Implantable Drug Delivery Systems
Engineering Polymer Systems for Improved Drug Delivery
Luis Solorio, Angela Carlson, Haoyan Zhou, Agata A. Exner, Pages: 189–225, 2014
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# PART III

# IMPLANTABLE POLYMERIC DRUG DELIVERY SYSTEMS

# 7

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Luis Solorio, Angela Carlson,
Haoyan Zhou, and Agata A. Exner

*Department of Radiology, Case Western Reserve University, Cleveland, OH, USA*

## 7.1 INTRODUCTION

Delivery of therapeutics to their intended site of action is a complex process filled with numerous barriers. As described in the previous sections, polymeric platforms currently under development for intravenous (IV) delivery help achieve therapeutic drug levels at the target site by protecting agents in micro or nano-constructs. These constructs, in turn, can be manipulated by numerous techniques to be target specific, capable of stimulus-triggered release, detected by various imaging modalities and used for concurrent diagnosis and therapy. Despite the most sophisticated modifications, all of these systems are nonetheless susceptible to the unrelenting transport issues associated with IV administration. Particularly when the therapy objective is site specific, IV administration results in systemic distribution and then refocusing of the delivery to the target site. While this strategy has numerous benefits, in some instances an alternative approach, that at the outset concentrates the therapeutic at the local site, can be of considerable advantage.

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Implantable polymeric systems provide a platform for site-specific therapeutic delivery. In stark contrast to IV delivery, implantable systems are designed to be loaded with a high concentration of the therapeutic agent and implanted at a site only once to deliver a specified level of drug over an extended period of time. The fundamental concept underlying this approach is referred to by many as "controlled drug release." In essence, the implantable formulations, constructed of either degradable or nondegradable polymers, are able to modulate, through a wide range of parameters, the rate of released drug(s) for a period of hours, weeks, or months. Why is this of interest? The primary reason is patient compliance. This may seem like a simplistic goal, but at the core, a therapeutic agent needs to be administered at regular increments in order to keep its plasma concentration within the therapeutic window. If administration is frequent (as often is the case with labile proteins, for example) and requires multiple injections, patient compliance will undoubtedly decrease. Hence, the idea of loading an implant with a drug, placing it into a site and removing the patient from the equation, should improve the overall effectiveness of any number of agents. Such implants have been utilized clinically for decades providing long-term delivery of contraceptives, hormones, and other therapeutic agents.

In addition to improving patient compliance, implantable delivery systems have also been investigated as a means of local drug administration with the primary goal of maximizing drug concentrations in the immediate vicinity of the implants, while reducing systemic drug exposure to minimize unwanted side effects associated with the drug. This is of particular interest in administration of agents with an extremely narrow therapeutic window. The main applications of such devices have been in the treatment of solid tumors with potent anticancer agents, drug eluting stents for reduction of restenosis, and delivery of antibiotics for treatment of periodontal disease.

In this chapter, we discuss the application of polymeric implants in delivery of therapeutics. The following sections outline the role of both nondegradable and degradable implants in systemic and local drug delivery. We expound on the concepts behind controlled release and discuss specific examples of each system that are already utilized in the clinic. We first discuss the application of nonbiodegradable polymers such as silicone and poly(ethylene-vinyl acetate) copolymers in surgically implantable devices. We examine the differences between reservoir devices, where the drug is entrapped within a polymer membrane, and matrix devices, where the drug is distributed throughout the polymer network, and introduce the mathematical models describing drug release profiles from these implants. We also examine specific properties of implants affecting release rate (eg., membrane porosity, pore/mesh size of polymer network, affinity of drug to polymer), and the advantages and disadvantages of this approach. The second part of this chapter discusses implants formulated with biodegradable polymers. We review the formulation techniques, polymer degradation mechanisms, and how these impact implant performance and drug release, and additional factors influencing drug release. Two types of formulations, namely, implantable and injectable, are discussed along with pertinent concepts and case studies. Finally we discuss the relevant challenges associated with these types of implants and provide an overview of the future cutting-edge research directions currently underway in this exciting field.

## 7.2 NONDEGRADABLE POLYMERIC IMPLANTS

Early attempts at the temporal control of drug administration included tablet coatings that slowly dissolve, suspensions (solid insoluble drugs in a liquid vehicle), as well as emulsions (immiscible liquids combined to form a liquid drug in a liquid vehicle) [1]. Not until the 1960s did the concept of using nondegradable implants for sustained release of therapeutic agents become popular [1–3]. Nondegradable polymers were used because they are relatively inert and biocompatible while offering a simple means of controlling the release via diffusion through a semipermeable matrix [2, 3]. Judah Folkman first proposed that silicone capsules could be used as a drug carrier for a zero order release system due to the constant non-degrading matrix composition and fixed geometry [4]. Silicone has many advantages, for use as a drug eluting polymer depot, in that it is relatively inert, flexible, easily modified, and provides almost constant, linear release of the loaded drug. Modifications can be achieved by adjusting the degree of cross-linking which allows researchers to create tunable periods of controlled long-term drug release [5]. Silicone has been used in several commercially available contraceptive implants such as Norplant® (Leiras, Helsinki, Finland) and Jadelle® (Schering Oy, Berlin, Germany) [2]. Additionally, silicone has been used to deliver antibacterial drugs such as metronidazole and invermectin [6, 7] as well as chemotherapeutic drugs such as carmustine [8, 9].

Another nondegradable polymer commonly used for controlled release applications is poly(ethylene-*co*-vinyl acetate) or EVAc. EVAc is typically used as a drug eluting matrix and can deliver a range of therapeutics from proteins to low molecular weight (Mw) drugs [10, 11]. Clinically, this system has been employed to deliver the drug pilocarpine in order to treat glaucoma (Ocusert®, Johnson and Johnson—formerly Alza Corp.) [12]. EVAc is also used in contraception applications, delivering the hormone etonogestrel from an implantable rod commercially known as IMPLANON® (Organon, Oss Netherlands) [2]. While polydimethylsiloxane (PDMS) and EVAc are two of the most widely used nondegradable polymers in the field of drug delivery, several other polymer systems have been developed over the years. Polyvinyl alcohol (PVA) mixed with ethyl vinyl acetate (EVA) is utilized in Vitrasert (Bausch and Lomb, Rochester, NY), a commercial implant that delivers genciclovir into the eye to control cytomegalovirus retinitis common in AIDS patients [13]. Polyurethane is utilized not only as a covering for silicone breast implants but has also been used as an antibacterial coating for implants [14, 15].

### 7.2.1 Reservoir Versus Matrix Drug Delivery Systems

As introduced briefly in Chapter 1, most implantable controlled delivery systems can be classified into one of two structure categories: reservoir or matrix systems. Reservoir systems are defined as formulations in which the polymer is used to form a hollow membrane casing that encapsulates a drug reservoir (Fig. 7.1) [5, 16, 17]. In a reservoir system a drug does not need to be dissolved to be loaded into the implant, just encased within the device. One drawback for these release vehicles is that the sole driving force of release is diffusion, and as such the larger the drug is, the slower the

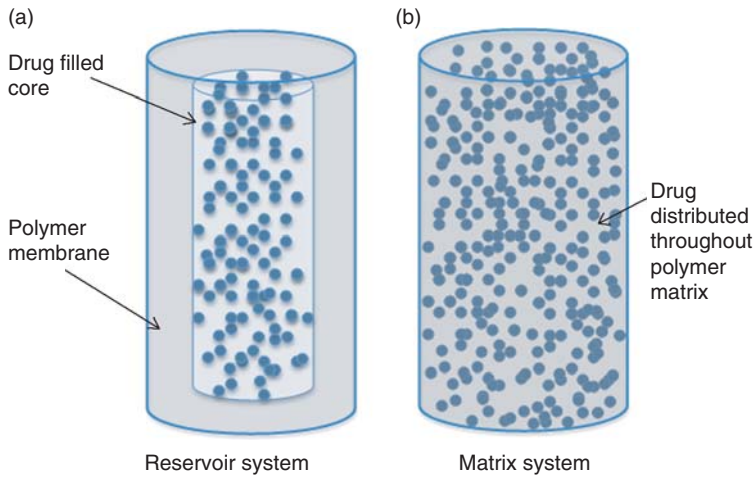


Figure 7.1. Schematic representation of a reservoir system (a) and matrix system (b).

release rate will be. Additionally, if the membrane of the implant is ruptured, a bolus release of drug may occur, which could be fatal for the patient [5, 18]. A common example of a reservoir system is the Norplant silicone contraceptive implant. Release from a reservoir system is driven by diffusion through a number of barriers. First the drug must travel through the polymer membrane, then through the tissue surrounding the implant and finally into the blood stream. Release from a reservoir system can be modeled using Fick's first law (Eq. 7.1) [19]:

$$J = -D_{\mathrm{d:p}} \frac{\mathrm{d}c}{\mathrm{d}x} \tag{7.1}$$

where $J$ is the flux of the drug, $D_{\mathrm{d:p}}$ is the diffusion coefficient of drug through the polymer and $\mathrm{d}c/\mathrm{d}x$ is the concentration gradient of the drug through the membrane [19]. This equation assumes that diffusion is one-dimensional, the diffusion coefficient is constant and the concentration gradient of drug through the membrane is relatively constant which is plausible only if there is a constant high concentration of drug at the membrane's inner edge [19]. To describe how diffusion changes the drug concentration over time, Fick's first law can be combined with a mass balance equation to derive Fick's second law (Eq. 7.2) [5].

$$\frac{\partial c}{\partial t} = D_{\mathrm{d:p}} \frac{\partial^2 c_{\mathrm{p}}}{\partial x^2} \tag{7.2}$$

where $D_{\mathrm{d:p}}$ is the diffusion coefficient of drug through the polymer, $c_{\mathrm{p}}$ is the concentration of the drug in the matrix, $t$ is time, and $x$ represents the spatial coordinate system of the drug within the matrix. This equation assumes that the drug diffuses into an infinite sink condition, that the implant is a flat plane, and that there is no convection, generation, or consumption of drug within the reservoir. With these assumptions,

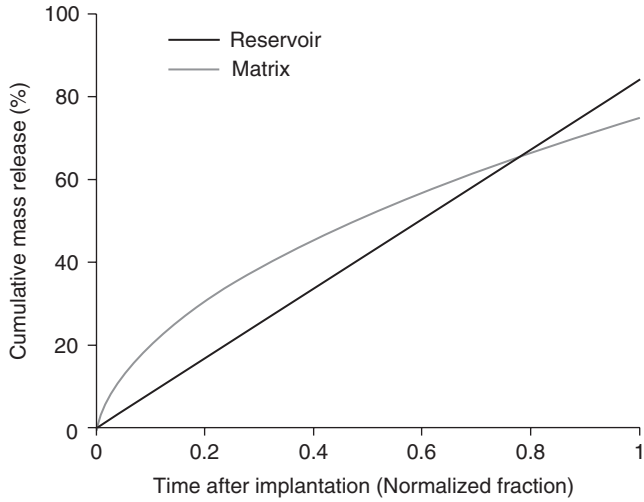


Figure 7.2. Comparison of the release profile from a matrix and reservoir implant.

release from a reservoir system is relatively linear (zero-order) as modeled in Fig. 7.2 [8, 20, 21]. Fick's second law can be modified to describe a spherical or cylindrical implant by changing the coordinate system of the equation.

A matrix based device can be described as a system in which the drug is distributed homogenously (in an ideal scenario) throughout the polymer [5]. This type of drug delivery system is often utilized when the desired drug release rate cannot be controlled sufficiently by use of a biocompatible polymer membrane [22]. The typical release profile from a matrix based implantable device follows first-order kinetics if the matrix is assumed to not swell or degrade [23, 24]. First there is an initial burst release of drug, followed by a slower release until equilibrium is reached (Fig. 7.2). One of the biggest advantages of matrix systems relative to reservoir systems is that there is no hazard of a bolus release of the drug, unless the entire system is damaged. However, one drawback of the release kinetics observed with matrix systems is that the release rate decreases over time [16, 22]. While zero-order release is ideal in many applications, for certain drugs such as leuprolide acetate (which is used to treat prostate cancer), a zero-order release profile would not be adequate. For an effective treatment, this therapy requires a high initial dose of drug followed by a lower maintenance dose [25]. Thus, the first-order release observed in a matrix delivery system can be beneficial.

