Polymeric Systems for Controlled Drug Release

Kathryn E. Uhrich

Department of Chemistry, Rutgers University, Piscataway, New Jersey 08854-8087

Scott M. Cannizzaro and Robert S. Langer*

Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Kevin M. Shakesheff

Department of Pharmaceutical Science, University of Nottingham, Nottingham NG7-2RD, U.K.

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I. Introduction

A. Need for Controlled Release Systems

Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance and convenience. Such systems often use synthetic polymers as carriers for the drugs. By so doing, treatments that would not otherwise be possible are now in conventional use. Although the introduction of the first clinical controlled release systems occurred less than 25 years ago, 1997 sales of advanced drug delivery systems in the United States alone were approximately $14 billion dollars.[1] In this paper, we examine the breadth, the mechanisms, and rationale for controlled drug delivery and then focus our attention on some of the major families of synthetic polymers being used in the field.

This review examines the chemical issues involved in the design of synthetic polymers used in the controlled release of drugs. Before considering the variety and the evolution of these polymeric structures, it is necessary to examine the motivation for achieving controlled release. This field of pharmaceutical technology has grown and diversified rapidly in recent years. Understanding the derivation of the methods of controlled release and the range of new polymers can be a barrier to involvement from the nonspecialist.

All controlled release systems aim to improve the effectiveness of drug therapy.[1,2] This improvement can take the form of increasing therapeutic activity compared to the intensity of side effects, reducing the number of drug administrations required during treatment, or eliminating the need for specialized drug administration (e.g., repeated injections). Two types of control over drug release can be achieved, temporal and distribution control.

B. Methods of Controlled Release

In temporal control, drug delivery systems aim to deliver the drug over an extended duration or at a specific time during treatment. Controlled release over an extended duration is highly beneficial for drugs that are rapidly metabolized and eliminated from the body after administration. An example of

* To whom correspondence should be addressed. Telephone: (617) 253-3107. Fax: (617) 258-8827.

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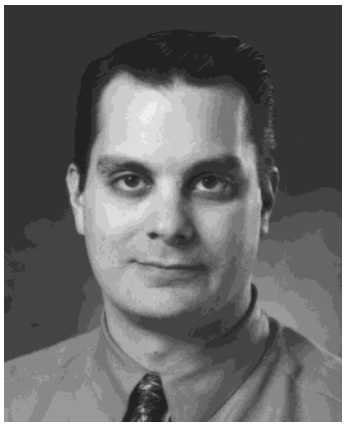
Kathryn E. Uhrich was born in Aberdeen, SD, in 1965. She received a B.S. degree in Chemistry from the University of North Dakota (1986) and M.S. (1989) and Ph.D. (1992) degrees from Cornell University. She held post-doctoral positions at AT&T Bell Laboratories and at the Massachusetts Institute of Technology (1993–1995), before moving to her present post as Assistant Professor of Chemistry at Rutgers, The State University of New Jersey. Trained in organic and polymer synthesis, her research interests have included linear and dendritic polymers, photoresists, and biomaterials for bone replacement. Her current research activities are in the design, synthesis, and characterization of novel, organic polymers that have medical relevance.



Scott M. Cannizzaro was born in Schenectady, NY (1967). He earned his B.S. degree in Chemistry from Sienna College (1990) and his Ph.D. degree from Duke University in Organic Chemistry (1995). He trained in drug delivery and tissue engineering as a NIH Fellow at MIT (1995–1997). While at MIT he had a winning entry in the 50K Business Plan Competition, a nationally recognized entrepreneurial award. He then joined Arthur D. Little, a technical consulting firm, as a manager in the Technology Products & Development group. While at ADL, he advised clients on medical devices and drug delivery systems. He also managed internal research efforts for the development of novel biomaterials. Recently, Dr. Cannizzaro has joined Surface-Logix (Boston, MA), a company based on microfabrication from soft lithography. He will be responsible for the company's efforts in polymers and biomaterials.

this benefit is shown schematically in Figure 1 in which the concentration of drug at the site of activity within the body is compared after immediate release from 4 injections administered at 6 hourly intervals and after extended release from a controlled release system. Drug concentrations may fluctuate widely during the 24 h period when the drug is administered via bolus injection, and for only a portion of the treatment period is the drug concentration in the therapeutic window (i.e., the drug concentration that produces beneficial effects without harmful side effects). With the controlled release system, the rate of drug release matches the rate of drug elimination

Robert Langer is the Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering at MIT. He received his B.S. degree from Cornell University in 1970, a Sc.D. from MIT in 1974, both in chemical engineering, and honorary doctorates from ETH (Switzerland) in 1996 and Technion (Israel) in 1997. He has written over 600 articles, 400 abstracts, and 360 patents, and edited 12 books. He has also received over 80 major awards including the Gairdner Foundation International Award, Lemelson-MIT prize, ACS's Applied Polymer Science and Polymer Chemistry Awards, AICHE's Professional Progress, Bioengineering, Walker and Stine Materials Science and Engineering Awards. In 1989, Dr. Langer was elected to the Institute of Medicine of the National Academy of Sciences, and in 1992 he was elected to both the National Academy of Engineering and the National Academy of Sciences. He is the only active member of all three National Academies.

Kevin Shakesheff was born in Ashington, Northumberland, U.K., in 1969. He received his Bacheclor of Pharmacy degree from the University of Nottingham in 1991 and a Ph.D. from the same institution in 1995. In 1996 he became a NATO Postdoctoral Fellow at MIT, Department of Chemical Engineering. He is currently an EPSRC Advanced Fellow at the School of Pharmaceutical Sciences, The University of Nottingham. His research group investigates new methods of engineering polymer surfaces and the application of these engineered materials in drug delivery and tissue engineering.

and, therefore, the drug concentration is within the therapeutic window for the vast majority of the 24 h period. Clinically, temporal control can produce a significant improvement in drug therapy. For example, when an opioid pain killer is administered to a patient with terminal cancer, any time that the drug concentration is below therapeutic concentrations the patient experiences pain. A temporally controlled release system would ensure that the maximum possible benefit is derived from the drug.

In distribution control, drug delivery systems aim to target the release of the drug to the precise site of activity within the body. The benefit of this type of control is shown schematically in Figure 2 in which

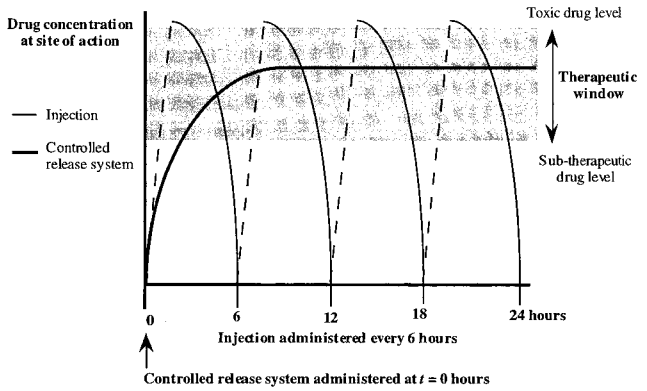


Figure 1. Drug concentrations at site of therapeutic action after delivery as a conventional injection (thin line) and as a temporal controlled release system (bold line).

