CHAPTER

APPLICATIONS OF POLYMERS IN PARENTERAL DRUG DELIVERY

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8.1 INTRODUCTION

Oral delivery of formulations have been the most commonly accepted and convenient form of drug delivery. However, these typical dosage forms are only effective where instant effects of the drugs are required in acute conditions. Nonetheless, these formulations still bear the disadvantage of variability in absorption from gastrointestinal (GI) tract and well-known first-pass metabolism in liver reducing the systemic bioavailability of drugs. These have been the key reasons for leaning toward parenteral drug delivery, especially intravenous (IV) injections, that can offer direct access to the systemic circulation with complete drug bioavailability, and, therefore, can reach the site of drug action rapidly.

Also, in chronic therapeutic indications such as pain management, central nervous system disorders, and endocrine diseases, a constant drug concentration must be maintained within its therapeutic window for a longer duration of time. All these problems led to the introduction of a new concept of controlled drug delivery. Initially, various oral sustained release products such as mucoadhesive tablets and floating tablets were developed in quick succession, but these were limited to delivering a drug for a few hours to not more than a day, due to the physiological conditions throughout the GI tract. Moreover, more prevalent parenteral systems were only injectable aqueous solutions which did not provide prolonged release characteristics. Advancements in the polymer science have broadened the scope of application of parenteral administration toward whole new categories of products serving dedicated medication needs. Initially, changing chemical structure of drugs was been utilized to stabilize the drug molecule in the in vivo condition, but this may alter its pharmacological response and metabolic and/or elimination profile (Notari, 1973). This was furthered by chemical linking of protein/peptide drugs with polyethylene (PE) glycols (PEGs) which led to modification to improve their biological half-lives and provide better stability of these biomolecules in blood. Moreover, prolongation of action for parenterally delivered drugs can be achieved by various methods ranging from rate controlled intravenous infusion to use of oily injections and more advanced biomaterials such as micro and nanoparticulate systems to create long-acting injectables (LAIs; Ritschel, 1973).

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Parenteral formulation strategies are advancing toward manufacturing of complex injectables with sophisticated and robust manufacturing processes. This has led to availability of variety of formulations such as aqueous and oily solutions and suspensions, lyophilized injections, micelles, solid implants, in situ forming implant systems and particulate systems including microspheres. In all these areas, polymers play a major role with different functional outputs ranging from stabilizing a particulate system in solution for shelf-stability to providing controlled drug release for weeks to months. Also, quest for safe and effective parenteral therapy has now evolved to encompass several parenteral delivery modes, including intravenous, subcutaneous—SC, intramuscular—IM, intraperitoneal, intrathecal, intravitreal, intravesical, intraarticular, and intratumoral. A specific polymeric delivery system can be chosen based on the route of administration and desired therapeutic need considering the physicochemical, biological, or toxicological constraints associated with the formulation. With that said, evolution of polymers have shown major advancement in prolonged release injectables (aka LAIs; Danhier et al., 2012; Notari, 1973; Kreuter et al., 2003) and nanoparticulate injectables. Growth in this area is driven by unmet medical needs and economic advantages to patients.

With growing need of personalized and patient-centered formulations, polymeric drug delivery systems are gaining wide acceptance. Commercially marketed polymeric implants and microspheres are proof of this. Also, wide range of delivery systems has opened its own scientific field with specific challenges associated with the development of polymeric formulations. A thorough understanding of polymer properties entangled with drug properties and formulation characteristics is required for successful development. This chapter will focus on role of polymers in parenteral formulations, polymer properties, polymeric drug delivery systems, formulation considerations, and various polymer types and their utilities.

8.2 ROLE OF POLYMERS IN PARENTERAL DRUG DELIVERY

Polymers have a widespread multifunctional role in drug delivery. The major role in drug delivery is played in the prolonged release/controlled release formulations. However, there are several other areas in which polymers' roles and functionalities are evolving which could be considered. All these polymers differ in their characteristics to be suitable for the function for which they are used. Role of polymers in parenteral drug delivery may be divided into followings depending on their functionalities.

1. *Polymers as drugs*—Polymers that themselves serve a therapeutic action. Examples include plasma-volume expanders or antithrombotic polymer solutions.

   Usually, polymers are used as excipients or as drug carriers; however, in some cases they may act as therapeutic agents, for example, polyoxyethylene−polyoxypropylene block copolymer has hemorheological and thrombolytic properties that could be of benefit in myocardial infarction and other thrombotic conditions. Similarly, plasma-volume expanders are solutions of high molecular weight (MW) polymers that help boost the blood volume and restore blood hemodynamic in conditions of hemorrhage or circulatory shock (Farrugia, 2011). Such formulations include albumin, dextran, or starch-based solutions for intravenous infusion. Another example is sodium hyaluronate injectables available for intraarticular injection for pain management in osteoarthritic patients and for anterior eye chamber injection to prevent damage to corneal endothelium.

2. *Polymers as nonbiofunctional excipients*—Nonbiofunctional polymers here are defined as polymers which are do not play role in the drug release or drug pharmacokinetics-pharmacodynamics (PKPD) modification. These polymers are usually important in immediate release products formulation aspects as manufacturing aid or to maintain shelf-stability of formulations.

   These polymers do not play important role in drug release characteristics directly. However, they are required for proper functioning of the drug. Examples include the polymers that are required for stability of drug suspension such as DEPO-MEDROL, methylprednisolone acetate injectable suspension, which uses PEG 3350 as suspending agent. Also, some research has gone into the use of polymers as bulking agent in lyophilization. Such polymers include starch and dextran. A few examples of polymers use as formulation component as a stabilizer formulation are given in Table 8.1. Some protein-based formulations also contain some polymers as a process impurity. Examples include Autoplex-T and Prolastin injections which contain PEG.

Table 8.1 Nonbiofunctional Polymers as Formulation Components.

Polymer	Product Name—Formulation Type (Function)	Ref.[a]
Albumin	Intron A—powder for injection (stabilizer)	Aoki et al. (2014)
	Rebif—interferon beta-1a solution (stabilizer)	Asano et al. (1985)
	Zevalin—ibritumomab tiuxetan solution kit (albumin supplied separately as a formulation buffer)	Azevedo and Reis (2004)
	Procrit—epoetin alfa solution (stabilizer)	Bae and Kataoka (2005)
Polyethylene glycol (PEG)	Depo-Medrol—methylprednisolone acetate injectable suspension (PEG 3350 as suspending agent)	Balthasar et al. (2005)
	Depo-Provera—medroxyprogesterone acetate injectable suspension (PEG 3350 as suspending agent)	Banga and Chien (1988)
	Invega Sustenna—paliperidone palmitate extended-release injectable suspension (PEG 4000 as suspending agent)	Batrakova et al. (1996)
Carboxymethyl cellulose	Plenaxis—powder for reconstitution (complexing agent to create suspension and to provide drug release for 1 month)	Bhattacharya et al. (2000)
	Triesence—triamcinolone acetonide injectable suspension (suspending agent)	Bos et al. (2004)
Dextran-40	Mylotarg—lyophilized cake or powder for injection (bulking agent)	Burns et al. (2010)
	Etopophos—lyophilized powder for reconstitution (etoposide phosphate) injection (cryoprotectant/bulking agent)	Burt et al. (1999)
Povidone	Ryanodex—lyophilized powder of dantrolene sodium for injectable suspension (povidone K12 as cryoprotectant/bulking agent)	Calhoun and Mader (1997)
	Alkeran—lyophilized powder of melphalan hydrochloride for injection (cryoprotectant/bulking agent)	Carelli et al. (1989)

[a]*Readers are referred to read these references for details on formulation.*
Note: CMCellulose, Carboxymethyl cellulose

3. Polymers as biofunctional excipients
   Biofunctional polymers are referred herein to the polymers which play active role in pharmacokinetics−Pharmacodynamics of drug. These polymers are usually used in prolonged release products or as drug carriers in vivo.
   a. *Polymers for prolonged release products*—Polymers which play specific role in drug release and hence bioavailability/pharmacokinetic behavior of drug, that is, LAIs
   b. *Polymers as carrier systems for drug in blood*—Polymers that act as carrier for drug in blood so that the pharmacokinetics (PK) of polymer/polymeric system govern the PK of drug, that is, injectable nanoparticles, polymer−drug conjugates, and protein−drug conjugates (PDCs) and also they may enhance the effectiveness of the drug and/or reduce their toxicity.

LAIs and polymeric nanoformulations (including polymer−drug conjugates) have been the center of parenteral formulations R&D due to their wide acceptance for chronic and critical diseases. LAIs have advanced from solid implants that need to be removed after completion of therapy to biodegradable implants with evolution of polymers from nonbiodegradable polymers to more biocompatible and biodegradable polymers and newer technologies to formulate microparticulate and in situ polymeric drug delivery systems. On the medical side the maintenance of therapeutic doses over longer periods of time improves the therapeutic efficacy as it lessens the dosing frequency and improves patient comfort (Ranade and Cannon, 2011). Second, reduced patient visits to hospitals, reduced hospitalizations and monitoring compared to that associated with delivery of their opposite counterparts (intravenous infusions or frequent bolus injections or oral solids) provide cost-advantage. Examples, are birth-control implants such as Jadelle and Nexplanon which provide therapeutic action for 5 and 3 years respectively and sustained release injectables of peptide hormone analogues such as Lupron Depot (1−6 months implants), Zoladex (1- and 3-month implants) and Vantas (12 months implant).

Another area in which a rapid growth is seen is nanoparticulate systems where polymers are important carriers for drug to modify its pharmacokinetic properties for better therapeutic outcomes and/or to reduce its toxicity. Success of Abraxane, albumin bound paclitaxel nanoparticles for cancer treatment, made by nanoparticle albumin bound (NAB) technology has triggered extensive research in nanoparticulate drug delivery systems.

Regardless of the functionality of the polymers used as a part of a therapeutic system, they should have some of the primary characteristics (Oak et al., 2012). Polymers used in parenteral delivery should be:

1. Biodegradable—degrades into small molecule that are easily eliminated by body.
2. Biocompatible—no toxicological effects with polymer itself or its degradation products. There should be minimum undesirable effects such as systemic toxicity, carcinogenicity, and immunogenicity.
3. Easy to manufacture with minimum difficulties in achieving sufficient uniformity and low dispersity of MW.
4. Devoid of process by-products (chemical contaminants) and microbial contamination or pyrogens as well as other contaminants that may cause biological harm.
5. Easy to entrap suitable amount of drug with tunable release profile where controlled release is required

6. Of low cost may also be a factor when choosing a specific polymer while planning delivery strategies.
7. Of enough physicochemical stability to survive through various stages of drug development (manufacturing process, sterilization process, interaction with packaging, temperature excursions during shipping, and handling and storage) and delivery (dilutions, interaction with dilution fluids, in-use stability after injection until end of prolonged release period).

8.3 IN VIVO DISPOSITION OF POLYMERS

Irrespective of what function a polymer serves in drug delivery system, all polymers should be biocompatible, and it is important to consider their in vivo disposition or elimination which gives the direct indication of their biocompatibility. Some implants that are of nondegradable polymers need to be removed after completion of therapy, that is, solid implants such as Jadelle or Nexplanon need to be removed surgically after they are depleted of drugs. Such systems are suitable for administration via IM, SC or intradermal (ID) route but not IV route. Similarly, polymeric systems which are administered intravenously should be made of biocompatible as well as biodegradable polymers and they or their degradation products should be easily eliminable from kidney.