Park et al. [23] derived an approximate equation to model release at the early stages of a planar non-swelling matrix implant from Fick's second law (Eq. 7.3):

$$\frac{M_t}{M_\infty} \cong 4\left(\frac{D_{d:p}t}{L^2\pi}\right)^2 \tag{7.3}$$

where $M_t$ is the amount of drug inside the matrix over time, $M_\infty$ is the total amount of drug in the matrix initially (and it is assumed that $M_t/M_\infty$ is less than 60%), $D_{d:p}$ is the diffusion coefficient of drug through the polymer, $t$ is time, and $L$ is the length of the implant through which the drug must diffuse [23, 26]. This equation assumes that there is no change in the dimensions or degradation of the implant during the time of release [26]. Further modification of Fick's second law from Equation 7.3 can approximate release from a nonswelling matrix at the end of the release period ($0.4 \leq M_t/M_\infty \leq 1$) (Eq. 7.4) [27].

$$\frac{M_t}{M_\infty} \cong 1 - \left(\frac{8}{\pi^2}\right) \exp\left[\frac{\left(-\pi^2 D_{d:p} t\right)}{L^2}\right] \tag{7.4}$$

There are advantages and disadvantages to both the reservoir and matrix implant designs. Ultimately, the desired release profile will dictate which design can be used.

### 7.2.2 Factors Affecting Release from Nonbiodegradable Polymer Implants

Unlike the preformed degradable or *in situ* forming implants discussed later in this chapter, nondegradable implants have a fixed geometry and will not degrade or erode once placed within the body. Therefore, the number of factors affecting the release of the preloaded drug from these implants can be reduced to factors that alter the concentration of drug outside of the implant (which are discussed in detail later in this chapter) and factors that affect the diffusivity of the drug through the matrix such as (i) the size of the pore in the polymer membrane or matrix, (ii) the degree of pore connectivity and tortuosity within the matrix, (iii) the distribution of drug throughout the implant, and (iv) and the affinity of the drug for the polymer [8, 28].

The release from a nondegradable reservoir polymer implant system is primarily dependent on the size of the polymer's pores with respect to the size of the drug that will diffuse through them. Studies have shown that a macroporous polymer (0.1–1 μm) has pores much larger than the loaded drug, and will therefore have greater release over time. Microporous polymers (5–20 nm) release less drug because the pore size is often only slightly larger than the drug molecule, which reduces mass transport [24]. If the drug is larger than the pores, the drug will not diffuse out through the interconnected porous network (which have high diffusivity coefficients), but instead the drug must diffuse through the polymer rich domains (which has diffusivity coefficients that are orders of magnitude smaller) [18, 24, 29].

All reservoir and matrix implants can be considered to be a collection of interconnected pores and the degree of interconnectivity of these pores plays a large role in the release of drug from the preloaded matrix implant. If there are several pathways for the drug to diffuse through, a larger concentration of drug can be released over time from the implant (Fig. 7.3). Additionally, the tortuosity of the pores can play a role in altering drug release. Tortuosity is a measure of how twisted and curved the porous network is [30]. Much like traveling cross country, it is always better to

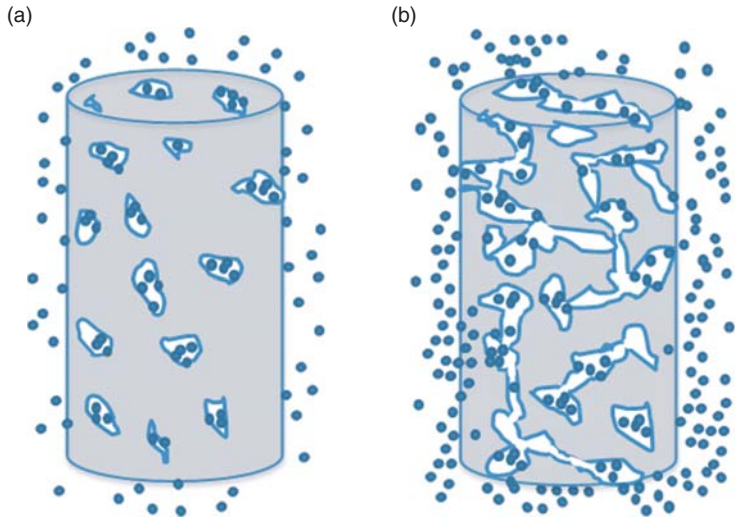


Figure 7.3. (a, b) Schematic showing the effect of increased pore interconnectivity on drug release.

fly direct. The more tortuous the path, the longer it takes for the drug to reach its destination outside of the implant [10, 30].

The fraction of drug that is dissolved at any time during the implant lifetime also plays a role in release. In both reservoir and matrix systems there is a direct relationship between drug solubility in the surrounding interstitial fluid of the implantation environment and drug concentration in a dry implant. The higher the drug solubility the faster the release as only dissolved drug is available for diffusion [8, 20, 31, 32]. Distribution of drug throughout the implant matrix can also be a factor in the release profile with homogenous distribution at a low loading density contributing to lower immediate burst release [8, 19, 24].

Another factor that can affect the release of drug from a nondegradable implant is the affinity between the drug and the polymer. The degree of drug hydrophobicity with respect to the polymer will determine whether hydrophobic interactions will counteract or further facilitate the diffusional movement. A hydrophilic drug encapsulated within a hydrophobic polymer will diffuse out rapidly while a hydrophobic drug within a hydrophobic polymer will diffuse out more slowly because of its lack of affinity with the physiological hydrophilic environment surrounding the implant [5]. Drugs may also interact and bind with functional groups on the polymers which will decrease the overall release from the implant. One of the assumptions of purely diffusional release is that the drug is free to move randomly throughout the system and if the drug interacts and binds with polymer functional groups, that free random movement is limited resulting in overall slower release [1, 24]. Release from nondegradable

implants can be modified by choosing a polymer with the appropriate properties in order to tailor the release profile to fit the desired application.

### 7.2.3 Clinical Example and Summary

One of the first and most commercially successful controlled release devices was Norplant, a female contraceptive implant developed in the 1970s [2, 33]. Norplant was successful because it was more effective in preventing pregnancy for a longer duration than any other contraceptive available at the time. The platform was composed of six flexible, silicone cylinders that released a synthetic hormone called levonorgestrel for effective contraception for up to 5 years [33, 34]. Norplant was a reservoir drug delivery system with a very slow, constant release rate; the capsules release 50 μg of levonorgestrel per day for the first 400 days after implantation, followed by a relatively steady release of 30 μg/day for the next 3000 days (or ∼8.5 years) [33]. Norplant was typically implanted in a fan-like configuration in the subderma of the patient's upper arm in a minimally invasive outpatient procedure. The first clinical trials for Norplant began in 1980 and within a few years, it was approved by more than 50 countries [34, 35]. By 1992, Norplant was used by over 600,000 women in the United States alone [34, 35]. Post implantation, trials encompassing thousands of women over a ten year period were conducted in which the safety, efficacy, and release from Norplant were scrutinized. Low percentages of women receiving Norplant complained of headaches and weight gain because of the continued use of the hormone. Other more serious complaints such as hair loss, hypertension, uterine fibroids, and breast cancer were reported in less than 1% of the thousands of women surveyed [36, 37]. The most frequent complication seen with Norplant was the difficulty with which the implants were removed. Owing to the long implantation period, fibrous tissue occasionally formed in the area of the implants, making removal difficult. The removal procedures could also be painful and result in incomplete removal because of implant fracture and/or scarring in the area. In extreme cases, sonography was used to determine the exact location of the remaining rod [38]. The difficulty of implant removal seen with the Norplant rods is a common drawback of nondegradable implants.

While synthetic, nondegradable implants are still in use today, a large majority of the research and upcoming clinical applications revolve around the use of biodegradable polymers. This transition is a result of increased control over the release profile, as well as a reduction in possible complications and the number of required procedures, as removal is no longer necessary [1, 8, 11].

## 7.3 BIODEGRADABLE POLYMERIC IMPLANTS

Biodegradable polymeric implants provide a useful means of controlled drug release without the need for the surgical removal of the implants after their expiration. While degradation results in more complicated implant design, these systems can provide additional, more flexible avenues by which dissolution of drug can be modulated. In this section, we describe the process of drug release from preformed polymer implants

and *in situ* forming systems along with the factors that influence implant performance. The mechanisms of polymer degradation and erosion and the factors that influence or alter both processes are discussed. We are also review factors that affect implant-host interactions with the most common biodegradable polymers found in Food and Drug Administration (FDA) approved devices, and provide an overview of clinical applications using these polymers.

### 7.3.1 Degradation and Erosion

While a specific polymer cannot be approved by the FDA, there are five polymers commonly found in FDA approved devices that have demonstrated an appropriate host tissue response for their designated applications (Fig. 7.4). The polyetherester polydioxanone has been approved for use as suture clips and bone pins marketed as OrthoSorb [17]. The slow degrading semicrystalline poly(caprolactone) has been used for the controlled release of contraceptives and as a suture formerly marketed as Capronor and monocryl [17, 39]. Poly(PCPP-SA anhydride) has been used in the field of drug delivery in order to treat residual tumor cells after surgical resection and are marketed as the Gliadel Wafer® [5, 17, 40]. Finally, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymer (PLGA) have been used as degradable sutures, bone pins, and drug delivery vehicles marketed as the Leupron depot, Atrigel, Eligard, Atridox, Dexon, and Vicryl [17, 25, 41–45].

Biodegradable implants lose mass over time as a function of polymer degradation and erosion. Polymer degradation refers to the process by which the repeating structural units of the polymer chain are cleaved resulting in a reduction in Mw (Fig. 7.5). This can be facilitated by a number of factors [5, 46, 47]. For example,

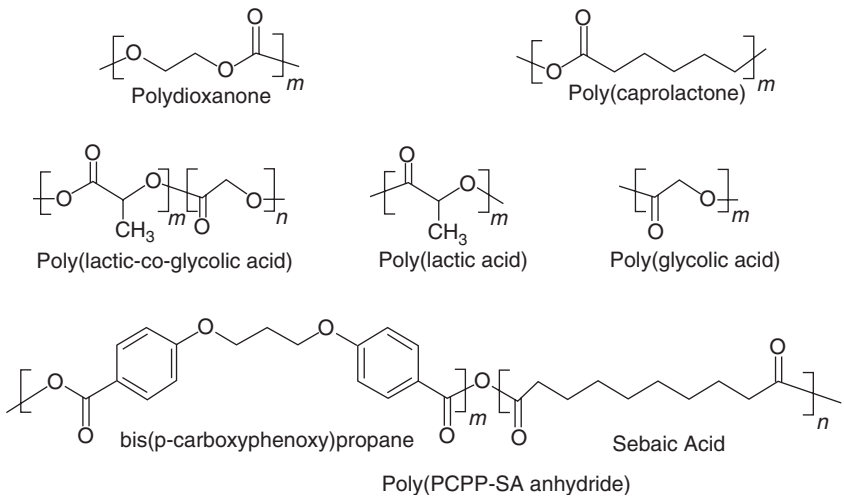


Figure 7.4. Chemical structures of the polymers commonly used in FDA approved devices.

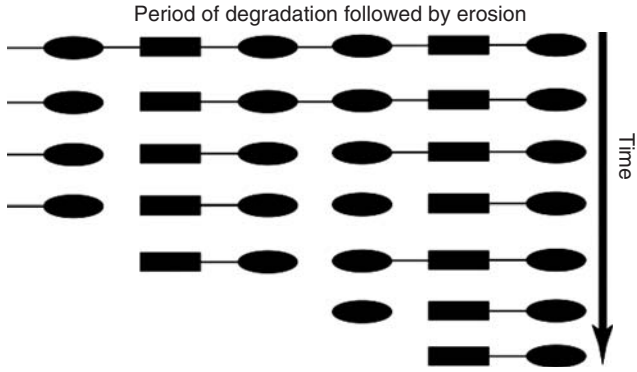


Figure 7.5. Schematic of the degradation and erosion process, where the ellipses and squares represent the subunits of the polymer backbone, and the lines represent the degradable bonds. The top row is the nondegraded polymer. The loss of the lines represents the degradation process while the loss of subunits over time represents erosion after degradation has occurred.

enzymes can catalyze the polymer degradation process which is sometimes referred to as biodegradation. Polymer degradation can also be initiated by external factors such as the presence of UV light, mechanical perturbation, as well as $\gamma$-radiation, which is used to sterilize the polymers for clinical applications [46]. For drug delivery purposes, the most common method of degradation occurs through hydrolysis (occurring in both polyesters and polyanhydrides), which is the cleavage of the polymer backbone because of the interactions of the polymer with water [46–48].

