PDA microsphere. Reproduced with permission from Zheng et al. [53]

Table 2 Various types of biodegradable polymeric agrochemical carriers. Reproduced with permission from Sikder et al. [19]

Polymer used	Agrochemical used	Release property	Nature of carrier	Applied crop/ plants	References
Poly(PEG-co-PLGA)	Metolachlor	Diffusion control	Micelle	*Oryza sativa*, *Digitaria sanguinalis*	[19]
Polyethylene glycol-aliphatic diacid conjugate	Imidacloprid	Diffusion control depends on diacid	Micelle	Mango, guava	[55]
Polylactide	Imidacloprid	Diffusion control	Nanoparticle	Rose, sunflower, wheat	[56]
PCA−PEG−PCA triblock copolymer	Imidacloprid	Diffusion control depends on PEG chain	Nanoparticle	Corn, millets, barley	[56]
Cross-linked polymer (acrylamide–itaconic acid)	Potassium nitrate	Depends on the nature of cross-linking agent	Cross-linked nanoparticle	Rice, tomato, sugarcane, legumes	[57]
PHB, PHBV, poly(vinyl alcohol)	Ametryn	Release depends on surface property of the particle	Particle formed by emulsion	Corn, sugarcane, banana, pineapple	[58]
Poly(ε-caprolactone)	Atrazine	Release depends on morphology and loading content	Nanocapsule/ nanosphere	Corn, sorghum	[59]

Nevertheless, the use of biodegradable polymeric materials for pesticide distribution poses a number of challenges. Most important one is the greater expense of these materials as compared to conventional delivery methods. In addition, the rate of degradation of these materials can differ based on environmental circumstances, which can influence their efficacy. Biodegradable polymeric materials can reduce environmental pollution and increase agricultural production while reducing the risks connected with agrochemical abuse. Future creation of more effective and cost-effective biodegradable polymeric materials for agrochemical distribution is anticipated, even though there are still obstacles to be surmounted.

2.4 Herbicides and Polymeric Biocides

Weeds are unwanted vegetation that disrupts agricultural output. They fight for resources with crops, resulting in significant output loss. Herbicide-based weed control is a highly efficient and dependable vegetation management approach. Herbicides account for a sizable portion of the worldwide pesticide industry. However, herbicides are lost in the agroecosystem in a variety of ways (like chemical breakdown, photo-degradation, microbial decomposition, run-off, leaching, and volatilization), reducing herbicidal action and polluting the ecosystem and groundwater [60].

The adverse effects of biologically active compounds are mitigated by a novel controlled release formulation method. This method safeguards the agent delivery, enables controlled release to the target, and maintains its optimal concentration for a predetermined period of time, resulting in high precision and longevity [12, 34, 59]. Two techniques - solvent evaporation and ion gelation method [60] are used to mix biological agents and polymeric materials to attain controlled release rate of agents, from encapsulation or heterogeneous dispersion of them. The polymeric biocide has many advantages, including the ability to use lower amounts than conventional biocides because it releases the required amount of active agent over a long period of time, reducing the number of applications. Since, a single application lasts a long time, thus eliminating the time and cost of repeated over applications. As a result, less active materials are required, reducing ecotoxicity, and eliminating the need for widespread application [59, 61].

Factors such as chemical properties of the active agents, their structure, nature of the active-agent-polymer bonding (esters, urea, urethanes, amides, acetals), the distance of the active agent from the polymer backbone, and presence of a permanent spacer group to prevent steric hindrance etc., influence the release rate of the active group from the polymer matrix and the duration of its effective action. Chemical makeup of the polymer backbone and groups encircling the functional moieties, dimensions and structure of the polymer molecule are controlled by polymerizing parameters, comonomers, solubility, cross-linking, and stereochemistry [17, 19, 31].

2.5 Polymeric Molluscicides

Mollusks are soft-bodied crustaceans of the Mollusca family. They are typically fully or partly encased in a calcium carbonate shell produced by the soft mantle that covers the body. Snails and slugs account for almost 80% of their population. These organisms thrive on the crop plant by eating leaves, fruits and seeds thereby reducing crop yield and quality. An effective way to tackle them is by using molluscicides. These are biologically active compounds which kills molluscs by interfering with their biological pathways while remaining unharmful for humans. Some majorly used molluscicides include metal salts (iron (III) phosphate, aluminium sulphate), Metaldehyde, niclosamide and acetylcholinesterase inhibitors. Since molluscicides are responsible for controlling various molluscs, significant quantities of these compounds are required to combat bilharziasis by controlling and eradicating schistosoma snails in tropical countries where cultivated areas are expanding. Bayer Co. created and marketed niclosamide (5,2-dichloro-4'-nitrosalicylanilide) as an active molluscicide to cure bilharziasis under the brand name of Bayer 73. However, large-scale use of this molecule has resulted in fiscal and environmental toxicity problems [62].

Molluscicides have been chemically combined with functionalized polymers in an attempt to enhance snail eradication while decreasing the negative effects of using a comparatively large dosage of niclosamide. Polymeric molluscicides containing Niclosamide via ionic and covalent interactions have thus been made by chemically modifying polymers like gelatin and alginate [63].

There are some drawbacks to compostable polymeric materials for agrochemical delivery. Regulating pesticide release from biodegradable plastics is difficult. Polymer, pesticide, and ambient factors affect the release rate, making it difficult to predict and control [16]. Storing and application of biodegradable polymers and herbicides must be steady. Heat, light, and moisture degrade agrochemicals, lowering their efficacy. If mishandled, biodegradable plastics can also degrade [64]. Biodegradable material and pesticide compatibility can be tricky. The agrochemical must spread through the polymer matrix and fight it without weakening or losing its mechanical properties to reach the target [50].

Biodegradable polymers are less popular for agricultural applications because they are more expensive. Manufacturing, refining, and application costs must be examined to ensure the technology is financially viable. Regulating compostable polymeric pesticide dispersal systems is tough. To ensure safety and efficacy, regulatory agencies may require extensive testing and evaluation of these new systems [12].

3 Superabsorbent Polymers

Superabsorbent polymers (SAPs) are defined as polymers that can absorb and retain large quantities of aqueous solutions or body fluids, relative to their own weight (Fig. 10) [65]. SAPs absorb and store water by forming a network of cross-linked polymer chains that trap water molecules [66]. It is usually a highly hydrophilic substance with a cross-linked network structure that is commonly available as micro-beads. These beads are capable of absorbing and retaining significant amounts of water or aqueous solutions, even when subjected to pressure [67]. These SAPs beads are classified as non-degradable petroleum based SAPs, degradable natural polymer based SAPs and degradable synthetic polymer based SAPs (Fig. 11).

Biodegradable polymers have been utilized as a super absorbent polymers in agriculture to improve soil water retention and nutrient availability. Because these polymers have the ability to absorb and hold a large quantity of water and gently release it to the soil over time. This lowers the need for regular irrigation while also enhancing plant development. Starch-based polymers, cellulose-based polymers, and polyacrylamide (PAM)-based polymers are the most frequently used superabsorbent polymers for soil enhancement. Starch-based polymers are produced from maize or potato starch and have a high capacity for water absorption, making them ideal for use

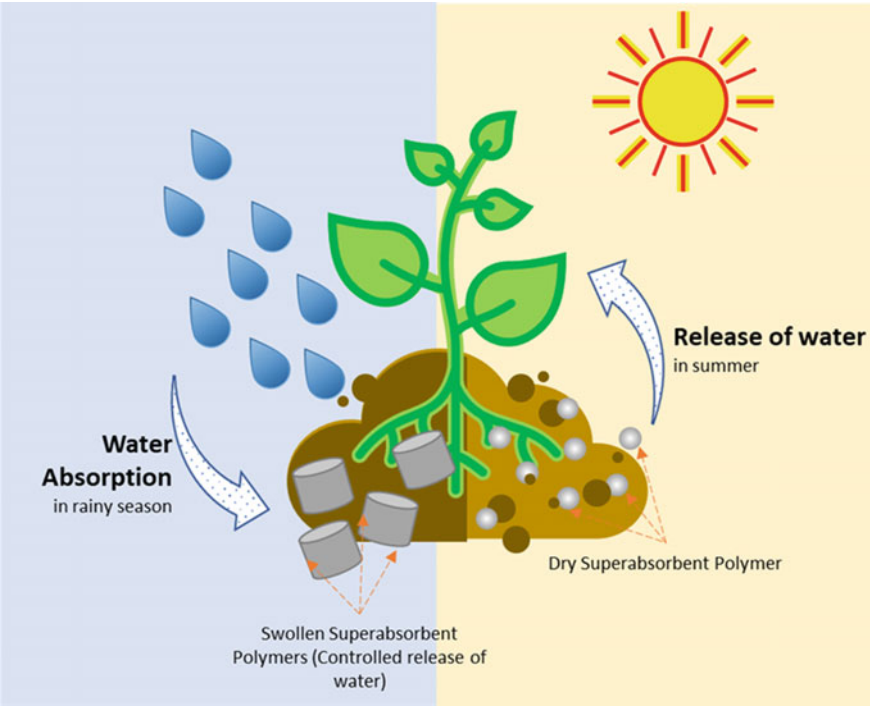


Fig. 10 Functioning of superabsorbent polymers for water retention inspired from [65]

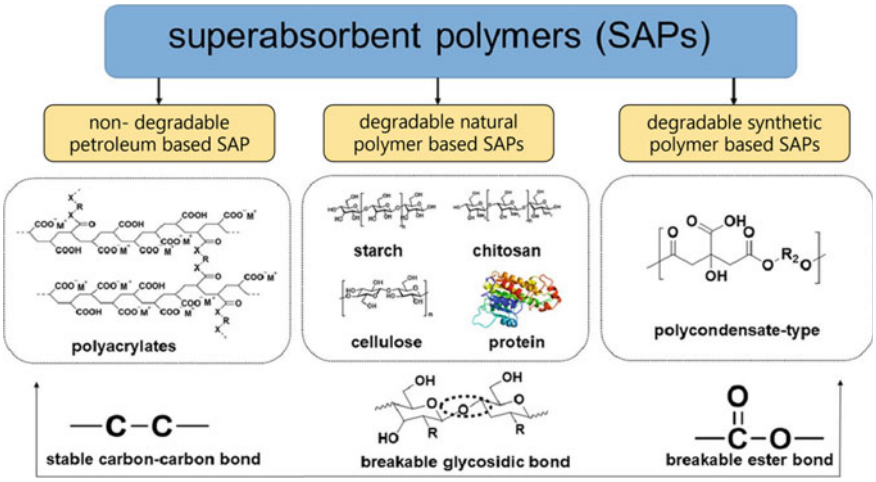


Fig. 11 Classification of superabsorbent polymers. Reproduced with permission from Chen et al. [68]

in sandy soils. Because of their exceptional water-holding ability and biocompatibility, cellulose-based polymers such as carboxymethyl cellulose (CMC) and hydroxypropyl methylcellulose (HPMC) are also widely used [18, 40, 46]. Researchers have synthesized SAP using acrylic acid and they modified the SAP particles by cross-linking it with polycations (Fig. 12) [69]. This SAP absorb and store water by forming a network of cross-linked polymer chains that trap water molecules through capillary forces, electrostatic, and hydrogen bonding [69]. Cellulose-based polymers are frequently used as seed coverings to provide water to plants during sprouting [70]. In a study, researchers found that inclusion of SAP improved the ability of dirt and sand to retain water. The water retention ability of the soil rises as the quantity of SAP in the soil increases. Biodegradability of the carboxymethylcellulose/acrylic acid super absorbent polymer (CMC/AAc SAP) was monitored. It was observed that CMC/AAc SAP showed around 40% weight reduction in 4 weeks under compost environmental conditions. The findings of the experiments indicate that the SAP has a beneficial impact on the germination of wheat and lady's finger seeds as well as the development of juvenile plants due to its high water retention capacity [71]. Another form of biodegradable superabsorbent polymer used in horticulture is cellulose-based polymers. Biodegradable superabsorbent polymer was synthesized from maleylated cotton stalk cellulose (MCSC) based cross-linker and acrylic acid (AAc) (MCSC-g-PAA) using UV photopolymerization as a green and environmentally benign form of initiation and biodegradable MCSC as cross-linker [72]. These polymers can soak water up to 100 times their weight and are obtained from sustainable sources such as wood pulp or cotton.