Fate of polymer and especially its distribution throughout the body after in vivo administration (Fig. 8.1) must be considered to develop an optimal polymeric drug delivery system (Bae and Kataoka). Systemic parenteral delivery is desired when administered drug needs to reach remote location in body through blood, while several local administration routes can be employed for limiting spread of drug to other organs to avoid toxicity or adverse effects. Nevertheless, each route requires special considerations in terms of selection of polymer.

By understanding the physical and chemical behavior of polymers inside the biological environment, one can develop safe polymeric carriers for drug encapsulation without exposing the drug to the external environment and the host immune system. This is important specifically for the targeted delivery of proteins, peptides, and diagnostic/imaging agents to the target sites such as cancer tissue (Yih and Al-Fandi, 2006; Unezaki et al., 1996). In the following sections the intravenous route has been discussed as one of the parenteral routes for understanding the polymeric behavior after injection. High MW polymers normally cannot penetrate blood vessels easily and, thus, after intravenous administration, these polymers reside in the vascular spaces. If these polymers are water soluble enough, they can be moved to the kidney for excretion. The upper cut-off limit of any material to be excreted into the urine via the kidney is a MW of 50 kDa and a size of 6 nm (Seymour et al., 1987). Apart from these, if the polymer carries any surface charge, this may affect the excretion because the capillaries of the kidneys are negatively charged and, thus, positively charged polymers get filtered (Takakura et al., 1990; Takakura and Hashida, 1996). Alternatively, if the polymer is not soluble in aqueous biological media, it can be engulfed by the host defense system, the reticuloendothelial system (RES), even though it is not processed by the kidneys. However, if the polymer administered overcomes all the physiological barriers, there are still fundamental problems related to the amount of the polymer used to maintain the bioavailability of drug. To increase the bioavailability of a drug, one may increase the amount of polymer, but this causes potential side effects because of polymer accumulation and, furthermore, it is very hazardous when

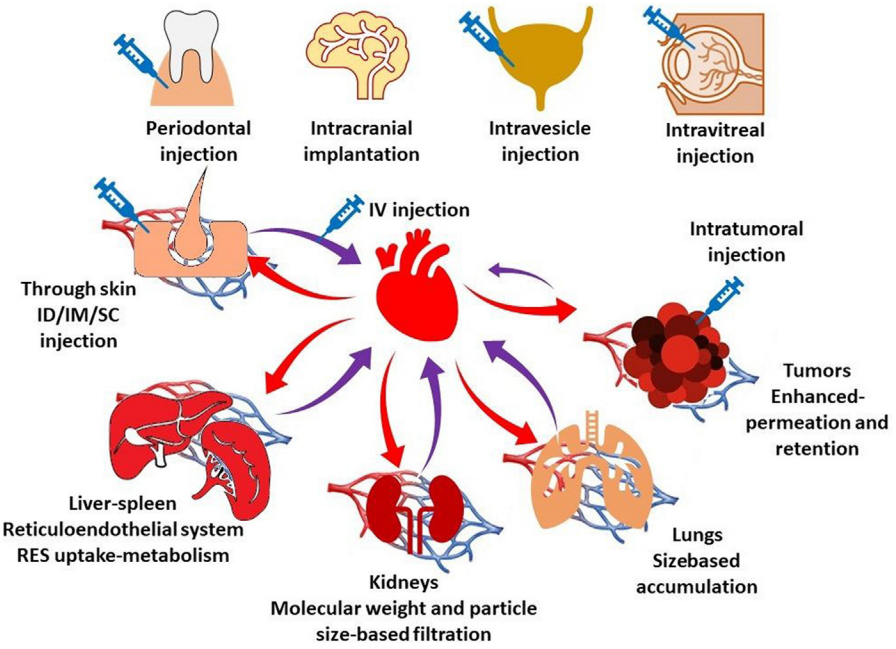

FIGURE 8.1

In vivo distribution of polymers after parenteral administration via different routes. Some local delivery routes that are used for parenteral administration of polymer-based drugs are also shown. RES indicates reticuloendothelial system, red arrows indicate arterial blood flow, purple arrows indicate venous blood flow, and syringes indicate injection sites.

repeated doses are required. On a safe side a minimum optimal amount of polymer should be used for parenteral delivery of therapeutics and after drug delivery, the polymer should be either biodegraded into nontoxic metabolites or easily excreted from the body without being accumulated.

8.4 FACTORS INFLUENCING POLYMERIC PARENTERAL DELIVERY

Factors influencing polymeric parenteral delivery have been divided into polymer properties, drug properties, and formulation properties. This section will majorly cover the factors influencing the drug delivery through polymeric LAIs, nanoparticulate systems or polymer–drug conjugates.

8.4.1 POLYMER PROPERTIES

8.4.1.1 Molecular weight

Majorly, three polymeric delivery systems get affected by the MW of the polymer: LAIs, polymer–drug conjugates, and nanoparticulate systems for intravenous administration.

In case of LAIs, MW of the polymer is one of the factors, which affects the matrix properties and erosion rate. MW of the polymers needs to be carefully chosen to provide certain period of drug release. MW affects majority of other physicochemical properties of polymer such as crystallinity, rate of degradation, and glass transition temperature. The crystallinity affects water diffusion through polymer matrix and drug release as well as processability of the polymer. Hence, it is important to select appropriate MW and evaluate other physicochemical properties based on the requirement of the manufacturing.

In contrast, for intravenous administration, MW of polymers plays a more important role. Proteins, peptides, or polysaccharides of MW $\geq$ 40 kDa can be used due to their biodegradability. Examples include use of antibodies, albumin, and polyglutamate. However, for nonbiodegradable polymers such as PEG and HPMA, restriction on MW applies based on the excretion threshold by kidney to ensure their complete elimination from body. Hence, PEG $<$ 40 kDa and HPMA with MW $<$ 45 kDa should be employed for intravenous delivery (Singh et al., 2012). For example, various grades of polyvinyl pyrrolidone (PVP) exist, yet only the low MW grade is suitable for parenteral applications (Akers, 2006).

The physical characteristics of a polymer, such as solubility, crystallinity, degradation rate, glass transition temperature, and viscosity in solution, are governed by its MW (Chakravarthi et al., 2007). Surface erosion, and thus diffusion, is dependent on the MW of the matrix forming polymers. Usually, polymers with low MW have low viscosity and tensile strength and show rapid degradation. Thus during parenteral polymeric drug delivery, choosing a polymer with suitable MW is crucial. Polydisperse heterogeneous polymers, a result of inefficient polymer synthesis, degrade more quickly than homopolymers of a similar MW (Chakravarthi et al., 2007).

8.4.1.2 Crystallinity

Crystallinity depends on the polymer composition. Crystallinity of the polymer plays is highly important factor in LAI formulation. The higher the crystalline nature of a polymer, the lower the drug release would be. Taking example of polyesters of lactic acid, pure polylactic acid (PLA) is semicrystalline in character while polyester of racemic mixture lactic acid (DL-lactic acid) is amorphous. Degradation of semicrystalline polyesters occurs in two stages with amorphous portions of polymer degrades initially which allows more solvent access to degrade crystalline portions of the polymer in the second stage. Crystallinity also affects the mechanical strength of the drug delivery system. Highly crystalline polymers show brittle characteristics while, amorphous polymers show lack of mechanical strength and hence generally a suitable mix of both forms is used (Chakravarthi et al., 2007). Some polymers such as polycaprolactone (PCL) are highly crystalline as well as hydrophobic and hence might take months to years to completely degrade. Hence, modification of the polymer by blending more amorphous polymers such as PLA or polylactic acid-co-glycolic acid (PLGA) or alkylamines improves their degradation rate making them more suitable for drug delivery (Lin et al., 1994).

8.4.1.3 Hydrophobicity

Many factors, such as polymer MW, its branching and water solubility of monomers, are responsible for hydrophobicity of a polymer. A particulate carrier system comprising a hydrophobic polymer exhibits lower aqueous ingress causing slower polymer biodegradation and hence drug release. But this can be altered by including excipients such as hydrophilic polymers or water-soluble

components to create pores upon hydration inside the biological media to promote degradation rate and drug release. Polyaspartic acids are very hydrophilic in nature and SA at different ratios is copolymerized with these polymers to obtain the desired degradation profile (Shieh et al., 1994). Biodegradation can be augmented from 8 months to almost 2 weeks by the copolymerization. Hydrophobicity is also important for cellular uptake of vesicular and particulate systems. Surface modifications of hydrophobic polymers using hydrophilic polymers such as PEG protect against the opsonization process and eventually RES uptake.

8.4.1.4 Biodegradation of polymers

Biodegradable polymers consequently degrade via a controlled mechanism in vivo into their metabolites by various metabolic pathways and can then be eliminated easily. For drug delivery it is crucial that the delivery system degrades at a predetermined rate to provide controlled release of the encapsulated drug. Thus a polymer should have a continuous mass loss characteristic to achieve subsequent doses and to ensure proper pharmacodynamic effects. Degradation products of the polymer also alter the pattern of the matrix erosion and ultimately affect the release profile. Apart from this the degraded polymeric moieties may induce alteration in cellular function, tissue regeneration, and host response (Azevedo and Reis, 2004). As recommended by various regulatory bodies, including the US Food and Drug Administration, the polymer intended to be used for parenteral application must be biocompatible and nontoxic. Hence, it is important to understand the degradation mechanism of the polymer determining the degradation kinetics, changes in mechanical properties of degraded polymer, and identification of degradation products.

After administration, polymers may undergo various kinds of degradation processes. The polymer degrades because of chemical, physical, mechanical, or biological interactions depending on the route of administration, physicochemical properties of delivery system, and biological response to administration. Chemical and enzymic degradation are the two major types for biodegradation of delivered biodegradable polymeric material. Most of the biodegradable polymers undergo chemical or enzymic hydrolysis and a few follows chemical and enzymic oxidation-dependent degradation. Oxidation usually is an elimination process of degraded polymers/polymer fragments, while hydrolytic degradation is the major degradation pathway for polymers used in LAIs and polyester drug delivery systems which affects the drug release. Apart from these pathways, polymers may degrade by mechanical or thermal processes.

8.4.1.4.1 Chemical and enzymatic oxidation

Upon exposure to biological fluid and tissue, polymers may be degraded by chemical and/or enzymatic oxidation. The host immune system cells such leukocytes and macrophages produce highly reactive oxygen species (ROS) such as superoxide (O^{2-}), hydrogen peroxide, nitric oxide, and hypochlorous acid from. These reactive species lead to oxidative degradation of polymer chains. These degradation mechanisms usually play secondary role in polymer elimination but not quite important role in drug release mechanism. During numerous inflammatory immune responses, efforts have been made to study the effect of the previously listed oxidative species in the degradation of polymeric materials. Degradation of aliphatic polyesters is affected superoxide (Lee and Chu, 2000). Superoxide, through nucleophilic attack on the ester bonds, accelerates polyester degradation. Similarly, enzymatic oxidation of polymers is mediated by enzymes such as peroxidase,

catalase, and xanthine oxidase. Williams and Zhong (1991) discuss how these ROS and oxidative enzymes can impact the polymer degradation under biological conditions.

8.4.1.4.2 Chemical and enzymic hydrolysis

Hydrolytic biodegradation refers to the cleavage of one or more chemical bonds in the polymer backbone by attack of water molecules. The biological fluid first contacts the hydrolysable bonds on the surface of the polymer matrix and then gets absorbed inside the matrix. Following hydrolysis, the polymer degrades into nontoxic easily eliminable metabolites. Hydrolysis can be catalyzed by chemicals such as acids, bases, or by the enzymes in the biological fluids. The degradation rate for hydrolysis mainly depends on the hydrophilicity and hydrophobicity of the polymer. The following is the order or general pattern for the susceptibility of a polymer toward hydrolytic degradation.

