Chapter 5
Biodegradable Polymers in Drug Delivery Systems

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Abstract This chapter is focused on the use of biodegradable polymers in long acting injectable drug delivery systems with an emphasis on marketed products. An overview is provided of how the chemical structures and physical properties of these polymers impact functionality of drug delivery systems and how to strategically select polymers for different applications. Detailed examples of biodegradable drug delivery systems are discussed with respect to routes of administration and disease states. The reader will gain information on polymer selection for different applications and on how to integrate knowledge of materials science and formulations to strategically design drug delivery systems for different pathological states.

5.1 Introduction

During the past several decades, considerable research and development efforts have focused on biodegradable polymers for biomedical applications [1]. Medical applications of biodegradable polymers range from sutures in wound management to antiadhesive coating agents in stent devices [18, 26, 31–33, 41, 53]. The first suture using a synthetic polymer, polyglycolide suture (Dexon™), was introduced in 1969. Owing to the availability of safety and long-term clinical data, and their predicable degradation profiles, biodegradable polymers have been utilized in various controlled drug delivery systems [13, 29].

Controlled drug delivery can involve both rate and target control [6, 42], allowing for predictable dissolution rates, optimizing drug release to achieve concentrations

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within the therapeutic index in vivo, and targeting of specific cells, tissues, and organs. Consequently, controlled drug delivery is able to reduce the frequency of administration, reduce systemic side effects, and increase patient compliance. Controlled drug delivery is flexible and can utilize various routes of administration routes, including the oral, buccal, transdermal, ocular, nasal, pulmonary, and parenteral routes. However, the need for biodegradable polymeric delivery systems is mainly in the parenteral area.

Numerous parenteral, polymeric controlled delivery technologies have been successfully developed and validated, and many products are currently on the market, including nanoparticle systems, microspheres, hydrogel implants, and prodrugs [22, 38, 40, 47]. These systems are administered via intravenous, subcutaneous, and intramuscular injection. Biodegradable polymer delivery systems degrade safely in the body, eliminating the need for surgical extraction. In addition, biodegradable polymers tend to have improved biocompatibility with respect to foreign body response compared to nondegradable polymers.

In 1989, the US Food and Drug Administration (FDA) approved the first biodegradable polymeric controlled drug delivery system Lupron® Depot for the treatment of advanced prostate cancer [2]. Lupron® Depot is leuprolide encapsulated into poly(D,L-lactide-*co*-glycolide) (PLGA) microspheres. The depot is a suspension dosage form administered intramuscularly, providing long term leuprolide delivery. PLGA slowly hydrolyzes in the body, delivering leuprolide over periods of weeks to months. In recent years, numerous biodegradable polymeric delivery systems including Trelstar® Depot, Zoladex®, and Eligard® have been introduced into the market. Section 5.3 includes a detailed discussion of these delivery systems.

The aim of this chapter is to provide an overview of applications of biodegradable polymers in marketed parenteral drug delivery systems. Most of these applications are in the form of particulate and in situ controlled drug delivery systems. Formulation design and selection of biodegradable polymers as well as strategies for controlled delivery and targeting delivery are discussed.

5.2 Classification of Biodegradable Polymers

A polymer is a large molecule composed of many repeating smaller structural units called monomers that are connected by covalent chemical bonds. Biodegradation is the chemical breakdown of materials in a physiological environment where the material is degraded by enzymes or is hydrolysed [14, 46]. Depending on the source, biodegradable polymers are classified as either synthetic or natural (biologically derived). Examples of both kinds are listed in Table 5.1.

There are several requirements that must be met for biodegradable polymers to be used in parenteral drug delivery systems, as discussed by Naira and Laurencin [33]. Biodegradable polymers used in parenteral drug delivery systems should be naturally and completely eliminated from the body and the polymers and degradants