The use of biodegradable polymers as soil superabsorbents has several benefits, including reduced water usage and nutrient leaching, improved plant development and output, and reduced soil erosion. These polymers can be tailored to particular

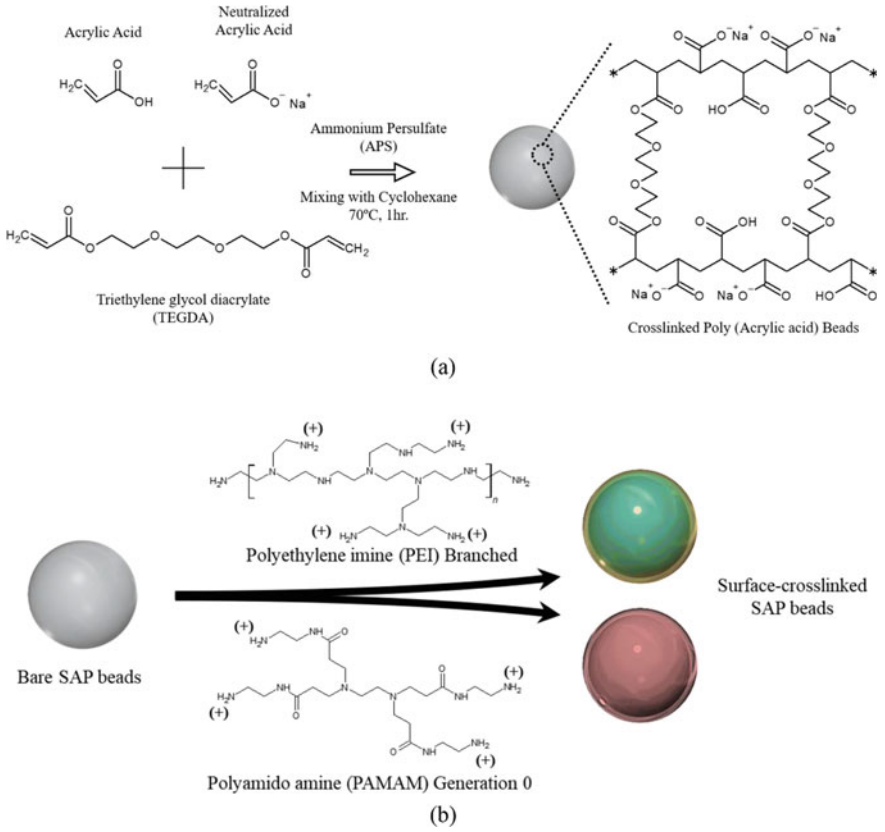


Fig. 12 **a** Schematic of synthesis of SAP using acrylic acid, neutralized acrylic acid and, TEGDA (Triethylene glycol diacrylate) and **b** incorporation of PEI (Polyethylene imine) and PAMAM (Polyamido amine) branches for surface cross-linking. Reproduced with permission from Lee et al. [69]

soil conditions and plant needs, and their biodegradability prevents them from accumulating in the ecosystem. Chitosan has a high-water absorption capacity and is frequently used as a soil amendment to increase water retention and prevent fertilizer leaching [73]. It is a biodegradable polymer made from chitin; a natural polymer found in crab exoskeletons. It has been shown to boost crop yields in a range of products such as rice, wheat, and maize.

A study demonstrated that cornstarch-based SAPs can also improve the soil's water-holding capacity, keeping more water conserved more nitrogen in the soil, and thus boosting water and nitrogen availability to tomato plants when compared to soil-only and soil-with-fertilizer-only regimens. Moreover, water and nutrient retention rates ranging from 35 to 91% based on SAP quality are extremely hopeful for water and nutrient conservation. Increased nutrient availability is also linked to greater water availability [74].

Another polymer water-soluble polymer polyvinyl alcohol (PVA) is used to make hydrogels, which are used as soil conditioners, seed coatings, and plant development boosters. To increase water retention and decrease soil erosion, nowadays, PVA is frequently combined with other biodegradable polymers like starch, gelatin and cellulose [64, 75].

While superabsorbent polymers have shown great potential in increasing soil quality and plant development in farming uses, they do have some drawbacks. One of the primary concerns about the use of superabsorbent polymers in agriculture is their possible environmental effect. While biodegradable polymers can decompose naturally, they may discharge hazardous compounds into the earth or water as they decline, which can be detrimental to the ecosystem and human health [55, 64]. Some polyacrylic acid based superabsorbent polymers can have an effect on soil acidity, which can contribute to a decrease in soil health and plant development if not used properly. Because superabsorbent polymers are expensive, their use in agriculture may be limited, especially for small-scale farmers who may not have the means to engage in them [16]. Superabsorbent polymers can influence nutrient availability, possibly leading to imbalanced plant development if not used appropriately [76].

Government agencies control the use of superabsorbent polymers in agriculture, and getting their permission can be a time-consuming and costly procedure [1, 4, 77] with limited understanding. The use of superabsorbent polymers in agriculture is a comparatively novel area, and much remains to be discovered about their optimal application rates, long-term impacts on soil health, and interactions with other agricultural inputs [55, 64].

4 Conclusion and Future Scope

Agriculture has always been regarded as a source of food, energy, and fiber for humans. Opportunities have emerged as a result of trends and external events that have affected production and patterns. Numerous publications discuss how improved soil conditions have led to an increase in the yield of various plants. This chapter highlights the importance of using biodegradable polymers in the agricultural sector. Biodegradable polymers are considered a better alternative to conventional non-degradable polymers because they can serve several purposes, including mulching, seed coatings, plant nutrition, protection from pests, soil enhancement, and targeted delivery of agrochemicals. Biodegradable mulch film, for example, can retain water, protect against weeds, release agrochemicals, and prevent pests. Seed coatings, on the other hand, can protect seeds from pest and pathogen, thus promoting growth.

Biodegradable polymers can also serve as carriers for herbicides, pesticides, and plant nutrients, and can be designed in different shapes and sizes depending on the desired activity. SAPs (super absorbent polymers) can improve soil water retention and aeration while encapsulating plant nutrients and growth promoters. In terms of super-swelling behavior, chemistry, and creating a variety of applications, SAPs have produced a very appealing field. As we replace synthetics bio-based materials like

polysaccharides and polypeptides, the environment we walk in is becoming greener. Making natural-based SAPs seems clearer in light of the high cost and rising price of crude oil. This opens the door for more advancement in this field in the near and far future. It is possible to create biodegradable polymers using waste streams from the agroindustrial sector and yearly regenerated crops. A more hygienic and secure method of conducting chemistry is through the use of enzymes, microorganisms, or plants to produce monomers and polymers. However, the requirement for developing low-cost methods that would support the phytostabilization of severely metal-contaminated soils has been partly addressed by biodegradable polymers. Despite challenges such as availability of raw materials, processing conditions, and high costs, the use of biodegradable polymers in the agricultural sector is growing, and research in this area remains prominent.

While biodegradable polymers offer a sustainable solution, further research is needed to understand their potential impact on the environment and determine the most effective methods for their disposal. Current technologies are limited, and there are no 100% biodegradable, bio-based, and economically attractive polymers with the best mechanical properties. As the population grows, the need for better and more sustainable technologies in agriculture will continue to rise, making the development of biodegradable polymers an essential area of research.

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Chapter 10
Bio-polymeric Green Composites for Thermal Energy Storage Applications

Soumyadip Dutta, Chandrani Sarkar, and Sampa Saha

1 Introduction

Industrial and economic development is largely ruled by the net energy production and consumption. Starting from the stone age, human beings are looking for energy resources to sustain their life, and even in this twenty-first century after several technological advancements, we are still looking for sustainable and reliable energy resources. This everlasting exploration seems to be because of the harsh realization of the human civilization on how different human activities have been exploiting the environment through the emission of green-house gases leading to pollution and global warming. According to the researchers, constant burning of fossil fuels can take this world to an alarming stage where earth will not be a suitable place for any of the living beings to stay anymore. Mostly the energy consumed by the human population comes after several energy conversions and energy wastage at different stages of energy dissipation. Primarily the mechanical energy trapped from different sources are converted into electrical energy for electricity supply at household and industrial scale. The chemical energy inside the batteries is utilized to get electrical energy. But the researchers are mostly inquisitive about the restoration and utilization of thermal energy because of the on-going research of this versatile and valuable energy form.

The current civilization is mostly dependent on the non-renewable energy resources but its high depletion rate and its tendency to harm the environment has caused the world to look for alternatives to fulfil the accelerated energy demands of

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the rising population. Different countries are coming up with the idea and implementation of electric mobility and utilization of solar energy. Dependency on solar energy has its corresponding disadvantage of being inoperative in the absence of daylight. As a sustainable method of storing energy, thermal energy storage (TES) systems have attracted interest and attention from all over the world. The TES system can be of two types—Sensible heat storage (SHS) system and Latent heat storage (LHS) system [1] (see Fig. 1). A thermal energy storage system means to store and release energy according to the requirement which proves out to be more flexible in manufacturing and functioning. SHS simply works by absorbing heat energy on increasing the temperature or releasing the energy on its temperature fall [2]. For example, materials like cast iron, reinforced concrete and NaCl [3] are known to be good SHS systems having a working temperature around 200–500 °C. LHS works by the change of phase and absorbing and releasing the latent heat –for example, materials like paraffin wax, fatty acids and glycols [1]. The concept of latent heat is very simple but useful at the same time. Latent heat is stored or released in a greater efficiency and amount as compared to sensible heat which enhances its applicability to bridge the gap between rising energy demand and supply. The materials which are used for thermal energy storage and make this wonder happen are called phase change materials (PCM). PCMs are finding applications in wide areas ranging from passive cooling of buildings, thermoregulated textiles and cold chain logistics to solar power harvesting [4].

One major problem of using PCMs without a good supporting matrix is that the PCMs tend to leak from the storage medium due to constant expansion and compression in volume during phase transition. But the interaction of the PCM with the matrix material plays a crucial role in its melting and freezing behavior and so polymers have been highly appreciated as a matrix material with which the PCM

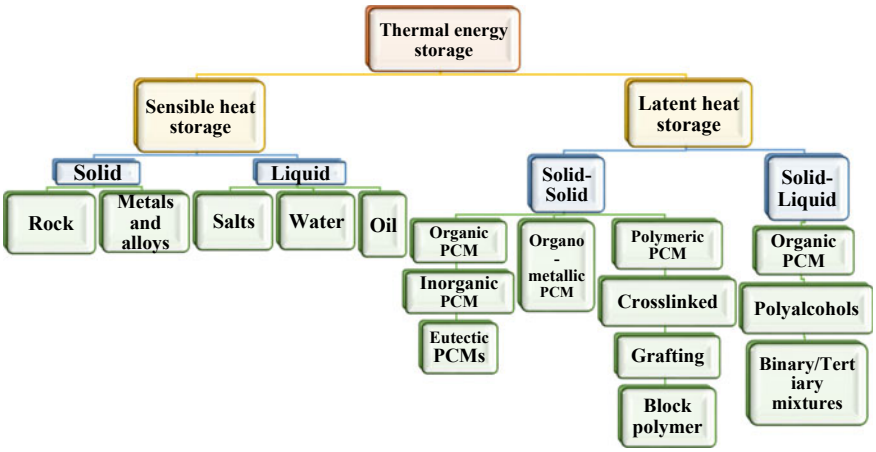

Fig. 1 Flowchart showing classification of thermal energy storage systems. Redrawn from ref. [5]

has good compatibility. Even the researchers have been convinced about the flexibility of polymers for necessary physical or chemical modifications to enhance its compatibility with the PCM and give reproducible properties. Also, the increasing environmental awareness caused the scientific community to consider biopolymers as a suitable matrix for shape stabilization of the product due to its biocompatibility and increasing tendency of the civilization to move towards green revolution [5]. Use of bio-polymers to replace the traditional synthetic polymers has multifaceted benefits such as reduction in plastic pollution, reduction in carbon footprint, sustainable development through green technologies etc. A major problem of synthetic polymers is the leaching of harmful chemicals from the product during use and also after discarding, which can lead to various diseases like cancer. This can be averted with increased use of biopolymers as they are biocompatible and biodegradable so they would not interfere with nature's harmony. So, the focus of this chapter will be on the exploration of various biopolymers used to encapsulate PCM to fabricate TES. In order to understand the TES, we would like to discuss about PCM first and then on their entrapment in bio-polymeric materials.

2 Phase Change Materials

Phase change materials (PCM) help to utilize the latent heat of phase transition at almost constant temperatures and makes the surrounding environment cool at high-temperature and warm at low temperature (Fig. 2). It can undergo solid–solid [6], solid–liquid [1] and liquid–gas [7] phase transition to perform its thermoregulatory function.

2.1 Working Principle of PCMs

Phase change is a process in which the material changes from one state of matter to another-thus absorbing or releasing the heat during a change of phase. In order to explain the concept of utilization of latent heat in phase change materials let's take an example of water. The heat energy required to melt the 1 g of ice from 0 °C ice to 0 °C water is 334 J/g [8] and the heat required to raise the temperature of 0 °C water to 1 °C water is 4.18 J/g. Hence this proves that the latent heat of melting is almost 80 times more than the sensible heat required to raise the temperature of the PCM. Solid–solid PCMs have a very high-temperature of phase transition [6] (<250 °C) thus limiting its application as it is beyond the temperature range of practical usage. Liquid–gas PCMs come with the great advantage of very high enthalpy of fusion but cannot be stored due to its huge variation in volume [1]. The solid–liquid PCMs have emerged as the most researched and used PCM material, which shows less volume variation during phase transition and has a phase transition temperature in the application range, thus making the material more appreciable and explorable. In

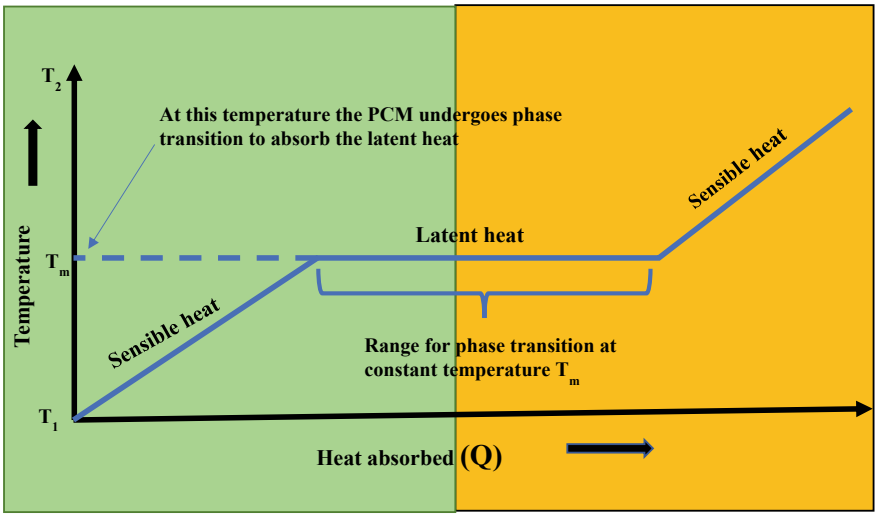

Fig. 2 Phase transition curve of phase change materials. Redrawn from [1]

solid to liquid phase transition, the ambient temperature should be near the melting temperature of the material, so that it can melt and absorb the heat and reduce the surrounding temperature, on cooling when the temperature reaches its solidification or fusion temperature, the material gets rid of the heat thus making the surrounding warm. It is to be noted that during phase transition, the absorption or emission of heat takes place at a constant temperature (isothermally). PCMs are the most appealing material in this domain of thermal energy storage which has popularized the process of phase change and utilization of latent heat. This is because, as previously said, latent heat is a very huge amount of heat compared to sensible heat and it mostly gets wasted. So PCMs and their shape stabilization and appropriate fabrication techniques help to make use of this latent heat.