(1) > (2) > (3) > (4) where:

(1) is a hydrophilic polymer with bonds prone to hydrolysis,
(2) is a hydrophobic polymer with bonds prone to hydrolysis,
(3) is a hydrophilic polymer with bonds not prone to hydrolysis, and
(4) is a hydrophobic polymer with bonds not prone to hydrolysis.

For example, despite the absorption of a relatively large amount of water, poly-*N*-vinylpyrrolidone is not prone to hydrolysis (Azevedo and Reis, 2004). Generally, biodegradable polymers contain amides, anhydrides, carbonates, esters, glycosides, orthoesters, ureas, and urethanes as hydrolysable bonds. In contrast to this, polymers possessing covalent bonds in their backbone (e.g., C−C) with a lack of hydrolysable bonds require a longer time to degrade in vivo.

Enzymes are biocatalysts, which accelerate the rate of biological reactions in all living bodies. One of the important reactions catalyzed by enzymes is hydrolysis. Hydrolysis is mainly governed by a group of enzymes termed hydrolases that mainly include esterases, glycosidases, proteases, and phosphatases. Sufficient concentration of hydrolytic enzymes is present in plasma to carry out hydrolysis of the administered polymer and other exogenous material to facilitate the elimination of these materials from the body. It has been shown that biodegradation of polymer polyurethane increased up to 10 times in the presence of cholesterol esterase compared to buffer alone (Santerre et al., 1994).

In hydrolysis the rate of degradation is affected by various parameters which include MW, copolymer ratio, polydispersity, and crystallinity (Winzenburg et al., 2004). Some of these factors are explained as follows:

- *Crystallinity*: Crystallinity of the polymer is one of the most important properties as amorphous regions of polymer matrix are more accessible to biological media. Usually, degradation decreases by increasing the crystallinity of polymer (Jones, 2004).
- *Structure of the polymer*: Polymers possessing the structure, which resists the contact between the hydrolysable bonds and water, display slower hydrolysis (Malmsten, 2001).
- *Temperature*: Generally, the degradation increases with increasing temperature (Grit et al., 1993).
- *pH*: The rate of hydrolysis increases at lower and higher pH values (Leong et al., 1985; Achim et al., 1994).

- *MW*: Increase in MW provides strength to the polymer and ultimately decreases the degradation (Alonso et al., 1994).
- *Hydrophilicity* of the polymer, that is, water solubility and water permeability, will predominantly determines the rate of polymer degradation and pattern of degradation (i.e., bulk erosion or surface erosion). However, polymer evolving acidic or basic groups as a result of polymer breakdown may lead to autocatalysis, for example, polyesters and orthoesters.
- *Glass transition temperature* determines the permeability and mobility of molecular chains. Mobility of the chains plays a key role in enzymic attack. Furthermore, cleaved polymer fragments that are trapped inside polymer matrix allow faster degradation by developing autocatalytic hydrolysis. This mainly contributes to the degradation of polyester polymers such as polylactic. This may also contribute to the degradation of such polyesters of lactic and glycolic acid.
- *Surface morphology and physical dimensions:* (e.g., size and surface-to-volume ratio) are vital during phagocytosis, an advanced stage of biodegradation.

Ultimately all these factors influence the drug release pattern. For example, a highly hydrophobic and crystalline polymer, poly-ε-caprolactone (PCL), degrades very slowly compared to PLGA which is amorphous in nature and relatively less hydrophobic (Winzenburg et al., 2004). Thus varieties of degradation profile (ranging from days to months) can be achieved using different polymers. Examples of these polymers are activated carbon−carbon polymers, polyamides and polyurethanes, polyesters and polycarbonates, polyacetals, polyketals, polyorthoester (POE), and inorganic polymers. However, controlling the release pattern from a polyester polymer is quite difficult because of its characteristic to erode from bulk changing the microenvironment of polymeric matrix over time. In such case the drug release is controlled by a mixed phenomenon of polymer swelling, diffusional release of drug, and polymer erosion, which is quite difficult to predict (Heller, 1987; Li and Vert, 1999; Pitt, 1992).

Erosion and drug release: The molecular degradation of polymers leads to degradation of the polymeric drug delivery system in different physicochemical phenomenon that affects the drug release. Erosion can occur either as a bulk phenomenon or as a surface phenomenon depending on the polymer type. For example, polyesters undergo bulk erosion. Ingress of water causes initial haphazard hydrolytic cleavage of polymer chain leading to formation low MW fragments and even monomer units. Once the low MW fragments that are small enough to get dissolved in water are formed, the polymer matrix erosion starts. Usually polymer chain cleavage rate is slower than water ingress rate. pH plays one of the most important role in polymer bulk erosion (Leong et al., 1985; Li et al., 1990). As the degradation products of polyesters and some other polymers are usually acidic in nature, they create a low pH microenvironment which then catalyzes faster scission of acid labile hydrolysable bonds and hence faster erosion, so-called autocatalytic polymer degradation. This phenomenon is more distinct in bulk rather than on the surface due to accumulation of acidic monomers inside bulk causing more pronounced pH drop which is not that evident on surface due to availability of physiologic of dissolution media which usually dilutes the monomers released on surface. Other polymers such as polyanhydrides (PAs) and POEs predominantly exhibit surface erosion (Middleton and Tipton, 2000). In these cases, polymer degradation is much rapid than water ingress which causes outer layers of polymeric carrier to erode first. This can be seen as more uniform release of drug as autocatalytic component of erosion is less pronounced and

protection of drug from such acidic environment as well as any physiologic fluid. Including salts such as sodium sulfate in these polymers modifies the erosion kinetics by facilitating diffusion of water into the polymer matrix and causing pH dependent autocatalytic degradation in the matrix due to pH sensitivity of POEs. Similarly inclusion of inactive ingredients such as itaconic, adipic, or suberic acid has been reported to affect the polymer degradation and release of drug (Maa and Heller, 1990).

8.4.2 DRUG PROPERTIES

8.4.2.1 PKPD of drugs

From PKPD point of view, important characteristics a drug should have depend on the desired effect level. For LAIs, drugs should be potent so that a small dose is needed to keep drug levels in therapeutic window for longer duration of time. This makes hormonal drugs such as estrogens, progesterone, and GnRH (gonadotropin releasing hormone) analogues ideal candidates for LAIs due to their high potency. Also, most of the drugs which are developed as LAIs have longer $t_{1/2}$. Hence, for slow release formulations of drugs that have shorter metabolic $t_{1/2}$, it is difficult to achieve desired therapeutic levels faster leading to therapy failure. As a rule of thumb, longer the $t_{1/2}$ and smaller the dose, longer the release period can be designed into the formulation. For example, etonogestrel has elimination $t_{1/2}$ of about 25 h; hence, it is possible to make LAI that can provide release up to years, while leuprorelin acetate has half-life of about 3 h and longest duration LAI available is for up to 6 months. This directly correlates with MW of drug as well. For example, for levonorgestrel which is a small molecule, 3 yearlong LAI is available. While for insulin or other antidiabetic peptide drugs which have higher MWs, LAIs are available that last from a day to only a few weeks. Dose of the drug also puts a constrain on the amount of excipient which can be used and hence, the content of polymer, as limitations of implant size or injection volume cannot be irrationally large.

In case of polymer–drug conjugates, protein, or peptide drugs are used instead of small molecules as in this situation drugs usually have lower circulation half-lives, and polymer provides longer retention time in blood and hence at the target site. Examples include PEGylated peptide/proteins such as PEG-asparaginase and PEG-interferons (Kolate et al., 2014). In case of PDCs, conjugation might reduce the efficacy of the common drugs used for anticancer therapy. In such cases, drugs that are highly active, that is, cellular toxins are used to conjugate with polymers so that lower dose administration can provide high activity while taking advantage of targeting efficacy of proteins (Yewale et al., 2013; Vhora et al., 2015). Such formulations include highly active antibody–drug conjugates (ADCs) and other PDCs.

8.4.2.2 Physicochemical properties of the drugs

For all formulation types, one of the important factors to consider for selection of drug is the solubility of the drug that affects manufacturing process of formulation development as well as biological properties of the formulation in terms of drug release. Solubility in biological milieu determines the intrinsic release rate from drug delivery system. Physicochemical properties of drug usually put restriction on the available manufacturing processes. Development of LAI of water-soluble drugs (water-soluble small-molecules or peptide hormones) requires use of specific techniques such as

double emulsification and microfluidics for effectively encapsulating the drug inside hydrophobic PLA/PLGA polymer core. For example, Nutropin depot is made by cryogenic spray drying, Trelstar, Sandostatin LAR, Somatuline LA are prepared by phase separation methods and Lupron Depot, Vivitrol and Risperdal Consta are prepared by double emulsification techniques to suite the stability of drugs. Also, each formulation uses specific base form or salt form of drug (i.e., risperidone, naltrexone, leuprolide acetate, triptorelin acetate, or pamoate) for effective encapsulation in microsphere formulations.

8.4.2.3 Drug–polymer interactions

Physicochemical interactions occurring between a drug and a polymer are mainly dependent on their chemical characteristics which include charge density, solubility, and hydrophobicity. For LAIs, properties of the drug delivery system might be different from that of the polymer itself, as such interactions might affect the glass transition temperature or degree of crystallinity (Chakravarthi et al., 2007). Such interaction of drugs with polymer are usually hydrophobic interactions in which hydrophobic regions of the drug interact with hydrophobic regions of the drugs or hydrogen bonding between hydrogen-donor and hydrogen acceptor groups of drug and polymer. Some of the biodegradable polymers contain terminal functional groups such as acid terminated PLA possesses carboxylic groups which can create ionic bonds with drug affecting the degradation rate of polymer and hence release characteristic. This chemically formed complex is difficult to destroy in a biological system and, thus, diffusion is delayed when compared to physically encapsulated or attached drug molecules. There are chances that basic drugs will interact with acidic groups and vice versa. Furthermore, polymer degradation may occur such as in ester polymers where basic drugs may lead to catalytic cleavage of ester bonds. Such interactions must be taken care of before using a polymer in a formulation. Numerous analytical techniques are used to study the drug–polymer interactions such as differential scanning calorimetry, thermogravimetric analysis, solid-state ^{13}C-NMR, and FTIR (Heller et al., 1990b; Chakravarthi et al., 2007).

In certain formulations, drug–polymer interaction is specifically built into creating conjugation products as described in case of polymer–drug conjugates. In such formulations the pharmacodynamic properties of the drugs might be altered due to the permanent nature of the conjugation. Hence, such systems are usually designed with biodegradable linkers that allow the cleavage of polymer from drug for optimum therapeutic activity (Yewale et al., 2013; Vhora et al., 2015). While for others, drug–polymer interaction takes place through ionic interactions due to inherent negative charge of drug with positively charged polymers. Example of such delivery system is polymeric gene delivery systems in which therapeutic genes (siRNA, mRNA, or pDNA) are complexed with positively charged polymers such as polylysine or arginine and histidine-based cationic polymers.

8.4.2.4 Drug stability in formulation

Small molecules in general are more tolerant toward harsh conditions of use of organic solvents or processing parameters than protein or peptide-based drugs. Hence, it is important to use appropriate manufacturing methods that suite the requirements of the drug. Hot-melt extrusion can be used for drugs such as etonogestrel, while double emulsification techniques with use of microfluidics are being used and/or developed for handling protein/peptide drugs. Moreover, shelf-life is always a major concern for both types of drugs even though protein/peptide-based drugs are more prone to

degradation or conformational changes. Hence, thorough stability studies should always be a part of the initial development plan to assess shelf-stability and in-use stability.