After the polymer begins to degrade, the loss of the oligomers and monomers to the surrounding environment facilitates a reduction of polymer mass, and is known as erosion [5, 17, 46, 47, 49]. When erosion is enhanced by physiological processes, it is referred to as bioerosion [5]. As erosion is simply the loss of mass over time, it does not always require degradative processes in order to occur. In the case of a matrix containing water-soluble components, erosion can occur simply through dissolution of the matrix [5], such as a cookie crumbling in milk or a bar of soap reducing in size with use. Erosion is a process that can occur solely on the surface of the implant through a process known as surface erosion (which is the case in the soap example), or throughout the bulk of the polymer, which is then referred to as bulk erosion, as in the cookie example (Fig. 7.6). The primary factor that determines whether the polymer will be surface eroding or bulk eroding is the reaction kinetics of degradation. If the rate of polymer degradation is faster than the rate of water diffusion into the polymer, then the polymer will be surface eroding. If the rate of water diffusion is faster than the reaction kinetics, then the polymer will be bulk eroding [50].

It is the presence of hydrolysable bonds in the polymer backbone that allows for tunable degradation and erosion profiles; therefore, the choice of chemical bond is a critical factor in controlling the rate of degradation and the method by which the polymer will erode. The three most common chemical bonds found in controlled

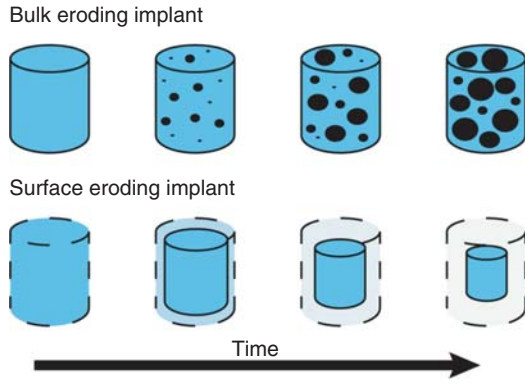


Figure 7.6. Schematic illustrating the difference between bulk and surface erosion.

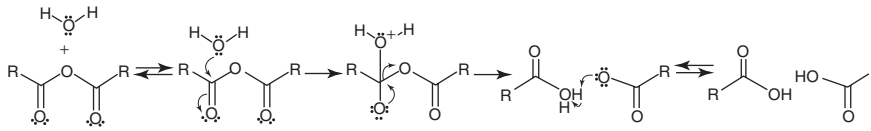

Figure 7.7. Anhydride reaction with water; arrows represent the movement of electrons.

release devices listed in order of reactivity are: anhydrides, esters, and amides [46, 51]. While both esters and amides require either acidic or basic conditions in order for hydrolysis to occur, the reactivity of anhydrides is high enough that hydrolysis occurs under neutral conditions, only requiring the presence of moisture in the air to initiate degradation [51, 52]. The reaction begins when the oxygen of water acts as a nucleophile, and attacks one of the anhydride carbonyls, which leads to the elimination of one carboxylic acid and the formation of a second (Fig. 7.7).

As esters are less reactive than anhydrides, an acidic or alkaline environment is needed for their hydrolysis. When the hydrolysis is acid-catalyzed, the reaction is a reversible process, requiring the presence of excess water or removal of degradation by-product [51, 52]. The two stage reaction begins when a free hydrogen cation associates with the carbonyl, which allows water to act as a nucleophile, forming a tetrahedral intermediate that facilitates the alcohol to act as a leaving group (Fig. 7.8) [52]. When the reaction occurs in an alkaline environment, free hydroxyl anions act as a nuclophile. The nucleophilic attack leads to the formation of a tetrahedral intermediate causing the elimination of an alcohol. Like acid-catalyzed hydrolysis, this reaction leads to the formation of a carboxylic acid and an alcohol, but it is not an equilibrium reaction and will continue until the polymer has completely degraded. The hydrolysis of amides is similar to esters and can occur in either alkaline or acidic environments. However, because the bond is less reactive than an ester linkage, stronger conditions are required in order for hydrolysis to occur [51, 52]. Both ester

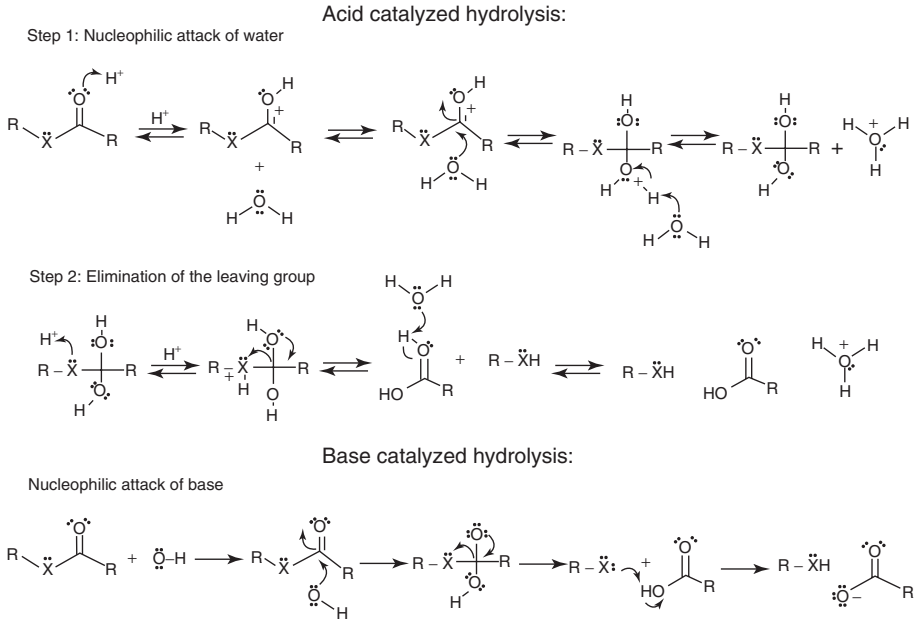


Figure 7.8. (a) Hydrolysis of an ester in an acidic and alkaline medium resulting in the formation of an alcohol and carboxylic acid, arrows represent the movement of electrons. (b) Hydrolysis of an amide in an acidic medium resulting in the formation of an alcohol and amine, arrows represent the movement of electrons.

hydrolysis and amide hydrolysis leads to the formation of a carboxylic acid, but unlike ester hydrolysis the eliminated group from amide hydrolysis is an amine (Fig. 7.8).

While the chemical bond used to form the polymer backbone is an important factor in controlling the rate of polymer degradation, the groups adjacent to the reactive bond can also be important factors. For example, the methyl group found on PLA, leads to a slower degradation rate than what is observed in PGA because of the presence of the hydrophobic moiety, which sterically hinders the nucleophilic attack of water [46, 53, 54]. As the erosion profile of a polymer is sensitive to both the rate of degradation as well as the rate of water uptake, parameters that decrease the influx of water can be used to alter the erosion profile of the implant. Therefore, the polymer hydrophobicity is an important parameter in controlling whether the polymer will be a surface or bulk eroding polymer.

Crystallinity is a measure of the polymer ability to form a structured array, which occurs as a result of the chain regularity, and is typically reported as a percentage of crystallinity [55]. Owing to the close packing inherent in crystalline domains, the free volume for diffusion is lower in the crystalline regions, which can decrease diffusion coefficients by several orders of magnitude and play a role in altering the rate of polymer degradation [48, 56]. Owing to the random nature of polymers, there will always be amorphous domains such that a polymer can never be purely

crystalline [17]. Crystalline domains can be present initially, or can form as a result of oligomer formation caused by polymer degradation, leading to latent crystallization [46, 56, 57].

In addition to polymer crystallinity, the glass transition temperature ($T_g$) has been shown to play a role in altering the free volume available for diffusion. The $T_g$ is the temperature at which the polymer transitions from a glassy state into a rubbery state. When a polymer is above the glass transition temperature, the free volume is higher, which results in an increased diffusivity [56]. Even the physical dimensions of the polymer can be used to transition a system from bulk eroding to surface eroding [50]. For systems that have low water absorption and rapid degradation kinetics, the implants would have to be extremely small in order to behave as a bulk eroding system. For example a poly(anhydride) disk would need to be smaller than 75 μm thick in order to behave as a bulk eroding system [50]. Conversely, polymer disks that rapidly absorb water with slow degradation kinetics would have to be significantly thicker to behave as a surface eroding system. A poly($\alpha$-hydroxy-ester) would need to be at least 7.4 cm thick to surface erode, while a poly(amide) which is even less reactive would need to be at least 13.4 m thick [50].

### 7.3.2 Biocompatibility

With the insertion of any material into the body, understanding how the host and implant will interact is imperative. Biocompatibility describes the ability of an implanted material to maintain performance without initiating a negative host response [17, 58, 59]. Biocompatibility is often evaluated based on the inflammatory and healing responses of the body to a particular implant [58]. The tissue response continuum, as explained by Anderson et al. [58] organizes the host response to implantation into a sequence of events characterized by the cell types which are present. Phase I, or the acute and chronic inflammatory phase occurs over the course of the first two weeks, and is initiated by the implantation or direct injection of the device. During phase I, neutrophils, monocytes, and lymphocytes will be present with monocytes becoming the dominant cell type within days of implantation. Phase II is characterized by an excess of monocytes and macrophages, leading to the development of a fibrous capsule around the implant. The duration of the second phase is determined by the rate of polymer degradation, and can take as little as 50 days or more than 400 days [58, 60–63]. Phase III is dominated by the degradation of polymer and an increase of fibrous tissue filling the void left behind by the eroding polymer [58]. Histological evaluation of the tissue response has proven useful in categorizing the effect of introducing an implant to the local environment.

One major concern when using a degradable device is the toxicity of the degradation by-products. In the case of PLA, PGA, and their copolymer PLGA, the polymer was designed to degrade into natural metabolites. The hydrolytic degradation of these polyesters results in the formation of lactic and/or glycolic acid, based on the original polymer used [59, 64, 65]. In healthy tissues with high clearance, these intermediates are metabolized by the body into carbon dioxide and water and show no adverse

effects on introduction of the material to the body [66]. However, in situations where the clearance is low, which may occur as a result of a diseased state or be a function of injection site with low metabolism and overall clearance, the effect of elevated levels of acidic by-products must be considered. Therefore, the clearance rate of these compounds is an important parameter in implant design.

Other factors to consider when evaluating biocompatibility of a device are additives such as fillers, plasticizers, stabilizers, and excipients. Additives are typically used to modify an implant's properties and to reduce manufacturing costs [67]. For example, fillers and plasticizers are typically used to alter the mechanical properties of the implants and even used to change the outer membrane behavior of some pills [67–75]. The plasticizer di(2-ethylhexyl)phthalate (DEHP) has been used to soften the poly(vinyl chloride) polymer used to make blood storage bags since 1955 [73, 74]. Plasticizers typically increase the flexibility of the plastic by disrupting the crystallinity of the polymer, and increasing the free volume of the material, which lowers the glass transition temperature of the material [76]. Fillers such as carbon black and silica have been used to reinforce the mechanical properties of polymeric devices. The interaction of fillers with the polymer matrix is complex, and reinforcement is not a result of a single interaction [67]. One way in which the fillers can reinforce polymers is by forming a network (when the filler concentration is above the percolation threshold) within a material that provides additional mechanical support [70, 71, 77], and second by interacting with the polymer which alters the chain mobility of the polymer [70, 72, 77]. Other common additives such as stabilizers are used to protect the degradable units within a polymer backbone. Common examples of stabilizers include antioxidants such as vitamin E which has been used to reduce oxidative stress that degrades the amorphous domains in poly(etherurethanes), which are commonly used in medical devices [78]. Excipients are additives which are used to improve drug solubility and biodistribution, but are completely inert in the host, such as cyclodextran [79, 80]. These ring shaped molecules have two distinct domains, a hydrophobic interior and a hydrophilic exterior [79]. When put in contact with poorly soluble drugs (such as doxorubicin), the drug interacts with the interior domain, and the hydrophilic exterior interacts with the aqueous environment leading to improved drug solubility [79].