Table 5.1 Examples of natural and synthetic biodegradable polymers

Natural biodegradable polymers	Synthetic biodegradable polymers
Proteins: collagen, gelatin, albumin, elastin, fibrin	Polyesters: Poly(glycolic acid), Poly(lactic acid), Poly (lactic-glycolic acid), Poly(caprolactone) (PCL)
Polysaccharides: chitosan, dextran, alginate, hyaluronic acid	Polyanhydrides
	Polyorthoesters
	Polyurethanes
	Tyrosine-derived polycarbonates
	Polyphosphazenes

should be nontoxic and non immunogenic. They should also be compatible with the therapeutic agent(s) and excipients, and should not interfere with the therapeutic effects of the drug. From a manufacturing and CMC (chemistry, manufacturing and controls) standpoint, the polymer should be easy to synthesize and characterize, batches should be reproducible, and the polymer should be stable and easily sterilized. The manufacturing process should be simple and economic to manufacture and scale-up. From a business standpoint, polymers should be applicable to various drugs, including small molecules, proteins, and nucleic acid-based drugs.

5.2.1 Natural Polymers

Natural polymers, listed in the left column of Table 5.1, are present in plants or animals, as proteins and polysaccharides [41]. Most natural polymers are water-soluble and must be crosslinked to from a water insoluble polymer network. The extent of crosslinking can affect drug release rates from delivery systems prepared using these polymers. The crosslinking process can involve heat and/or the application of chemical agents, such as glutaraldehyde and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC, carbodiimide) [34]. EDC reacts with the amine and carboxyl groups on the polymer to form amide groups. Glutaraldehyde reacts with the amine groups on polymer to form a Schiff base.

Natural polymers vary in molecular weight and composition and hence can exhibit considerable lot to lot variability. They are less pure and their physicochemical properties are less easy to control when compared to synthetic polymers. In addition, they can elicit a strong immunogenic response. Most natural polymers undergo enzymatic degradation in vivo. Degradation of natural polymers depends on the degree of crosslinking and other physicochemical properties of natural polymers such as purity, and molecular weight, as well as the availability and concentration of enzymes at the local in vivo site. These conditions affect the drug release profile from delivery systems prepared using natural polymers. Natural polymers typically lack a reproducible degradation rate and typically have a short drug release half life. Collagen and gelatin are the most common natural polymers used in marketed products, and these are discussed below.

5.2.1.1 Collagen

Collagen is a fibrous protein found in connective tissue. Collagen consists of three polypeptide chains intertwined to form a right handed triple helix (tertiary structure). Each of the individual polypeptide chains forms a left handed helix (secondary structure). There are more than 22 different types of collagen currently identified in the human body. Type I collagen is the most abundant protein present in mammals and is the most thoroughly studied protein. The three polypeptide subunits of Type I collagen have similar amino-acid compositions. Each polypeptide is composed of about 1,050 amino acids, containing approximately 33% glycine, 25% proline, and 25% hydroxyproline with a relative abundance of lysine.

Native collagen is water insoluble, and for many pharmaceutical applications collagen is modified to improve its water solubility. Collagen undergoes enzymatic degradation in the body via enzymes, such as collagenases and metalloproteinases. Drug release from collagen matrices is controlled by varying the degree of crosslinking and other physical properties such as porosity, density, and degree of degradation by enzymes in vivo.

Collagen is a major component of the extracellular matrix and natural collagen is, therefore, an ideal matrix material for tissue engineering and wound dressing applications. Product examples include AlloDerm® and Sulmycin® implants, applications of which are discussed in Sect. 5.3.

5.2.1.2 Gelatin

Gelatin, denatured collagen, is a modified natural polymer formed by hydrolysis of fibrous insoluble collagen. Gelatin is typically isolated from bovine or porcine skin or bone by partial acid hydrolysis (Type A) or partial alkaline hydrolysis (Type B) [43]. This processing breaks up the collagen tripolypeptide, generating single polypeptide chains.

Structurally, gelatin molecules contain repeating sequences of glycine–X–Y triplets, where X and Y are frequently proline and hydroxyproline. These sequences are responsible for gelatin's ability to form a gel when saturated by water. Gelatin is zwitterionic, since it contains amino acids bearing acidic carboxyl (glutamic and aspartic acid) side chains, and basic ε-amino (lysine), guanidinium (arginine) and imidazole (histidine) groups. The isoelectric point (pI) of gelatin molecules is defined as the pH value at which the net average charge due to ionization of the acidic and basic groups is zero.