8.4.3 FORMULATION CHARACTERISTICS

8.4.3.1 Particle size of nano/microparticulate systems

The size distribution is an important factor in the performance of polymeric particulate carriers because a wide distribution range indicates significant changes in drug loading, its release kinetics which ultimately affect its pharmacokinetics, and in vivo performance. Specifically for nanoparticles, which are mainly taken into cells by endocytosis, particle size can have major effect on bioavailability of the drug and its efficacy (Chiang, 2007; Pathak et al., 2007). Drug diffusion from a particulate delivery system having large particle size may be slow compared to that from small particles or a colloidal dispersion because in the latter case the drug has a shorter path to cover for diffusion. To illustrate this, PLA microspheres containing etoposide were prepared with a different range of sizes, that is, <75, $75-180$, and $180-425\ \mu m$, and the drug release was evaluated. Particles below $75\ \mu m$ showed a faster release due to extensive increase in the surface area compared to that with larger sized particle fractions. Apart from diffusion, particle characteristics are also critical for intravenous administration. Larger particles may cause discomfort and pain as well as other biological complications. Apart from these factors the size of a particle may influence the circulation period in blood and penetration through leaky vasculatures.

8.4.3.2 Implant size/depot size

As described earlier, dose of a drug puts a limit on the amount of the drug that can be devised into a single administration for LAIs. Polymeric injectable has the volume equal to the amount of drug and amount of polymer used. Large dose drugs need to be formulated with less amount of polymer or need to be divided into more frequent dosage regimen (weekly or monthly compared to every 3 or 6 months). Moreover, drug properties become central in drug release compared to low-dose drugs in which polymer become the major regulator of drug release. Hence, thorough consideration should be made on the desired target profile for polymeric drug delivery systems. Also, micro/nanoparticles require larger volumes compared to implants as they required enough amounts of solvents to maintain their particle characteristics.

8.4.3.3 Drug loading

The release kinetics of a molecule may be modified by its initial loading inside the polymeric matrix. Generally, the diffusion rate is higher for aqueous and polymer soluble drugs and also for drugs which are not chemically interacting with the polymers during encapsulation. A higher initial release is observed for polymeric drug carriers with a higher drug loading. These types of systems have rapid pore formation within the matrix because of the higher drug to polymer ratio which ultimately causes higher diffusion of the drug (Li, 2005).

8.4.3.4 Porosity

Controlling the porosity and rate of pore formation is an alternate way of tuning the drug delivery systems. Calcium chloride has been used as a channel forming agent and porous PLGA

microparticles have been prepared to check the effect of this pore forming agent (Ravivarapu et al., 2000). Calcium chloride containing microspheres showed a higher surface area and porosity, and slightly lower drug encapsulation. A porous polymeric carrier may provide faster onset of action compared to nonporous carriers.

8.4.3.5 Surface properties

Surface charge on the polymeric particles is vital because of its influence on the particles' distribution throughout the body and level of cellular uptake (Vhora et al., 2014). A positive charge on the particles favors a higher intracellular concentration as cell membranes are negatively charged. For example, a higher amount of etoposide was found in the brain and bone after encapsulating it into positively charged nanoparticles made up from tripalmitin (Reddy et al., 2004). Furthermore, the exterior of particles can be altered to attach targeting moieties to restrict the distribution at the target site. Some of the surface modifiers described previously, such as PEG, PVP, and dextran, guards particles from being captured by RES, thereby increasing their blood residence time (increased half-life) and improving bioavailability (Chakravarthi et al., 2007).

8.5 POLYMERS FOR PARENTERAL DELIVERY

Polymers suitable for injectable drug delivery can be classified into nonbiodegradable and biodegradable polymers. While nonbiodegradable polymers are still in use for certain LAIs, but their applicability is limited to solid implants such as Jadelle. Majority of the drug delivery systems utilize biodegradable polymers that provide flexibility in terms of their characteristics to suite drug properties and to achieve tunable release profile for small molecules as well as large biomolecules.

8.5.1 NONBIODEGRADABLE POLYMERS

Prevalent research in controlled drug delivery started to take place in 1960s when biocompatible polymers such as PE and silicone rubber were conceptualized (Desai et al., 1965; Folkman and Long, 1964; Pitt and Schindler, 1983). However, nonbiodegradability of these polymers limited their applicability because of two major reasons (Rogers, 1965; Crank and Park, 1996; Lacey and Cowsar, 1974): (1) they require surgical removal of drug depleted implant and they sometimes create local unwanted toxicity issues and (2) polymeric diffusion-controlled release was excellent to achieve desirable drug release kinetics, but it was solely dependent on polymer permeability and other physicochemical properties. Nonbiodegradable polymers used in parenteral drug delivery include only those used in the development of LAIs of reservoir type systems with a drug core enclosed by the nonbiodegradable polymer layer which governs the drug release by limiting the diffusion. Solvent molecules travel through membrane inside the core and solubilize the drug and solubilized drug molecules diffuse outside the delivery system. In this era of modern pharmaceutics, nondegradable polymers are generally not much in use nowadays due to the issues associated with their nonbiodegradability. These polymers

include polyacrylamide, silicone elastomers, and ethylene vinyl acetate copolymer (EVAC; Rajendra et al., 2010; Sutar et al., 2008).

Earlier silicone elastomer matrices were shown to provide prolonged delivery of macromolecules for >3 months (Rajendra et al., 2010; Sutar et al., 2008). Modifications such as the addition of a hydrophilic pore forming component and controlling the loading in the matrices have been shown to alter the release pattern from these polymers, for example, polydimethylsiloxane (Rajendra et al., 2010). Various peptides such as insulin, bovine serum albumin with chymotrypsin, pepsin, and a dipeptide (glycine−tyrosine) have been shown to have a sustained release profile upon encapsulation within silicon elastomers (Hoth and Merkle, 1991; Carelli et al., 1989).

EVAC is the most frequently used nondegradable but biocompatible polymer in drug delivery as it offers control over release rates of the embedded drug molecules (Banga and Chien, 1988; Heller, 1993). Insulin implants made of EVAC have been shown to provide controlled release of insulin for over 3 months in rats (Edelman et al., 1996). Although nonbiodegradable, its inert nature and no toxicity after parenteral administration is the reason for interest in these polymers for parenteral drug delivery.

PEG is another polymer that belongs to the category of nonbiodegradable polymers; however, it has evolved as a biocompatible polymer which is easily eliminated by kidneys without toxicity issues. Wide range of PEG-based polymers with different MWs is available to serve specific formulation needs. PEGs and PEG-based surfactants are used as wetting agents, suspending agent, emulsifiers, solubilizers, stabilizers, etc. PEG is also most widely used polymer for improving the circulation half-lives of protein/peptide drugs (Kolate et al., 2014).

8.5.2 BIODEGRADABLE POLYMERS

Biodegradable polymers possess immense potential for delivering various drug molecules by parenteral routes (Izhar et al., 2001; Kumar and Kumar, 2001; Mukherjee et al., 2008; Saito et al., 2001). They land themselves in three classes depending on their sources: natural, semisynthetic, and synthetic. In this sections, block or graft copolymers that have proven to be very promising biopolymers have been detailed. These polymers can easily be manipulated for their physicochemical properties by changing the ratio of the monomer unites/block or by addition of new blocks in linear or branched configurations. Synthetic polymers specifically provide a preferential advantage of manipulation in wide range of characteristics compared to naturally occurring polymers (Lewis, 1990).

Regardless of the origin and chemical properties, biodegradable polymers should share one or more of the following properties:

- They should have stability and compatibility with the drug molecule.
- They should have a biocompatible and biodegradable nature.
- They should be easy to produce in different scales.
- They should be amenable to sterilization.
- They should have the flexibility to give multiple release profiles.

Different polymers used in polymeric parenteral drug delivery are described in the next sections.

8.5.2.1 Synthetic polymers

Synthetic polymers comprise of a linear or branched chain structure made of covalently attached repeating monomers. Polymerization of monomeric units can be attained by addition and condensation reactions in the presence of an optimal physical and chemical environment. Generally, synthetic biodegradable polymers are favored for drug delivery over their natural counterparts due to the ease of producing these polymers with predictable and reproducible physicochemical properties (Ranade and Hollinger, 2004).

8.5.2.1.1 Polyesters

Polyesters are most widely used polymer for parenteral drug delivery due to the availability of extensive toxicological and degradation data proving their biocompatibility, availability with wide range of physicochemical properties, foreseeable biodegradation kinetics, ease of synthesis with varying monomer ratios and tunable MWs, versatility to be fabricated into different macro/micro/nano drug delivery systems while having approval for parenteral use by majority of regulatory bodies (Vhora et al., 2019a). These are some of the key features, which have made these polymers stand out compared to other synthetic polymers.

Commonly used linear biodegradable polyesters (Fig. 8.2), such as PLA, PGA, and PLGA, play a prominent role in prolonged release injectables (Lewis, 1990). In vivo biodegradation of these polyesters is affected by acid/base catalyzed reactions. They are biocompatible, nontoxic, and easily metabolizable. Lactic acid and glycolic acids are produced upon degradation of these polyesters, which can be removed by the Krebs cycle (citric acid cycle). A slow rate of accumulation of the biodegradation products makes these polymers very safe (Panyam and Labhasetwar, 2003). PLGA is one of the widely used polyesters, in which the mole ratio between lactide to glycolide can be modified to attain the desired polymer with altered physical and chemical characteristics, and all such grades are commercially available. As being a hydrophilic counterpart, increasing the amount of glycolide in PLGA increases the biodegradation rate. Apart from PLGA, PLA and PGA have been extensively evaluated in drug delivery. PLA degrades very slowly, and the degradation time may be several years, whereas for PGA, it is several months. However, PLGA has an even shorter

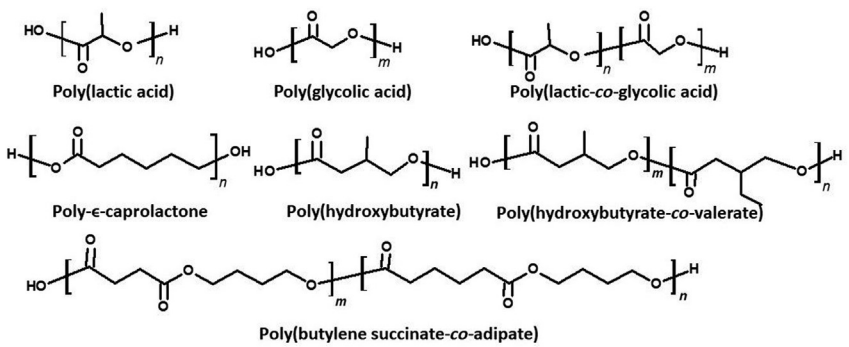

FIGURE 8.2

Structures of some widely used polyesters used in parenteral drug delivery.

biodegradation time of up to a few weeks (Holland et al., 1986; Mehta et al., 1994). Thus changing monomer stereochemistry, ratio of monomers, chain linearity, and MW to an optimal level, one may attain the desired performance characteristics of these polymers (Lewis, 1990).

Interestingly, it was observed that in the presence of surfactants, these polymers show a more controlled release profile (Burns et al., 2010). Stereo-irregularity in the lactide domain and a more crystalline behavior of a polymer governs the degradation time. The pattern followed for degradation can be summarized as poly-L-lactide (crystalline and stereo-irregular) > poly-DL-lactide (amorphous and stereo-irregular) > polyglycolide (crystalline and stereoregular). Despite its numerous benefits, PLGA is inferior in terms of drug loading, specifically for protein or peptide drugs, compared to hydrogels and dextran, which are hydrophilic in nature. The acidic microenvironment of PLGA with a pH of about 2.0 may degrade acid labile bioactive molecules and cause denaturation in the case of peptide molecules (Gehrke et al., 1998).