Some additives not only alter implant behavior, but also have desirable therapeutic properties. For example, the use of a triblock copolymer Pluronic® has been shown to reduce the diffusivity of drug from polymer implants, but these additives have also been shown to inhibit a cell's ability to recover from heat, sensitizing the cell to elevated temperatures [81–85]. Therefore, the effect of additives used must be carefully evaluated to insure that the additive does not induce a negative effect.

### 7.3.3 Implantable Systems

Drug eluting depots provide a unique way in which plasma concentrations of the delivered therapeutic can be maintained within a narrow window as well as providing a means for achieving elevated local concentrations of drug while limiting systemic involvement [82, 86]. In addition to improving patient compliance, controlling drug release via implantable systems can reduce systemic side effects and patient

discomfort [9, 25, 82, 87, 88]. Pre-formed polymer implants have a defined geometric structure, which leads to predictable and reproducible release and degradation profiles for extended periods of time. The therapeutic agent can be trapped homogenously within the encapsulating matrix or formed as a composite for more complex release profiles [82]. While both degradable and nondegradable implants are dependent on the properties of the encapsulating polymer matrix, as the implants degrade over time there is no need for surgical removal [5, 9, 82, 87, 88].

Fabrication of preformed polymer implants can be achieved using a number of techniques including: compression molding, melt casting, solvent casting, and extrusion [9, 81, 86]. Implants fabricated using compression molding are made by first mixing the polymer and drug in a piston shaped mold, then applying elevated pressure at 5–10 °C above $T_g$ to create disk or rod shaped implants [86, 89, 90]. The low fabrication temperature is beneficial for maintaining activity of reactive drugs, since the drug may not be homogenously distributed, there can be a large variability in drug release [86]. Implants formed using melt molding require that the polymer is elevated above $T_m$, resulting in a viscous solution in which the drug can be homogenously mixed and subsequently solidified in a mold of the desired geometry [86]. The fabricated implant has a reproducible release profile, but the elevated temperature can result in a loss of therapeutic activity if the drug is sensitive to temperature, especially when proteins are used as therapeutics [86]. Solvent casting is performed by dissolving the polymer in a volatile solvent, with drug if the drug is soluble. If the drug is nonsoluble then the powdered drug is homogenously distributed into the polymer solution. The solution can then be added to a mold of the desired geometry and maintained at a lowered temperature so that the solvent will evaporate off slowly [86]. Solvent casting provides a technique with which to fabricate implants loaded with heat sensitive drugs, but this technique has a number of disadvantages. The phase inversion dynamics intrinsic to solvent evaporation can lead to a porous microstructure, resulting in implants with poor mechanical properties, as well as have the potential to deactivate the therapeutic agent [86]. Additionally, because of the amount of time required for the solvent to evaporate, the suspended drug may not stay homogenously distributed in the matrix [86].

Dual release can be achieved through processes known as dip coating, where the preformed implants are dipped into a polymer solution containing a water soluble component such as NaCl or poly(ethylene oxide) and drug in order to form a thin outer membrane [82, 88, 89]. Once implanted into the tissue, the aqueous environment leads to the dissolution of the soluble component and an initial burst release from the porous outer membrane [82, 89]. Ultimately it is the properties of the drug and the desired application that will dictate the fabrication technique used to make the implant.

Drug release is not only affected by the geometry of the implant; the rate of dissolution can be affected by factors such as the ratio of polymer relative to other components in the implant, how the drug is loaded into the implant, the crystallinity of the polymer, the crystallinity of the drug, as well as implant microstructure [16, 46, 49, 56, 57, 86, 91–94].

Percolation theory provides an ideal means by which the effect of drug loading can be evaluated on implant behavior. In percolation theory the matrix is envisioned

as a lattice of interconnected points, and the introduction of drug removes a point from the lattice. Initially, the reduction of points in the lattice does not overly disrupt the lattice stability, but as the number of points in the lattice continue to disappear so does the stability of the system. The critical point at which the polymer no longer forms a connected network, is referred to as the percolation threshold [47, 95, 96]. In addition to the percolation threshold, polymer crystallinity can play a role as to where the drug partitions within the system [57, 92]. Typically drug diffuses through the implant pores; therefore, high interconnectivity leads to elevated release.

Similar to nondegradable systems, factors such as the size of the drug diffusing through the polymer network, the affinity of the drug with the polymer, and the tortuosity of the porous network all influence release from the implant [5]. The key difference is that diffusivity of degrading implant systems change as a function of polymer degradation. Simple models of release for bulk eroding systems assume that polymer degradation follows first-order kinetics, leading to an exponential increase in diffusion with respect to time [56].

$$\frac{\mathrm{d[COOH]}}{\mathrm{d}t} = k[\mathrm{COOH}][\mathrm{H_2O}][\mathrm{Ester}] \tag{7.5}$$

$$D_{\mathrm{eff}} = D_0 \mathrm{e}^{kt} \tag{7.6}$$

$$\frac{\partial c}{\partial t} = D_{\mathrm{eff}} \frac{\partial^2 c_{\mathrm{d}}}{\partial x^2} \tag{7.7}$$

In Eqs. 7.5 and 7.6, [COOH] refers to the concentration of carboxylic acid, [$H_2O$] refers to the concentration of water, [Ester] refers to the total concentration of degradable esters, $k$ is the first-order degradation kinetic constant of the polymer, $D_{\mathrm{eff}}$ is the effective diffusivity as a function of the degradation kinetics, $D_0$ is the initial diffusivity at time zero before degradation begins, and $t$ is time [56]. The first-order degradation kinetics can be determined from the changes in polymer Mw over time and makes the simplifying assumption that there is a near constant concentration of both the hydrolysable esters and water [48, 97, 98]. The effective diffusivity coefficient can then be used with the general models of diffusion. The result of degradation is an increase in release over time as the polymer diffusivity changes (Fig. 7.9). For surface eroding systems, release of drug is typically proportional to the rate of polymer erosion [86]. For *in vivo* systems, evaluating drug release is more complex because of the presence of cells and microvascularization in the tissue space [9, 89, 99, 100]. Evaluation of release from these systems requires multidimensional analysis of the implant and surrounding tissue, with careful consideration of the boundary conditions between the implant and tissue interface. For this system, the rate of drug distribution within the surrounding tissue involves investigating the diffusion of drug within the

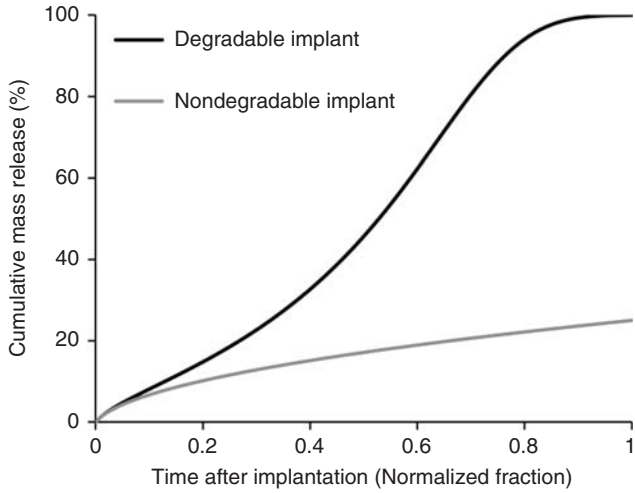


Figure 7.9. Cumulative release over time from a degrading and nondegrading polymer implant.

tissue space from the implant, the elimination of the drug by the vasculature, and the metabolism of the drug by the cells [9, 89, 99, 100].

$$\frac{\partial C}{\partial t} = D\nabla^2 C - v\nabla C - kC \tag{7.8}$$

where $k$ is the rate of drug metabolism, the $v$ accounts for the velocity of the surrounding vasculature, and $D$ is the diffusivity of drug from the implant to the surrounding tissue [9]. A result of diffusion-based local release is that the metabolic activity of the cells and the removal of drug as a function of the microvasculature limits the distribution distance of the drug within the tissue.

### 7.3.4 Clinical Example of Preformed Polymer Implants

Preformed implants have been successfully implemented as a means for adjuvant therapy, most notably in the form of a surface eroding polyanhydride polymer disk that is inserted directly into the resected tissue space and used to treat malignant gliomas [40, 82, 88, 101–103]. These wafers, commercially known as the Gliadel® wafers (MGI Pharma, Inc., Bloomington, USA) received FDA approval in September of 2006 and are currently the only commercially available solid intratumoral chemotherapeutic device [82, 88, 103]. As these devices were approved by the FDA, they have been used in over 20,000 patients in the United States alone [103].

The wafers are composed of a 20:80 molar ratio of poly(bis[*p*-carboxyphenoxy]) propane:sebacic acid (PCPP:SA), and loaded with the lipophilic anticancer drug carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea, or BCNU) [103]. The disks slowly

erode over the course of 2–3 weeks, with degradation by-products eliminated in the urine or as $CO_2$ from the lungs [104]. These implants are fabricated to have a 7.25 mm radius and are 1 mm thick loaded with 3.85 wt% drug, and have an average weight of 200 mg [103]. As many as eight wafers can be implanted into the resected tissue space and are used to treat cancer cells that may not have been removed during the surgical procedure. This reduces the risk of recurrence by eliminating residual cancer cells along the tumor periphery. These implant systems have shown modest success in the treatment of malignant gliomas by increasing the chance of survival up to 50%, and increasing the median survival times by 2 months [105].

### 7.3.5 Injectable Systems

Injectable *in situ* forming implants (ISFIs) are liquid formulations comprised of biodegradable polymers mixed with bioactive therapeutic agents which can be injected into a target tissue. Once in place, the solution forms a solid or semisolid depot from which drugs can be released in a controlled manner. This liquid to solid phase transition takes place in response to a stimulus such as temperature, pH, enzymatic activity, or solvent miscibility. In recent years, ISFIs have garnered increased attention because of their versatility, ease of manufacturing, potential for improved patient compliance, and minimally invasive placement using needles as small as 21-gauge for the implant injection. This is in contrast to preformed implant systems which often require local anesthesia and minimally invasive surgical placement [106]. ISFIs can be divided into five categories based on the mechanism of transition from liquid to solid: (i) thermoplastic pastes, (ii) thermally induced gelling systems, (iii) *in situ* cross-linked systems, (iv) *in situ* solidifying organogels, and (iv) *in situ* precipitating or phase inverting implants [107]. Table 7.1 summarizes each of these categories.

Thermoplastic pastes (or thermopastes) are polymers that can be injected in the molten form and solidify as they cool down to body temperature. These polymers typically have a low melting temperature, ranging from 25 to 65 °C, and have an intrinsic viscosity ranging from 0.05 to 0.8 dl/g (determined and measured at 25 °C) [108]. Common thermopastes include PLA, PGA, PCL, and poly(trimethylene carbonate) [108, 109].