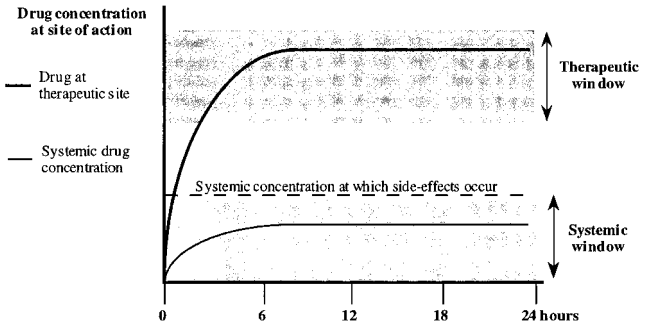


Figure 2. Drug delivery from an ideal distribution controlled release system. Bold line: Drug concentrations at site of therapeutic action. Thin line: Systemic levels at which side effects occur.

drug concentrations at the site of activity and side-effect production are compared. There are two principle situations in which distribution control can be beneficial. The first is when the natural distribution causes drug molecules to encounter tissues and cause major side effects that prohibit further treatment. This situation is often the cause of chemotherapy failure when bone marrow cell death prevents the patient from undergoing a complete drug treatment. The second situation is when the natural distribution of the drug does not allow drug molecules to reach their molecular site of action. For example, a drug molecule that acts on a receptor in the brain will not be active if it is distributed by the patient's blood system but cannot cross the blood−brain barrier.[3]

A large number of classes of drugs can benefit from temporal or distribution controlled release. These classes include chemotherapeutic drugs,[4,5] immunosuppressants,[6] antiinflammatory agents,[7−9] antibiotics,[10] opioid antagonists,[11] steroids,[12] hormones,[13] anesthetics,[14] and vaccines.[15] Recently, the need to develop new controlled release strategies has been intensified by advances in the design of peptide drugs and emergence of gene therapy. These biotechnology-derived agents may dominate the next generation of drug design. However, their clinical success may be dependent on the design of controlled release devices that ensure that the drugs reach their target cells precisely at the required time. A discussion of the pharmacological and clinical motivations for controlling the release of the specific drug classes referred to above is beyond the limit of this article; however, a number of excellent reviews are available.[16,17] In addition, it should be noted that controlled release technology is not confined to pharmaceutical applications but has also proven beneficial in agricultural[18] and cosmetic industries.[19]

C. Scope of Polymer Systems

In this review, a number of polymer backbones that are potentially degradable are detailed in the text. This restriction certainly does not reduce the impact and significance of C−C backbones for controlled release applications but is simply a mechanism to focus on an important subset of materials. To illustrate the diverse range of functionalities available—from nonbiodegradable systems based on C−C backbones to heteroatom-containing polymer backbones that may confer biodegradability—Table 1 is provided that overviews polymers used in controlled release applications as a function of the composition of the polymer backbone.

II. Mechanisms of Controlled Drug Release Using Polymers

A diverse range of mechanisms have been developed to achieve both temporal and distribution controlled release of drugs using polymers. This diversity is a necessary consequence of different drugs imposing various restrictions on the type of delivery system employed. For example, a drug that is to be released over an extended period in a patient's stomach where the pH is acidic and environmental conditions fluctuate widely will require a controlled release system very different from that of a drug that is to be delivered in a pulsatile manner within the blood system. An important consideration in designing polymers for any controlled release mechanism is the fate of the polymer after drug release. Polymers that are naturally excreted from the body are desirable for many controlled release applications.[20,21] These polymers may be excreted directly via the kidneys or may be biodegraded into smaller molecules that are then excreted. Nondegradable polymers are acceptable in applications in which the delivery system can be recovered after drug release (e.g., removal of patch or insert) or for oral applications in which the polymer passes through the gastrointestinal tract.

From a polymer chemistry perspective, it is important to appreciate that different mechanisms of controlled release require polymers with a variety of physicochemical properties. This requirement has stimulated the evolution of the new polymers that will be discussed in section IV. Before consideration of these polymers, the major mechanisms of controlled release and polymeric characteristics that are required to carry out these mechanisms will be briefly described.

A. Temporal Controlled

Most drug molecules need to be dissolved in the aqueous environment of the patient and freely diffuse within that media before they can act on their target receptors. Polymeric devices that achieve temporal

Table 1. Summary of Polymer Structures Based on Backbone Composition

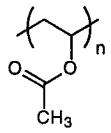
Backbone Structure	Examples	Notes
C-C	**Poly(ethylene)** (PE) 	Zero-order temporal control achieved by diffusion from matrices.[125] Tetanus toxoid released by pulsatile kinetics.[126] Prolonged pseudo-first order release of acetoaminophen in gastrointestinal tract.[127]
	Poly(propylene) (PP) 	Biocompatibility improved by albumin grafting to surface.[128] Ophthalmic drug delivery applications.[129] Accurel® used to release agents active in vapor state.[130]
vinyl-based C-C	**Poly(vinyl chloride)** (PVC) 	Membrane devices formulated to release volatile agents into air and non-volatile agents into aqueous solutions.[131]
	Poly(vinyl alcohol) (PVA) 	Water-soluble copolymer of vinyl alcohol and vinyl acetate is formed by hydrolyzing poly(vinyl acetate). Surface stabilizer in microsphere formulation.[132,133] Bioadhesive hydrogels.[134]
vinyl-based C-C	**Poly(ethylene-vinyl acetate)** p(EVAc) 	Employed as rate controlling membrane in Ocusert®.[23] Drug permeability tailored by ratio of vinyl acetate present. Used in magnetically controlled temporal release,[135,136] ultrasound-stimulated release, subcutaneous implant for cancer pain relief,[137] and chemotherapeutic agents.[138]
	Poly(enol-ketone) (PEK) 	Produced by controlled oxidation of PVA.[139]

Table 1 (Continued)

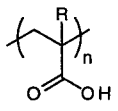
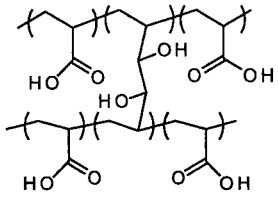
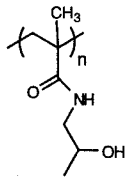
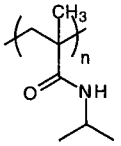
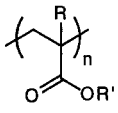
Backbone Structure	Examples	Notes
	Poly(acrylic acid) (PAA)  R = H (acrylic) = CH_3 (methacrylic)	Bioadhesive polymer.[134] Hydrogels of PAA reversibly swell as function of pH.[140]
	Poly(carbophil) 	PAA-based hydrogel loosely cross-linked with divinyl glycol. Mucoadhesive properties allow temporal and distribution control.[141]
vinyl-based C-C	**Poly(acrylamides)** e.g., poly(N-(2-hydroxypropyl) methacrylamide) p(HPMA) 	Plasma expander used as polymer-drug conjugate for distribution control.[142] Enzyme cleavable side chains employed to target release at colon.[32] Hydrolytically degradable hydrogels produced by cross-linking with N,O-dimethacryloyl hydroxylamine linker.[143] Component of photosensitive delivery system.[144]
	Poly(N-isopropyl acrylamide) e.g., p(NIPAAm) 	Pronounced negative thermosensitivity. Used in stimuli sensitive systems.[140,145]
	Poly(acrylates)  R = H (acrylic) = CH_3 (methacrylic) = CN (cyanoacrylate)	Employed as surgical adhesive due to polymerization in water at room temperature. Controlled drug release applications reported in polymer-drug conjugate[146] and topical applications.[147] Bone cements with hydrophilicity tailored to facilitate protein release.[148]

Table 1 (Continued)