Expanding applications of PLGA in drug delivery led to the development of polycaprolactone (PCL). PCL degrades slowly, even slower than PGA and PLGA and, thus, is more suitable for formulation of LAIs. Further biodegradation can also be decreased by allowing less accessibility of the ester bonds to the external media. PCL provides high permeability to many types of drug molecules and is also safe to use in vivo. PCL being semicrystalline in nature, its melting temperature, permeability, and biodegradation can be affected by the level of crystallinity. For example, PCL with more crystallinity exhibits reduced permeability by reducing the solute solubility as well as by increasing the diffusional path. Some drugs, which have been encapsulated in PCL, are chlorpromazine and L-methadone which have zero-order release kinetics for 6 days. One of the block copolymers of PCL, PCL-*b*-polyethylene oxide (PCL-*b*-PEG), has been used for preparing polymeric micelles to solubility enhancement of low water-solubility drugs (Allen et al., 2000).

There are several examples of in situ gelling systems prepared using synthetic triblock copolymers. Examples include copolymers which are made of PLA, PLGA, PEG, polyhydroxy butyrate (PHB), polysebacic acid−lactic acid (poly(SA-LA)), etc. Triblock copolymers such as PLGA−PEG−PLGA (Chen et al., 2005), PCL−PEG−PCL polymers (Liu et al., 2008a), PCLA−PEG−PCLA (Petit et al., 2015), mPEG-poly(sebacic acid-DL-lactic acid)-mPEG (mPEG-poly(SA-LA)-mPEG) (Zhai et al., 2009), and poly(PEG−PPG−PHB urethane) (Loh et al., 2007) are worth noting here. However, only a few have reached to veterinary and clinical trials such as InnoCore Pharmaceuticals' InGell technology which is evaluated in pet canine back pain trial and BTG international's ReGel formulation which is evaluated in clinical trials.

One ReGel product loaded with paclitaxel (OncoGel) is made of thermally reversible PLGA−PEG−PLGA polymer as in situ gelling system without use of any organic solvents. It is to be administered intratumorally in solid tumors for local drug delivery for 6 weeks. A number of preclinical studies have demonstrated regional drug release and reduced tumor burden with an acceptable toxicity profile (Elstad and Fowers, 2009). Clinical trials evaluating OncoGel for treatment of solid tumors of breast, pancreas, and esophagus (DeWitt et al., 2017; DuVall et al., 2009; Vukelja et al., 2007) have shown that it was safe but failed to improve overall tumor response with standard of care. However, it was able to improve tumor burden in another trial in conjunction with radiation therapy (DuVall et al., 2009). Veterinary trial in horses with intraarticular administration of ReGels loaded with celecoxib showed sustained drug release with no adverse effects. Development of ReGel is currently ongoing for biomolecules.

Organic solvents used in in situ forming implants might affect the protein stability, therefore, InnoCore Pharmaceuticals is developing a new formulation InGell which is a PCLA−PEG−PCLA triblock copolymer. The hydrophilic PEG moieties help keep the protein structure intact. Two different systems are being developed by using different PCLA and PEG blocks lengths to a gamma polymer (GP) which show temperature sensitive in situ implant formation at body temperature, and a liquid polymer is liquid at room temperature and hence eliminates need of a solvent and shows similar temperature sensitive in situ gelling characteristics as GP. Both these systems avoid organic solvents in contrast to Atrigel which require *N*-methyl pyrrolidone (NMP) as a solvent. Moreover, both polymers can solubilize hydrophobic small molecules providing high drug loading (up to 25%). PCLA−PEG1500−PCLA−based InGel loaded with celecoxib provided up to 30 days of drug release after intraarticular injection study in gelding (Petit et al., 2015). Animals studies have demonstrated safety after SC injection and intradiscal injection (Tellegen et al., 2018). InGell is also being evaluated as protein delivery system.

8.5.2.1.2 Polyamino acids

Use of polyamino acids in drug delivery has been exhaustively investigated because it generates nontoxic degradation products after metabolism. However, immune responses after administration have always been a major obstacle for the use of synthetic polyamino acid especially when three or more different amino acids behave as a monomer. Thus synthetic polyamino acids are restricted to two or three amino acid sequences. The limitation further extends to the fact that these synthetic polymers are not as favorable for parenteral as other classes of polymers. Despite of all these problems, many polyamino acids, such as polylysine, polyarginine, polyglutamate, and polyaspartate, have been studied for use in parenteral drug delivery (Jeong et al., 1999; Huille et al., 1999). Some short peptides are being used as targeting ligands for nanocarriers examples include polyaspartate, polyglutamate, or poly(aspartate−serine−serine) (Zhang et al., 2012; Vhora et al., 2019b).

Currently, polyamino acids of cationic amino acids (lysine, histidine, and arginine) have advanced in delivery of nucleic acids. However, their application is restricted to local delivery such as pulmonary delivery (Konstan et al., 2004) or, if injected, to localized injections such as ID (Sirnaomics, 2016). A polypeptide polymer series that was extensively evaluated in preclinical models for gene delivery was copolymers of histidine and lysin known as HKP (histidine lysine polymers) (Zhou et al., 2017; Leng and Mixson, 2005). A series of HKP polymers were tested which ultimately translated to use of a specific variant H3K4b used in clinical trial for delivery of siRNA targeting transforming growth factor-β1 and COX-2 enzymes for hypertrophic scars (NCT02956317; Konstan et al., 2004). Intratumor injection of dsRNA molecules stabilized by polylysine and critical micelle concentration (CMC) is being evaluated in several clinical trials by Oncovir Inc. as an immunomodulator for treatment of cancer. The delivery system is termed poly-ICLC (polyinosinic−polycytidylic acid stabilized with polylysine and carboxymethyl cellulose) and registered as Hiltonol (NCT03262103).

8.5.2.1.3 Polyphosphazenes

These are relatively new polymers compared to other classes of polymers. The hydrolytic stability of these polymers is not determined by changes in the backbone structure but by changes in the side groups attached to an unconventional macromolecular backbone. Polyphosphazenes can adopt desired flexibility and this makes them unique carriers for drug delivery. Polyphosphazene

microspheres encapsulating naproxen and succinyl sulfathiazole were prepared by Veronese et al. (1999). Polyphosphazenes were also evaluated for delivery of proteins and vaccines (Payne and Andrianov, 1998). Polyphosphazene blend hydrogels have been tested in vitro and in vivo as a self-cross-linkable, thermosensitive injectable carrier, which show sol−gel transformation upon SC injection. Tailored drug release can be accomplished through control of cross-linking of the polymer (Potta et al., 2010). Moreover, Linhardt et al. (2016) have developed tetrapeptide substituted polyphosphazene which show molecular self-assembly to nanostructures. In vitro evaluation of tetrapeptide substituted polyphosphazene showed sustained release of imiquimod with the combination of enzymatic and hydrolytic release mechanisms (Linhardt et al., 2016). Despite the in vitro or preclinical studies, this polymer has not translated to clinical trials.

8.5.2.1.4 Polyorthoesters

POEs are synthesized by transesterification reaction of a diethyl orthoester with a diol. Linear as well as cross-linked versions of this polymer have been explored in drug delivery for more than last three decades. Some of the drugs that have been delivered successfully using these polymers are 5-fluorouracil (Maa and Heller, 1990), levonorgestrel (Heller et al., 1985a,b), norethindrone (Heller et al., 1990b), cyclobenzaprine hydrochloride (Sparer et al., 1984), and insulin (Heller et al., 1990a). There are four different types of POE, POE I which is prepared by transesterification of a diol with diethoxytetrahydrofuran, POE II which is prepared from a diol and a diketene acetal, POE III which is obtained by a reaction between a triol and an orthoacid and POE IV and POE IV which is POE II backbone modified with lactic and glycolic acid units. Among all, POE IV is the most promising as a drug delivery carrier because of a lactic acid moiety in the backbone structure which gives a mechanical and thermal strength to the polymer. Solid and semisolid forms of POE are available, of which formal is used to prepare particulate delivery systems, while the latter is used in injection preparations. Use of a semisolid POE for drug incorporation is quite advantageous because of ease of manufacturing using an organic solvent-less or nonthermal process. This phenomenon is again very beneficial for heat sensitive drug molecules such as proteins and peptides. These are also surface eroding polymers made of POE, drug release from which can be controlled by manipulating their structural features, and MW. Drug release can be obtained, according to need, ranging from a few days to months. Radiation sterilization may also be used for the sterilization of POE. Recently, wide range of PEG-based block copolymers of POE have also been evaluated in drug delivery research (Einmahl et al., 2001).

8.5.2.1.5 Polyanhydrides

PAs are polymers that can be prepared by a polycondensation reaction of diacid monomers and which then degrade in to biocompatible metabolites (Katti et al., 2002). These are surface eroding polymers, which can be eroded by hydrolysis of labile anhydride bonds, to attain drug release from the matrix. The homo-PA exhibits zero-order rate kinetics for both drug release as well as hydrolytic degradation (Li, 2005). Unsaturated PA can be cross-linked to give higher physical stability. Manufacturing process, ratio of polymer components, and hydrophobicity of polymer can be tuned to get controlled erosion to get an anticipated drug release. This surface erosion characteristic is specifically used to protect proteins and peptides from exposure to the outer biological environment by two ways, that is, first encapsulating them inside the core and second there is a restricted entry of fluids into the core area (Tabata et al., 1993). In contrast to PLGA, these polymers supplement

nonsignificant change in the pH upon degradation and, thus, provide a better climate for encapsulated drug molecules. Biodegradable PA ester implants which degrade into salicylic acid have been investigated (Erdmann et al., 2000). Polifeprosan 20, a polyanhydride copolymer made of 20/80 mole ratio of poly[bis(*p*-carboxyphenoxy)] propane and sebacic acid has been used to develop intracranial implant Gliadel (Aoki et al., 2014).

8.5.2.2 Natural polymers

Though natural polymers are not as desirable as synthetic polymers, the use of natural biodegradable polymers in parenteral delivery has also become an area of active research. Natural polymers are readily available and may be amenable to chemical modification. These are relatively cheap compared to synthetic polymers. Many varieties of biodegradable polymers have been investigated and some of them have shown promising potential as polymeric matrices for drug delivery. Two mostly relevant classes are proteins such as collagen, gelatine, albumin, immunoglobulins, hemoglobin, and fibrinogen and polysaccharides such as chitosan, starch, dextran, inulin, cellulose and hyaluronic acid (Sinha and Trehan, 2003). Natural biodegradable polymers such as alginate, pectin, or hyaluronate can be easily modified to produce semisynthetic polymers without losing their biodegradability. These modified polymers may have desired characteristics such as thermogelling properties, mechanical strength, and degradation rates (Ranade and Hollinger, 2004).

8.5.2.2.1 Protein and peptides

Proteins and peptides are the most extensively used polymers for parenteral administration. There exists wide variety of drug delivery systems developed using protein/peptides, that is, nanoparticles, microparticles, hydrogels, and PDCs. Some of the proteins used in parenteral drug delivery research are shown in Fig. 8.3.