Conversely, thermally induced gelling systems are liquid at room temperature, and form a gel at temperatures above the lower critical solution temperature (LCST). Lower critical phase separation is governed by the balance between hydrophobic and hydrophilic moieties on the polymer chain and is driven by the negative entropy of mixing. The Gibbs free energy change for the mixing of two phases is negative below the LCST and positive above. When temperature increases to the LCST, the hydrogen bonding between polymer and water becomes energetically unfavorable compared to polymer–polymer and water–water interactions. Then an abrupt transition occurs as the hydrated hydrophilic molecule quickly dehydrates and changes to a more hydrophobic structure [110]. A number of polymer modifications can be used to alter the temperature at which this transition occurs [106, 111, 112]. Examples of this system include poly(*N*-isopropyl acrylamide) (poly(NIPAAM)), PEO–PPO–PEO

TABLE 7.1. Summary of *In Situ* Forming Implant (ISFI) Categories

| ISFI Category | Formation and System Requirements | Representative Polymers |
|---|---|---|
| Thermoplastic pastes | Polymers injected in the molten state and form an implant when cooling down to body temperature<br>Low melting temperature of 25–65 °C and an intrinsic viscosity from 0.05 to 0.8 dl/g, at 25 °C are required [108] | poly(D,L-lactide)<br>poly(glycolide)<br>poly(Ɛcaprolactone)<br>poly(trimethylene carbonate)<br>[108, 109] |
| Thermally-induced gels | Temperature is used to control critical phase separation in thermosensitive polymers.<br>Systems are liquid at room temperature, and form a gel at and above the lower critical solution temperature (LCST) [106, 111, 112] | poly(*N*-isopropyl acrylamide)<br>poly(ethylene oxide)<br>PEO–PPO–PEO triblock copolymers poly(ethylene oxide)-poly(L-lactic acid)<br>PEG–PLGA–PEG<br>[113, 114, 165, 115, 116] |
| Cross-linked systems | Polymer chains cross-linked to form solid polymers or gels<br>Cross-linking source can be: heat initiation, photon absorption, and ionic mediated reactions [166] | poly(D,L-lactide-*co*-caprolactone) PEG-oligoglycolylacrylates alginate 1,2-bis(palmitoyl) glycero-3-phosphocoline<br>1,2-bis(myristoyl)-glycero-3-phophocoline<br>[118–121] |
| *In situ* solidifying organogels | Amphiphilic organogels are waxy at room temperature and form a cubic liquid crystal phase on injection into aqueous medium<br>Glycerol esters of fatty acid-based systems are most common [122] | Amphiphilic lipids<br>oils such as peanut oil<br>waxes<br>[124–126] |
| *In situ* precipitating systems | Implant forms through a process called phase inversion where solvent diffuses into the aqueous environment while water diffuses into polymer system [129, 130]<br>Typically comprising water insoluble polymer dissolved in a water miscible, biocompatible solvent | poly(DL-lactide)<br>poly(DL-lactide-*co*-glycolide)<br>poly(DL-lactide-*co*-Ɛcaprolactone)<br>Poly(ethylene carbonate)<br>Fluoroalkyl-poly(ethylene glycol)<br>[106, 107, 118, 131] |

copolymers (Pluronics®), and PEG–PLA as well as PEG–PLGA–PEG copolymers [113–117].

*In situ* cross-linked polymer systems form cross-links at the injection site because of heat, photon absorption, or ionic mediated interactions. On initiation of the cross-linking reaction, the solutions can then transition into a solid polymer depot or gel *in situ*. Polymers such as PCL, PEG-oligoglycolylacrylates, alginate, 1,2-bis(palmitoyl)-glycero-3-phosphocoline (DPPC), 1,2-bis(myristoyl)-glycero-3-phophocoline (DMPC) have been used with *in situ* forming cross-link systems [118–121]. For example, a photon initiated biodegradable hydrogel drug delivery system introduced by Hubbell et al. [119] consists of a polymer with at least two free radical-polymerizable regions (PEG-oligoglycolylacrylates), a photosensitive initiator (eosin dye) and a photon source (visible light). The polymer begins to cross-link and form a network after it is exposed to the photoinitiator and light source. The formed networks can be used to deliver drugs at a controlled rate.

*In situ* solidifying organogels are amphiphilic organogel waxes at room temperature and transition into a cubic liquid crystal phase on injection into aqueous medium [122]. Cubic liquid crystal phases are unique structures formed by amphiphilic molecules which organize into a tortuous array of hydrophilic and hydrophobic domains [123]. This unique structure provides regions for both hydrophilic and hydrophobic drugs to accumulate, and because of the tortuous paths, provide a means of controlling release from these structures [122]. Amphiphilic lipids, oils such as peanut oil, waxes, and glycerol esters of fatty acids are among the most commonly used organogels for drug delivery applications [124–126].

Another class of ISFI uses phase sensitivity to elicit a transition into a solid drug eluting depot, and will be the focus of the remainder of the chapter. Phase sensitive ISFI are comprised of a water insoluble biodegradable polymer dissolved in an organic biocompatible solvent [127, 128]. Drugs can be suspended into this polymer solution with mechanical agitation or dissolved directly into the polymer solution [118, 127]. Counter transport of solvent and water begins the instant the polymer solution is in contact with an aqueous environment. The solvent/nonsolvent exchange results in the precipitation of the polymer, forming an implant once the water concentration becomes sufficiently high to stabilize the tertiary system [129, 130]. The transition into a solid depot is known as phase inversion. These implants have received significant attention as the phase transition only requires contact with an aqueous environment while other ISF categories typically require an external initiator such as heat or light. The phase inversion process is illustrated in Fig. 7.10. Common polymers used in this system are PLGA, PCL, PLA, poly(ethylene carbonate), sucrose acetate isobutyrate, and fluoroalkyl-ended poly(ethylene glycol) [106, 107, 118, 131].

Earlier in this chapter we examined how polymer degradation and erosion affect drug release. ISFI behavior and resulting drug release are also dependent on these processes, however phase inversion can also significantly alter the release profile. Phase inverting systems are typically classified into two categories, fast phase inverting (FPI) implants and slow phase inverting (SPI) implants [91–93, 128, 132]. FPIs require a highly water miscible solvent such as *N*-methyl-2-pyrrolidone (NMP) or dimethyl sulfoxide (DMSO) [91, 132]. The high solvent miscibility results in a rapid rate of phase

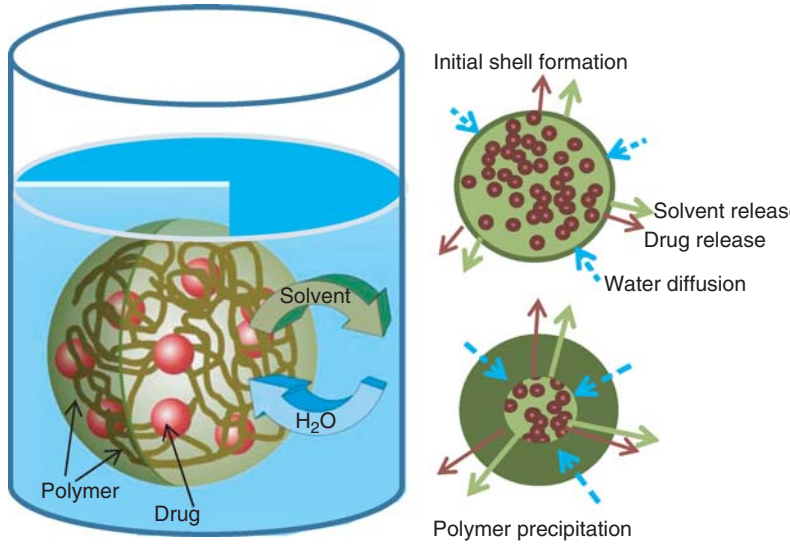


Figure 7.10. Schematic representation of the phase inversion process.

inversion, leading to the formation of a thin, dense shell which acts as a diffusional barrier. Inside the interfacial polymer shell, droplets called polymer-lean domains form, which consist of both solvent and nonsolvent. Owing to the reduced nonsolvent/solvent exchange, polymer-lean domains begin to expand [133]. As a result, the implants develop a vast network of interconnected pores and macrovoids (Fig. 7.11) [134–137]. As a consequence of the resultant morphology, drug release is elevated. Initially, there is a burst release of drug, followed by a diffusion facilitated phase which will begin to plateau as the drug trapped within the interconnected porous network is depleted (Fig. 7.11). Finally, the release rate increases as the polymer degrades and the diffusivity of the drug increases [137, 138].

SPIs require a solvent that has low miscibility in water, such as ethyl benzoate. The low miscibility of the solvent reduces the counter transport responsible for phase inversion, leading to a slow rate of polymer precipitation [91, 93, 128, 136]. The slow rate of solvent exchange leads to the formation of a dense matrix with low diffusivity and negligible pore formation [134, 139]. The absence of the porous network observed with FPI systems, forces drug to diffuse through the viscous polymer. Therefore, a nearly zero-order release can be achieved with this system. These solutions often have a high viscosity (especially when compared with FPIs), which can make injection extremely difficult. Combined solvent systems have also been developed to achieve intermediate release profiles [93, 140–143]. The combination of NMP and triacetin has been shown to reduce the rate of drug release [144], changing the morphology into a less porous structure [93]. Also the addition of water miscible solvents has been shown to decrease the solution viscosity and improve the injectability of SPI systems [142, 145, 146].

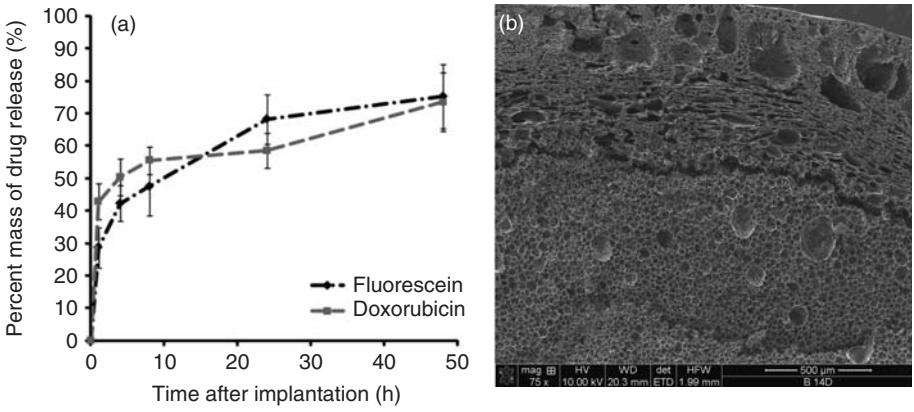


Figure 7.11. (a) Doxorubicin/fluorescein (drug/drug model) release profile showing FPI effects. (b) Morphology of an FPI system as imaged by scanning electron microscope (SEM). Adapted from Reference [137] with kind permission from Springer Science and Business Media.

Additives have also been used to modify the release rate from FPI systems. The surfactant Pluronic® has been used to reduce burst release by decreasing the diffusivity of drug within the porous network [147, 148]. The hydrophobic PPO block of Pluronic is hypothesized to incorporate with the polymer phase, while the hydrophilic PEO block extends into the polymer-lean region. When the concentration of Pluronic is significantly high, the additive fills the interconnected pores and acts as a barrier for diffusion and reduces the burst release [147]. If the Pluronic concentration exceeds the percolation threshold, there will no longer be a sufficient mass of polymer available resulting in an elevated release of drug [148]. Other additives that have been reported to effectively reduce the rate of drug release are heptanoate and glycerol [149]. While the majority of the additives are utilized to reduce burst release, some additives such as polyvinylpyrrolidone (PVP) and aliphatic esters have the opposite effect, which have been shown to increase the drug release [93, 150].

Like the cosolvent system, a combined polymer system can also be used to control drug release profiles and fit the specific delivery requirements [151–155]. Many studies have been done to tune the drug release profile by changing the polymer properties such as the Mw of the polymer and the polymer concentration in the solvent [148, 156–158]. For instance, Lambert and Peck studied changing solvent, polymer Mw, polymer concentration in the system to manipulate the release of FITC-bovine serum albumin from PLGA implants. They found that for high PLGA Mw (75–115 kDa) higher polymer concentration will lead to smaller burst release. For low Mw (10–15 kDa), the initial burst of drug release was eliminated by a much higher concentration of polymer in solution [159]. The results are shown in Fig. 7.12.

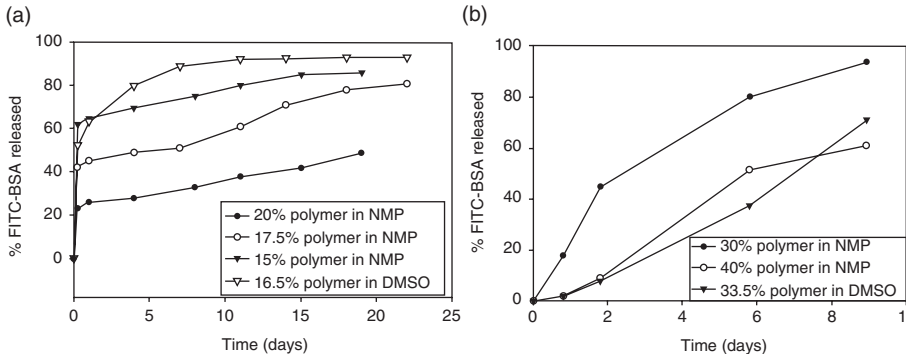


Figure 7.12. (a) FTIC-BSA release from high MW 50:50 system, polymer concentration is between 15–20%. (b) FITC-BSA release from low MW 50:50 system, polymer concentration is between 30–40%. Reprinted from the Journal of Controlled Release, Reference [159], Copyright (1995), with permission from Elsevier.