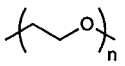
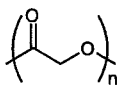
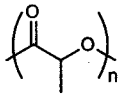
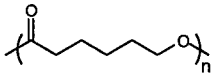
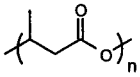
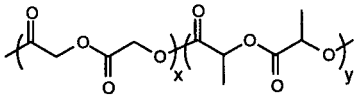
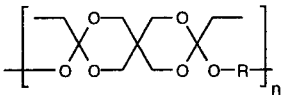
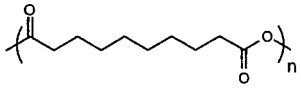
Backbone Structure	Examples	Notes
C-O	**Poly(ethylene glycol)** (PEG) 	Also termed poly(ethylene oxide) (PEO). Used as diffusion-limited tablet formulation,[149] cross-linked hydrogels,[150] and polymer-drug conjugates.[29,151] Employed as a component of block copolymer systems. **Section B.2.**
C-O, C=O	**Poly(glycolic acid)** (PGA)  **Poly(lactic acid)** (PLA)  **Poly(ε-caprolactone)** (PCL)  **Poly(3-hydroxybutyrate)** 	*copolymer:* **Poly(lactic acid-*co*-glycolic acid)** (PLGA)  Biosynthetic poly(ester) often employed as copolymer with hydroxyvalerate monomer.[152] **Section B.1.**
C-O, C=O	**Poly(ortho esters)** e.g., 3,9-diethylidene 2,4,8,10-tetraoxaspiro [5.5]undecane-based polymers (DETOSU) 	**Section C.**
	Poly(anhydrides) e.g., poly(sebacic anhydride) 	**Section D.**

Table 1 (Continued)

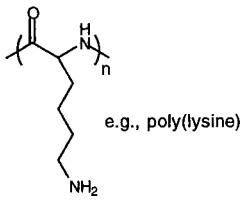
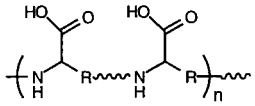
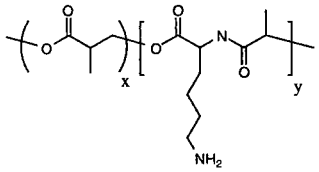
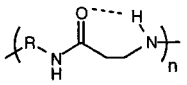
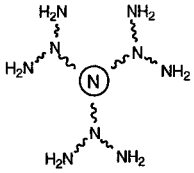
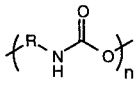
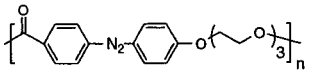
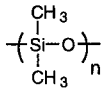
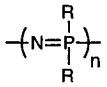
Backbone Structure	Examples	Notes
C-N, C=O	**Poly(amino acids)**  e.g., poly(lysine) **pseudo-poly(amino acids)** 	**Poly(lactic acid-*co*-lysine)** (PLAL)  **Section E.**
C-N, C=O	**Poly(amide-enamines)** 	Hydrolyzable polymer with hydrophilic and hydrophobic segments. Potential for diffusion controlled drug release.[139]
	Poly(amido amines) (PAMAM) **dendrimers** 	Complexes with DNA to form conjugates for gene therapy.[153,154]
other C-N, C-O, C=O	**Poly(urethanes)** 	Hard and soft segment polymers containing PEG for temporal controlled release.[155] Azo-containing polymers used to control site of polymer-drug conjugate degradation.[156] Anti-infectious biomaterials containing antibiotics.[10]
	Azopolymer poly(ether-ester) 	Azo bond degraded by bacteria in colon thereby generating colon-specific delivery of chemotherapeutic and other drugs.[157-159]

Table 1 (Continued)

Backbone Structure	Examples	Notes
silicon-based Si-O	**Poly(dimethylsiloxane)** 	Temporal controlled release of rifampicin from shunt.[160] Bone infections treated with crosslinked matrix.[161]
phosphorus-based P=N, P-O	**Poly(phosphazenes)** 	Amino acid side chains generate flexible materials that degrade to amino acid, phosphate and ammonia poly[bis(glycine ethyl ester)phosphazene].[116] PEG-modified nanoparticles for site-specific drug delivery.[118] **Section F.**

controlled release protect drug molecules from this aqueous living environment for preprogrammed periods of time. This protection can involve delaying the dissolution of drug molecules, inhibiting the diffusion of the drug out of the device, or controlling the flow of drug solutions.[22] These mechanisms are shown in Figure 3. Mathematical descriptions of release mechanisms have been described previously.[23]

Polymers employed to delay drug dissolution aim to slow the rate at which drug molecules are exposed to water from the aqueous environment surrounding the drug delivery system. This may be achieved by a polymer coating or matrix that dissolves at a slower rate than the drug.

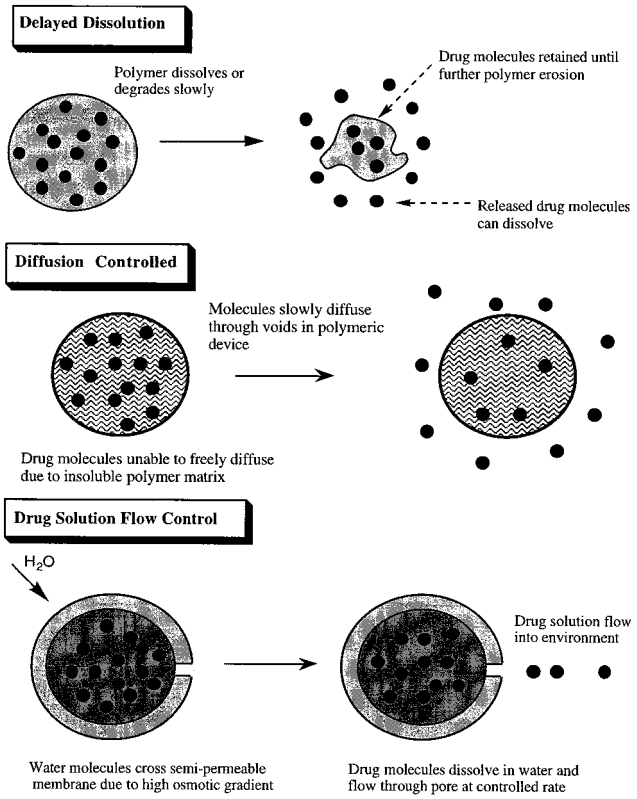


Figure 3. Examples of mechanisms of temporal controlled release.

In diffusion-controlled release, drug molecule diffusion within an aqueous solution is inhibited by the insoluble polymer matrix in which drug molecules must travel through tortuous pathways to exit the device. Polymer chains such as those in a cross-linked hydrogel form the diffusion barrier. The barrier to diffusion can be decreased by swelling of the hydrogel, for example, which creates voids in the gel structure. Such hydrogels may also benefit from bioadhesive characteristics which allow them to reside within the gastrointestinal tract for extended time periods. Polymers used for diffusion-controlled release can be fabricated as either matrices in which the drug is uniformly distributed or as a rate-limiting membrane that protects the drug reservoir from the living environment.

Devices that control the flow of drug solutions sometimes utilize osmotic potential gradients across semipermeable polymer barriers to generate pressurized chambers containing aqueous solutions of the drug. This pressure is relieved by the flow of the solution out of the delivery device. The rate of flow is controlled because flow is restricted to fluid transport through a micrometer scale to larger diameter pore or pores.