Collagen: Collagen is a fibrous protein that can be fabricated into different physical forms (films, filaments, fibers, microsponges, etc.). Its nontoxic and biocompatible nature makes it a great alternative for tissue engineering applications as well as drug delivery. It can be isolated in large amounts and it has well established physicochemical and immunological properties. Collagen has four chemical structures: primary, secondary, tertiary, and quaternary and appears in different forms (around 19 types reported in humans). Generally the collagen matrix exhibits poor loading capacities for drug molecules; however, modification by cross-linking with glutaraldehyde has helped to deliver vascular endothelial growth factor with a significantly reduced degradation for a prolonged time (Tabata et al., 2000). Many other growth factors such as hepatocyte growth factor, platelet-derived growth factor, and basic fibroblast growth factor have also been studied by their incorporation into collagen matrices. One major problem with collagen for its parenteral use is its high immunogenicity because of its animal origin and also its conformational changes during processing. Efforts are being made to prepare a delivery system from collagen without any harsh treatment, which may affect the structure of collagen, that is nonimmunogenic in nature. Collagen can be converted to gelatine by acid- or base-catalyzed hydrolysis. Collagen itself has poor physicochemical properties which are not suitable for parenteral use, such as unwanted swelling, poor mechanical strength, and low elasticity under in vivo biological conditions (Gehrke et al., 1998). Collagen was used as skin-augmentation injectables for dermal filling; however, complications have been noted with these types of injections which limit their application in drug delivery as well (Lucey and Goldberg, 2014). Such complications include early nonhypersensitivity reactions such as injection

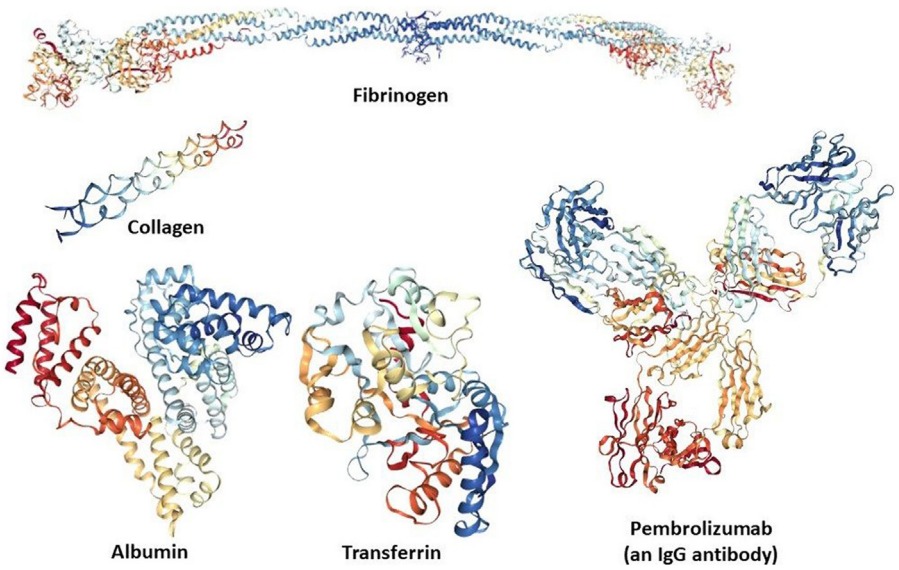

FIGURE 8.3

3D structures of some proteins used in parenteral drug delivery (structures created with the PDB ID and associated publications: collagen (Kawahara et al., 2005), fibrinogen (Kollman et al., 2009), albumin (Bhattacharya et al., 2000), transferrin (Yang et al., 2000), pembrolizumab-an IgG antibody (Scapin et al., 2015) using NGL viewer (a web application for molecular visualization) by Rose et al. (2018), and RCSB PDB. *PDB ID*, Protein data bank identifier; *RCSB PDB*, research collaboratory for structural bioinformatics - protein data bank; PDB101.rcsb.org

site reactions, discoloration, maldistribution, infection and rare but serious vision loss, and hypersensitivity reactions such as delayed type IV hypersensitivity and rarely type I hypersensitivity. Late stage reactions such as granuloma, foreign body reactions, and infections develop weeks or even years after administration (Lucey and Goldberg, 2014).

Gelatine: Gelatine which find their use in drug delivery and cell culture and tissue engineering is a natural protein derived from collagen or by recombinant deoxyribonucleic acid (DNA) technology (Yang et al., 2004; Olsen et al., 2003). Depending on the method used for manufacturing, that is, acid catalyzed or base catalyzed hydrolysis, type A (acid treated) and type B (base treated) gelatines are available. The backbone structure is mainly composed of a heterogeneous mixture of glycine, proline, and hydroxyproline. Gelatine degrades in vivo to endogenous amino acids through pH and enzymatic pathways. Enzymatic degradation is done by matrix metalloproteinases (Nagase, 2001), especially MMP-2 and -9 (gelatinase A and B, respectively) which are overexpressed in tumors (Roomi et al., 2009). Hence, gelatine is a carrier of choice for the development of nanoparticles and preparing PDCs for drug delivery in cancer as it can preferentially cleaved inside tumors and reducing the toxicity to noncancer tissues. Gelatine microspheres are also explored for intraarticular administration (Saravanan et al., 2011). Gelatine particles have been manufactured using a desolvation technique of adding a nonsolvent for gelatine into aqueous gelatine solution to

precipitate gelatine into a particulate form (Coester et al., 2000). The particles obtained can be separated and hardened by glutaraldehyde as there is an aldehyde crosslink between the gelatine molecules. Gelatine particles can also be prepared by an oil-in-water or water-in-oil-in-water multiple emulsification process. Paclitaxel, methotrexate, and doxorubicin are some of the examples of the drugs delivered by gelatine particles (Chakravarthi et al., 2007). Recently, this polymer has also been used for gene delivery for delivering DNA, double-stranded oligonucleotides, and small interfering ribonucleic acid (siRNA) inside the cells (Xu et al., 2012; Jing and Amiji, 2011). Antibody grafted gelatine nanoparticles have also been investigated for targeted lymphocyte uptake (Balthasar et al., 2005).

Albumin: Albumin is widely used for delivering therapeutic drugs in the systemic circulation. As it is an endogenous protein, it is nonantigenic, nontoxic, and readily available. Albumin is an acidic water-soluble polymer, which is a very robust protein compared to others. Properties such as its stability in wide pH range (pH 4−9), solubility in 40% ethanol, and lack of deleterious effects upon heating at 60°C for up to 10 h make it a suitable carrier for parenteral use. Apart from these factors, albumin is also preferentially taken up into tumors and inflamed tissues. Human serum albumin has much less toxicity and immunogenicity compared to bovine serum albumin and other proteins due to its biodegradability and endogenous nature. Various fascinating uses of albumin have been reported in drug delivery ranging from enhancing blood circulation time (e.g., Albuferon, Albulin-G, Albiglutide, and Albugranin) and drug targeting (e.g., Abraxane; Kratz, 2008). Market approval of Abraxane, the first nab (NAB) technology product of Paclitaxel from Abraxis Biosciences, LLC, was a landmark in polymeric parenteral drug delivery for breast cancer treatment. This led to several other nab products of docetaxel and rapamycin to be developed that reached the clinical trials (Kratz, 2008).

8.5.2.2.2 Polysaccharides

These polymers of mono/di/trisaccharide mainly come from natural sources, for example, alginate from algae, pectin and guar gum from plants, xanthan gum and dextran from microbial sources, and chitosan and chondroitin from animals (Liu et al., 2008b). Some polysaccharides are polyelectrolytes depending on the surface charge which make them suitable for specific applications such as to improve cellular uptake or to load drug through ionic interactions. Chitosan which has amine groups belong to cationic polysaccharides, while others such as alginate, pectin, hyaluronic acid, pectin have carboxylic acid groups belonging to anionic polysaccharides (Kida et al., 2007; Liu et al., 2008b). Polysaccharides can be easily tuned for their chemical and biological properties using its hydroxyl, carboxyl, and amino groups (Lee et al., 2000).

Polysaccharides are less preferred for parenteral delivery compared to synthetic polymers and even proteins. While several find application in injectable drug delivery, only few are approved for injectable use with limited application to local injections such as intrabursal, intraarticular, or IM administration. These include methyl cellulose, sodium hyaluronate, carboxymethylcellulose, and its sodium salt (Fig. 8.4). Hyaluronic acid, in the form of sodium salt, has been evaluated in several clinical trials and approved under the names of Nuflexxa, Hyalgan, MonoVisc, Supartz, Gel-One, etc. for injectable delivery in osteoarthritis for pain management in patients not responding to nonpharmacological therapy and analgesics (Stitik et al., 2017; Huang et al., 2011). Hyaluronic acid sodium injection (BioLon and OphtHA) is also used in a surgical aid during ophthalmological surgeries (cataract removal, lens implantation, or other anterior segment surgeries). It provides

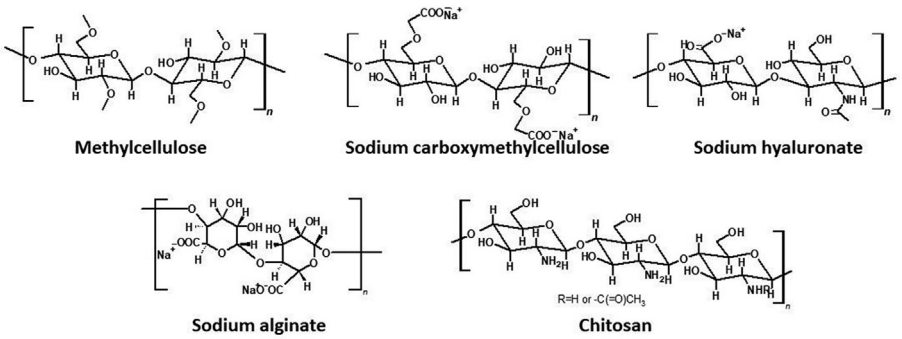

FIGURE 8.4

Structure of some common polysaccharides used in parenteral delivery.

protection to corneal endothelium and to maintain a deep anterior chamber during procedure. Sodium CMCellulose is also used for intraarticular and IM injectables. Other polymers find their application in preclinical studies include xanthan gum and sodium alginate (Shao et al., 2014; Choi et al., 2018). Chitosan has been extensively investigated in drug delivery but yet does not have regulatory approval for pharmaceutical use in parenteral preparations.

8.6 POLYMERIC PARENTERAL DRUG DELIVERY SYSTEMS

The general standards during selection of any polymer for the use in parenteral delivery systems are to match the mechanical properties, safety profile inside the body, and the degradation rate required (Mishra et al., 2008). Detailed account of various types of controlled- and prolonged-release drug delivery systems, their characteristics and factors influencing their therapeutic performance can be found in Vhora et al. (2019a). Some polymeric drug delivery systems in the market are shown in Table 8.2.

8.6.1 POLYMERIC IMPLANTS

Implants are cylindrical or other shaped devices, which are injected or implanted into the SC tissue with a large bore needle. Polymeric implants were the major prolonged release products used for hormonal drugs. These systems include:

- nondegradable polymeric implants and
- biodegradable polymeric implants

Nondegradable implants generally include elastomers most commonly silicon and polyethyl-*co*-vinyl acetate. Drug particles are uniformly distributed throughout the polymer matrix where leakage of the drug occurs by diffusion through the matrix or by erosion or a combination of both. Polymeric biodegradable implants comprise physically entrapped drug molecules in matrices or

Table 8.2 Some Biodegradable Parenteral Polymeric Systems.