### 7.3.6 Clinical Applications of ISF Implants

A number of ISF implant systems have been used in clinical applications. Products such as Eligard® (Sanofi-Aventis Inc., France), Atridox® (Zila Inc, Fort Collins, CO), and Zoladex® (AstraZeneca, UK) all use ISF technology [106]. Eligard is a formulation of leuprolide acetate (a luteinizing hormone-releasing hormone (LHRH) agonist) in the polymer solution Atrigel® (Atrix Laboratories, Fort Collins, CO), which consists of PLGA (PLA:PGA=75:25) dissolved in NMP [94, 127, 160]. Leuprolide acetate can be released for a period of up to 6 months from this system [161], and suppresses plasma testosterone levels which inhibits prostatic tumor growth.

Atridox is another ISFI system that uses Atrigel® to deliver the antibiotic doxycycline for the treatment of periodontal disease for a period of 21 days [106, 162]. As administration is minimally invasive, Atridox requires no anesthesia and can be administered in the dentist's office. The SABER® (Durect Corp., Cupertino, CA) delivery system utilizes a high viscosity polymer, sucrose acetate isobutyrate (SAIB), and a hydrophobic solvent such as benzyl benzoate to provide a depot with low viscosity and slow solvent diffusion for release times ranging from several hours to several weeks. Zoladex® is also a marketed product using this system to treat prostate cancer [106, 162].

### 7.3.7 Phase Inverting Implants and their Characterization

Most implantable systems are preformed using relatively standardized and reproducible manufacturing processes ensuring consistent shape and size [14]. The reproducible geometry provides them with a more consistent release behavior when

compared to injectable systems. However, preformed implants require surgical placement and subsequent surgical removal if the implants are nondegradable, such as silicon elastomers [14]. For injectable phase inverting systems, the preparation is much simpler and the implants are administered with a simple injection. The release of drugs from both preformed systems and ISF systems is dependent on the surrounding physiological environment. Local micro-vasculature, cell metabolism of drugs, and potential interactions between drugs and the extracellular matrix will all reduce the distribution volume of drug in the tissue [9, 89, 99, 100]. Furthermore, owing to the *in situ* forming nature of injectable systems, the implant shape and size are not consistent and highly dependent on mechanical and chemical properties of the local environment. Thus their drug release profiles are more difficult to control [16, 17]. One study by Patel et al. [37] demonstrated that the poor *in vitro* and *in vivo* correlation of ISFIs was, in part, a result of the various physical properties of the surrounding environment.

In order to better understand the behavior of this system *in vivo*, recent research has focused on the development of noninvasive characterization techniques able to quantify longitudinal implant behavior. Ultrasound imaging is a technique recently applied for this purpose by Solorio et al. [157] (Fig. 7.13). In this technique, a transducer linearly emits short bursts of ultrasonic waves into a sample and echoes that reflect from materials of different properties are recorded. The backscattered signal can be characterized as a function of acoustic impedance which is determined by the material density and speed of sound in the material. Therefore, as the polymer system goes through the phase inversion process, the acoustic impedance changes, resulting in the development of an echo signal which can be detected by ultrasound [157]. This technique provides unique properties such as real time visualization of the phase inversion process and can be used to trace shape and composition changes

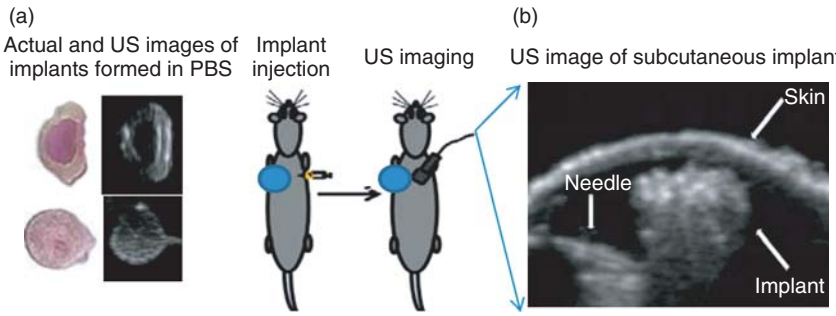


Figure 7.13. ISF implant formation imaged with ultrasound. (a) Images of two different implants formed in PBS along with photos of their cross-section. Dark areas on ultrasound image indicate more water-like core while lighter areas indicate precipitated polymer. (b) Ultrasound image of implant injection subcutaneously; arrows highlight the needle, skin and implant. Adapted from the Journal of Controlled Release, Reference [157], Copyright (2010), with permission from Elsevier.

of the implants over time. The technique is noninvasive, allowing an entire set of *in vivo* time course data to be collected using the same implant, thereby reducing environmental variability and the number of animals used [156].

Two other imaging techniques have been used to characterize injectable implant behavior: dark ground optics and electron paramagnetic resonance (EPR) [138]. Dark ground optics fuses both a dark ground fringe image and a reflected light image. The dark ground image shows the polymer distribution of the reactive index near the diffusion front while the reflected light image shows the solidification of the polymer. The fused image can be used to obtain information such as diffusion coefficients, liquid–liquid phase separation, and gel formation [163]. This method is simple and fast; however, it cannot be used to analyze implants *in vivo* [138].

EPR is based on interactions between electrons and a magnetic field. Electrons are aligned with the magnetic field that has been applied in a resonator, and, at the resonance frequency, unpaired electrons of the sample will be excited [138]. EPR can be used as an *in vivo* characterization technique, but the type and accuracy of the data collected are limited. For instance, the size and shape of the injected implant cannot be determined by EPR alone because EPR is more sensitive to mobility and kinetics of solvent/nonsolvent exchange. The direct biological environment influence of implant formation is also not available from EPR [164]. Furthermore, small Mw paramagnetic spin probes are required during the measurement, introducing another variable that can affect implant performance [157].

## 7.4 CONCLUSIONS AND FUTURE PERSPECTIVES

Implantable delivery systems are capable of overcoming many issues associated with enteral and IV administration of therapeutic agents. When used as a subcutaneous or intramuscular “storage depot” for extended systemic delivery, they can considerably improve the dosage schedule and can maintain an agent within its therapeutic window without inconveniencing the patient. They can also be used to focus the delivery of an agent at the desired site of action whether it is a solid unresectable tumor, an artery, or the eye. While not without issues, in many cases the strategies have been able to revolutionize the standard of care.

The evolution of implantable systems has been relatively rapid and has occurred with the changing needs of the clinical applications. Like the shift from nondegradable to more patient friendly biodegradable polymers used in their formulation, implants continue to adapt to the unyielding slew of new information, new technology, and new tools available for their design, engineering, and analysis. Continuing discovery and deeper understanding of the implants themselves and the impact of the implantation site on implant behavior *in vivo* has narrowed the criteria needed for engineering reproducible, successful systems.

Outstanding challenges still remain. With all implants, improved control, and on-demand modulation of drug release are of interest to many. Understanding the factors most influential in the poor *in vitro–in vivo* correlations of many implantable systems, and improving implant formulations to overcome these factors are also necessary.

Along the same lines, the development of more sophisticated *in vitro* phantoms that can better mimic the eventual clinical application is also of crucial importance. Such phantoms would permit simple, inexpensive, yet accurate, testing of new implantable formulations, streamlining research, discovery, and translation. Finally, for implants delivering drugs locally, an array of tools that can characterize their performance (implant formation, drug release, polymer degradation) *in vivo* is of great importance for the advancement of the field. Research into all of these aspects is ongoing and producing exciting developments every day. Advancements in implant technology will continue to escalate and increase future academic, industrial, and clinical interest.

## 7.5 KEY POINTS

- Administration from an implantable drug depot facilitates improved patient compliance over time, especially when dosing is frequent and inconvenient.
- Implantable technology can be used to achieve special and temporal control of drug delivery.
- Biodegradable implants are more patient friendly than nonbiodegradable implants.
- Patient compliance can be further improved by using injectable systems that form biodegradable networks *in vivo*.

## 7.6 HOMEWORK PROBLEMS

1. Re-create the release of Norplant in graphical format as well try to model the release by using a modification of Fick's first law.
2. What is the difference between erosion and degradation, how can these parameters be used to predict changes in drug release over time?
3. What effect does reaction kinetics have on determining whether a material will behave as a surface eroding or bulk eroding material? What parameters dictate how a material will erode? Predict what effect changes in the surrounding solution pH (i.e., a pH of 13 vs. a pH of 7) may have on degradation kinetics for a poly($\alpha$-hydroxy-ester), will it always behave as a bulk eroding polymer regardless of the solution pH?
4. Using the given assumptions for the first-order degradation kinetics, solve the underlying problem and describe how this can be used to determine the rate kinetics. Apply this equation to the general solution and demonstrate the effect that degradation kinetics have on cumulative drug release.
5. What are the benefits of local delivery, and what effect does the metabolic activity of the surrounding tissue have on the spatial distribution of drug released from these implants?
6. What causes the burst release of drug from the ISFIs and what can be done to eliminate this burst release?

## REFERENCES


1. Langer R. Implantable controlled release systems. Pharmacol Ther 1983;21(1):35–51.
2. Shastri PV. Toxicology of polymers for implant contraceptives for women. Contraception 2002;65(1):9–13.
3. Pillai O, Panchagnula R. Polymers in drug delivery. Curr Opin Chem Biol 2001; 5(4):447–451.
4. Folkman J, Long DM. The use of silicone rubber as a carrier for prolonged drug therapy. J Surg Res 1964;4:139–142.
5. Saltzman WM. Drug Delivery: Engineering Principles for Drug Therapy. Oxford University Press; 2001. 198 Madison Ave., New York, New York 10016
6. Maeda H, Brandon M, Sano A. Design of controlled-release formulation for ivermectin using silicone. Int J Pharm 2003;261(1–2):9–19.
7. Malcolm RK et al. Controlled release of a model antibacterial drug from a novel self-lubricating silicone biomaterial. J Control Release 2004;97(2):313–320.
8. Dash AK, Cudworth GC. Therapeutic applications of implantable drug delivery systems. J Pharmacol Toxicol Methods 1998;40(1):1–12.
9. Saltzman WM, Fung LK. Polymeric implants for cancer chemotherapy. Adv Drug Deliv Rev 1997;26(2–3):209–230.
10. Hsu TT, Langer R. Polymers for the controlled release of macromolecules: effect of molecular weight of ethylene-vinyl acetate copolymer. J Biomed Mater Res 1985;19(4):445–460.
11. Pillai O, Dhanikula AB, Panchagnula R. Drug delivery: an odyssey of 100 years. Curr Opin Chem Biol 2001;5(4):439–446.
12. Okabe K et al. Intraocular tissue distribution of betamethasone after intrascleral administration using a non-biodegradable sustained drug delivery device. Invest Ophthalmol Vis Sci 2003;44(6):2702–2707.
13. Dhillon B, Kamal A, Leen C. Intravitreal sustained-release ganciclovir implantation to control cytomegalovirus retinitis in AIDS. Int J STD AIDS 1998;9(4):227–230.
14. Basak P et al. Sustained release of antibiotic from polyurethane coated implant materials. J Mater Sci Mater Med 2009;20:213–221.
15. Schierholz JM et al. Controlled release of antibiotics from biomedical polyurethanes: morphological and structural features. Biomaterials 1997;18(12):839–844.
16. Siepmann J, Siepmann F. Modeling of diffusion controlled drug delivery. J Control Release 2012;161(2):351–362.
17. Ratner BD. Biomaterials Science, Second Edition: An Introduction to Materials in Medicine. 2nd ed. Elsevier Academic Press; 2004;24-28 Oval Road, London NW1 7DX, UK.
18. Peppas NA, Gurny R. Relation between the structure of polymers and the controlled release of active ingredients. Pharm Acta Helv 1983;58(1):2–8.
19. Langer R. Polymer-controlled drug-delivery systems. Acc Chem Res 1993;26(10): 537–542.
20. Baker R. Controlled Release of Biologically Active Agents. Vol. 40. New York: John Wiley & Sons, Inc.; 1987.