2.2 Classification of PCM

Phase change materials are broadly classified into two categories—Inorganic PCM and Organic PCM.

Materials like salt hydrates [9], metals [10] and alloys fall into the category of inorganic PCMs (see Table 1). They have the advantage of high latent heat of fusion and high thermal conductivity. They are also known for their good flame retardancy. Inorganic PCMs have a high heat storage density of about 300–400 kg/dm^3 [1] which is almost double than that of the organic PCMs. These materials are available over a wide range of phase change temperatures. But the drawback which have hindered their widespread use are supercooling [11] which makes it an inappropriate material

Table 1 Thermal properties of different inorganic PCMs [9–11]

Compound	Melting temperature, T_m (°C)	Heat of fusion, ΔH_m (kJ/kg)
Salts		
$AlCl_3$	192	280
$LiNO_3$	250	370
$NaNO_3$	307	172
KNO_3	333	266
KOH	380	150
$KClO_4$	527	1253
LiH	699	2678
$MgCl_2$	714	452
Salt hydrates		
$Na_2P_2O_7{\cdot}10H_2O$	70	184
$Ba(OH)_2{\cdot}8H_2O$	78	266
$(NH_4)Al(SO_4)_2{\cdot}12H_2O$	95	269
$MgCl_2{\cdot}6H_2O$	117	169
$Mg(NO_3)_2{\cdot}6H_2O$	89.3	150

for repeated use due to the growing non-uniformity in melting and freezing transition. Its tendency to phase separates on repeated heating and cooling and its corrosiveness towards metals limits their use. Eutectic mixtures which is a mixture of salt hydrates are also used as inorganic PCM. The mechanism of inorganic PCM, for example of salt hydrates, is different than that of organic PCMs, in the former case, it is followed by hydration and dehydration of the salt [9]. On heating, the salt hydrate on reaching the melting temperature gives solid anhydrous salt and water in liquid state. On cooling solid salt hydrate is formed from the binary phase by the release of the heat of fusion. Some examples are calcium chloride tetrahydrate, sodium carbonate decahydrate and magnesium chloride hexahydrate having melting temperature in the range of 14–60 °C and enthalpy of 120–260 °C [12].

Organic PCMs include alcohols [13], paraffin waxes [1], fatty acids [14] and glycols [15] which are known for their broad transition temperature range from 0 to 200 °C and high latent heat of fusion, high heat storage density, non-toxic nature, biocompatibility, very low supercooling tendency, good chemical stability and a much better and sustainable energy resource (see Table 2 for the details of some important organic phase change materials).

The main advantage of using PCM for thermoregulation over other materials used in this application is its ability to make use of the latent heat during phase transition which usually gets wasted. Moreover, as discussed before, this latent heat which

Table 2 Thermal properties of different organic PCMs [1, 16–20]

PCM	Melting temperature, T_m (°C)	Heat of fusion, ΔH_m (J/g)	Molecular weight (g/mol)
Tridecane	4.5	231	184.37
Tetradecane	5.7	217	198.34
Nonadecane	31.5	230	268.50
Eicosane	36.5	240	282.50
Heneicosane	40.0	161	296.58
Docosane	43.6	157	310.61
Fatty acid			
Capric acid	30.8	159	172.26
Lauric acid	42.8	191	200.32
Tridecylic acid	41.8	157	214.34
Myristic acid	52.8	194	228.37
Pentadecylic acid	52.5	165	242.40
Palmitic acid	62.4	204	256.43
Stearic acid	69	214	284.48
Arachic acid	75	227	312.53
Alcohols			
Dodecanol	24.1	216	186.34
Tridecanol	31.6	223	200.36
Tetradecanol	37.8	231	214.39
Hexadecanol	49.1	238	242.45
Octadecanol	57.8	246	270.50
Nonadecanol	61.1	255	284.53
Eicosanol	64.5	247	298.55
Docosanol	70.4	263	326.61
Polymer-molecular weight			
PEG-600	17–22	127	
PEG-1500	48.83	164.6	
PEG-4000	58.8	205.7	
PEG-8000	63	189.5	
PEG-10000	67	197.2	

is being absorbed or released by the PCM is very huge in amount as compared to sensible heat. Thus, the heat charging and discharging ability of a PCM can bring a considerable, appreciable and desirable difference in temperature which can almost disrupt the use of different air conditioners if commercialized at an industrial scale, probably with lower price.

3 Shape Stabilized PCMs (SSPCMs)

3.1 Definition and Working Principle

The shape and structure of a matrix material helps to hold the PCM so that it can get a framework to perform its functions. Here the PCM is entrapped inside a molecular network by some chemical bonding or physical interactions like H-bonding [21] or forming a core–shell structure where the PCM forms the core [22]. Such interactions between the PCM and the framework helps to prevent its leakage and enable it to be used for longer cycles of subsequent heating and cooling (Fig. 3). Till now researchers have used metallic and inorganic shells to hold the PCM because of their high conductivity and re-usability for long term applications. But the major drawback in the rigidity of such matrix cannot inhibit the seepage of PCMs from them. This is the reason why the scientific community became so inquisitive of using polymeric framework to hold the PCM. The polymeric framework not only provides flexibility to the volumetric variations of the PCM but also provided high surface area for good heat charging and discharging. Polymer, being an insulator is expected to lower the enthalpy of the product. But the researchers have found several ways of chemical modification of the shape-stabilized product, incorporating different conductive fillers like carbon nanotubes [23], graphene platelets [24], carbon black [25], silver nanofibers [26] and various other conductive architectures to produce a form-stable, shape stabilized PCM incorporated product. Even different fabrication techniques like solution casting [27], electrospinning [28], vacuum impregnation [29], extrusion [29], wet composite spinning [30], physical adsorption, intercalation and exfoliation [31] have been reported to show different thermal characteristics for the same amount of PCM loading. But during exploration of such a versatile matrix for TES, downturns of polymeric framework were overlooked because of the resourcefulness and flexibility in designing a shape stabilized product and its function to endure repeated thermal shock.

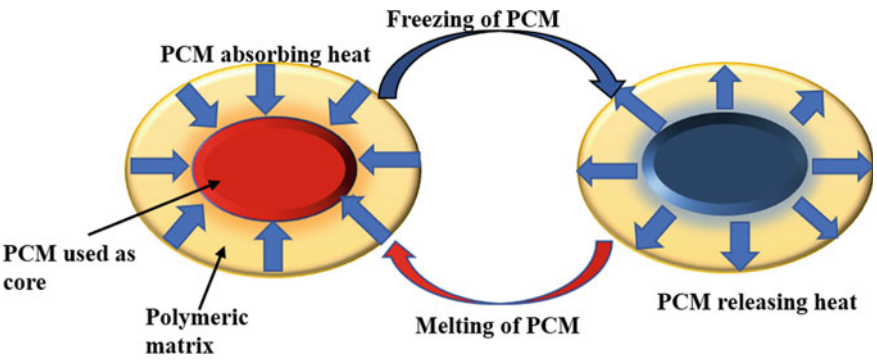

Fig. 3 Schematic representation of the working principle of polymeric shape stabilized phase change material. Redrawn from [1]

3.2 Recent Advancement in Shape Stabilization

Microencapsulation of PCM inside polymeric capsules by emulsion or solution polymerization is being popularized to produce PCM loaded microcapsules which shows high heat transfer efficiency due to increased surface area. A porous supporting framework are being discussed recently due its high storage capacity, good PCM and heat entrapment, high pore volume [32] and hence high surface area. The interaction between the PCM molecules and the pore surface helps to prevent leakage by different hydrophilic and hydrophobic interactions [33], Vander Waal's and hydrogen bonding-like in case of graphene [34] based and cellulose based aerogel [35], expanded graphite [36] and metal foam based PCM [37]. Such interactions are also governed by the pore size, pore geometry, porosity etc. Here the thermal conductivity is increased where the number of interconnected pores is more than the closed pores. Bigger pores tend to be more interconnected which makes the material more thermally conductive [38]. Incorporation of PCM inside a 3D printed matrix [39] helps to fabricate products having high porosity and light weight which helps to increase the PCM loading. Even among the metals, 3D aluminum honeycomb [40] network provides high thermal conductivity and excellent mechanical properties. Even copper shells [41] are extensively used to load PCM. Recently a new shape-stabilized PCM system has been developed where the supporting material is a metal–organic framework (MOF) [42] having very high porosity and surface area for high heat transfer efficiency. Even a conductive pathway by bridging graphitic sheets has been used by employing expanded graphite to trap high loading of PCM. Researchers have also fabricated some 3D structures of polymeric network where the PCM is swollen by physical interactions or chemical cross-linking of polymers or grafting, like in case of polyurethane based PCM [43]. This type of composite can easily absorb extra heat from the source producing the heat and dissipating that through passive radiative cooling and convection currents.

3.3 Applications of SSPCM

PCMs have been well explored for various applications (Fig. 5). PCM based vest body cooling system for the application of thermoregulatory textiles [44], Mine rescue chamber cooling system [45], Heat exchangers and other heat venting systems [46, 47], Thermoregulatory textiles for soldiers working at conditions like at a temperature of 45–50 °C [48], Appropriate packaging for medicines and vaccines to eradicate the use of refrigerated trucks [49], PCM filled jacket for heat cabinets to trap solar energy, even the convection from the heat charging and discharging of the PCM can also be trapped to generate power and used in water pumps for water suction [50] PCM incorporated in construction materials on rooftop, walls and ceilings to keep the temperature of the building at a comfortable level and reduce the use of electricity

for air conditioners and air coolers, as depicted in Fig. 4. Recently microencapsulated PCM have been used in concrete gypsum or bentonite-based wallboard for the purpose of thermoregulation in order to reduce the maximum and minimum temperature of the walls and rooftop of the building [51, 52]. The National Aeronautics and Space Administration (NASA) has shown the utility of PCM in space suits to protect the astronauts from abrupt temperature changes in space [53]. PCM have also been used for heat panels in high thermally conductive carbon fiber reinforced polymer composite for micro-satellites where the PCM helped to increase the apparent heat capacity with small mass gain and the supporting matrix helped in heat dissipation [54]. PCM loaded packets helped to absorb the heat of exothermic electrochemical reactions in Li-ion batteries due to their high latent of fusion [20, 55]. Thermal shielding for different flexible electronics and electronic gadgets involves PCM based composites. For example, PCM has been employed in expanded graphite-based composite that can be used for electro-driven TES system [56]. Moreover, shape stabilized PCM may be applied for passive radiative cooling in buildings [57, 58].