Formulation	Product Name	Polymer Used	Distributor	Active Ingredient	Indication
Microparticles	Lupron Depot	PLA	Abbot	Leuprolide acetate	Prostate cancer
	Enantone Depot, Trenantone, Enantone Gyn	PLA	Takeda	leuprolide acetate	Prostate cancer
	Nutropin Depot	PLGA	Genentech	Growth hormone	Pediatric growth hormone deficiency
	Suprecur MP	PLGA	Aventis	Buserelin acetate	Prostate cancer
	Decapeptyl SR	PLGA	Ipsen	Triptorelin acetate or pamoate	Prostate cancer
	Sandostatin LAR	PLGA	Novartis	Octreotide acetate	Acromegaly
	Somatuline LA	PLGA	Ipsen	Lanreotide	Acromegaly
	Trelstar	PLGA	Pfizer	Triptorelin pamoate	Prostate cancer
	Vivitrol	PLGA 75:25 L:G ratio	Alkermes	Naltrexone	Alcohol dependence
	Risperdal Consta	PLGA 75:25 L:G ratio	Janssen/ Alkermes	Risperidone	Schizophrenia
	Parlodel LAR	PLG−glucose	Novartis	Bromocriptine	Parkinson's disease
Implants (biodegradable)	Profact Depot	PLGA 75:25 L:G ratio	Sanofi-Aventis	Buserelin acetate	Prostate cancer
	Zoladex	PLGA 50:50 L:G ratio	AstraZeneca	Goserelin acetate	Prostate cancer
	Ozurdex	Mix of PLGA 50:50 L:G ratio capped and uncapped	Allergan	Dexamethasone	Noninfectious uveitis
	Gliadel	Polifeprosan 20 (polyanhydride copolymer consisting of poly[bis(*p*-carboxyphenoxy)] propane and sebacic acid)	Arbor	Carmustine	Malignant glioma
	Suprefact	PLGA 75:25 L:G ratio	Sanofi	Buserelin acetate	Prostate cancer

Table 8.2 Some Biodegradable Parenteral Polymeric Systems. ***Continued***

Formulation	Product Name	Polymer Used	Distributor	Active Ingredient	Indication
Implants (nonbiodegradable)	Nexplanon	EVA	Merck	Etonogestrel	Birth-control
	Jadelle	Silicon	Bayer	Levonorgestrel	Birth-control
	Retisert	PVA and silicon elastomer and silicon adhesive	Bausch & Lomb	Fluocinolone acetonide	Chronic noninfectious uveitis
	Vantas	Hydroxyethyl methacrylate, hydroxypropyl methacrylate	Endo	Histerelin acetate	Prostate cancer
In situ forming implant	Eligard	PLGA with carboxyl end-group and PLGA with hexanediol end-group with different lactic acid:glycolic acid ratios (L:G ratio)	Sanofi-Synthelabo	Leuprolide acetate	Prostate cancer
	Perseris	PLGA with 80:20 L:G ratio	Indivior	Risperidone	Schizophrenia
	Sublocade	PLGA 50:50 L:G ratio	Indivior	Buprenorphine	Opioid use disorder
	Atridox	PLA	Tolmar/Zila Therapeutics	Doxycycline hyclate	Periodontitis

EVA, *Ethylene vinyl acetate;* PVA, *polyvinyl alcohol.*

microspheres. Examples of biodegradable polymers are PLGA and poly-*p*-carboxyphenoxypropane-*co*-sebacic acid.

Biodegradable implants release a drug molecule at a sustained rate with parallel degradation of the polymer into nontoxic metabolites, thus avoiding surgical removal. In this system, hydrolytically labile polymers form a matrix with a physically uniformly dispersed drug. Implants can easily be removed if there is a need to discontinue treatment unlike particulate systems such as microparticles or nanoparticles. Special devices are also available such as trocars for implanting prefabricated implants, generally under anesthesia. Using biodegradable polymers sustained systemic as well as sustained local delivery of various drugs have been achieved. A few examples are systemic release of LHRH (luteinizing hormone releasing hormone) agonists (Asano et al., 1985) and somatostatin analogue (Rothen-Weinhold et al., 1999), and sustained local release of anesthetics (Le Corre et al., 1997) as well as antibiotics (Calhoun and Mader, 1997) have been achieved. Standard hot-melt extrusion or injection molding methods are used to manufacture these types of implants in different shapes and sizes (flat films, rolled implants, rods, and so on). Research on implantable drug delivery then progressed to the development of in situ implants, which are usually polymer solution or suspension in biocompatible organic solvent administered by SC or IM route using conventional 21- or 22-gauge needles. This technique removes the discomfort associated with the implantation procedure. Atrigel, developed by the Atrix laboratory, uses NMP or triacetin

which are biocompatible solvents to dissolve biodegradable polymers such as PLGA, PLA or PCL, and drug molecules (Wong and Hu, 2004). This drug−polymer−organic solvent system, once administered, dissociates the organic solvent in the physiological environment of the surrounding tissue leading to subsequent water permeation into the polymer solution/suspension resulting in aggregation of the polymer and in situ implant formation. Modifying the polymer properties, choosing appropriate solvent system and altering the ratio between the polymer and the organic solvent can help achieve desirable control on drug release profile. A product delivering leuprolide acetate for up to 4 months has been recently approved. This system offers several advantages such as ease of manufacturing, simplicity in administration, and cost-effectiveness. However, limitations for the use of organic solvents and concentrations of polymers used in parenteral routes and burst effects (almost 30%−40% within few hours) are some of the disadvantages of this technique. Burst effect may lead to toxicity for some the drugs such as leuprolide acetate. Alza Corporation developed the Alzamer Depot system which is developed with the aim of reducing the burst release using appropriate solvent system. PLGA-based Zoladex contains goserelin acetate for the treatment of prostate carcinoma. A Gliadel Wafer is another commercially available implant system comprising PA copolymer matrix poly[bis(*p*-carboxyphenoxy) propane:SA] for delivering carmustine for brain cancer treatment. This can be placed in the brain after tumor removal and thus overcoming the requirement for the drug to cross the blood−brain barrier (BBB) and simultaneously reducing the systemic toxicity and enhancing drug effectiveness.

8.6.2 MICROPARTICLES

Microparticles including both microcapsules and microspheres are generally fine spheres usually less than 1000 μm in diameter (Yang and Alexandridis, 2000). Microspheres can have homogeneous drug distribution throughout the polymer matrix. Alternatively, a drug can be captured inside a polymer coating creating a reservoir system (also called microcapsules). One more type of microparticles includes a drug adsorbed onto the particle surface by the means of different applications such as physical, ionic, or chemical interactions. In the past few decades, microparticles for parenteral applications were mainly investigated as a controlled release drug delivery carrier, and they were all were based on biodegradable polymers. There was remarkable success in encapsulating a peptide macromolecule into the ester polymer (PLGA), and in recent years, this led all researchers to concentrate on this polymeric carrier for sustained release applications. Though microparticles range from 1 to 1000 μm, for injection purposes, particles should be smaller than 125 μm to avoid complications in physiological conditions (Jain, 2000). Microparticles can be injected using hypodermic injection needles, unlike the surgical methods used for sustained release implants. A variety of methods are used to prepare microparticles including most common techniques such as phase separation (coacervation), spray drying, and solvent evaporation. All these methods influence the final characteristics of microparticles prepared, and some of the expected characteristics of this delivery system are:

- The physicochemical stability of the encapsulated active ingredient should be maintained throughout the process.
- Manufacturing should end with optimal drug loading, maximum encapsulation, and maximum yield.

- Microparticles should be able to provide suitable drug release at intended rate for suitable time period.
- The particles produced should possess the needed flowability and syringeability.
- Manufacturing process should be simple, reproducible, and easily scalable.

8.6.3 NANOPARTICLES

Nanoparticles share similar morphological characteristics with microparticles except the particle size which is in the submicron range for nanoparticles. Nanoparticles made up from biodegradable polymers are most suitable for parenteral use. If not biodegradable the polymers, which are easily eliminated from body, can be used. Either way, selection of polymer depends on the therapeutic application, biocompatibility, and desired release rate. Release rates ranging from hours to several months can be achieved with this carrier system (Labhasetwar et al., 1997). As discussed earlier, all particulate systems including nanoparticles in the systemic circulation are prone to uptake by the RES. Unless otherwise intended, this phenomenon may lead to extensive clearance of the drug from the plasma. If given intraperitoneally, these nanoparticles are taken up by lymphatic system. However, this may help in some of the disease conditions specifically in acquired immunodeficiency syndrome. RES uptake can be reduced or prevented by the means of steric stabilization of nanoparticles using the PEGylation technique providing improved residence time in blood.

Nanoparticles are best suited for targeted delivery strategies. Many researchers have attached different ligand or targeting moieties to the nanoparticles' surface and have achieved significant concentrations of drug at the target sites. Compared to free drug nanoparticles, bound anticancer drugs have found to show prolonged drug retention at the tumor site, reduced tumor growth, and better survival of tumor bearing mice (Akhtar et al., 2000). Currently, research is also envisaged to overcome the BBB by parenteral administration of nanoparticles for sustained release of drug inside the brain tissue, also for a vaccine delivery system for transporting therapeutic peptides or protein antigens into immune cells (Willis, 2004).

8.6.4 POLYMERIC MICELLES

Micelles provide apparent advantages in the delivery of small molecule drugs having limited water solubility. Because of the high solubilization capacity for hydrophobic drugs, small particle size, thermodynamic stability, and, more interestingly, prevention of rapid clearance by the RES, polymeric micelles hold a promising place in the parenteral drug delivery (Kabanov et al., 2002). In polymeric micelles the CMC plays the same significant role as nonpolymeric low MW surfactants. In the initial stages of the micelle formation, at concentration similar to CMC or slightly higher than CMC, loose aggregates are formed with a small amount of water in the core (Torchilin, 2001). Once the polymer concentration increases, the residual water from core is eliminated making more stable and compact micelles which are smaller in size. In general, micelles with a lower CMC value are considered to be more stable physiologically because in the biological system upon dilution with almost 6 L of blood volume, micelles with a high CMC dissociates and the content may leach out, while at low CMCs, micelles still maintain their integrity and protect the drug molecule inside the core. Usually, block copolymers tend to form polymeric micelles due to the hydrophobic block making the core and hydrophilic block making the shell,

so-called core−shell structure (Kataoka et al., 2001). Hydrophobic chains of copolymer form core solubilizing a much higher concentrations of hydrophobic drug, while the core is covered by hydrophilic portions of copolymer protecting micelles from aggregation, precipitation, cell adhesion, or protein binding (Kakizawa and Kataoka, 2002). Further chemical manipulation of polymers can lead to the desired level of drug solubilization (Huh et al., 2005). Drug solubility relies on the compatibility of the polymer with drug and interaction (hydrophobic interaction, ionic interaction, or hydrogen bonding) between the drug and the polymeric core (Kwon and Kataoka, 1995). However, stability of this polymeric carrier gets lowered with an increased amount of drug loading (Burt et al., 1999). The highly hydrated nature of PEG makes it a common component of di- and triblock polymers and a steric stabilizer (Kwon, 1998; Torchilin and Trubetskoy, 1995). Some of the examples of block and graft copolymers and their supramolecular assemblies in water are shown in Fig. 8.5.

A most common example of a triblock copolymer used to prepare micellar systems is Poloxamer (Pluronic) which are made of ethylene oxide (hydrophilic component) with propylene oxide (hydrophobic component). Various drug molecules such as diazepam, indomethacin (Lin and Kawashima, 1985, 1987), Adriamycin (Yokoyama et al., 1998, 1994; Kwon et al., 1997), anthracycline antibiotics (Batrakova et al., 1996), and polynucleotides (Kabanov et al., 1995) have been shown to be solubilized inside the poloxamer micellar core. The toxicity of drugs such as doxorubicin is also diminished after incorporation into polymeric micelles. Other polymers used for micellar solubilization of hydrophobic drugs include polyaspartic acid, PGA, PLA, PEG−PE, PEG-*b*-polyaspartic acid, PEG−PLA, and PEG-poly-L-lysine. Polymer blocks comprising anionic and cationic amino acids, that is, aspartate or lysine provide ionic complexation potential as well for creating electrostatic interaction with opposite charge drugs and improve their loading.