Many temporal controlled release devices use the above mechanisms to provide sustained release of drug at a constant rate. Another form of temporal controlled release is responsive drug delivery in which drug is released in a pulsatile manner only when required by the body.[24] Much work in this area has as its eventual goal the delivery of insulin to diabetics. Insulin requirements fluctuate throughout the day as patient food intake and activity change blood glucose levels. Current insulin formulations require repeated injections daily and careful control of glucose intake. Responsive drug delivery hopes to

revolutionize insulin therapy with the design of systems that release insulin in response to increased blood glucose levels. In general, responsive drug delivery systems have two components: a sensor that detects the environmental parameter that stimulates drug release and a delivery device that releases drug. For diabetes treatment, responsive drug delivery systems have been proposed that use the enzyme glucose oxidase as the sensor.[25] When blood sugar levels rise, glucose oxidase converts glucose to gluconic acid resulting in lowered pH. This pH decrease is then used as the signal for insulin release. Release is achieved by pH-sensitive polymers that either swell or degrade in acidic environments.[26]

The concept of responsive drug delivery can be used for any drug therapy in which a sensor and delivery device can be coupled. Signals that have been employed to trigger drug release have been reviewed by Langer[27] and include the following: *magnetic* signals in which magnetic beads are distributed within a polymer matrix and cause a rearrangement of that matrix when a magnetic field is applied; *electrical* signals in which pore size, permeability, and other factors are controlled by electrically stimulated polymer swelling; *ultrasonic* signals in which the intensity, frequency, and duration of ultrasound increase release for both nondegradable and biodegradable polymeric systems; *pH* systems in which ionizable groups within polymer gels control polymer chain interactions; and *temperature* systems in which thermosensitive hydrogels swell and collapse in response to temperature variations.

B. Distribution Controlled

The simplest method of achieving distribution control is to implant the drug delivery system directly at the site. This method has been successfully described in the delivery of chemotherapeutic agents to malignant gliomas using poly(anhydrides) by Brem et al.[4] During treatment, polymer disks containing carmustine are implanted in cavities created after surgical removal of the tumor. This distribution control is highly beneficial given that 90% of malignant gliomas recur within 1 in. of the original tumor site. In general, direct implantation is suitable for distribution control only if the site of drug action is accessible without risk to the patient and the drug is unable to leave this site, e.g., the drug is unable to pass through the blood−brain barrier.

For the majority of diseases that require distribution controlled release of drug, a targeting mechanism must be employed that allows the delivery system to find the desired target.[17] Polymers are used in two types of delivery systems for these applications, colloidal carriers and polymer−drug conjugates. In colloidal formulations, the polymer encapsulates drug within micro- or nanoparticles.[28] In polymer−drug conjugates, the drug is covalently coupled to the polymer. In these forms of distribution controlled release, the polymer acts as a carrier but is not responsible for targeting the delivery device.[29] Biological molecules such as immunoglobulins and carbohydrates are frequently utilized as targeting moieties. However, there are several examples of targeting in which distribution control is an inherent property of the polymeric carrier. Polymer surfactants such as block copolymers of poly(ethylene glycol) and poly(propylene oxide), also referred to as pluronics, alter the distribution of colloidal carriers around the body.[30,31] The change in distribution depends on the ability of the surfactant polymer to change protein adsorption on the particle surfaces (section IV.B.2). In another case, the polymer drug−conjugate contains a spacer molecule that is site-specifically cleaved. One application of this targeting approach is the delivery of drugs to the colon, and site-specific cleavage is ensured by the presence of linkages that are only degraded by bacteria present in that section of the gastrointestinal tract.[32]

III. Polymers Used for Controlled Drug Release

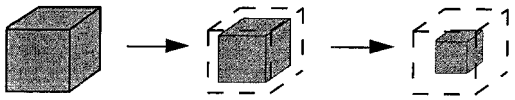
A. Overview

Classification of polymers in controlled release applications can be difficult due to the inherent diversity of structures. However, it is beneficial to attempt this classification because it can highlight common properties within groups of polymers. In broad terms, polymers may be classified as either biodegradable or nonbiodegradable. Biodegradable systems have garnered much of the recent attention and development in drug delivery systems because nonbiodegradable systems need retrieval or further manipulation after introduction into the body.

In the realm of degradable polymers, there exists another level of classification based upon the mechanism of erosion. The term “degradation” specifically refers to bond cleavage, whereas “erosion” refers to depletion of material. Degradation is a chemical process; erosion is a physical phenomena reliant on dissolution and diffusion processes. Two mechanisms of polymer erosion can be identified, surface and bulk erosion. In practical terms, these two mechanisms represent extremes. For most biodegradable polymers both mechanisms will occur, but the relative extent of surface or bulk erosion varies radically with the chemical structure of the polymer backbone.

Surface erosion occurs when the rate of erosion exceeds the rate of water permeation into the bulk of the polymer. This is often considered to be a desirable mechanism of erosion in drug delivery because the kinetics of erosion, and hence the rate of drug release, are highly reproducible. Furthermore, the magnitude of erosion may be changed by simply changing the surface area of the drug delivery device. The slow rate of water permeation into surface eroding devices has a further beneficial effect of protecting water labile drugs up to the time of drug release. Examples of surface eroding polymers discussed in this review are the poly(anhydrides) and the poly(ortho esters). Both of these classes of biodegradable polymers possess highly labile groups that ensure rapid hydrolysis of polymer chains encountering water molecules. Water permeation is retarded by designing the polymers with hydrophobic monomer units. Alternatively, hydrophobic excipients can be added to stabilize the polymer bulk. In ideal surface erosion, the erosion rate is directly propor-

tional to external surface area. Surface erosion can lead to zero-order drug release provided that diffusional release is limited and the overall shape remains constant.



Idealized Surface Erosion

Bulk erosion occurs when water molecules are able to permeate into the bulk of the polymer matrix at a quicker rate than erosion. As a consequence, polymer molecules in the bulk may be hydrolyzed and the kinetics of polymer degradation/erosion are more complex than for surface eroding polymers. The majority of biodegradable polymers used in controlled drug delivery undergo bulk erosion, including the very important poly(ester) materials. While the more limited predictability of erosion and the lack of protection of drug molecules are inherent disadvantages to bulk eroding devices, these properties do not inhibit their successful employment as drug delivery devices. In addition, many new applications in controlled release use nano- or microparticle formulations that possess massive surface areas resulting in bulk and surface eroding materials possessing similar erosion kinetics.

Within the scope of biodegradable systems, natural polymers, particularly those in the poly(saccharide) family (e.g., starch, cellulose, and chitosan), are being investigated.[33] They are referred to as biopolymers, and synthesis of this class of polymers is limited to the manipulation of bulk material to enhance their viability. Due to the physicochemical limitations of natural materials, there is significant exploration of synthetic materials which can be readily tailored to offer properties for specific applications. For example, degradation of synthetic polymer can be limited to 1 week or 1 month, depending on the desired range of therapeutic effect. The ability to design biomaterials with specified release, mechanical, and processing properties has opened opportunities for synthetic chemists in the controlled release arena.

Historically, homopolymers such as the poly(esters) (section III.B) were first in the discovery process for synthetic biomaterials due to their availability. As properties are defined and utilized from homopolymer systems, copolymer systems emerge that combine and merge desired function for more effective systems. Biodegradable materials possess chemical functionalities that are unstable within living environments, e.g., anhydride, ester, or amide bonds. The most common routes of biodegradation in vivo are hydrolysis and enzymatic cleavage resulting in scission of the polymer backbone. However, for some polymers, cleavage of a side chain results in a water-soluble polymeric product that can be excreted. Biodegradation is frequently a desirable property for controlled release applications because metabolism and excretion of the polymer results in complete removal. In the presence of enzymes, rates of biodegradation are enhanced. The role of degradative enzymes is to both facilitate the mechanism as well as increase the degradation rate.