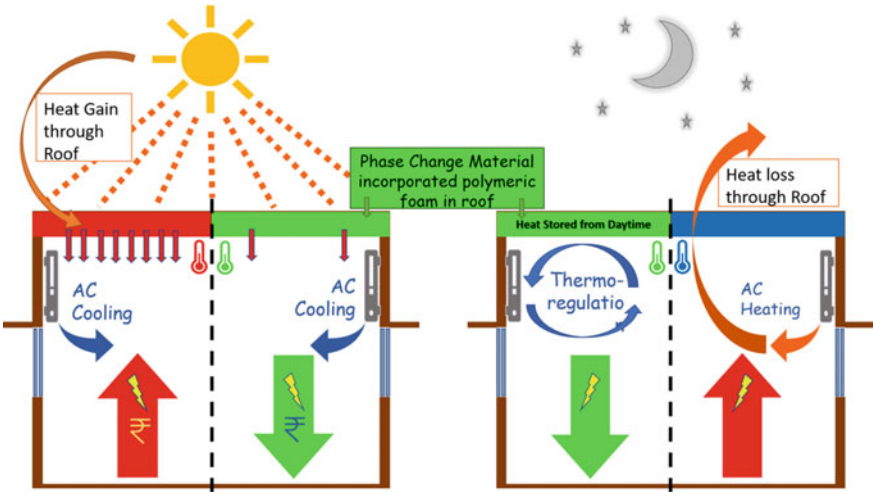

Fig. 4 PCM loaded polymeric roofing helps in temperature regulation of buildings during daytime and night-time. Redrawn from ref. [7]

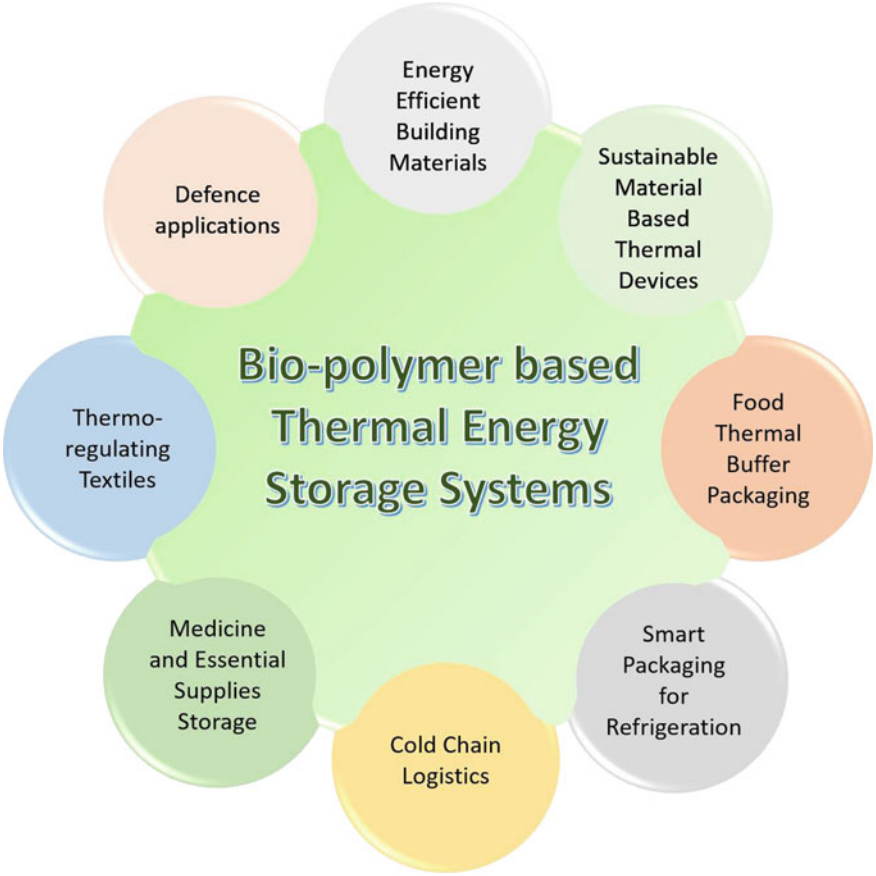

Fig. 5 Different applications of bio-polymer-based thermal energy storage systems

4 Bio-polymeric Matrix Stabilized PCMs

4.1 State of the Art and Applications

Polymer is such a type of material which gives strength due to its high molecular weight and flexibility due to the entanglements in the long chain and depending upon different types of physical and chemical interactions, it has a diverse field of application. These long chain molecules can easily be tuned in terms of its structure and properties as per their application. Metallic frameworks have very high conductivity but their endurance to volumetric expansion of the PCM in the molten state is very poor. Hence researchers have come up with the idea of incorporating conductive fillers inside the supporting polymeric matrix which not only enhances the heat transfer efficiency but also increases the mechanical strength so that it can work in extreme

climatic conditions. For applications of macro or micro-encapsulation of PCM inside a polymeric matrix, it provides a very conducive platform for different volumetric variations of the PCM. Moreover, such PCM loaded microcapsules provide high surface area for better heat transfer. The polymeric frameworks also provide good thermal and chemical stability and protect the PCM from the external environment. But since the world is moving towards Green revolution, so in that case also polymers have proved their expertise as we have biocompatible and biodegradable polymers too.

Bio-polymers, unlike synthetic petroleum sourced polymers, are not harmful to nature. They show excellent biocompatibility, non-toxicity, good mechanical properties, and sustainability [13]. Many researchers have utilized various bio-polymers as PCM-based TES systems' support systems and have found excellent results [59–64]. However, bio-polymers have a low thermal conductivity, limiting their application area. Bio-polymers do not jeopardize the ecological balance of nature. There is always a concern regarding the toxicity of the supporting material when we use synthetic polymers like polystyrene [65], poly(methyl methacrylate) [1], urea formaldehyde [1], melamine formaldehyde [1] and polyurethane [43]. These materials are not biodegradable and even with due course of time synthetic polymers like urea and melamine formaldehyde release toxic formaldehyde during their service life which leads to environmental pollution [1]. Hence bio-polymers like chitosan, poly(hydroxy butyrate-co-hydroxy valerate), polylactic acid [1], polycaprolactam [59], cellulose etc. have been used to build networks for PCM loading.

Globally a lot of effort is being put into sustainable building materials, and biopolymers are extremely lucrative due to their availability, non-toxicity, biodegradability, easy processability and commercial availability. Many material scientists are reporting bio-polymeric support for PCMs in TES systems.

A research group utilized carboxymethyl cellulose as the structural component, where stearic and lauric acid were used as the PCM. The latent heat storage value was ~115 J/g, which is much lower than the pristine PCM. The composite was observed to undergo 100 heating and cooling cycles (Fig. 6c), exhibiting around 5% reduction in thermal energy storage capacity. The loss of heat storage capacity coupled with low value of the same makes the system less effective for long term applications [63]. The direct synthesis of carbon aerogel from biomass is a viable method for creating supporting materials for phase transition materials (PCMs). In a recent work, hydrothermal and post-sintering techniques were used to create carbon aerogels (CCA and PCA) made from carrots and pumpkins. The carbon aerogels' specific surface area and pore distribution were assessed using N_2 adsorption–desorption isotherms. It was discovered that the specific surface area of the carrot carbon aerogel sintered at 800 °C (CCA800) was 33.80 $m^2\ g^{-1}$, which is individually 168%, 165%, and 287% higher than the specific surface areas of the carrot carbon aerogel sintered at 1000 °C (CCA1000, 12.59 $m^2\ g^{-1}$), pumpkin carbon aerogel sintered at 800 °C (PCA800), and pumpkin carbon aerogel sintered at 1000 °C (PCA1000). The carbon aerogels exhibited a high loading of palmitic acid (PA)/thiol-ene resin (TE) composite as a PCM without leakage because of its porosity (Fig. 6b). In comparison to 50PA/TE, 50PA/TE@PCA1000 display increased thermal conductivity by 60.5%, and a

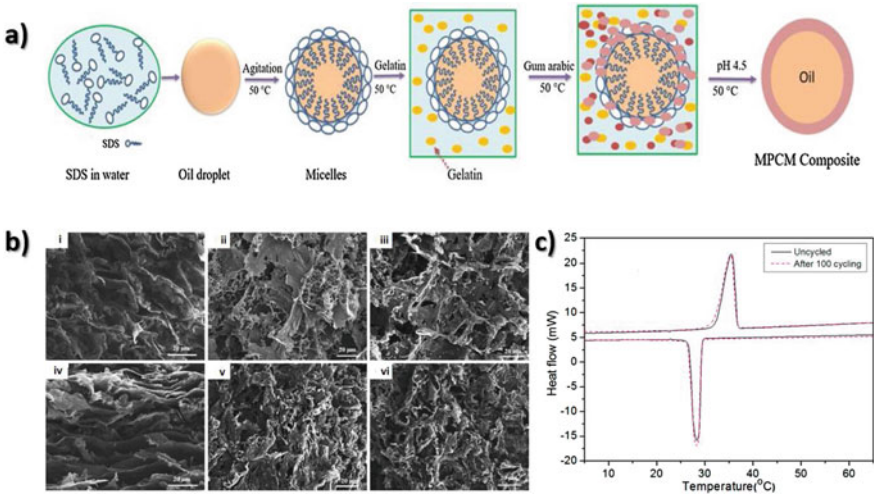

Fig. 6 **a** Schematic representation of MPCM composite synthesis with GE/GA shell (Reprinted with permission from Ref. [67]. Copyright 2020, Elsevier.), **b** SEM images of carrot derived (i) aerogel, (ii) CCA800, (iii) CCA1000 and pumpkin derived (iv) aerogel, (v) PCA800, (vi) PCA1000. (Reprinted under Creative Commons license from Ref. [64]. IOP publishing Ltd), **c** DSC curve of CPCM1 before and after 100 thermal cyclings. (Reprinted with permission from Ref. [63]. Copyright 2015, Elsevier)

DSC (differential scanning calorimeter) analysis revealed that it had a latent heat of 88.26 J/g [64].

Guo et al. reported the successful encapsulation of paraffin wax inside polymeric walls of Polylactic acid for use in thermal energy storage. They achieved ~80% of the value of heat absorption in the composite to that of pure Paraffin. However, the bio-polymeric shell was unable to stop PLA leakage of PCM from the system, which decreased its energy storage capacity over repeated thermal cycles. Instantaneously, they proposed supplementary techniques for restricting phase change material from seepage, such as complex cellular architecture, inter-penetrating polymer network structure etc., which could be used to reduce heat loss in the shell structure, improve energy utilization proficiency, improve thermal conducting properties, and increase energy storage effectiveness [66].

Recently Balaji reported using lotus stem as fibrous filler in epoxy resins where paraffin wax was used as PCM. The composites were fabricated into plate-like structures and further stacked into cuboid block-like formations. The thermal energy storing capacity of the whole block was found to be around 19.22 kJ, which was much lower than the neat PCM used. The thermal stability was improved by incorporating natural fiber reinforcements but provided little improvement in the mechanical strength of the composites. Low thermal conductivity and even lower thermal energy storage capacity make the platform unattractive for practical usage [68]. Singh and co-workers utilized capric acid encapsulated composites, which was made by using protein-polysaccharide (Gelatin, GE/Gum Arabic, Ga) interactions (Fig. 6a).

High mechanical and thermal stability were reported as they used glutaraldehyde as the cross-linker and heat deflecting silica coating correspondingly. The thermal characteristics were found to be similar even after 50 thermal cycles. However, the core–shell structures showed rapid loss of PCM materials at a 30–170 °C temperature, limiting their applicability [67].

By using a multiemulsification and cross-linking technique, Liu and colleagues were able to create chitosan microcapsules with many uses that contained Fe_3O_4 and n-eicosane as PCM. The end product, the microcapsules, demonstrated good thermal energy release-storage capabilities, high thermal storage capacity, and a latent heat storage value of about 80 J/g [69].

In an intriguing study, Zhang and colleagues used coacervation technology to create eco-friendly side-chain crystallizable octadecyl acrylate encased chitosan. With a transition temperature range of 32–47 °C and a maximum encapsulation effectiveness of 69%, they were able to achieve a melt enthalpy of 136 J/g. The microcapsules were evaluated for medical use, where a suspension of microcapsules and PVA was made, and then coated uniformly over a bandage. Chitosan has antibacterial qualities that inhibit bacterial invasion. According to the study, it is possible to maintain a comfortable temperature at the site of the wound where the bandage is placed, aiding in wound healing [70].

Microencapsulation of phase change materials (PCM) in a polymeric shell is very important to prevent phase change materials (PCM) from leaking into the environment. These microcapsules should ideally provide a platform for storing and releasing PCM's latent heat without requiring any physicochemical change of the core (PCM) or shell (polymer) constituents. The composition of shell materials influences several features of PCM capsules, including heat transfer efficiency, thermal conductivity, water dispersibility, and durability. Using the emulsion solvent evaporation method, a random copolymer of poly (methyl methcrylate-co-2-hydroxyethyl methacrylate) poly (MMA-co-HEMA) with an optimum ratio of 75/25 methyl methacrylate (MMA)/2-hydroxyethyl methacrylate (HEMA) was used as the shell material to encapsulate paraffin wax (PCM). The microcapsules were manufactured with a shell thickness of 0.8 μm and a high encapsulation efficiency of 92.34% and heat storage capability of 99.85%. PHEMA (poly(2-hydroxyethyl methacrylate) with water absorbable shells have improved heat conductivity from 0.1 to 0.49 W/(mK) at 25 °C as compared to the dry capsule. After 500 heating/cooling cycles, the capsules show no substantial change in thermal characteristics or water dispersibility, indicating that they are durable. The thermal behavior of this innovative water dispersible microencapsulated PCM was tested after it was blended with natural rubber latex at various blend ratios to determine its applicability. The biodegradable natural rubber based composite that was created had a strong thermoregulation property as well as increased mechanical strength [71].

A simple fabrication technique for producing novel porous microcapsules encapsulating n-Eicosane as phase change material (PCM) with a random copolymer of poly (methyl methacrylate0.9-co-2-hydroxyethyl methacrylate0.1) (poly(MMA0.9-co-HEMA0.1) as shell material has been developed. The porous microparticles (particle size: 31.8 ± 9 μm; porosity: 30 ± 13%; shell thickness: 1.60 ± 0.2 μm)

with a hollow core (shell thickness: 1.60 ± 0.2 μm) were synthesized using hot water aided double emulsion (water/oil/water) technique. Surprisingly, the microcapsule system was discovered to entrap >95% n-Eicosane, resulting in a considerably high thermal energy storage capability (95%). High phase transfer repeatability and long durability were observed in porous microcapsules with a phase transition enthalpy of 160 J/g. The heat charging and discharging conditions for the microcapsules were also disclosed by the non-isothermal and isothermal differential scanning calorimetric studies. Infrared thermography demonstrated that in comparison to clean hydrophobic PCM, porous particles with partially hydrophilic shells (due to the poly-HEMA unit) had better water dispersibility and efficient thermal management. As a result, the microencapsulated phase transition material in porous microcapsules can be a clever mix of good thermal energy storage and wettability. Because of the acceptable phase transition temperature (37 °C) demonstrated by the selected PCM, such microcapsules could potentially be used as thermal energy storage materials for space conditioning in buildings (n-Eicosane). Our research showed that water dispersible porous polymeric particles may store a substantial amount of thermal energy (>95%), which has never been reported before [72]. Using the similar concept, biodegradable polymer-based porous particles can be fabricated and applied for the same purpose.