Similar to collagen, preparation of gelatin often presents lot-to-lot variability including a distribution of polypeptide fragments of different sizes, different isoelectric points (pI), and different gelling properties. Consequently, the physiochemical properties of gelatin vary depending on the method of extraction, the amount of thermal denaturation employed, and electrolyte content of the resulting material. To overcome the variable nature of gelatin preparations, manufactured recombinant

Table 5.2 A list of the pros and cons of synthetic versus natural polymers

Classification of polymer	Pro	Con
Natural	Hydrophilic	Possible immunogenicity
	Biocompatible	Require purification
	Cell/tissue specific binding affinity	Lot-to-lot variation
	Safe	Less controlled raw material specifications
	Readily available	Less controlled degradation
		Short release profile
Synthetic	Design desired physicochemical feature, such as copolymer	Require ligands attached to achieve cell/tissue specific binding affinity
	Easy to add functional groups to allow crosslinking and surface modification of chemical moieties to improve functionality of polymer	Require synthesis
	Precise controlled release profile	Scale up challenges
	No immunogenicity	Hydrophobic
	Control of mechanical and physical properties of polymer such as branching	

gelatins have been introduced [35]. Recombinant technology eliminates many of the variables and drawbacks associated with tissue derived material. This allows the production of gelatins with defined molecular weights and pIs, guaranteed lot to lot reproducibility, and the ability to tailor the molecule to match a specific application.

Gelatin is usually crosslinked to form a water insoluble polymer network. Gelatin has relatively low antigenicity, so it is useful in parenteral dosage forms. Gelatins have been used commercially as plasma expanders, vaccine bases, and absorbable sponges (e.g., Gelfoam® or Spongel®).

5.2.2 Synthetic Polymers

In the first half of twentieth century, development of materials synthesized from glycolic acid and other α-hydroxy acids was abandoned because the resulting polymers were unstable for long-term industrial uses. However, this instability, leading to biodegradation, has proven to be immensely important in medical applications over the last three decades. The second column of Table 5.1 lists common synthetic biodegradable polymers currently in use for research and commercial applications [16]. Synthetic polymers have predictable and reproducible degradation rates and controlled release profiles that overcome some of the disadvantages of natural polymers.

Table 5.2 lists the pros and cons of natural and synthetic polymers [29]. Synthetic polymers which contain only a single type of repeating unit are known

as homopolymers, while polymers containing a mixture of repeating units are known as copolymers [23]. The physical properties of polymers depend on the structure of the polymer, including the type of monomer, the length of the chain and arrangement of monomers within the polymer. For example, custom design of the branching of the polymer chains can alter intermolecular forces and consequently affect bulk physical polymer properties. In general, long-chain branches may increase polymer strength, toughness, and the glass transition temperature (T_g) due to an increase in the number of entanglements per chain. Similarly, altering monomer arrangement in a copolymer can be used to control physicochemical and mechanical properties, such as crystallinity, tensile strength, and degradation profile. Depending on comonomer content and method of synthesis, alternating, random, and block copolymers, and grafted copolymers can be produced [23].

A disadvantage of synthetic polymers is that they usually cannot bind with receptor binding ligands on cells. To overcome this obstacle, research on the conjugation of polymers with receptor binding ligands and natural polymers coated on synthetic polymers is gaining attention to achieve site specific delivery [12, 51].

The most common synthetic polymers used in marketed drug delivery applications are discussed below. Other listed in Table 5.1, e.g., poly(orthoesters), have not yet been commercialized.

5.2.2.1 Poly(α-esters)

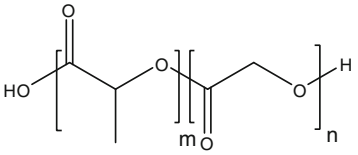
Polyesters and their copolymers are the most commonly used polymers in parenteral drug delivery systems. The major disadvantages of this family of polymers should be addressed, including release of acidic degradation products, processing difficulties and limited range of mechanical properties. Degradation of polyesters is mainly by hydrolysis of ester linkages in the presence of water to release acidic degradation products. In general, incorporation of a buffer in polyester formulations containing protein and other acid labile therapeutics can improve the local environment by helping prevent acid catalyzed degradation. The limited range of mechanical properties can be addressed by incorporating other polymers.