Table 1 provides an overview of polymeric systems used in controlled release as a function of chemical makeup of the polymer backbone with corresponding references. Table 1 includes a diverse range of functionalities: from nonbiodegradable systems based on C−C backbones to potentially degradable heteroatom-containing polymer backbones. In the remainder of this review, a number of polymer backbones that may confer biodegradibility will be detailed in the text. This restriction certainly does not reduce the impact and significance of C−C backbones for controlled release applications but is simply a mechanism to focus on an important subset of materials.

B. Poly(esters)

Poly(esters) are the best characterized and most widely studied biodegradable system. The synthesis of poly(esters) has received as much attention as the degradation of these materials. A patent for the use of poly(lactic acid) (PLA) as a resorbable suture material was first filed in 1967.[34] The mechanism of degradation in poly(ester) materials is classified as bulk degradation with random hydrolytic scission of the polymer backbone.

Poly(esters) have been extensively employed in drug delivery applications and comprehensively reviewed.[35−38] The predominant synthetic pathway for production of poly(esters) is from ring-opening polymerization of the corresponding cyclic lactone monomer. The more prominent poly(esters) and their starting materials are shown in Figure 4.

Polymerization of the cyclic lactone alone is usually too slow to produce high molecular weight material (>20 000 amu). The rate of ring opening for the cyclic lactone can be increased by activation of a Zn- or Sn-based catalyst with the carbonyl ester. However, the introduction of a catalyst invites concerns over traces of potentially cytotoxic material. Thus, stannous octoate $Sn^{II}(CO_2CH(^nBu)(Et))_2$ is commonly used because it has FDA approval as a food stabilizer.[35] Alternatively, resorbable Fe(II) salts have been uti-

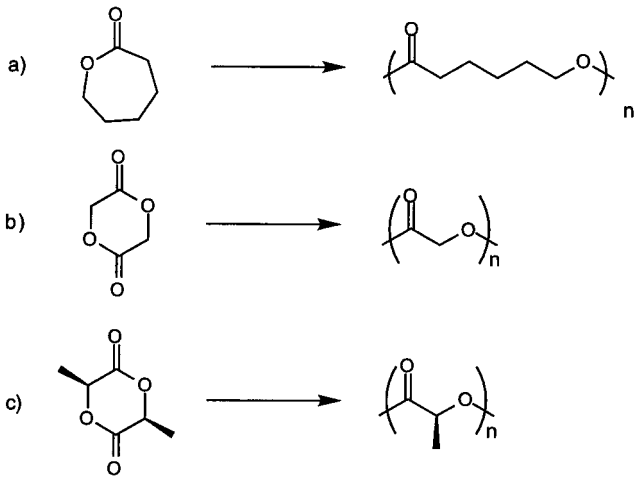


Figure 4. Ring-opening polymerization of selected cyclic lactones to give the following: (a) poly(ϵ-caprolactone) (PCL); (b) poly(glycolic acid) (PGA); (c) poly(L-lactic acid) (PLA).

lized as initiators for lactide polymerization above 150 °C.[39] Zinc powder and CaH_2 have also been evaluated as potential nontoxic catalysts for copolymer formation of poly(lactic acid) (PLA) with poly(ethylene oxide) (PEG).[40]

1. Poly(lactic acid), Poly(glycolic acid), and Their Copolymers

Poly(esters) based on poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers, poly(lactic acid-*co*-glycolic acid) (PLGA), are some of the best defined biomaterials with regard to design and performance. Lactic acid contains an asymmetric α-carbon which is typically described as the D or L form in classical stereochemical terms and sometimes as the *R* and *S* form, respectively. For homopolymers, the enantiomeric forms are poly(D-lactic acid) (PDLA) and poly(L-lactic acid) (PLLA). The physicochemical properties of optically active PDLA and PLLA are nearly the same, whereas the racemic PLA has very different characteristics.[41] For example, racemic PLA and PLLA have T_g's of 57 and 56 °C, respectively, but PLLA is highly crystalline with a T_m of 170 °C and racemic PLA is completely amorphous.

The stereochemical dependence of PLA from D- and L-lactide (DD and LL cyclic dimers of lactic acid enantiomers) has also been studied as a function of the catalyst.[42,43] Diad and tacticity concerns for the polymerization with Sn- and Zn-based initiators have shown a preference for DD/LL and LL/DD heterotactic additions. Such stereoregular concerns are known to affect the mechanical, thermal, and biological properties of PLA.[42]

Because the naturally occurring lactic acid is L (or *S*), PLLA is considered more biocompatible. The polymers are derived from monomers that are natural metabolites of the body; thus degradation of these materials yields the corresponding hydroxy acid, making them safe for in vivo use. Biocompatibility of the monomer is the foundation for biocompatibility of degradable polymer systems. To this end, the degradation products often define the biocompatibility of a polymer—not necessarily the polymer itself. Even though PLGA is extensively used and represents the gold standard of degradable polymers, increased local acidity due to the degradation can lead to irritation at the site of the polymer employment. Introduction of basic salts has been investigated as a technique to control the pH in local environment of PLGA implants.[44]

From a physical level of understanding, poly(esters) undergo bulk degradation. PLA homopolymers degrade slower than PGA homopolymers on the basis of crystallinity as well as steric inhibition by the pendent methyl group of PLA to hydrolytic attack. However, the complexity of PLA, PGA, and PLGA degradation has been demonstrated by Vert[45] and does not conform to a simple model. Vert and coworkers have demonstrated that a size dependence for hydrolytic degradation exists for PLA systems. Other research efforts suggest that PLA-derived microparticles will degrade faster than nanoparticles derived from PLA.[46,47] This is modeled on a diffusion−reaction phenomena. An autocatalytic effect at the interior of larger devices is thought to contribute to the initial heterogeneous degradation of larger devices as acidic byproducts cannot readily diffuse out from the interior as is the case for smaller constructs. Extensive degradation studies have also been reported for PLA, poly(caprolactone) (PCL), and their copolymers both in vitro[48] and in vivo.[49]

Studies in hydrolytic degradation for poly(esters) have focused on understanding the effects of changes in polymer chain composition. A distinguishable effect based on end group composition for poly(ester) degradation demonstrated that terminal carboxyl groups have a catalytic effect on hydrolysis for PGA.[50] The ability to tailor rates of protein release from PLGA microspheres was derived from the understanding of end-group effects.[51] The commercial developmental process for formulating poly(esters) with selected drug candidates has been reviewed.[52] The aforementioned review highlights the development of poly(ester) matrices containing human growth hormone that sustained levels of a therapeutic protein in humans for 1 month from a single dose.[13]

2. Poly(ethylene glycol) Block Copolymers

Poly(ethylene glycol) (PEG) is also referred to as poly(ethylene oxide) (PEO) at high molecular weights. Biocompatibility is one of the most noted advantages of this material. Typically, PEG with molecular weights of 4000 amu is 98% excreted in man.[53]

One of the emerging uses for inclusion of PEG in a controlled release system arises from its protein resistivity.[54] The hydrophilic nature of PEG is such that water hydrogen bonds tightly with the polymer chain and thus excludes, or inhibits, protein adsorption. Many research groups are investigating attachment of PEG chains to therapeutic proteins; PEG chains at the surface allow for longer circulation of the protein in the body by prolonging biological events such as endocytosis, phagocytosis, liver uptake and clearance, and other adsorptive processes.[55−59]