Zhang and colleagues used cellulose acrylate as a framework to store poly(n-alkyl acrylate), and they were able to accomplish this using 83 wt% PCM and also an enthalpy value of about 95 J/g was observed for the system. Since this copolymer offered good temperature control and TES had a degradation temperature of only 280 °C, it was suggested that it can be used in the textile and temperature-sensitive pharmaceuticals sectors [73]. Samui and colleagues created a novel, quick, and economical method for making PCM utilizing microwave technology with the aim of increasing the PEG loading while preparing the mixtures of cellulose acetate and PEG to make form-stable PCMs. Without any leakage from the matrix, a very high storage capacity of up to 96.5 wt% PEG was achieved, along with an exceptional enthalpy value of 155 J/g; but it came up short of virgin PEG's enthalpy [74] (Table 3).

Over the past ten years, research has focused on the shape stabilization of organic PCMs; nevertheless, the poisonous nature of synthetic polymer-based shell material poses a risk. In an effort to reduce leakage problems, various biopolymers are used as a skeleton. However, a bio-polymeric framework has the drawback of having low heat conductivity, which can be overcome by the combination of conductive fillers and nanomaterials. Due to their superior surface-to-volume ratio, nanoparticles are doped in PCMs to improve thermal conductivity and boost the nucleation rate during the charge–discharge of thermal energy. The integration of hybrid nanofillers, particularly hybrid nanofluids with mixed nanoparticles, has been increasingly popular because it enhances the rate of heat transmission and has a shape-stabilizing effect. Thus, a significant future scope lies in this area to develop more efficient green composite based TES.

Table 3 Different biopolymers used for encapsulation of PCM and their applications

Biopolymer	PCMs	Method of synthesis	Melting temperature, T_m (°C)	Heat of fusion, H_m (J/g)	Application	Reference
CA	PEG	Coaxial electrospinning	62	53	Thermal energy storage (TES)	[75]
Ethyl cellulose	n-hexadecane	MW assisted blending	60.56	155.35	–	[74]
CA	Capric-myristic and stearic acid	Immersion polymerization	21.4	76.6	Temperature regulation	[76]
Ethyl cellulose	Lauric acid and stearic acid	Emulsion solvent evaporation	19.5	147.1	TES	[77]
Cellulose diacetate	PEG	Physical blending	52.07	104.5	–	[78]
PVA	Plant oil mixture	Electrospinning	38.46	84.72	–	[79]
PVA	80 wt% erythritol	Electrospinning	118.74	262.7	TES	[80]
PVA	Stearic acid	–	67.4	132.6	TES	[81]
PVA	40 wt% paraffin	Wet spinning	31.2	55.4	Thermoregulating fibers	[82]
PVA	Biobased n-dodecanol	In-situ polymerization	31.8	200.4	TES	[83]
PCL	80 wt% paraffin	Precipitation	56.6	129.1	Temperature buffering in food storage	[84]
PCL	Dodecane	Electrospinning	−8.31	73.71	Smart thermoregulating packaging	[85]
PCL	Rubitherm RT5	Electrospinning	7.5	140	Food refrigeration and packaging	[86]
Chitosan	PEG-4000	Solution casting	57.18	152.16	TES	[87]
Chitosan-silk fibron	n-eicosane	Coacervation	37	93.04	–	[88]

(continued)

Table 3 (continued)

Biopolymer	PCMs	Method of synthesis	Melting temperature, T_m (°C)	Heat of fusion, H_m (J/g)	Application	Reference
Chitosan–gelatin	n-hexadecane	Phase coacervation	31.9	115	TES	[89]
PLA	Dodecane	Electrospinning	−9.71	20.08	TES	[85]
PLA	Paraffin	Solvent evaporation	58.2	176.6	TES	[66]
PLA	Biobased palmitic acid	Solvent evaporation	62.1	70.1	TES	[90]

CA= Cellulose acetate , PVA= Poly (vinyl alcohol), PCL=Polycaprolactone , PLA= Polylactic acid

5 Conclusion

In this chapter, an effort has been made to explore bio-polymeric matrix-stabilized PCMs for thermal energy storage applications based on renewable biopolymers. The thermal conductivity, heat latent, phase transition temperature, supercooling degree, shape stability and thermal cycling stability of PCMs have been explored in the chapter. An overview of the various bio-polymeric materials used as support for SSPCMs has been discussed along with their applications and recent advancements in the field of research. PCMs stabilized in a polymeric matrix behave thermally very differently from PCMs in bulk. As a result, mesopores and small macropores are most helpful in preventing PCM leakage. Excellent pore volume, porosity, and specific surface area ensure high thermal energy storage density. Comparatively, carbon-based supporting materials, particularly interconnected three-dimensional highly graphitized network based carbon materials, are more successful at improving the thermal conductivity of pure PCMs. The majority of current studies on SSPCMs are for organic PCM-based low temperature thermal energy storage systems. However, there is still a lack of research on high-temperature thermal energy storage devices that use inorganic PCMs embedded in high-temperature stable porous materials. For various thermal energy storage devices, it has taken a lot of work to create changeable SSPCMs with good thermal and mechanical properties. Even though several composite PCMs have made some noteworthy improvements with improved performances, raising the awareness of composite PCMs. Future research will need to address a number of difficulties, including the limited heat conductivity of bio-polymeric supports, the time-consuming inclusion of PCMs, the low loading amount, etc. The creation of biopolymer supported SSPCMs composite has a number of interesting elements and difficulties that demand intensive research.

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Chapter 11
Biodegradable Anisotropic Polymeric Particles and Their Emerging Applications

Subhashree Subhasmita Pradhan, Chandrani Sarkar, and Sampa Saha

1 Introduction

Nature has always been a source of motivation for the development of anisotropic functional materials which show distinct features of a machine or substance that point in opposite directions due to the heterogeneous structures or ingredients they include when compared to their isotropic counterparts [1, 2]. Their essential characteristics for various physicochemical and biomedical applications are directly affected by the precision with which polymeric material's morphology is controlled [3, 4]. For example, tooth enamel is the hardest mineral material in the human body because it contains highly mineralized, perpendicular collagen fibers. That architecture inspires the construction of aligned reinforcements in load-bearing materials to accomplish the highest possible mechanical performance in the required direction [5]. Similarly, it was discovered that prolate-shaped particles bind to cells more effectively than oblate-shaped or spherical particles due to the better interaction of anisotropic shaped particles with macrophages. However, oblate-shaped particles were seen to have enhanced cell uptake by 300% when compared with spheres, while prolate-shaped particles reserved cell uptake by 50%. In terms of their effectiveness as drug delivery vehicles, those with an anisotropic shape have longer circulation times and more precise targeting than their spherical counterparts [6]. Similarly, many articles have been written to show how anisotropy excels over its isotropic counterparts [7–22].

Anisotropy can arise from a variety of sources, like natural materials, synthetic materials, shapes, chemical composition, and surfaces. Anisotropy can be created in

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a variety of natural and manmade materials (synthetic), either as-is or after being subjected to various modifications Fig. 1. Taking biodegradability into account, we'll focus on the biodegradable polymeric materials that contribute to the generation of different types of anisotropy. However, shape anisotropy is a geometric property, as the name would imply, and there are many different shapes such as rod, disk, ellipsoid, cup, trojan, needle, cubic, cylinder, toroidal spiral, and so on [18, 23–32]. The particle composition, however, is consistent despite the anisotropy in shape. In the second case, it is the presence of different compositions in different directions of the same system, however, that causes compositional anisotropy to arise within a single system, examples include spherical particles with multiple compartments and the Janus particle, i.e., two dissimilar compartments with various compositions in a single particle. In contrast, surface anisotropy develops when isotropic or anisotropic particles are subjected to surface modifications or functionalization techniques that give rise to the formation of surface patches [23, 24]. Such a system can be generated by allowing spatioselective growth of the polymer chain from a specific part of a surface causing the particle to swell in water in a way that is not uniform, thereby introducing anisotropy into the particle system.

Over the past few years, the synthetic strategies for well-controlled anisotropic polymeric materials in terms of shape, size, functionality, composition, pattern, and special arrangement have been the focus of significant research and development. Seeded polymerization, microfluidic techniques, electrohydrodynamic jetting, clusterization, and self-assembly are some of the current breakthroughs in polymer science and production techniques that have made it possible to generate anisotropy by precisely controlling the geometry, morphology, surface properties, and functionalization of polymeric materials. Anisotropic polymeric materials have attracted a lot of attention because of their potential applications in fields as varied as aerospace, sensing, soft robotics, and tissue engineering, but so far, they have only been studied

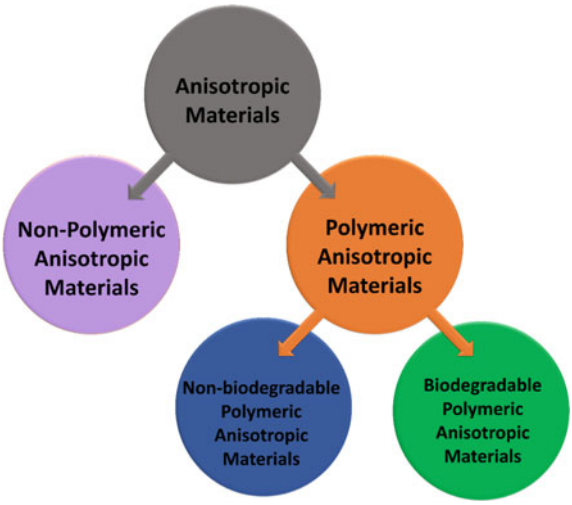

Fig. 1 Classification of anisotropic materials

in their potential as targeted and triggered biomedical carriers, Pickering emulsion stabilizers, and catalysts.

Recent studies should also move their focus to sustainably generated anisotropic materials along with the aforementioned classification, production, and uses of those materials. Biodegradability must be a concern as most of these anisotropic polymeric materials are prepared from synthetic or non-biodegradable sources, which leads to serious end-user problems and an additional route for environmental pollution. Unfortunately, not much studies have been reported to determine the origins (synthetic/natural), degradability, and ultimate purpose of these anisotropic polymeric materials. An in-depth investigation into biodegradable anisotropic polymeric materials is the focus of this chapter.

2 Classification of Anisotropic Particles

An organized comprehension of anisotropic biodegradable materials can be obtained by classifying the former according to their source, shape, and the material from which they are composed Table 1. Let us discuss them in the following section.

2.1 Based on Source

Beginning with the source we proceed to divide it into biodegradable and non-biodegradable, but biocompatible categories.

Anisotropy Originating from Natural Polymers

Biodegradable polymeric materials have come a long way in their use and development for various applications in recent years. Biodegradable polymers can be produced in one of two ways: either naturally, by microbes, animals, and plants; or artificially/synthetically, by chemical synthesis from biological starting components (such as corn, sugar, starch, etc.). Synthetic chemicals used in the production of biodegradable polymers come from petroleum sources. Here are detailed examples of biopolymers that can be used to create anisotropic particles. Some examples of biodegradable polymers, Cellulose and its derivatives [6] are utilized in the fabrication of anisotropic polymeric materials such as rod-shaped [3], spindle-type [4], and anisotropic cellulose particles [5, 8, 9, 12]. Another example, Dextrans, which serves as a coating on biodegradable material, and is used to create anisotropic polymeric particles by being coated over various anisotropic and isotropic particles [9–11].

Table 1 Classification of anisotropic biodegradable polymeric materials

Based on source	
Natural polymer generating anisotropy	Synthetic polymer generating anisotropy
Cellulose [3–5, 8, 9, 12]	Polylactic acid [14–21]
Sugar derivatives [7]	Poly(lactic-co-glycolide) [27–32]
Starch derivatives [9, 12]	Polycaprolactone [33–38]
Based on type of anisotropy	
Anisotropy by shape	
Type of shape	Examples of polymers
Crescent [14], cup [2, 16], trapezoidal [17], cylindrical [21], disk-shaped particles, cellulose (rod-shaped) [3], spindle-type [4]	PLA
Ellipsoid [29], rods [30], disk [31, 32]	PLGA
Spindle-type [54]	Cellulose
Wormlike [26]	PEG–PCL
Cell shaped [57]	Chitosan
Anisotropy by composition	
Biphasic (disk) [18, 19]	PLA/PLGA
Sphere, microcylinders (biphasic) [46]	PLGA/PLGA/gold nanoparticles
Sphere (biphasic) [58]	PLGA/PCL
Spheres (biphasic) [20]	PLGA/PLLA
Spheres (biphasic) [59]	Pectin/pectin or pectin/alginate
Surface anisotropy	
Anisotropic patchy particle [60]	PLA/PLGA+ alkyne functionalized PLGA
Anisotropic patchy particle [61]	PLA/PLGA+ acetylene functionalized PLGA
Polymer brush-modified anisotropic cup particles [15, 16]	PLA-Poly (MMA-co-BEMA)
Based on type of substrate	
Type	Reference n
Flat/rectangular	Cellulose, spindle-type [3, 53, 54]
Spherical	PLA, PLGA, PCL, cellulose, PEG [3–8, 10–16, 18–21, 23, 29, 31–33, 56]

Synthetic Polymers Generating Anisotropy

When it comes to making anisotropic biopolymeric materials, polylactic acid (PLA) is by far the most popular choice. They can adapt to a wide range of shapes, compositions, and surface anisotropies like PLA-based crescent [14], cup [15, 16], Trapezoidal [17], cylindrical [21], disk-shaped [18] and Janus [19, 20] type biodegradable particles, etc. Secondly, Polycaprolactone which has been reported in the making process of Disk like, hemispheres [23], ice-cream cones [24], Janus hemispherical

[25–27], biphasic [2] and wormlike [28] anisotropic biodegradable polymeric particles. There is a copolymer consisting of PLA and PGA (Polyglycolide acid). Some prominent examples of anisotropic particles prepared out of these copolymers include ellipsoid [29], rods [30], disk [20, 31] shaped, and non-spherical [18, 32] polymeric particles.