21. Mantanus J et al. Near infrared and Raman spectroscopy as process analytical technology tools for the manufacturing of silicone-based drug reservoirs. Anal Chim Acta 2011;699(1):96–106.
22. Siegel RA. Pharmacokinetic transfer functions and generalized clearances. J Pharmacokinet Biopharm 1986;14(5):511–521.
23. Ferrero C, Massuelle D, Doelker E. Towards elucidation of the drug release mechanism from compressed hydrophilic matrices made of cellulose ethers. II. Evaluation of a possible swelling-controlled drug release mechanism using dimensionless analysis. J Control Release 2010;141(2):223–233.
24. Grassi M, Grassi G. Mathematical modeling and controlled drug delivery: matrix systems. Curr Drug Deliv 2005;2:97–116.
25. Ravivarapu HB, Moyer KL, Dunn RL. Sustained suppression of pituitary-gonadal axis with an injectable, in situ forming implant of leuprolide acetate. J Pharm Sci 2000; 89(6):732–741.
26. Fu Y, Kao WJ. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Expert Opin Drug Deliv 2010;7(4):429–444.
27. Park K, Shalaby W, Park H. Biodegradable Hydrogels for Drug Delivery. Vol. 191. Technomic publishing company; 1993 851 New Holland Ave, Box 3535, Lancaster, PA, 17604.
28. Saltzman WM, Langer R. Transport rates of proteins in porous materials with known microgeometry. Biophys J 1989;55(1):163–171.
29. Ballal G, Zygourakis K. Diffusion in particles with varying cross-section. Chem Eng Sci 1985;40(8):1477–1483.
30. Fournier RL. Basic Transport Phenomenon in Biomedical Engineering. Taylor and Francis; 1999 325 Chestnut St., Philadelphia, PA, 19106.
31. Higuchi T. Rate of release of medicaments from ointment base containing drugs in suspension. J Pharm Sci 1961;50:874–879.
32. Lee PI. Novel-approach to zero-order drug delivery via immobilized nonuniform drug distribution in glassy hydrogels. J Pharm Sci 1984;73(10):1344–1347.
33. Sivin I. International experience with NORPLANT and NORPLANT-2 contraceptives. Stud Fam Plann 1988;19(2):81–94.
34. Sivin I et al. The performance of levonorgestrel rod and Norplant contraceptive implants: a 5 year randomized study. Hum Reprod 1998;13(12):3371–3378.
35. Meirik O, Fraser IS, d'Arcangues C. Implantable contraceptives for women. Hum Reprod Update 2003;9(1):49–59.
36. Mansour D. The benefits and risks of using a levonorgestrel-releasing intrauterine system for contraception. Contraception 2012;85(3):224–234.
37. Pritts EA et al. Angiogenic effects of norplant contraception on endometrial histology and uterine bleeding. J Clin Endocrinol Metab 2005;90(4):2142–2147.
38. Berg WA, Hamper UM. Norplant implants: sonographic identification and localization for removal. AJR Am J Roentgenol 1995;164(2):419–420.
39. de la Puerta B et al. In vitro comparison of mechanical and degradation properties of equivalent absorbable suture materials from two different manufacturers. Vet Surg 2011;40(2):223–227.
40. Attenello FJ et al. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. Ann Surg Oncol 2008;15(10):2887–2893.

41. Dunn RL, Garrett S. The drug delivery and biomaterial attributes of the ATRIGEL technology in the treatment of periodontal disease. Expert Opin Investig Drugs 1998; 7(9):1483–1491.
42. Gad HA, El-Nabarawi MA, El-Hady SSA. Formulation and evaluation of PLA and PLGA in situ implants containing secnidazole and/or doxycycline for treatment of periodontitis. AAPS Pharmscitech 2008;9(3):878–884.
43. Sartor O. Eligard (R) 6: a new form of treatment for prostate cancer. Eur Urol Suppl 2006;5(18):905–910.
44. Paajanen H et al. Randomized clinical trial of tissue glue versus absorbable sutures for mesh fixation in local anaesthetic Lichtenstein hernia repair. Br J Surg 2011;98(9):1245–1251.
45. Sakamoto A et al. An investigation of the fixation materials for cartilage frames in microtia. J Plast Reconstr Aesthet Surg 2012;65(5):584–589.
46. Gopferich A. Mechanisms of polymer degradation and erosion. Biomaterials 1996; 17(2):103–114.
47. Gopferich A. Polymer bulk erosion. Macromolecules 1997;30(9):2598–2604.
48. Alexis F. Factors affecting the degradation and drug-release mechanism of poly(lactic acid) and poly[(lactic acid)-co-(glycolic acid)]. Polym Int 2005;54(1):36–46.
49. Gopferich A, Langer R. Modeling of polymer erosion. Macromolecules 1993;26(16): 4105–4112.
50. von Burkersroda F, Schedl L, Gopferich A. Why degradable polymers undergo surface erosion or bulk erosion. Biomaterials 2002;23(21):4221–4231.
51. Wade LG. Organic Chemistry. Prentice Hall; 2003 Upper Saddle River, NJ 07458.
52. Morrison RT, Boyd RN. Organic Chemistry. 6 ed. Prentice Hall; 1992 Upper Saddle River, NJ 07458.
53. Jager J, Jan BF, Engberts N. Inhibition of water-catalyzed ester hydrolysis in hydrophobic microdomains of poly(methacrilic acid) hypercolis. J Am Chem Soc 1984;106:3331–3334.
54. Seo T et al. Ester hydrolysis by poly(allylamines) having hydrophobic groups: Catalytic activity and substrate specificity. J Macromol Sci Part A 1996;33:1025–1047.
55. Callister WD. Fundamentals of Materials Science and Engineering. Somerset, NJ: John Wiley & Sons, Inc.; 2004.
56. Siepmann J, Gopferich A. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv Drug Deliv Rev 2001;48(2–3):229–247.
57. Hurrell S, Cameron RE. The effect of initial polymer morphology on the degradation and drug release from polyglycolide. Biomaterials 2002;23(11):2401–2409.
58. Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev 1997;28(1):5–24.
59. Williams DF, Mort E. Enzyme-accelerated hydrolysis of polyglycolic acid. J Bioeng 1977;1(3):231–238.
60. Visscher GE et al. Effect of particle size on the in vitro and in vivo degradation rates of poly(DL-lactide-co-glycolide) microcapsules. J Biomed Mater Res 1988;22(8):733–746.
61. Visscher GE, Robison MA, Argentieri GJ. Tissue response to biodegradable injectable microcapsules. J Biomater Appl 1987;2(1):118–131.
62. Visscher GE et al. Biodegradation of and tissue reaction to 50:50 poly(DL-lactide-co-glycolide) microcapsules. J Biomed Mater Res 1985;19(3):349–365.

63. Visscher GE et al. Biodegradation of and tissue reaction to poly(DL-lactide) microcapsules. J Biomed Mater Res 1986;20(5):667–676.
64. Ignatius AA, Claes LE. In vitro biocompatibility of bioresorbable polymers: poly(L, DL-lactide) and poly(L-lactide-co-glycolide). Biomaterials 1996;17(8):831–839.
65. Schakenraad JM et al. Enzymatic activity toward poly(L-lactic acid) implants. J Biomed Mater Res 1990;24(5):529–545.
66. Kulkarni RK et al. Biodegradable poly(lactic acid) polymers. J Biomed Mater Res 1971; 5(3):169–181.
67. Chabert E et al. Filler-filler interactions and viscoelastic behavior of polymer nanocomposites. Mater Sci Eng 2004;381(1–2):320–330.
68. Abdul S, Chandewar AV, Jaiswal SB. A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). J Control Release 2010;147(1):2–16.
69. Bailly M, Kontopoulou M, El Mabrouk K. Effect of polymer/filler interactions on the structure and rheological properties of ethylene-octene copolymer/nanosilica composites. Polymer 2010;51(23):5506–5515.
70. Fritzsche J, Kluppel M. Structural dynamics and interfacial properties of filler-reinforced elastomers. J Phys Condens Matter 2011;23(3).
71. Koga T et al. Structure factors of dispersible units of carbon black filler in rubbers. Langmuir 2005;21(24):11409–11413.
72. Nunes RCR, Fonseca JLC, Pereira MR. Polymer-filler interactions and mechanical properties of a polyurethane elastomer. Polym Test 2000;19(1):93–103.
73. Sampson J, de Korte D. DEHP-plasticised PVC: relevance to blood services. Transfus Med 2011;21(2):73–83.
74. Shaz BH, Grima K, Hillyer CD. 2-(Diethylhexyl)phthalate in blood bags: is this a public health issue? Transfusion 2011;51(11):2510–2517.
75. Yu JG, Wang N, Ma XF. Fabrication and characterization of poly(lactic acid)/acetyl tributyl citrate/carbon black as conductive polymer composites. Biomacromolecules 2008;9(3):1050–1057.
76. Cadogan DF, Howick CJ. Plasticizers. In: Ullmann's Encyclopedia of Industrial Chemistry. Weinhein: Wiley-VCH; 2000.
77. Wang ZH et al. Novel percolation phenomena and mechanism of strengthening elastomers by nanofillers. Phys Chem Chem Phys 2010;12(12):3014–3030.
78. Schubert MA et al. Vitamin E as an antioxidant for poly(etherurethane urea): in vivo studies. J Biomed Mater Res 1996;32(4):493–504.
79. Stella VJ, He QR. Cyclodextrins. Toxicol Pathol 2008;36(1):30–42.
80. Thompson DO. Cyclodextrins - enabling excipients: their present and future use in pharmaceuticals. Crit Rev Ther Drug Carrier Syst 1997;14(1):1–104.
81. Exner AA et al. Enhancement of carboplatin toxicity by Pluronic block copolymers. J Control Release 2005;106(1–2):188–197.
82. Exner AA, Saidel GM. Drug-eluting polymer implants in cancer therapy. Expert Opin Drug Deliv 2008;5(7):775–788.
83. Krupka TM et al. Effect of intratumoral injection of carboplatin combined with pluronic P85 or L61 on experimental colorectal carcinoma in rats. Exp Biol Med (Maywood) 2007;232(7):950–957.

84. Krupka TM et al. Injectable polymer depot combined with radiofrequency ablation for treatment of experimental carcinoma in rat. Invest Radiol 2006;41(12):890–897.
85. Weinberg BD et al. Combination of sensitizing pretreatment and radiofrequency tumor ablation: evaluation in rat model. Radiology 2008;246(3):796–803.
86. Tamada J, Langer R. The development of polyanhydrides for drug delivery applications. J Biomater Sci Poly Ed 1992;3(4):315–353.
87. Langer R. Polymer implants for drug delivery in the brain. J Control Release 1991; 16(1–2):53–59.
88. Solorio L et al. Advances in image-guided intratumoral drug delivery techniques. Ther Deliv 2010;1(2):307–322.
89. Qian F et al. Combined modeling and experimental approach for the development of dual-release polymer millirods. J Control Release 2002;83(3):427–435.
90. Qian F, Szymanski A, Gao JM. Fabrication and characterization of controlled release poly(D,L-lactide-co-glycolide) millirods. J Biomed Mater Res 2001;55(4):512–522.
91. Brodbeck KJ, DesNoyer JR, McHugh AJ. Phase inversion dynamics of PLGA solutions related to drug delivery. Part II. The role of solution thermodynamics and bath-side mass transfer. J Control Release 1999;62(3):333–344.
92. DesNoyer JR, McHugh AJ. Role of crystallization in the phase inversion dynamics and protein release kinetics of injectable drug delivery systems. J Control Release 2001;70(3):285–294.
93. Graham PD, Brodbeck KJ, McHugh AJ. Phase inversion dynamics of PLGA solutions related to drug delivery. J Control Release 1999;58(2):233–245.
94. Ravivarapu HB, Moyer KL, Dunn RL. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. Int J Pharm 2000;194(2):181–191.
95. Caraballo I et al. Percolation theory: application to the study of the release behaviour from inert matrix systems. Int J Pharm 1993;96:175–181.
96. Leuenberger H, Rohera BD, Haas C. Percolation theory - a novel-approach to solid dosage form design. Int J Pharm 1987;38(1–3):109–115.
97. Tsuji H, Mizuno A, Ikada Y. Properties and morphology of poly(L-lactide). III. Effects of initial crystallinity on long-term in vitro hydrolysis of high molecular weight poly(L-lactide) film in phosphate-buffered solution. J Appl Polym Sci 2000;77(7):1452–1464.
98. Wu XS, Wang N. Synthesis, characterization, biodegradation, and drug delivery application of biodegradable lactic/glycolic acid polymers. Part II: biodegradation. J Biomater Sci Poly Ed 2001;12(1):21–34.
99. Weinberg BD et al. Modeling doxorubicin transport to improve intratumoral drug delivery to RF ablated tumors. J Control Release 2007;124(1–2):11–19.
100. Weinberg BD et al. Model simulation and experimental validation of intratumoral chemotherapy using multiple polymer implants. Med Biol Eng Comput 2008; 46(10):1039–1049.
101. Affronti ML et al. Overall survival of newly diagnosed glioblastoma patients Receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. Cancer 2009;115(15):3501–3511.
102. Noel G et al. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior gliadel implantation (Carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. Int J Radiat Oncol Biol Phys 2012; 82(2):749–755.