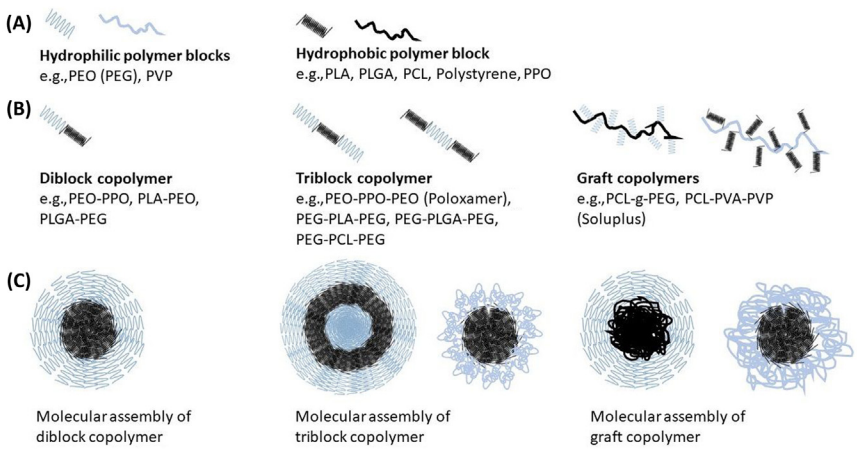

FIGURE 8.5

(A) Hydrophobic and hydrophilic blocks used in block or graft copolymers; (B) arrangement of hydrophobic and hydrophilic blocks in diblock, triblock, and graft copolymers and their examples; and (C) schematic representation of molecular assembly of different types of copolymers in aqueous environment.

8.6.5 HYDROGELS

A gelled network of either covalent crosslinks or just physical nature made with hydrophilic polymers forms a hydrogel. Covalently linked polymers forming hydrogels are known as chemical gels or thermoset hydrogels as these gels cannot regain their original shape once they are set. Physical gels are a noncovalently linked disordered structures (Park et al., 1993) and known as thermoplastic hydrogels because of their reversible nature after casting., Noncovalent types of attachments involved in these gels are hydrogen bonds, hydrophobic interaction, stereo-complex generation, ionic complexation, and crystalline structures. Recently, biodegradable hydrogels made of natural or synthetic polymers have advanced considerably for drug delivery. The biodegradation may be attributed to the degradation of polymeric backbone itself, degradation of crosslinks between polymer blocks and/or cleavage of hanging chains from the polymer backbone. As some protein or polysaccharides are prone to enzymatic degradation, site specific delivery can be possible using this novel hydrogel carrier (Kamath and Park, 1993). Many of the biodegradable polymers which have been developed exclude their usability for hydrogels due to their hydrophobicity. However, by combining hydrophilic polymers to these hydrophobic polymers, it is possible to develop biodegradable and swellable gels in the aqueous environment (Bos et al., 2004; Yang et al., 2002; Markland et al., 1999; Tanahashi et al., 2002).

Because of their biodegradable nature, the residues of polymers after drug release do not need to be removed and, thus, provide a natural removal process for elimination (Kamath and Park, 1993). Biodegradable hydrogels also provide a controlled release for protein therapeutics (Van Tomme and Hennink, 2007; Lin and Metter, 2006; Ito et al., 2007). Unlike microspheres, manufacturing process of hydrogels avoids organic solvents and thus reduces the toxicities related to these solvents. Use of hydrogels for encapsulation of macromolecules is also of interest.

Biodegradable hydrogels which are made as PLGA microparticles have been evaluated for use as injectable systems (Jiang et al., 2003; Holland et al., 2003). PLGA is the most extensively studied polymer; however, it has some issues related to drug release especially for therapeutic proteins and drug degradation due to low internal pH (van de Weert et al., 2000). To overcome these issues, hydrogels of biodegradable dextran modified with L-lactate or D-lactate have been prepared by organic solvent-less process of mixing aqueous solutions (Hennink et al., 2004). Furthermore, thermosensitive hydrogels can be designed to make this polymeric carrier most suitable for the delivery of proteins or genetic materials. Various biodegradable block copolymers of polyester and PEG (PEG−PLGA−PEG) have been examined thoroughly as carrier for therapeutic nucleic acids (Kissel et al., 2002; Li et al., 2003; Jeong et al., 2000). High loading efficiency and ease of scale-up make this technology more suitable. To target the drug to the desired sites various endogenous and exogenous stimuli such as pH, biochemical species (ROS, reductive environment, enzymes, etc.), ionic strength, magnetic, electrical, ultrasound, and thermal changes have been studied (Sabnis et al., 2009; Soppimath et al., 2002; Chen et al., 2004).

8.6.6 POLYMER−DRUG CONJUGATES

While polymer−drug conjugates cover a wide range of drug delivery systems, this section concentrates mainly on conjugates of natural or synthetic polymers, antibodies, and other proteins. The nanoparticulate drug delivery systems can also be polymer conjugated such as PEGylation to

improve circulation time and targeting ligand (majority of which are proteins) conjugation to improve tissue and cellular uptake.

Ringsdorf introduced the idea of polymer–drug conjugates (Ringsdorf, 1975). From then on, many polymer–drug conjugates were manufactured and tested for therapeutic efficiency, especially for cancer. Underlying premise for development of PDCs was based on the kidney's excretion threshold for macromolecules (≥40 kD for globular proteins, ≥45 kDa for synthetic polymers such as HPMA (hydroxypropyl methacrylamide) and ≥40 kDa for PEG) and tumor clearance threshold (≥40 kDa for globular proteins, >78 kDa for HPMA and >40 kDa for PEG) (Seymour et al., 1987; Singh et al., 2012). The first evidence of this was given by Matsumura and Maeda when they reported favored localization of polymeric carriers in tumors which was described as enhanced permeation and retention (EPR) effect (Matsumura and Maeda, 1986; Maeda et al., 2000). This indicates by employing certain MW of polymer for intravenous delivery, its blood $t_{1/2}$ can be improved simultaneously improving its tumor accumulation. Likewise, correlation can be made for macromolecules in terms of their hydrodynamic diameter, that is, greater EPR effect is observed with particles having hydrodynamic size ≥8 nm (Singh et al., 2012). These principles can be used for selecting appropriate proteins to achieve desirable circulation time and improved retention in tumor.

Polymer–drug conjugates offer numerous benefits, for example, prolonged circulation in blood by shielding macromolecules such as antibodies from immune system cells preventing or reducing any immune response (Rihova and Riha, 1985). Hydrophilic nature of the polymers such as PEG render surface properties of hydrophobic drug or immunogenic drugs hydrophilic and enable intravenous administration. Apart from these, conjugation provides enhanced therapeutic translation inside the cell and decreases efflux of the low MW drug molecules (Minko et al., 2000; Omelyanenko et al., 1998a,b).

Both natural and synthetic polymers can act as carriers for drugs. Biodegradable polymers from a natural origin, such as polysaccharides and polyamino acids, were used initially for drug delivery, with the idea that these macromolecules would be metabolized naturally to fragments for easy elimination from the body (Putnam and Kopeček, 1995). Unfortunately, the formation of a conjugate of a drug with a polymer may prevent the enzyme–substrate interaction. This finally prevents usually biodegradable macromolecule from degrading into fragments that can easily get eliminated from body and hence, renders these types of conjugates nonbiodegradable (Putnam and Kopeček, 1995; Crepon et al., 1991; Krinick and Kopeček, 1991). However, synthetic polymers are more appropriate and preferred because they can be tailor-made according to the biological requirements. Synthetically modified polymers containing specific three-dimensional structures with definite orientations of the functional group(s) and compositions are ideal for drug conjugation (Duncan, 2003). These are also nondegradable conjugates in a biological system but because of proper MW distribution can be eliminated by the renal pathway. Nonbiodegradable synthetic polymer-based conjugates to reach clinical trials are HPMA [*N*-(2-hydroxypropyl) methacrylamide] based. PK1 is a doxorubicin–HPMA conjugate which has reduced toxicity of free doxorubicin while showing therapeutic effectiveness in chemotherapy-refractory patients (Vasey et al., 1999). MAG-CPT which is a camptothecin (CPT)–HPMA conjugate (Schoemaker et al., 2002) and PNU-166945 which is paclitaxel–HPMA conjugate (Meerum Terwogt et al., 2001) are other examples of the same category. Several PEG–drug conjugates have reached clinical trials as well as market [reviewed by Kolate et al. (2014)]. CT-2103 (a.k.a. paclitaxel polyglumex or XYOTEX) is a

Table 8.3 Physicochemical and Biological Properties of Some Proteins Used for Development of Protein–Drug Conjugates.

Protein	MW (Da)	Hydrodynamic Diameter (nm)	Biological $t_{1/2}$
Fibrinogen	34,000	21.9	39.5 h
Albumin	66,500	7.2	15–20 day
Hemoglobin A	65,000	6.36	120 day
Transferrin	80,000	7.4	7–10 day
Immunoglobulins	150,000	10.6	7 to >20 day
Immunoglobulins	950,000	25.3	5–8 day
Gelatin	Variable	25–200	>5 h for 90 kDa

conjugate of paclitaxel to biodegradable polymer polyglutamate which has shown activity against several cancers (Zhao et al., 2018) and promising results in nonsmall cell lung cancer in Phase III studies (Langer et al., 2008).

PDCs: PDCs are essentially part of the polymer–drug conjugates as they have the same rational of development (Vhora et al., 2015). Protein binding, especially albumin binding, has been a well-known phenomenon which affects disposition of drugs after systemic administration. And as described earlier, proteins with certain MW longer circulation half-lives which increase their residence in blood and, hence, their conjugation with drugs was primarily designed to improve their residence in blood (Matsumura and Maeda, 1986). List of proteins that has certain physicochemical and biological properties for preferred use in development of PDCs are listed in Table 8.3. This led to advancement of an array of the so-called PDCs (more than 25 ADCs and more than five other PDCs) to reach clinical trials (Vhora et al., 2015). Most of the PDCs have been designed for cancer delivery because of a number of reasons including (1) cancer cells higher protein uptake to meet amino acids' demand to meet their uncontrolled growth, (2) longer residence in blood provides higher exposure to cancer tissue, (3) tumors' leaky vasculature which can have gaps as large as 1200 nm that allow interstitial accumulation of large macromolecules in tumor (Hobbs et al., 1998; Yuan et al., 1995; Noguchi et al., 1998), (4) tumors' inefficient lymphatic system that leads to poor drainage of large macromolecules which along with leaky vasculature provide EPR effect (Maeda et al., 2000), (5) normal tissues' nonsinusoidal vasculature with pore sizes of <12 nm (sometimes even around 1 nm) prevent these macromolecules from entering normal tissue preventing toxicity (Sarin, 2010).

8.7 SUMMARY

Polymeric drug delivery has grown tremendously in preceding two decades with increasingly biocompatible and biodegradable polymers being tested in animal and human trials for their drug delivery applications. Also, newer formulation strategies and manufacturing processes allow the development of wide range of delivery systems for delivery of small molecules, protein, and peptides as well as genetic drugs such as siRNA and mRNA. Biodegradable polymer-based LAIs are advancing at tremendous pace leading to more patient-friendly drug delivery systems. Also,

biodegradable polymers are playing a vital role in the growth of intravenously administered drug delivery systems in the form of nanoparticles, polymer−drug conjugates, and PDCs. Current growth in polymeric drug delivery systems requires thorough evaluations for safety and efficacy and overcoming unforeseen challenges. With adequate use of available tools and technologies, polymeric parenteral drug delivery systems will surely evolve to reduce healthcare burden, providing cheap and easy access medications to patients.

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