In addition to the aforementioned biopolymers, polymers such as polyhydroxy butyrate (PHB), polyhydroxy valerate (PHV), Poly (ortho esters), Polyanhydrides, Poly dioxanes, should be investigated further for their potential usage in the construction of anisotropic polymeric particles.

2.2 Based on the Type of Anisotropy (Shape, Composition, and Surface)

Since we have just given a cursory overview of the above group in the introductory paragraph, let us go into some more in-depth discussion of them here.

Shape

Particles that belong to this class have a uniformly smooth surface and are constructed from the same kind of substantial materials, but their dimensions in a straight line vary from one another. Therapeutic DNA, RNA, and gene delivery have all benefited from the use of anisotropic particles, which research has shown are more efficient than their spherical counterparts. It has been established in several outstanding reviews, that the shape of particles is an important attribute that impacts their performance, and as a result, researchers are motivated to emphasize on the explorations of non-spherical particles [27, 28, 33, 34]. Instances include, better antigen-specific T-cell activation was observed with elliptical particles than with spherical ones and rod-shaped particles improved biodistribution and delivery of the therapeutic agent. Micellar rod with a higher aspect ratio also showed improved delivery of the anti-tumor drug to the cancerous cells. PLGA particles having cylindrical-shape also showed effective delivery of the chemotherapeutic agent in an environmentally triggered fashion [35–38]. Microfluidics [39], lithography [40], seed polymerization [41], and electrospraying [42] are all examples of synthetic methods to produce anisotropic particles. A broad variety of anisotropic shapes have been created utilizing these techniques; significant ones are discussed in-depth below the fabrication section. Biopolymers such as PLA can able to generate a broad range of anisotropic shapes such as Crescent [14], cup [2, 16], Trapezoidal [17], cylindrical [21], disk-shaped particles, Cellulose (rod-shaped) [3], spindle-type [4], PLGA (ellipsoid) [29], rods [30], disk [31, 32], Polycaprolactone (Disk, hemispheres) [23], ice-cream cone [24], Janus hemispherical [23–25], biphasic [25], wormlike [26] etc.

Composition

Polymeric materials that exhibit anisotropy due to chemical heterogeneity fall within this category. Anisotropic compositional materials can be manipulated by altering their internal architecture. In this sense, we refer to particles like dumbbells, acorns, bicompartmental snowmen, and multicompartmental particles with an ordered polymer domain or composition [43]. Electrohydrodynamic-co-jetting [44], seeded polymerization [19], droplet microfluidics [45], self-assembly [46], and a few more technologies are prominently used to fabricate compositionally anisotropic particles.

Surface

These are patterned particles that have at least one well-defined patch on the surface. This patch represents the location on the materials' surface through which the particles experience anisotropy. Isotropic or anisotropic particles can be functionalized through the spatioselective change of their surfaces, which can result in the production of anisotropic surface particles or anisotropic patchy particles [2]. An additional fascinating category of patchy anisotropic particles would be those with polymer-brush-modified patches on their surfaces. Anisotropy can be created onto the particles, as has been demonstrated recently by several research groups [15, 16, 47], either by spatioselective attachment of polymer brush or by immobilization of polymer brush onto non-spherical (already anisotropic) particles. There is a plethora of approaches for creating patchy particles with different functions. Among these, post-modification techniques such as colloidal assembly, lithography, emulsion polymerization, and electrohydrodynamic-co-jetting techniques predominate [48–50]. Electrohydrodynamic-co-jetting is the most straightforward approach to producing biocompatible patchy particles since it allows for the simultaneous manufacturing of bicompartmental, tricompartmental, and multicompartmental particles with orthogonal functionalities. Spatioselective surface modifications/patch creation onto the surface of individual compartments is made possible by the presence of many, functionally distinct compartments within a single particle. Polymer brushes, which are an assembly of polymer chains attached to the surface via one end, have been reported to be immobilized onto substrates using a variety of methods during the past few years. The brushes can be 'grafted to' or 'grafting from' a surface. Polymer brushes use covalent or noncovalent interactions to attach themselves onto a surface via "grafting from or to" technique. Usually, surface-initiated polymerization techniques like atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT), ring-opening metathesis polymerization (ROMP), and nitroxide-mediated polymerization (NMP) have been employed to grow from initiator-immobilized substrates (NMP) [51]. ATRP has surpassed the others in popularity as the most practical and straightforward option. Biopolymers used for producing such types of anisotropic particles are cellulose [5, 8, 9, 12], PLA [19, 20], PCL [25, 52], etc.

2.3 Based on Type of Substrate

Substrate often refers to pre-existing materials that were either the source of or the target of modification in order to generate the anisotropy. Organic and inorganic substrates are the two most common types. It is possible to further categorize organic substrates into biodegradable materials and nondegradable materials. Biodegradable substrates can be flat rectangular or spherical. Biodegradable substrate can be used in any shape, as long as it is flat, rectangular, or round and either isotropic or anisotropic because they are amenable to further modification for getting anisotropy. Examples of flat surface/rectangular substrate [3, 53, 54], spherical [3–8, 10–16, 18–21, 23, 29, 31, 32, 55, 56].

3 Fabrication Techniques

Here, we will discuss in greater depth regarding the techniques we mentioned in Sect. 2 for creating anisotropic materials (Fig. 2).

3.1 Droplet Microfluidics

Droplet microfluidics allows the precise production of a wide range of particle shapes and compositions, including spherical and Janus particles. Direct encapsulation of actives or pharmaceuticals into polymeric particles is made possible by this method, which also has enormous potential in a wide variety of biomedical applications, including drug delivery and other biomedical applications [62, 63]. Microfluidic

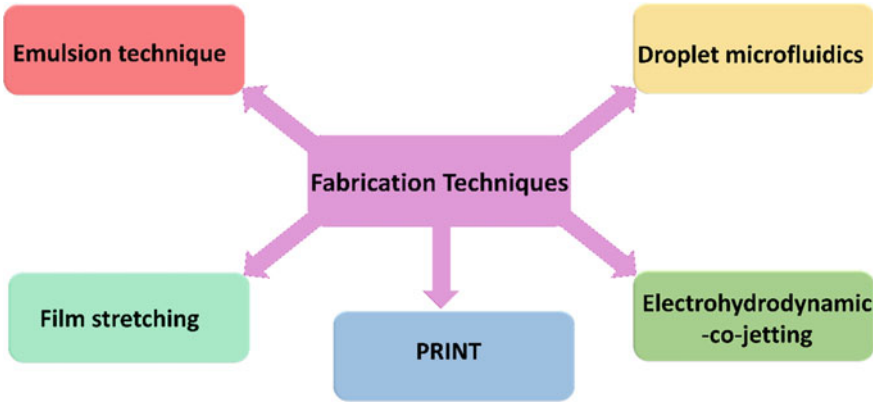

Fig. 2 Fabrication techniques for creating anisotropic materials re-drawn from [1, 2, 27]

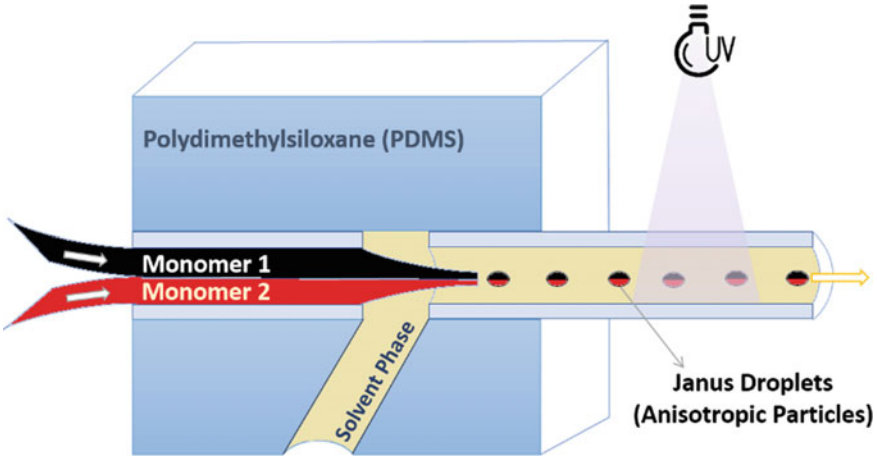

Fig. 3 Schematic illustration of anisotropic particle production using droplet microfluidics inspired from[63, 64]

devices, however, offer a flexible alternative to conventional emulsion approaches, allowing for the exact production of a single drop at a time, thus facilitating the manufacture of monodispersed particles and so resolving the challenges. Microdroplet synthesis into particles contains three basic steps: (1) droplet generation by microfluidic generator, (2) droplet shape via microchannel, and (3) particle solidification via microdroplet solidification [64] (Fig. 3).

3.2 Electrospraying (Electrohydrodynamic-co-Jetting)

Electrospraying, also known as electrohydrodynamic jetting, is another simple method for creating anisotropic polymeric micro/nanoparticles of predetermined shapes and morphologies for use in biomedical applications, such as drug encapsulation [42, 64–68]. Electrospraying requires a syringe with a needle attached to it, a syringe pump that regulates the flow rate of the polymer solution, a high-voltage source, and a grounded collector. The high-voltage applied to the drop of polymeric solution at the needle's tip causes electrostatic repulsive forces between the surface charges and coulombic forces exerted from the external field to overcome the droplet's surface tension, distorting it into a Taylor cone. In the case of low-viscous solutions, this Taylor cone sprays an electrified jet in the form of secondary droplets, leading to polymeric particle formation on the grounded electrode. Solution parameters (such as polymer concentration, viscosity, molecular weight of the polymer, electrical conductivity, etc.), processing parameters (such as applied voltage, flow rate, etc.), and equipment parameters (e.g., needle-to-collector distance, needle diameter, etc.) can all be adjusted to modify the size and shape of the polymeric particles.

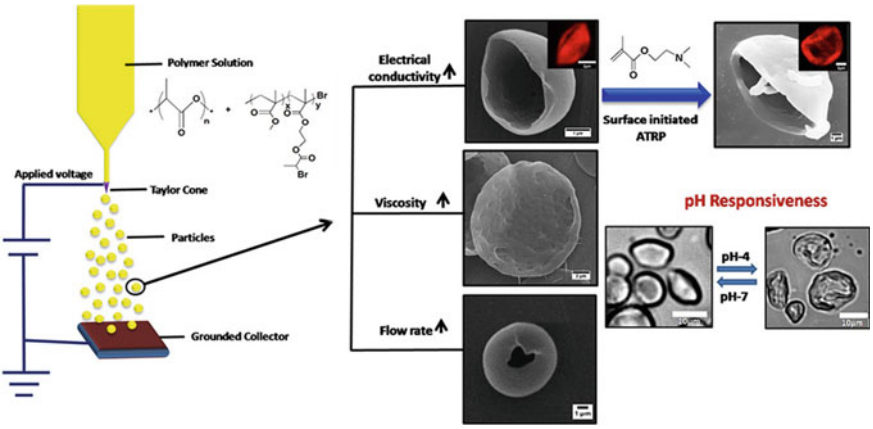

Fig. 4 Fabrication of anisotropic polymeric particles using electrohydrodynamic-co-jetting. Recreated with permission from Ref. [15]. Copyright 2019 Elsevier

In simple words changing the charge density, viscosity, and surface tension of a polymeric solution causes a change in the solution's morphology or overall appearance. The electrospraying method can be used with a wide variety of solvents, medicines, polymers, monomers, etc., which is just one of its many benefits. A narrow size distribution with a small standard deviation can be achieved, and the shape and size of the particles can be controlled with high precision [15] (Fig. 4).