PLA, PGA, and PLGA (Fig. 5.1(1))

Poly(lactic acid) (PLA) and poly(glycolic acid)(PGA) are homopolymers. The PLA homopolymer is stiff due to its highly crystalline nature, while PGA homopolymer is soft due to low crystallinity. Depending on the ratio of lactide to glycolide used for polymerization, different forms of poly(D,L-lactide-*co*-glycolide) (PLGA) ranging from mostly PLA to mostly PGA can be obtained [52].

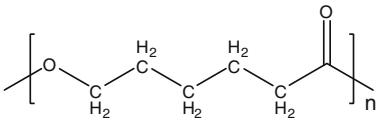
The degradation period of PLGA is between days and years and is a function of the polymer's molecular weight and the ratio of lactic acid to glycolic residues [40]. The higher the content of lactide units, the higher the molecular weight and crystalline content, and this results in slower degradation. PLGA undergoes hydrolysis in the body to produce the original monomers, lactic acid and glycolic acid.

1. Poly(lactic-*co*-glycolic acid) (PLGA).



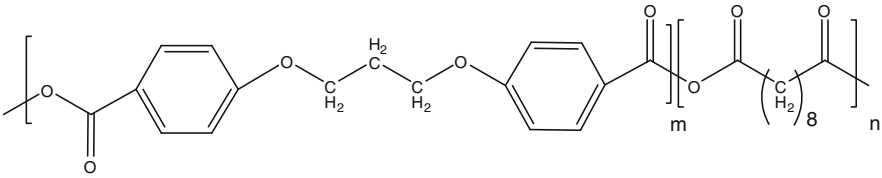
m: number of units of lactide
n: number of units of glycolde

2. Polycaprolactone (PCL)



n: number of units of caprolactone

3. Poly [bis(p-carboxyphenoxy) propane-sebacic acid (PCPP-SA)



m: number of units of bis(p-carboxyphenoxy)propane
n: number of units of sebacic acid

Fig. 5.1 Structures of biodegradable polymers. (**1**) PLGA. (**2**) Poly(ε-caprolactone). (**3**) Poly [(carboxyphenoxy propane)-(sebacic acid)] (PCPP-SA)

The acidic environment resulting from degradation can be overcome by formulating with a buffer to balance the pH and improve drug stability (e.g., for protein or peptide drugs) [50]. Since the two monomers are by-products of metabolic pathways in the body, there is minimal systemic toxicity associated with using PLGA for drug delivery or biomaterial applications.

Polymers prepared from glycolic acid and lactic acid are extensively used in biomedical applications, such as grafts, sutures and implants. Examples include polyglycolide suture (DEXON™) and PLGA used in sutures, surgical pins, and staples (i.e. Vicryl®, Quiet™ sutures or staples) [40, 52].

Poly(ε-caprolactone) PCL

PCL is an aliphatic poly(α-hydroxy acid) and semicrystalline polymer (Fig. 5.1(2)). The monomeric unit ε-caprolactone is relatively inexpensive and much research is

focused on polycaprolactone. The degradation of poly(α-hydroxy acids) depends on chemical hydrolysis of hydrolytically labile aliphatic ester linkages. Owing to its slow degradation, high permeability to many drugs and nontoxicity, PCL was initially investigated as a long term drug delivery vehicle, for example, the long-term contraceptive device Capronor®. This biodegradable PCL capsule device was implanted subdermally and was capable of long term zero order controlled release of levonorgestrel. PCL alone is stiff and has a slow degradation profile. A block copolymer of ε-caprolactone with glycolide offers reduced stiffness compared with pure PGA, and is sold as a monofilament suture by Ethicon, Inc., under the trade name Monocryl™. In 2009, the FDA also approved the commercial Monocryl Plus antibacterial suture (poliglecaprone 25).

5.2.2.2 Polyanhydrides

Polyanhydrides are characterized by aliphatic anhydride bonds that connect the monomer units of the polymer chain [21]. The hydrolytically labile backbone coupled with the hydrophobicity of the polymer precludes water penetration into the matrix, allowing polyanhydrides to undergo surface erosion. In vivo, polyanhydrides degrade into nontoxic diacid monomers that can be metabolized and eliminated from the body.