PLA−PEG copolymer systems (Figure 5) possess surfactant properties because the PEG block is very hydrophilic and the PLA block is hydrophobic. Therefore, when PLA−PEG is employed in a fabrication process that uses an aqueous external phase, e.g., particle fabrication by the double emulsion technique, PEG enriches the surface. The inclusion of PEG in copolymer systems imparts extremely beneficial surface properties within the body because of the ability to repel proteins within aqueous environments.[54] This repulsion inhibits the adsorption of proteins to the polymer surface and, therefore, prevents many polymer−cell interactions. For example, nanoparticles made from diblock PLA−PEG copolymer have increased blood circulation times (decreased clearance) in vivo above that of particles made from PLA alone.[60] Further studies demonstrated that PLA−PEG nanoparticles were inert toward proteins of the coagulation system.[61] Cannizzaro et al. have demonstrated that the PLA-PEG structure may act as the foundation for more complex biodegradable materials. They synthesized a PLA-PEG polymer to which a biotin molecule was grafted to the free end of the PEG chain. The new polymer was designed to simplify the

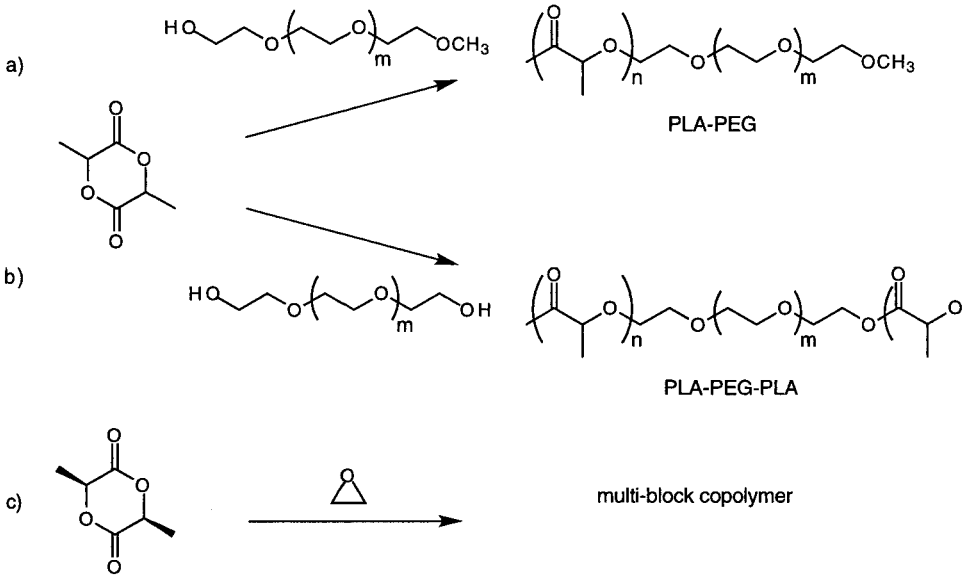


Figure 5. Synthesis of PLA−PEG copolymers: (a) PLA/PEG; (b) PLA/PEG/PLA; (c) a multiblock copolymer of L-lactide and ethylene oxide.

engineering of the polymer surface via the use of avidin−biotin interaction.[62]

PEG can be made with a range of terminal functionalities which lends to its easy incorporation into copolymer systems. PEG is commonly terminated with chain-end hydroxyl groups which provide a ready handle for synthetic modification. Diblock PLA/PEG and triblock PLA/PEG/PLA systems have been synthesized and characterized with various PLA contents.[40,63−66] The free hydroxyl groups of PEG are ring-opening initiators for lactide in forming the diblock or triblock materials (Figure 5a,b). Recently, Chen et al. have synthesized PLA−PEG multiblock copolymers from L-lactide and ethylene oxide, the monomer precursors for PLA and PEG, respectively (Figure 5c).[67] This approach is different in two respects: (i) use of bimetallic catalysts which proceed by anionic mechanisms; (ii) multiblock polymers are generated.

Han and Hubbell further demonstrated the synthetic utility for PLA−PEG systems by introducing acrylate moieties to form cross-linked systems.[68] Similarly, Jeong et al. prepared thermosensitive PLA−PEO hydrogels that exhibit temperature-dependent gel−sol transition for use as injectable drug delivery systems.[69]

C. Poly(ortho esters)

The motivation for designing poly(ortho esters) for drug delivery was the need to develop biodegradable polymers that inhibited drug release by diffusion mechanisms and allowed drug release only after the hydrolysis of polymer chains at the surface of the device.[70]

Most research on poly(ortho esters) has focused on the synthesis of polymers by the addition of polyols to diketene acetals. For example, Heller et al. have described the synthesis and application of the 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane (DETOSU)-based poly(ortho esters).[71] The basic structure is formed by the addition of the DETOSU monomer to a diol to form the chemical structure shown in Figure 6.

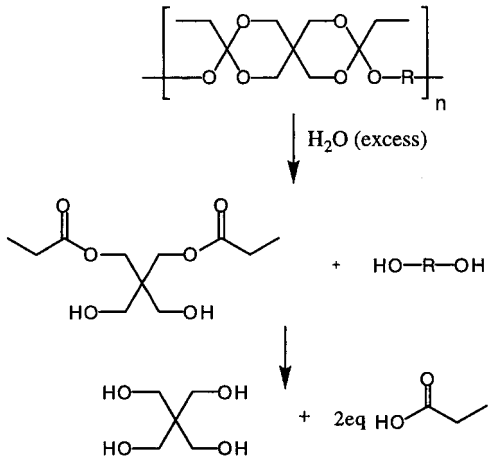


Figure 6. Degradation of the 3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane) (DETOSU)-based poly(ortho esters).

The DETOSU-based poly(ortho esters) contain acid labile ortho ester linkages in their backbone structure. Within aqueous environments, the ortho ester groups are hydrolyzed to form pentaerythritol dipropionate and diol monomers as breakdown products (Figure 6). The pentaerythritol dipropionate is further hydrolyzed to pentaerythritol and acetic acid.

Acid-catalyzed hydrolysis of these polymers can be controlled by introducing acidic or basic excipients into matrixes. Rates of hydrolysis can be increased by the addition of acidic excipients, such as suberic acid, as demonstrated by the zero-order release of 5-fluorouracil over a 15 day period.[72] Alternatively, basic excipients stabilize the bulk of the matrix but diffuse out of the surface region, thereby facilitating surface-only erosion. This approach has been employed in the temporal controlled release of tetracycline over a period of weeks in the treatment of periodontal disease.[73]

Recently, a number of changes in diol structure have been attempted to avoid the need for acidic

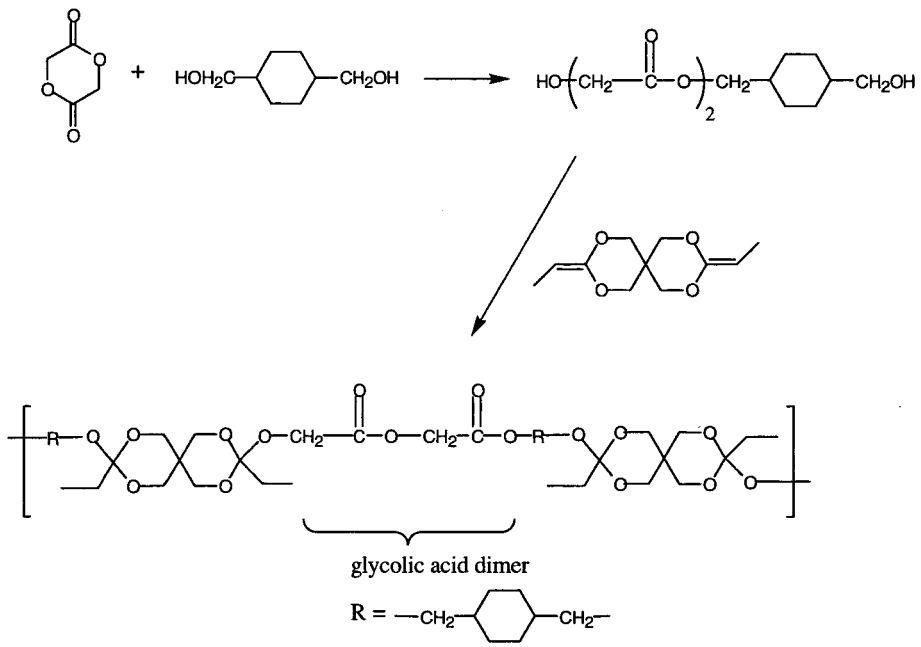


Figure 7. Synthesis of a poly(ortho ester) containing glycolic acid dimer.