3.3 Particle Replication in Non-wetting Templets (PRINT)

PRINT, or particle replication in nonwetting templates, is a cutting-edge soft lithography process that allows for the creation of particles of varying shapes and sizes, even down to the sub-100-nm range. It's a straightforward and easy method for controlling particle size, shape, and surface functionality, and for enclosing various bioactive chemicals [69–74]. The PRINT process casts molds from perfluoropolyether (PFPE) elastomers using silicon masters with predetermined patterns. Different patterned surfaces can be used to create a wide range of shapes. Liquid PFPE precursor is typically poured onto a silicon master, evenly distributed, and cured with light to create an elastomeric mold. Subsequently, using the roll to roll technique, a liquid monomer or polymer solution (preparticle liquid) is flooded into the mold, and the particle liquid is sucked into the cavities via capillary action. The particles are then consolidated using techniques including, thermal effect, lyophilization, ultraviolet irradiation, solvent evaporation, etc. To create polymeric particles, poly(dimethylsiloxane) (PDMS) is used as a mold material; it is then crosslinked using the soft lithography method. PVP [poly(vinylpyrrolidone)] layer imprinted on a PDMS mold has recently been used to create non-spherical PCL particles such as hemispheres and disks. Researchers

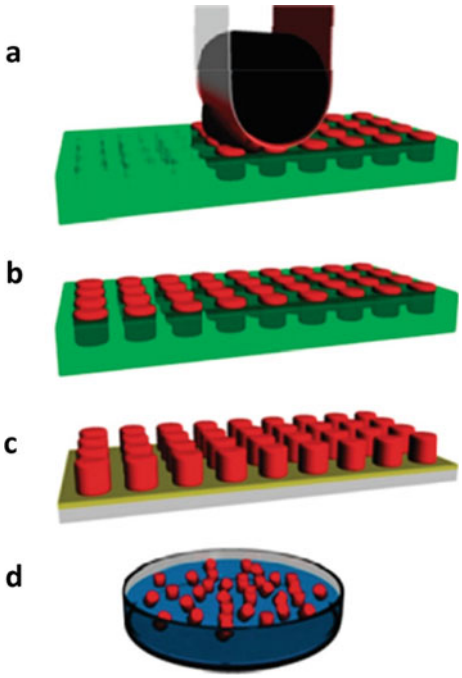

Fig. 5 The PRINT technique, depicted in a schematic form. **a** A roller (black) equipped with a high-surface-energy polymer sheet evenly distributes the preparticle solution (red) in the elastomeric mold (green), removing any excess solution as it goes. In step **b**, the particle solution is cast. Harvesting film is used to collect particles from the mold **c** (yellow). The particles in the solution become unbound after the film is dissolved, demonstrating **d** the fluidity of the solution. Recreated with permission from Refs. [69, 71] Copyright 2010 Elsevier

demonstrated the versatility of Fe_3O_4 nanoparticles by combining them with doxorubicin (DX) and using them as theranostics. Because the PEO phase dissolves in aqueous media during mold release, a PCL/PEO (poly(ethylene oxide)) immiscible polymer phase was also used to produce hemispherical hollow PCL particles [72] as shown in Fig. 5.

3.4 Film Stretching

This technique involves immobilizing previously fabricated particles in a thin film, heating the film above the Tg (glass transition temperature) of the polymeric particles, and then stretching the film, thus causing the particles to deform [75]. The polydispersity of fabricated particles is dependent on the polydispersity of the spherical stock particles, which can only be controlled by selecting the appropriate source spherical particles, but the film stretching method has the potential benefit of allowing the manipulation of many different shapes from a single stock of polymeric particles. Changing the ratio of stretching to compressing, the thickness of the film and the liquefaction method (in which particles are liquefied by using a solvent or heating the particles above Tg) have all been found to influence the particle's final form and size [75].

3.5 *Emulsion Technique*

The method is to be counted among the top sought-after approaches due to its ease of use, low cost, and scalability in the production of compositionally anisotropic particles [76–79]. It has been shown that this method may be used to manufacture compositionally anisotropic/Janus particles that are loaded with drugs, and the mechanism for controlling particle morphology has been identified. PCL and PLGA are two examples of biopolymers that have been employed to manufacture compositionally anisotropic particles through the application of this method [24, 52, 80] (Fig. 6).

Other procedures, notably those pertaining to grafting techniques [27, 81] like "grafting to" where polymer brushes are produced by reacting end-functionalized polymer molecules with a suitable substrate. However, when it comes to synthesizing polymer brushes with a high grafting density, the "grafting from" approach is the most promising method. And "grafting through" which is the combination of the above two. All of these are examples of advanced methods currently in use for producing anisotropy using biodegradable polymers.

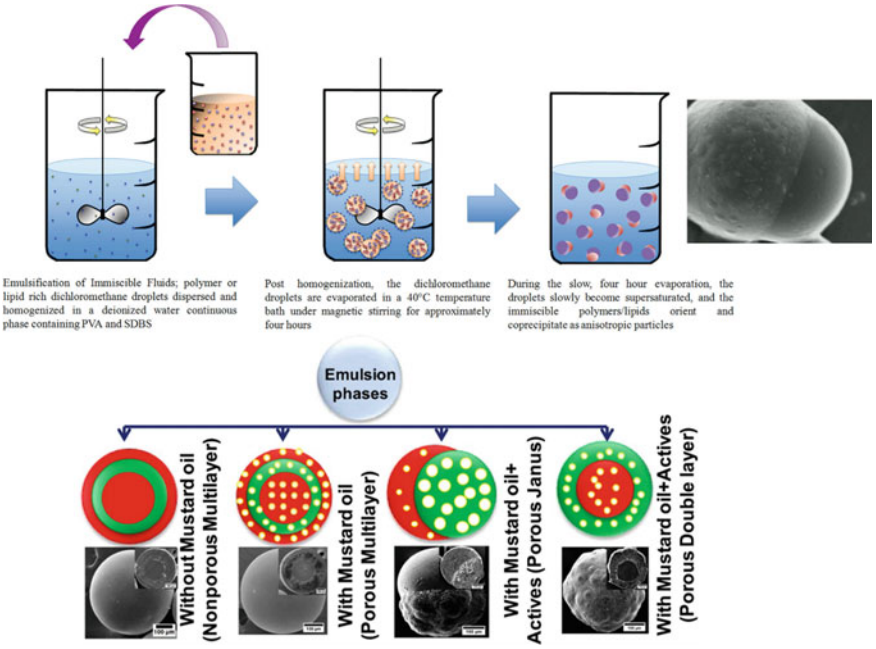

Fig. 6 The experimental procedure for making biodegradable anisotropic particles is depicted schematically above. Reproduced with permission from [51, 53, 80, 81]. Copyright 2012 ACS, 2020 Elsevier

4 Applications

Anisotropic particles, regardless of their form, composition, or surface anisotropy, have the potential to find applications in a wide variety of fields, including those in which their isotropic equivalents are already being utilized. In a variety of contexts, the use of anisotropic particles confers significant benefits above those of isotropic ones. Despite this, because the major focus of this article is on biodegradable anisotropic particles, a concise discussion on the numerous uses of these materials in a variety of fields has been stated below. Applications include targeted as well as triggered medication delivery, the Pickering emulsion stabilizer, Catalysis etc. (Fig. 7).

4.1 Targeted and Triggered Drug Delivery

Since the drug release rate is greatly influenced by the geometry of the carriers, many types of anisotropic particles have been studied in recent decades for use in drug delivery applications. By loading anisotropic brush-modified particles with anthracycline doxorubicin (DX) as a model anticancer drug and then studying properties like drug encapsulation and release performance, cytotoxicity, and cellular uptake, Zhao et al. [52] provide a compelling comparison of spherical micelle and anisotropic particles modified by polymeric brushes as transporters of therapeutics. Using dialysis, DOX was injected into a sphere of PCL-b-PEO. However, the wormlike molecular brushes were found to have a faster release of DX despite having lower drug loading efficiencies and drug loading content than the spherical micelles of

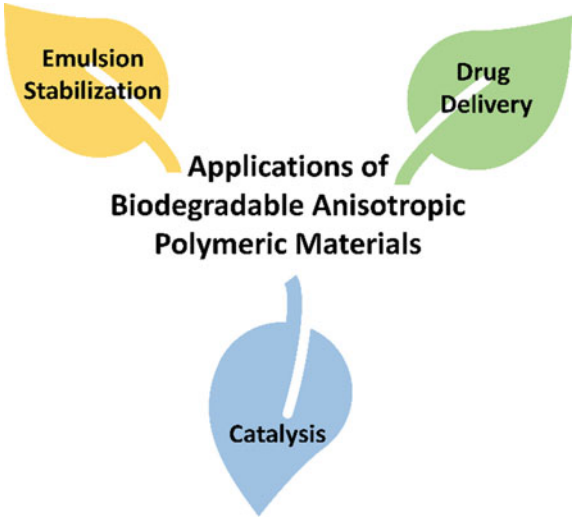

Fig. 7 Schematics for the application of biodegradable anisotropic polymeric materials

PCL-b-PEO diblock copolymers. The biocompatible PCL-b-PEO diblock copolymer was used to improve DX encapsulation because the hydrophobic core of the spherical micelles can expand as needed to accommodate more DX thanks to the flexibility of the chains within them. But polymer brushes could not identify additional drug molecules due to the PCL core's stiff backbone resulting in comparatively less DX loading. However, the in vitro release profile demonstrated that the wormlike brush resulted in a faster drug release than the spherical micelle. Again, this transpired because of the molecular brush's design, which allowed rapid transport of the medication from its central location to the surrounding environment. Furthermore, cellular uptake findings utilizing HeLa and HepG2 cells demonstrated that the wormlike brushes were easily internalized into HeLa and HepG2 cells within 1 h, in contrast to their spherical counterparts. It is possible that non-spherical polymeric core-based nanoparticles, when combined with brush-induced anisotropy, will be seen as a potential material in drug delivery systems, advancing the same line of research. Another example of wormlike micellar particles, consisting of PEG-b–PCL [poly(ethylene glycol)-b-poly(caprolactone)] block copolymer, with a diameter of 150 nm and a length of 1 mm, were created to encapsulate an anticancer medication like methotrexate [26]. When compared to spherical particles, which had a loading efficiency of 2.1 ± 0.08% and an encapsulation efficiency of 20.10% after being synthesized by ring-opening polymerization (ROP) (Full form), it was discovered that wormlike particles had a loading efficiency of 3.5 ± 0.14% and an encapsulation efficiency of 65.6 ± 0.12%. These values were significantly higher than those of the spherical particles (formed by self-organization rapid precipitation). In contrast, wormlike particles released methotrexate at a much slower rate, which is useful in situations where a constant supply of the drug is needed. The bicompartmental PLA/PLGA particles were disk-shaped, and they were loaded with levodopa (LD) and carbidopa (CD) to treat Parkinson's disease (PD), as was mentioned before [31]. Lack of dopamine is the root cause of Parkinson's disease, a neurodegenerative condition. Levodopa's ability to be absorbed in the small intestine, pass the blood–brain barrier, and be converted into dopamine makes it an effective treatment for PD. Carbidopa can be used instead of levodopa because only a fraction of an oral dose of levodopa reaches its intended side due to its metabolism by the 1-amino acid decarboxylase enzyme (AADC) (an AADC inhibitor). Because of this, it would be quite useful to have LD and CD sent together on a constant basis. Similar to the commercially available tablet Syndopa®, disk-shaped particles with anisotropic roughness were found to be an effective carrier for both LD and CD when placed in separate compartments, retaining the required drug ratios, LD/CD = 4:1. Due to their shape (disk) and chemical compositions in different compartments, the produced particles were anisotropic (Janus). The biphasic feature helped to independently control the drug release rate, and the disk form was favored because it provides a higher surface area for adherence to the intestine, boosting drug absorption. To investigate the impact of polymer hydrophilicity/hydrophobicity and crystallinity on drug release rate, two systems were created with either LD or CD in PLGA or PLA compartments (LD/CD = 4:1), and their release profiles were investigated. Because of the greater hydrophilic nature of amorphous PLGA, drug release occurs more rapidly from the

smooth PLGA compartment than from the crystalline PLA compartment. A bicompartmental particle system with LD in a PLGA phase and CD in a PLA phase has been shown to be a promising PD drug carrier, as it releases both medicines at similar and sustained rates (80% of drugs in the initial 5 h and 90% of drugs in 24 h). Anisotropy's function in defining the desired drug release profile was further demonstrated by the ease with which drug release rates for both medications could be manipulated due to differences in crystallinity between the two separate compartments (Fig. 8).

In another example, where researchers have discovered that particle form is a major factor in biodistribution. Numerous experiments have been conducted to determine whether the shape of a particle (rod, cylinder, quasi-hemispherical, spherical, and so on) affects its distribution in the body or not. A 2013 study by Chu et al. [37] discovered that smaller characteristics are preferable because they have a lower