Aliphatic polyanhydrides were introduced in 1932 as fiber forming polymers for textile applications. Owing to their hydrolytic instability and surface eroding nature, Langer et al. investigated this class of polymers for controlled drug delivery applications in the 1980s. Owing to its safe degradation, poly[(carboxyphenoxy propane)-(sebacic acid)] (PCPP-SA) (Fig. 5.1(3)) was used as a localized delivery vehicle for controlled delivery of the chemotherapeutic agent carmustine (BCNU) in the treatment of brain cancer (Gliadel®). A copolymer of 1:1 sebacic acid and erucic acid dimer is used in the polyanhydride implant (Septacin®) that contains gentamicin sulfate and was developed for sustained local delivery in the treatment of osteomyelitis.

5.3 Biodegradable Polymeric Drug Delivery

Biodegradable polymeric drug delivery systems are beneficial in treating many disease states, and are presented in various dosage forms. Table 5.3 lists currently marketed biodegradable polymeric drug delivery systems, indications for use, and durations of action.

Table 5.3 Biodegradable drug delivery systems on the market

Polymer	Product name	Therapeutic	Treatment	Duration of action	Delivery systems
PLA	Lupron Depot®	Leuprolide acetate	Peptide prostate cancer, endometriosis	1, 3, and 4 Months	Microparticles
PLA	Atridox®	Doxycycline hyclate	Chronic adult periodontitis	7 Days	In situ forming implant
PLGA	Trelstar Depot®	Triptorelin pamoate	Prostate cancer	1 and 3 Months	Microgranule suspension
PLGA	Risperdal® Consta®	Risperidone	Schizophrenia	2 Weeks	Microparticles
PLGA	Somatuline® LA	Lanreotide	Acromegaly	2 Weeks	Microparticles
PLGA	Arestin®	Minocycline	Periodontitis	3 Weeks	Microparticles
PLGA	ProFACT Depot ®	Buserelin acetate	Endometriosis and uterine leiomyoma	1 Month	Implant (Rod)
PLGA	SuprecureMP	Buserelin acetate	Endometriosis and uterine leiomyoma	1 Month	Microparticles
PLGA	Eligard®	Leuprolide acetate	Advanced prostate cancer	1, 3, 4 and 6 Months	In situ forming implant
PLGA	Zoladex®	Goserelin	Breast and prostate cancer	3 Month	Implant (rod)
PLGA	Ozurdex®	Dexamethasone	Macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)	3 Months	Intravitreal implant
PLGA	Vivitrol®	Naltrexone	Medication for alcohol and opioid dependence	1 Month	Implant
PLGA – Glucose	Sandostatin LAR® Depot	Octreotide	Acromegaly	1 Month	In situ forming implant
Polyanhydride PCPP:SA (80:20)	Gliadel®	Carmustine	Brain cancer	2–3 Weeks	Surgical implant
Collagen	CollaRx®	Gentamicin	Diabetic foot ulcer	7 Days	Surgical implant

5.3.1 Mechanism of Release from Polymeric Drug Delivery Systems

Drug release from biodegradable delivery systems occurs by a combination of drug diffusion, osmosis and polymer degradation or bioerosion. In general, degradation of polymers includes bulk erosion and surface erosion [3]. Bulk erosion leads to multiple channels of drug diffusion out of a polymeric system and consequently unpredictable or undesirable release profiles can be obtained, such as burst effects. Therefore, drugs with narrow therapeutic windows should not be used with polymers that undergo bulk erosion. On the contrary, surface erosion of polymeric drug delivery systems can display nearly zero order release kinetics, and if release occurs primarily by diffusion of drug near the surface, then approximately constant release rates are achievable.

Natural polymers are mainly degraded by enzymatic degradation and the degradation products are amino acids or sugars. On the contrary, most synthetic biodegradable polymers are degraded by hydrolytic degradation with little enzyme involvement, and the ultimate degradation products are monomers. Hydrolysis depends on the site of administration and manufacturing procedure as well as the physical properties of these polymers, such as hydrophobicity, crystallinity, glass transition temperature (T_g), impurities, molecular weight, polydispersity, degree of crosslinking, and geometry. In general, slow degradation can be achieved by selection of polymers with high molecular weight, high degree of crystallinity, high T_g, and high degree of crosslinking.