excipients. These new poly(ortho ester) structures address the problem of acidic excipient diffusion from matrices which leads to unpredictable degradation kinetics. Ng et al. described the synthesis of self-catalyzed poly(ortho esters) that contain glycolide sequences that can be hydrolytically degraded without excipient catalysis.[74] Once degraded, these sequences then catalyze ortho ester bond breakage, hence forming a self-catalyzing system. The synthesis of these polymers is shown in Figure 7.

A useful feature of the DETOSU systems is the ability to control the mechanical properties by changing the diol monomer ratios within the final polymeric structure. For example, Heller et al. have shown that the glass transition temperature of polymers containing a rigid diol monomer (*trans*-cyclohexanedimethanol) and a flexible monomer (1,6-hexanediol) could be varied between 20 and 105° by increasing the proportion of the rigid diol.[70] This control can also be achieved with the glycolide-containing polymers.[74]

A number of applications have been described for cross-linked poly(ortho esters) formed by the substitution of 1,2,6-hexanetriol for 1,2-hexanediol, for example. The triol monomer allows cross-linked materials to be formed that are semisolid materials.[75] It has been envisaged that these materials could be injected into the patient as a viscous liquid at slightly elevated temperatures that form nondeformable depot implants upon cooling.

A further modification of diol structure has been introduced to allow acid-catalyzed hydrolysis to be highly pH sensitive for applications requiring response. This modification involves the formation of a tertiary amine-containing polymer by incorporating *N*-methyldiethanolamine.[76] This polymer has been proposed as a material for the pulsatile delivery of insulin in which the drug delivery system includes the enzyme glucose oxidase. High glucose levels decrease environmental pH due to the activity of glucose oxidase. In turn, lowered pH increases the rate of poly(ortho ester) hydrolysis thereby increasing insulin release and creating a negative feedback mechanism.

D. Poly(anhydrides)

To obtain a device that erodes heterogeneously, the polymer should be hydrophobic yet contain water-sensitive linkages. One type of polymer system that meets this requirement is the poly(anhydrides). Poly(anhydrides) undergo hydrolytic bond cleavage to form water-soluble degradation products that can dissolve in an aqueous environment, thus resulting in polymer erosion. Poly(anhydrides) are believed to undergo predominantly surface erosion due to the high water lability of the anhydride bonds on the surface and the hydrophobicity which prevents water penetration into the bulk.[77] This process is similar to the slow disappearance of a bar of soap over time. The decrease in the device thickness throughout the erosion process, maintenance of the structural integrity, and the nearly zero-order degradation kinetics suggest that heterogeneous surface erosion predominates.

The majority of poly(anhydrides) are prepared by melt-condensation polymerization. Starting with a dicarboxylic acid monomer, a prepolymer of a mixed anhydride is formed with acetic anhydride. The final polymer is obtained by heating the prepolymer under vacuum to remove the acetic anhydride byproduct. The most widely studied poly(anhydrides) are based on sebacic acid (SA), *p*-(carboxyphenoxy)propane (CPP), and *p*-(carboxyphenoxy)hexane (CPH) (Figure 8).

Degradation rates of these polymers can be controlled by variations in polymer composition. The more hydrophobic the monomer, the more stable the anhydride bond is to hydrolysis. Aliphatic poly(anhydrides) (e.g., SA) degrade within days whereas

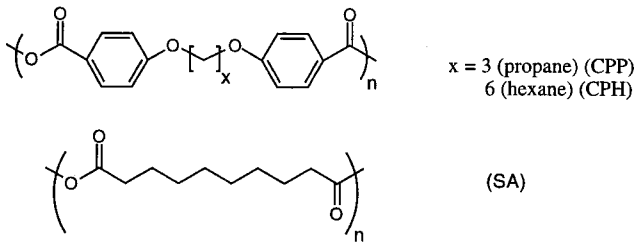


Figure 8. Structures of widely used aromatic poly(anhydrides) based on monomers of *p*-(carboxyphenoxy)propane (CPP) and *p*-(carboxyphenoxy)hexane (CPH) and aliphatic poly(anhydrides) based on sebacic acid (SA).

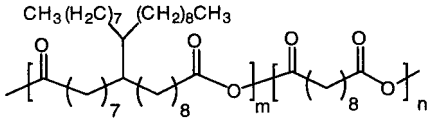


Figure 9. Poly(fatty acid dimer−sebacic acids) synthesized from hydrophobic dimers of erucic acid and sebacic acid.

aromatic poly(anhydrides) (e.g., CPH) degrade over several years.[77]

Poly(anhydrides) are best formed into drug-loaded devices by compression-molding or microencapsulation because of their high melting temperatures. A wide variety of drug and proteins, such as insulin, enzymes, and growth factors, have been incorporated into poly(anhydride) matrixes and their in vitro and in vivo release characteristics evaluated.[78,79] Leong et al. demonstrated[80] that reaction of the poly(anhydrides) with drug molecules containing nucleophilic groups did not occur during fabrication using solvent-casting techniques or when low temperatures are maintained during compression molding.

The biocompatibility of copolymers of SA and CPP has been well established. Evaluation of the toxicity of poly(anhydrides) show that they possess excellent in vivo biocompatibility.[81] Recent clinical trials have demonstrated that an intracranial device of SA/CPP copolymers improves the therapeutic efficacy of an antitumor agent, bischloronitrosourea, for patients suffering from a lethal type of brain cancer.[82]

Another type of poly(anhydride) is poly(fatty acid dimer−sebacic acid). These are synthesized from hydrophobic dimers of erucic acid and sebacic acid (Figure 9). They undergo surface erosion as indicated by the presence of an erosion zone, independence of erosion rate on device thickness, and low water contact in the polymer interior during erosion.[83] In vitro and in vivo elimination of the polymers is dependent upon monomer solubility. For example, the elimination time for polymers based on water-soluble monomers (shorter side chains) was 7−14 days, whereas for polymers based on monomers with low water-solubility (longer alkyl side chains) elimination took nearly 8 weeks.[84,85]

As the polymers degrade, most of the fatty acid dimers deposit on the surface of the polymer matrixes to effectively act as a diffusion barrier for the release of low molecular weight compounds (e.g., drugs or monomers) from polymer devices.[86]

1. Poly(anhydride–imides)

Poly(anhydrides) have been modified by inclusion of amino acids such as glycine and alanine into the

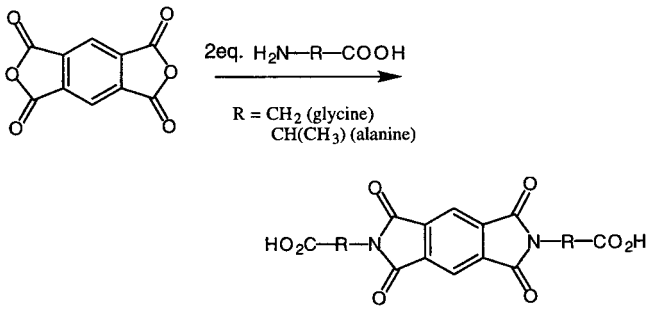


Figure 10. Poly(anhydrides) monomers that yield poly(anhydride−imides) include amino acids.

polymer backbone (Figure 10) to increase the mechanical properties (e.g., Young's modulus and compressive strength) of the poly(anhydrides).