103. Panigrahi M, Das PK, Parikh PM. Brain tumor and gliadel wafer treatment. Indian J Cancer 2011;48(1):11–17.

104. Fleming AB, Saltzman WM. Pharmacokinetics of the carmustine implant. Clin Pharmacokinet 2002;41(6):403–419.

105. Westphal M et al. Gliadel (R) wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. Acta Neurochir 2006;148(3):269–275.

106. Packhaeuser CB et al. In situ forming parenteral drug delivery systems: an overview. Eur J Pharm Biopharm 2004;58(2):445–455.

107. Hatefi A, Amsden B. Biodegradable injectable in situ forming drug delivery systems. J Control Release 2002;80(1–3):9–28.

108. Bezwada, RS. Liquid copolymers of epsilon-caprolactone and lactide. US Patent. 1995; p 15.

109. Einmahl S et al. A viscous bioerodible poly(ortho ester) as a new biomaterial for intraocular application. J Biomed Mater Res 2000;50(4):566–573.

110. Stile RA, Burghardt WR, Healy KE. Synthesis and characterization of injectable poly(N-isopropylacrylamide)-based hydrogels that support tissue formation in vitro. Macromolecules 1999;32(22):7370–7379.

111. Hoffman AS. Applications of thermally reversible polymers and hydrogels in therapeutics and diagnostics. J Control Release 1987;6:297–305.

112. Stile RA, Burghardt WR, Healy KE. Synthesis and characterization of injectable poly(N-isopropylacrylamide)-based hydrogels that support tissue formation in vitro. Macromolecules 1999;32(22):7370–7379.

113. Schild HG. Poly(N-isopropylacrylamide): experiment, theory and application. Prog Polym Sci 1992;17:163–249.

114. Alexandridis P, Hatton TA. Poly(ethylene oxide)–poly-(propylene oxide)–poly(ethylene oxide) block copolymer surfactants in aqueous solutions and at interfaces: thermodynamics, structure, dynamics and modeling. Colloid Surf 1995;96:1–46.

115. Jeong B et al. New biodegradable polymers for injectable drug delivery systems. J Control Release 1999;62(1–2):109–114.

116. Jeong B, Bae YH, Kim SW. Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers. J Control Release 2000; 63(1–2):155–163.

117. Jeong B, Bae YH, Lee DS, Kim SW. Biodegradable block copolymers as injectable drug delivery systems. Nature 1997;388:860–862.

118. Dunn RL, English JP, Cowsar DR, Vanderbelt DD, Biodegradable in-situ forming implants and methods of producing the same. USA. U.S.A Patent Application Date: 03 Oct 1988 Publication Date: 03 July 1990 Publication number 4938763.

119. Hubbell JA, Pathak CP, Sawhney AS, Desai NP, Hill JL, Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled release carriers. 1995: USA. U.S.A Patent Application Date: 01 March 1993 Publication Date: 25 Apr 1995 Publication number 5410016.

120. Viegas TX, Reeve LE, Henry RL, Medical uses of in-situ formed gels. USA. U.S.A Patent Application Date: 28 Dec 1993 Publication Date: 24 Dec 1996 Publication number 5587175.

121. Papahadjopoulos D et al. Phase transitions in phospholipid vesicles. Fluorescence polarization and permeability measurements concerning the effect of temperature and cholesterol. Biochim Biophys Acta 1973;311(3):330–348.
122. Engstrom S, Engstrom L. Phase-behavior of the lidocaine-monoolein-water system. Int J Pharm 1992;79(2–3):113–122.
123. Scriven LE. Equilibrium bicontinuous structure. Nature 1976;263(5573):123–125.
124. Ericsson B et al. Cubic phases as delivery systems for peptide drugs. ACS Symp Ser 1991;469:251–265.
125. Gao Z, Shukla AJ, Johnson JR, Crowley WR. Controlled release of contraceptive steroid from biodegradable and injectable gel formulations: in-vitro evaluation. Pharm Res 1995;12(6):857–864.
126. Gao Z, Crowley WR, Shukla AJ, Johnson JR, Reger JF. Controlled release of contraceptive steroids from biodegradable and injectable gel formulations: in-vivo evaluation. Pharm Res 1998;12(6):864–868.
127. Ravivarapu HB, Moyer KL, Dunn RL. Sustained activity and release of leuprolide acetate from an in situ forming polymeric implant. AAPS PharmSciTech 2000;1(1):E1.
128. McHugh AJ. The role of polymer membrane formation in sustained release drug delivery systems. J Control Release 2005;109(1–3):211–221.
129. Smolders CA et al. Microstructure in phase inversion membranes. Formation of macrovoids. J Membr Sci 1992;73:259–275.
130. Tsay CS, McHugh AJ. A technique for rapid measurement of diffusion-coefficients. Ind Eng Chem Res 1992;86(1):449–452.
131. Chandrashekar BL, Zhou M, Jarr EM, Dunn RL, Controlled release liquid delivery compositions with low initial drug burst. 2000: USA. U.S.A. Patent Filed Oct 28, 1998 Date of Patent: Nov. 7, 2000 Patent Number: 6,143,314.
132. Brodbeck KJ, Pushpala S, McHugh AJ. Sustained release of human growth hormone from PLGA solution depots. Pharm Res 1999;16(12):1825–1829.
133. Smolders CA et al. Microstructures in phase-inversion membranes .1. Formation of macrovoids. J Membr Sci 1992;73(2–3):259–275.
134. Smolders CA, Reuvers AJ, Boom RM, Wienk IM. Microstructure in phase inversion membranes. Formation of macrovoids. J Membr Sci 1992;73:259–275.
135. Vogrin N et al. The wet phase separation: the effect of cast solution thickness on the appearance of macrovoids in the membrane forming ternary cellulose acetate/acetone/water system. J Membr Sci 2002;207(1):139–141.
136. Raman C, McHugh AJ. A model for drug release from fast phase inverting injectable solutions. J Control Release 2005;102(1):145–157.
137. Solorio L et al. Effect of cargo properties on in situ forming implant behavior determined by noninvasive ultrasound imaging. Drug Deliv Transl Res 2012;2(1):45–55.
138. Solorio L, Solorio LD, Gleeson S, Exner AA. Phase inverting polymer systems in drug delivery and medicine. In: Ehlers TP, Wilhelm JK, editors. Polymer Phase Behavior. Nova Science Publishers, Inc; 2011. 400 Oser Ave Suite 1600, Hauppauge, NY 11788.
139. Tsay CS, McHugh AJ. A technique for rapid measurement of diffusion-coefficients. Ind Eng Chem Res 1992;86(1):449–452.
140. Chen S, Singh J. Controlled delivery of testosterone from smart polymer solution based systems: in vitro evaluation. Int J Pharm 2005;295(1–2):183–190.

141. Chen S et al. In vivo absorption of steroidal hormones from smart polymer based delivery systems. J Pharm Sci 2010;99(8):3381–3388.
142. Dhawan S, Kapil R, Kapoor DN. Development and evaluation of in situ gel-forming System for sustained delivery of insulin. J Biomater Appl 2011.
143. Singh S, Singh J. Phase-sensitive polymer-based controlled delivery systems of leuprolide acetate: in vitro release, biocompatibility, and in vivo absorption in rabbits. Int J Pharm 2007;328(1):42–48.
144. Liu QF et al. In vitro and in vivo study of thymosin alpha1 biodegradable in situ forming poly(lactide-co-glycolide) implants. Int J Pharm 2010;397(1–2):122–129.
145. Singh S, Singh J. Controlled release of a model protein lysozyme from phase sensitive smart polymer systems. Int J Pharm 2004;271(1–2):189–196.
146. Yapar A, Baykara T. Effects of solvent combinations on drug release from injectable phase sensitive liquid implants. Turk J Pharm Sci 2010;7(1):49–56.
147. DesNoyer JR, McHugh AJ. The effect of Pluronic on the protein release kinetics of an injectable drug delivery system. J Control Release 2003;86(1):15–24.
148. Patel RB et al. Characterization of formulation parameters affecting low molecular weight drug release from in situ forming drug delivery systems. J Biomed Mater Res A 2010;94A(2):476–484.
149. Bakhshi R et al. The effect of additives on naltrexone hydrochloride release and solvent removal rate from an injectable in situ forming PLGA implant. Polym Adv Technol 2006;17(5):354–359.
150. Mashak A et al. The effect of aliphatic esters on the formation and degradation behavior of PLGA-based in situ forming system. Poly Bull 2010. DOI: 10.1007/s00289-010-0386-7.
151. Packhaeuser CB et al. In situ forming parenteral drug delivery systems: an overview. Eur J Pharm Biopharm 2004;58(2):445–455.
152. Royals MA et al. Biocompatibility of a biodegradable in situ forming implant system in rhesus monkeys. J Biomed Mater Res 1999;45(3):231–239.
153. Okumu FW et al. Sustained delivery of human growth hormone from a novel gel system: SABER. Biomaterials 2002;23(22):4353–4358.
154. Tae G, Kornfield JA, Hubbell JA. Sustained release of human growth hormone from in situ forming hydrogels using self-assembly of fluoroalkyl-ended poly(ethylene glycol). Biomaterials 2005;26(25):5259–5266.
155. Ueda H et al. Injectable, in situ forming poly(propylene fumarate)-based ocular drug delivery systems. J Biomed Mater Res A 2007;83A(3):656–666.
156. Patel RB et al. Effect of injection site on in situ implant formation and drug release in vivo. J Control Release 2010;147(3):350–358.
157. Solorio L et al. Noninvasive characterization of in situ forming implants using diagnostic ultrasound. J Control Release 2010;143(2):183–190.
158. Liu H, Venkatraman SS. Effect of polymer type on the dynamics of phase inversion and drug release in injectable in situ gelling systems. J Biomater Sci Polym Ed 2012;23.
159. Lambert WJ, Peck KD. Development of an in situ forming biodegradable poly-lactide-co-glycolide system for the controlled release of proteins. J Control Release 1995;33:189–195.
160. Sartor O. Eligard: leuprolide acetate in a novel sustained-release delivery system. Urology 2003;61(2 Suppl 1):25–31.

161. Schulman C et al. Expert opinion on 6-monthly luteinizing hormone-releasing hormone agonist treatment with the single-sphere depot system for prostate cancer. BJU Int 2007;100(1 Suppl):1–5.

162. Solanki HK, Thakkar JH. Recent advances in implantable drug delivery. Int J Pharm Sci Rev Res 2010;4(3):168–177.

163. Mchugh AJ, Miller DC. The dynamics of diffusion and gel growth during nonsolvent-induced phase inversion of polyethersulfone. J Membr Sci 1995;105(1–2):121–136.

164. Kempe S et al. Non-invasive in vivo evaluation of in situ forming PLGA implants by benchtop magnetic resonance imaging (BT-MRI) and EPR spectroscopy. Eur J Pharm Biopharm 2010;74(1):102–108.

165. Jeong B et al. Biodegradable block copolymers as injectable drug-delivery systems. Nature 1997;388(6645):860–862.

166. D. Annavajjula, K. Yim, S.C Rowe. Drug Delivery System for Recombinant Human Growth Hormone with Photopolymerized Hydrogels. In: 28th International Symposium on Controlled Release of Bioactive Materials; 2001.