5.3.2 Selection of Biodegradable Polymer in Controlled Drug Delivery

The science of drug delivery systems is multidisciplinary, integrating polymer science, pharmaceutical science, clinical and molecular biology. A general knowledge of the indication of treatment, properties of excipients and therapeutic drugs, and how the characteristics of the drug carrier impact the in vivo and in vitro situation is imperative. It is necessary to know the intended use of the drug and the target drug product profile including desired frequency and duration of the drug to be administered as well as the desired drug release profile in vivo. With knowledge of the target drug product profile in mind, a design space can be formulated. For example, selection of excipients includes consideration of drug-excipient incompatibility as well as the toxicity profile and clinical outcome. The physicochemical and mechanical properties of polymers impact the drug delivery system and its in vivo performance. For example, choice of the molecular weight of PLGA and the ratio of the two comonomers affects the drug release profile. Particle size and surface charge of the delivery system can have an impact on drug targeting and pharmacokinetics. The manufacturing process should be robust and a correlation

between the scale-down and scale-up model should be established. Understanding of the impact of key process parameters and critical attributes of the product is required. Chemistry, manufacturing, and control (CMC) issues as well as clinical concerns of safety and efficacy are key to successful drug product development.

Selection of a biodegrable polymer for a particular application depends on the desired controlled formulation or dosage form, location and frequency of administration, and duration of action. For example, drug delivery systems for central nervous system (CNS) chemotherapy require well controlled release profiles, such as a zero order release profiles and avoidance of burst release and local toxicity. Biodegradable polymers with surface erosion should, therefore, be considered for application to CNS chemotherapy [27]. Biodegradable polymers with bulk erosion profiles, such as PLA or PLGA, may provide first order release profiles and are suitable for long-term treatments as well as those requiring higher therapeutic concentrations. For local drug delivery with short-term application within weeks, natural polymers such as gelatin or collagen can be considered since natural polymers have relatively short time degradation profiles.

5.3.3 Overview of Controlled Drug Delivery

Rate controlled drug delivery pre-designates the rate at which drug is delivered to the body. For example, release of active therapeutics may be extended over a long period (sustained release), it may be constant (zero order release), or it may be triggered by the environment (e.g., pulsatile release or feedback release).

Site specific or targeted delivery offers the advantages of reduced body burden and lower chance of systemic toxicity of the drugs, which is especially useful for highly toxic drugs such as anticancer agents [27, 28]. Site specific or targeted delivery includes passive and active targeting, as originally proposed by Paul Ehrlich [45]. Ehrlich suggested that drugs with special affinities, “magic bullets”, would directly reach the target pathological area following administration due to interactions between the drug and cells at the local site. This idea has led to the development of various targeted drug delivery systems that utilize targeting moieties to facilitate transport of drugs to or near to the physiological treatment site following systemic administration. Targeting moieties that identify certain cell lines or tissues are attached to the surface of “active” targeted drug delivery systems, or they may be attached directly to the drug. These targeting moieties include antibodies, enzymes, protein A, lectins, and sugars.

Active targeting is difficult due to the macrophages of the reticuloendothelial system (RES), which may remove particulate delivery systems from the vascular circulation, preventing them from reaching the target tissue site. Hydrophilic polymers on the surface of drug delivery systems provide a steric effect, which reduces protein adsorption on the surface of the polymer, consequently increasing their circulating half life [20, 23, 49]. An example is pegylated Stealth® liposomes. In this system, the flexible and relatively hydrophilic poly(ethylene glycol) (PEG)

chains induce a steric effect at the surface of the particles that reduces protein adsorption and RES uptake.

Passive targeting occurs when the drug carrier distributes naturally in vivo after administration, without using a specific targeting moiety. For example, particles in the size range 7–12 μm are usually filtered by the capillaries in the lung and, therefore, passively target the lung. Particles in the size range 0.3–2 μm are easily and rapidly taken up by macrophage cells and accumulate in the reticuloendothelial systems (RES). Consequently, diseases of the RES can be targeted by particles of this size.