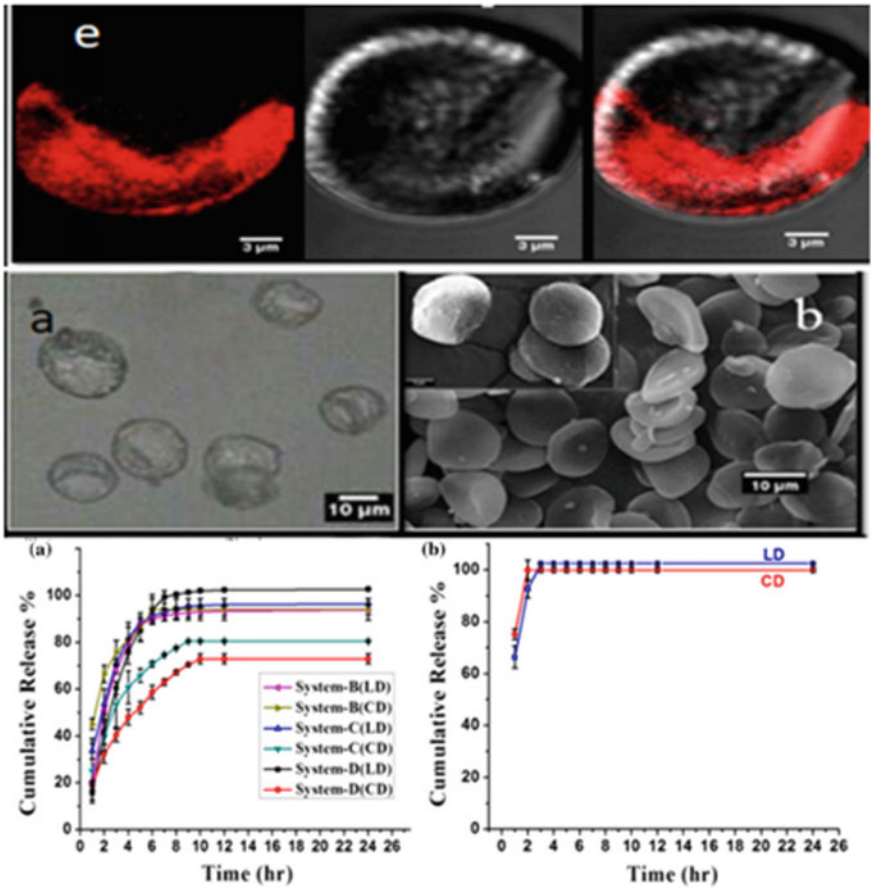

Fig. 8 Bicompartmental microparticles as a dual drug delivery system for Parkinson's disease management. Reproduced with permission from reference. Copyright 2019 Springer [31]

chance of being cleared by organs of the mononuclear phagocyte system (MPS) and thus have more time to perform their function inside the body. Regarding this topic, they reported the simple manufacture of docetaxel-loaded (a chemotherapeutic agent) monodisperse and shape-specific PLGA particles using the PRINT approach. Another PLGA-based anisotropic particle was reported [37] where the film stretching approach was used to alter the shape of spherical PLGA particles made using an emulsion process to prolate ellipsoidal and oblate ellipsoidal ones. Later, RBC (Red Blood Cells) was used to create a biomimetic lipid membrane by coating the particles. In this study, mice received intravenous injections of both coated and uncoated particles of spherical, prolate ellipsoidal, and oblate ellipsoidal shapes. The half-life of all the coated samples dramatically increased in contrast to the uncoated one, as shown by the blood samples collected at regular intervals. Half-life was the longest for prolate ellipsoidal RBCs, which were coated with RBCs, as opposed to spherical RBCs or oblate ellipsoids. After 24 h of incubation, the particles' distribution was studied across multiple organs, and it was discovered that the particle concentrations accumulated in each organ varied significantly depending on the particles' shapes. The accumulation of uncoated prolate ellipsoidal particles was lower in the liver after 24 h than that of oblate ellipsoidal and spherical particles, while it was higher in the heart. In addition, coated particles are concentrated in the spleen and uncoated particles in the kidney; this difference was likely attributable to the superior clearance and destruction of uncoated particles compared to coated ones. It is possible that non-spherical polymeric core-based nanoparticles, when combined with brush-induced anisotropy, will be seen as a potential material in drug delivery systems, for instance, spindle-type cellulose nanocrystals (CNCs) have been reported by Hu et al. [54] to possess biocompatibility in addition to excellent physical and chemical properties.

The aforementioned research certainly elucidates the significance of anisotropic drug carriers' morphology in the development of high-performing drug delivery systems. However, other classes' in-depth theoretical/computational investigation into the effects of anisotropy on particle properties needs to be carried out in order to facilitate particle design suited to a given application.

4.2 Catalysis and Pickering Emulsion Stabilization

While the study of metal catalysis for simple chemical reactions was quite popular, there is less enthusiasm for the subject because of the growing complexity of heterogeneous systems. New generation catalysts typically comprise of various polymers, biopolymers, and clay materials. There are many advantages of using biodegradable and milder catalysts in place of old and harmful ones, including atom economy, low energy demand, straightforward purification methods, more selectivity, and reduced pollution. Consequently, a hybrid system involving anisotropic polymeric materials such as metallic nanoparticles modified by polymer brushes was required to take the role of the ordinary metal catalyst [81–84]. Moreover, being amphiphilic in nature, polymer brush-modified Janus-type biodegradable polymeric particles may act as

interfacial catalysts to demonstrate catalysis at oil/water (o/w) interface. The o/w interface was stabilized by Pickering emulsion stabilizers which are nothing but amphiphilic solid particles.

In other words, for a stable emulsion to be created without the use of surfactants, solid particles known as Pickering emulsion stabilizers are adsorbents at the oil–water interface. Particle-stabilized emulsions is another name for them. They have carved out a niche for themselves in a variety of industries, including medicines, interfacial catalysis, oil recovery, pollution treatment, and others [85–88]. Amphiphilic polymer particles are frequently utilized as Pickering emulsion stabilizers, but their end-of-life consequences are rarely considered. Biodegradable polymer particles are increasingly being considered as potential stabilizers, in addition to their traditional use of functionalizing silicas and clay particles. However, most of the time they are only employed in specialized industries like healthcare, and there aren't many examples exploiting their eco-friendly nature useful in a wide range of contexts, including interfacial catalysis.

In a recent article by Ifra et al. [90] anisotropic Janus-type spherical microparticles (using PLA and copolymer of MMA (Methyl methacrylate) and 2(2-bromopropionyloxy)ethyl methacrylate (BEMA), poly(MMA-*co*-BEMA) with macroinitiators on only one side were manufactured using the electrohydrodynamic co-jetting method onto which pH responsive poly(DMAEMA) brushes were grown using SIATRP with the help of the macroinitiator, allowing for the production of amphiphilic Janus particles. Janus particles which were modified by the polymer brushes were then used to make stable an octanol/water emulsion similar to the Pickering emulsion; the stability of this emulsion can be modified by adjusting the pH; it was stable for more than four months. In addition, iron nanoparticles were electrojeted into one of the compartments, and gold nanoparticles (GNPs) were selectively immobilized onto the surface of brush-modified compartments only, to serve as the interfacial catalyst (acquired by in situ synthesis). In the end, the Janus particles were investigated to reveal two distinct catalytic processes, namely the dechlorination of TCE (trichloroethylene) by iron (0) nanoparticles and the PNP (*p*-nitrophenol) or MO (methyl orange) reduction by GNPs, both of which took place in two distinct phases (octanol and water) Fig. 9. While iron nanoparticles dechlorinated roughly 90% of TCE in about 7 days, presumably likely due to the trapping of TCE within the particles just like the freely available GNPs, they took only 1 min to completely reduce PNP or MO. The fact that they can be recycled and reused several times increases their appeal from a green chemistry standpoint and, by extension, their range of potential uses. In this study, researchers created unique amphiphilic Janus particles that show potential as a powerful interfacial catalyst for a wide range of organic processes, including the purification of polluted water.

Another example of a biodegradable polymeric system for the above application where the use of cellulose nanocrystals grafted with thermo-responsive poly (NIPAM) (poly(N-isopropylacrylamide)) (full form)brushes, were able to successfully construct heptane-in-water Pickering emulsions that can change their viscosity in response to temperature changes [5]. Over the course of four months, emulsions made with poly(NIPAM)-g-CNCs at concentrations of 0.05–0.5 wt% showed no

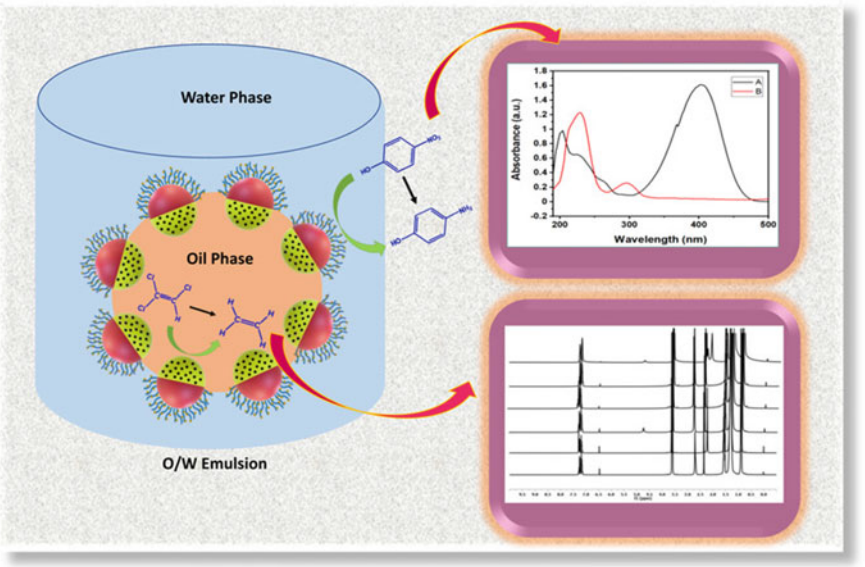

Fig. 9 Graphical illustrator of Pickering emulsion stabilization and catalysis using anisotropic colloidal surfactants decorated with dual metallic nanoparticles. Recreated with permission from Refs. [89, 91]. Copyright ACS 2022

signs of instability compared to the unmodified CNC. The resulting heptane droplets from poly(NIPAM)-g-CNCs had polydisperse drop size distributions, with sizes ranging from 30 to >100 nm depending on the quantity of grafted nanoparticles but when heated for 1 min at temperatures exceeding the LCST (lower critical solution temperature) of poly(NIPAM), entire emulsions were destroyed. Rheological tests shed light on the emulsion stabilization phenomenon by showing that the viscosity of the emulsion rose, as they got closer to the LCST of poly(NIPAM). The weakening of electrostatic and steric interactions of poly(NIPAM)-g-CNCs at the oil–water interface provides an explanation for the mitigating impact of salt under elevated temperatures. The aggregation of grafted nanoparticles at the oil–water interface was also observed as bigger layered sheets were assembled. The above piece of work indicates a significant advancement in biomedical and cosmetic applications that can be anticipated from the creation of thermally sensitive Pickering emulsions using naturally available biodegradable substrates with adjustable stability.

Problems associated with in situ ground water treatment using reactive Zero Valent Iron (ZVI) nanoparticles include rapid oxidation and severe agglomerations of ZVI, which ultimately impede their transport through the subsurface and actions towards degradation of non-aqueous phase liquid (NAPL) and water-soluble contaminants. To overcome the stated problem using biodegradable polymeric material, Kalpana et al. [91] used electrohydrodynamic co-jetting to create amphiphilic bicompartmental Janus particles (711 nm size) loaded with 50-nm ZVI nanoparticles. One of

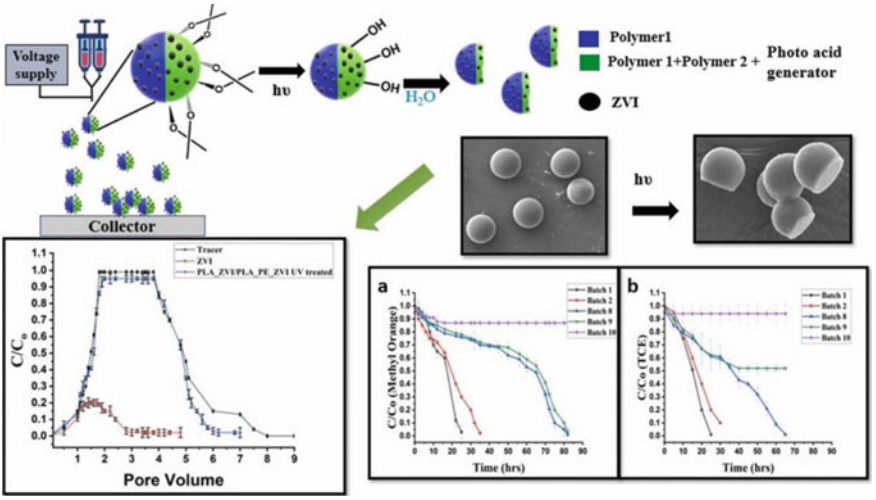

Fig. 10 Application of anisotropic particles for ground water remediation. Recreated with permission from Refs. [90]. Copyright 2022 Elsevier

the two compartments of the Janus particles comprised of PLA (polylactic acid), PE (hexamethylene 2,3-O-isopropylidenetartarate) and PAG (photo acid generator), whereas other hemisphere of the Janus particles was made of PLA only, though ZVI were present in both the compartments. When UV-irradiated, PAG part releases acid to deprotect PE's hydroxyl groups for making the PE compartment hydrophilic. The encapsulated ZVI nanoparticles were found to react and remove hydrophilic (methyl orange dye) and hydrophobic (trichloro ethylene) pollutants. UV-treated Janus particles were 9 times more reusable and had a far more stable dispersion (3 weeks) and reactivity (twenty-four days in polluted water) than the non-treated ones. Besides these, the fabricated amphiphilic Janus particles could remove contaminants at the NAPL/water interface in groundwater due to their low attachment efficiency onto sand particles (0.07) and great transportability (>95%) via porous media (sand column) (Fig. 10).

Applications for anisotropic particles are still in their infancy because their synthesis and modification involve intricate procedures. The vast majority of these substances are promising candidates for drug delivery and theranostic applications. Numerous unexplored applications exist for these materials.

5 Future Scope

Research on biodegradable anisotropic particles has rapidly evolved in recent years, from their construction to their applications across a wide range of fields. Different types of these materials, each with its specific size, shape, usefulness, and features

have been manufactured using selective synthetic techniques. Anisotropic particles can be synthesized using a wide number of synthetic processes like their spherical counterparts, or using the same method but adjusting the process parameters to achieve different results. Biodegradable anisotropic particles are gaining popularity as a research topic because of their potential to eliminate the drawbacks of spherical particles. There is still a lot to be overcome in their development, despite the many obstacles (such as poor repeatability, a lack of product, and a lack of command over form and particle size distributions). In conclusion, the prospective uses of biodegradable anisotropic particle need to be brought into the actual world. Collaboration between material scientists, chemists, biologists, and physicists is essential to this progress. Ultimately, interdisciplinary efforts will provide more well-designed functional materials and devices based on biodegradable anisotropic particles that exhibit fascinating features and have considerable future potential, particularly in the biomedical sector.

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Index

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