Site specific delivery or active targeting can be achieved using a targeting moiety on the surface of the drug carrier that targets a specific regional pathophysiological site. Site specific delivery also can be achieved using a localized delivery device that delivers the drug carrier to a given region of the body. For example, a microsphere suspension can be placed and retained at the angioplasty site of an injured artery via a balloon catheter [10, 19, 25]. The polymer used for particulate preparation, together with physicochemical properties of the dosage form (the particle size and porosity), dictates the release rate. In general, natural polymers have short degradation rates between days and weeks while synthetic polymeric microspheres can have degradation rates between months and years [15]. Drug release from carriers is dependent on the mechanism of release, diffusion of the drug through the polymer matrix and the size and the surface area of the carrier. In general, nanoparticulate systems have faster release rates compared to microsphere systems due to their larger surface area. Nanoparticulates with hydrophilic chains on the particle surface have a long circulation time in vivo.

5.3.4 Particulate Polymeric Drug Delivery Systems

Multiparticulate systems (microspheres, nanoparticles, micelles) can be efficiently localized at treatment areas and have less risk of dose dumping compared to large hydrogel implants [8]. These systems are also easy to administer to patients and depending on the application can be designed for long term release, minimizing the frequency of administration. The physicochemical characteristics of particulate systems, e.g., particle size, surface charge and surface hydrophobicity, and inclusion of targeting moieties, affect their distribution in the body. Colloidal systems easily travel in the blood circulation system to the targeted organs/tissues and are easily administrated via injection without the need for surgical incision. Microspheres and other large particulate systems are typically administered via subcutaneous or intramuscular injection for both local and systemic delivery.

Microspheres are solid spheres with particle sizes in the range 1–1,000 μm [7]. There are two types of microspheres, microcapsules and micromatrices. Microcapsules are vesicular systems where the drug is encapsulated in a cavity surrounded by a distinct polymeric membrane. Micromatrices are monolithic systems where drug is dispersed throughout the particles. Microspheres have the

ability to encapsulate a variety of drugs, including hydrophilic and hydrophobic agents, and small molecules and macromolecules, and can achieve sustained release of the agents over a period of days to years. A unique advantage of particulate systems is the ability to blend microspheres prepared with different types of polymers to modify the release profile.

5.3.5 *In Situ Injectable Implant Drug Delivery Systems*

In situ implant drug delivery consists of biodegradable polymers dissolved in biocompatible solvent systems, with drug either dissolved or suspended in the polymer solution [36]. Once the liquid polymer system is injected in the body, the polymer solidifies upon contact with the aqueous body fluids. The drug becomes encapsulated within the polymer matrix as it solidifies forming a depot system. The advantage of in situ injectable implants is that they combine long-term delivery with ease of administration. In addition, the manufacturing process is simple, cost effective and exhibits low batch-to-batch variation. Several mechanisms can be used to achieve solidification in vivo of injectable implants, including use of thermoplastic pastes, in situ crosslinking, in situ precipitation, and in situ solidifying organogels [17].

ATRIGEL® technology uses in situ precipitation, which is the most commercially available process and technology [11]. The biodegradable polymers include polyhydroxyacids, polyanhydrides, polyorthoesters and others. Solvents used to dissolve the polymers range from hydrophilic solvents such as *N*-methyl-2-pyrrolidone (NMP), to hydrophobic solvents such as triacetin and ethyl acetate. Of the latter NMP is the most frequently used due to its good solvency and safety/toxicology profile. Seven products have already been approved by the FDA using ATRIGEL® technology [11]. This technology can be used for parenteral as well as local drug delivery. An example of a parenteral product is Eligard®, an injectable leuprolide acetate suspension for prostate cancer treatment. Eligard® provides systemic release of leuprolide acetate and a range of drug release durations (1, 3, and 4 months) are available. Atridox® provides localized subgingival delivery of doxycycline for periodontal treatment. Nutropin® Depot is an injectable PLGA-encapsulated leuprolide acetate formulation for treatment of prostate cancer.

5.3.6 *Biodegradable Implant Drug Delivery Systems*

Biodegradable implants incorporating antibiotic and anti-inflammatory therapeutic agents are used for wound treatment. Collagen has been extensively investigated for the application of localized antibiotic delivery to wound areas, such as the Sulmycin® and Collatamp®G implants [48]. In 2009, the FDA approved commercial Monocryl™ plus antibacterial sutures based on poliglecaprone 25.

A synthetic polyanhydride copolymer (sebacic acid and erucic acid dimer; 1:1) is used in an implant, Septacin®, containing gentamicin sulfate for sustained local delivery to the site of infection for the treatment of osteomyelitis. To achieve prolonged drug delivery, formulation scientists have utilized different types of gentamicin salts in the collagen delivery system Septocoll® [44].

Gliadel® utilizes poly[(carboxyphenoxy propane)-(sebacic acid)] (PCPP-SA) as a localized delivery vehicle for the controlled delivery of the chemotherapeutic agent carmustine (BCNU) for the treatment of brain cancer. Ozurdex™ is a poly (D,L-lactide-*co*-glycolide) (PLGA) intravitreal implant containing the anti-inflammatory agent dexamethasone. Ozurdex™ eye implants used to treat retinal disease are placed at the rear of the eye to treat swelling caused by problems with retinal veins [24]. Profact® Depot is PLGA with encapsulated buserelin acetate for treatment of endometriosis. Zoladex® is PLGA with encapsulated goserelin for treatment of breast and prostate cancer.

Risperdal® Consta® PLGA microspheres contain risperidone, which are administered intramuscularly every two weeks for the treatment of schizophrenia and for the longer term treatment of Bipolar I Disorder.

5.3.7 Nucleic Acid Delivery

The success of biodegradable polymers in controlled drug delivery systems has led to promising applications in nonviral nucleic acid delivery. Quoting Leaf Huang, "the goal in developing non-viral nucleic acid vectors is to design a system that simultaneously achieves high transfection efficiency, prolonged gene expression and low toxicity" [9]. However, toxicity remains a challenge in this area as a result of the toxicity associated with cationic polymers and lipids. Accordingly, anionic delivery systems have been developed which combine low toxicity with similar or better transfection when compared to cationic systems [37].

Nucleic acid delivery has two essential requirements, namely therapeutic nucleic acids that can be expressed at a target cell, and a safe and efficient delivery system that can deliver therapeutic nucleic acid to the specific tissue or cell. Cationic polymers are mostly used in nucleic acid delivery because they can easily complex with the anionic nucleic acid molecules and condense nucleic acids into nanoparticles in the 100–300 nm range [39]. The resulting polyplexes protect nucleic acids from degradation by nucleases. Cationic polyplexes can also interact with the negatively charged cell surface and thereby can be taken up by cells via endocytosis. Once inside the cell, the polyplexes osmotically swell and eventually burst the vesicles, which then release the nucleic acids into the cytoplasm. The nucleic acids are then free to enter the nucleus.

Polylysine and chitosan are biodegradable cationic polymers commonly used in polyplexes. The physical properties of these cationic polymers [such as the molecular weight and the structure of the polymers (branched versus linear, etc.)] impact their transfection efficiency and cytotoxicity. The surface properties of complexes

also impact transfection efficiency [30]. For example, PEG conjugated with cationic polymers results in improved half-life of polyplexes, and further conjugation of ligands onto PEG-cationic polymer conjugates can improve the transfection efficiency by reducing nonspecific cellular uptake.

5.4 Future Directions in Controlled Drug Delivery

Significant effort is being devoted to developing tailor-made polymers with desirable functional groups to overcome the limitations of the current biodegradable polymers. Scientists are developing novel synthetic polymers with unique functional groups to increase the diversity of the polymer's structure or adapt available polymers to synthesize more desired block or graft copolymers. Furthermore, by understanding the physical properties of polymers and the impact of functional groups on the delivery system, a polymer library can be developed as a basis for synthesis of new biodegradable polymers with the desired properties.

Polymeric drug delivery has demonstrated success in various applications and provides advantages for various therapies. The future of drug delivery includes combination devices that have incorporated therapeutic agents and mediate local drug release at the device implant site [4, 5]. New tailor-made biodegradable polymers will address the needs of drug delivery for nucleic acid therapy, to improve transfection efficiency and reduce cytotoxicity.

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