The amino acids are incorporated by imide bonds at the amino terminus, leaving the terminal carboxylic acids available for activation by acetic anhydride.[87] The amino acid-containing units can then be copolymerized with activated monomers such as SA and/or CPH.

The poly(anhydride−imides) appear to undergo predominantly surface erosion similar to the poly(anhydrides).[88,89] IR and NMR spectral data verify the visual evidence that degradation of the poly(anhydride−imides) happens in several stages. Water is first absorbed into the matrix, with hydrolysis of the anhydride bonds occurring at the forefront of the inner erosion zone. Hydrolysis of the polymer backbone continues until the monomer units are solubilized in water. Finally, monomer units were removed by diffusion through the polymer matrix.[90]

2. Poly(anhydride–esters)

Other modifications of poly(anhydrides) include poly(anhydride−esters), which include two different types of hydrolytically cleavable bonds in the polymer backbone. In one example, low molecular weight carboxylic acid-terminated prepolymers of poly(ϵ-caprolactone) were coupled via anhydride linkages.[91] The intent of this research was to design polymers that displayed two-stage degradation profiles: anhydride bonds rapidly hydrolyzed to the poly(ester) prepolymers which degraded much more slowly.

In another example, carboxylic acid-terminated monomers that contain ester bonds are activated and then polymerized using the same chemistry described for the poly(anhydrides). A unique aspect of these poly(anhydride−esters) is that hydrolytic degradation of the polymer backbone yields a therapeutically useful compound, salicylic acid (Figure 11).[92]

As stated previously (section III.B.1), biocompatibility of polymers' degradation products typically define the biocompatibility of the polymers themselves. This work is the first example where the polymer's degradation products are potentially beneficial.

E. Poly(amides)

The most interesting class of poly(amides) for controlled release are the poly(amino acids). The

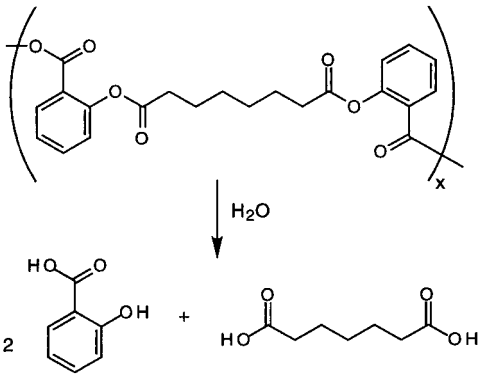


Figure 11. Poly(anhydride−esters) that degrade into salicylic acid, an antiinflammatory agent.

synthetic ability to manipulate amino acid sequences has seen its maturity over the last two decades with new techniques and strategies continually being introduced. An excellent review of the history of amino acid-derived polymers is given by Nathan and Kohn.[93] Poly(amino acids) have been used predominantly to deliver low molecular weight drugs, are usually tolerated when implanted in animals,[94] and are metabolized to relatively nontoxic products.[95] These results suggest good biocompatibility, but their mildly antigenic nature makes their widespread use uncertain. Another concern with poly(amino acids) is the intrinsic hydrolytic stability of the amide bond which must rely upon enzymes for bond cleavage. The dependence on enzymes generally results in poor controlled release in vivo.

The expense and difficulty in production of elaborate polypeptide sequences has limited the composition to homopolymers, predominantly poly(glutamic acid) and poly(aspartic acid). Poly(amino acids) are generally hydrophilic with degradation rates dependent upon hydrophilicity of the amino acids.[96,97] Amino acids are attractive due to the functionality they can provide a polymer. For example, poly(lactic acid-*co*-lysine) (PLAL) was synthesized using a stannous octoate catalyst from lactide and a lysine-containing monomer analogous to lactide (Figure 12). Inclusion of the amino acid lysine provides an amino group that allows for further modification of the PLAL system.[98] Recently, peptide sequences that promote cell adhesion have been attached to PLAL.[99]

The use of *N*-carboxyanhydride-activated amino acids was the first efficient method for production of amino acid homopolymers. Hrkach et al. have recently exploited the PLAL system by reaction with lysine *N*-carboxyanhydride derivatives to increase the systems functionality with a poly(lysine) graft.[100] PLAL has been formulated into microspheres that exhibit deep lung delivery from porous particles.[101]

Poly(amino acids) can be modified to enhance release or bioavailability of drug by attaching the drug molecule to the polymer via carboxylate bonds. An example is the attachment of the chloroformate derivative of norethindrone (a steroid) to poly[*N*-(3-hydroxypropyl)-L-glutamine].[102] The polymer conjugates were designed as insoluble particles for prolonged drug release and act by penetrating cells and then releasing drug by the action of lysosomal enzymes.[103] Enzymatic degradation of synthetic

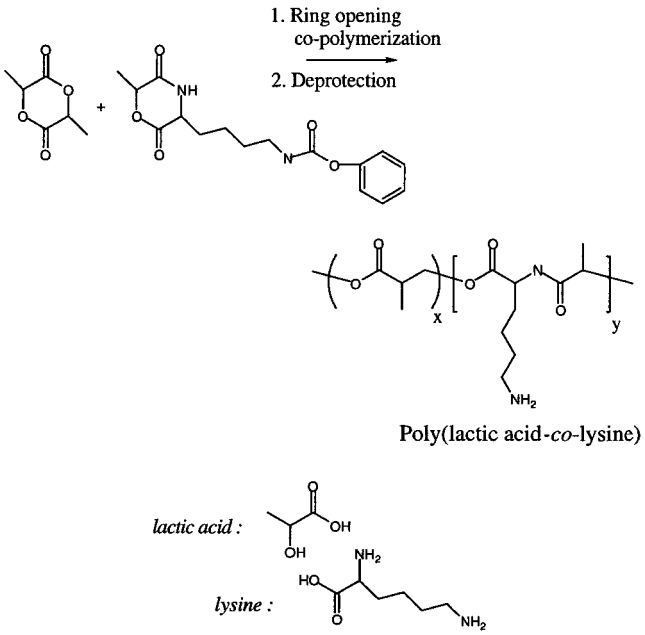


Figure 12. Poly(lactic acid-*co*-amino acid) (PLAL) polymer system.

polypeptides and poly(amino acids) along with an evaluation of their utility as drug delivery systems has been reviewed.[104]

1. Poly(iminocarbonates)

Poly(amino acids) are highly insoluble, nonprocessible, and antigenic when the polymers contain three or more amino acids.[105] To circumvent these problems, "pseudo"-poly(amino acids) synthesized from tyrosine dipeptide were investigated.[106] These degradable polymers are derived from the polymerization of desaminotyrosyl tyrosine alkyl esters. The general structure of these polymers is shown in Figure 13.

Tyrosine-derived poly(carbonates) are readily processible polymers that support the growth and attachment of cells and have also shown a high degree of tissue compatibility.[107] Tyrosine-derived poly(carbonates) are characterized by their relatively high strength and stiffness exceeding poly(esters) such as poly(ortho esters) but not poly(lactic acid) or poly(glycolic acid).[108,109]

The postulated mechanism of in vitro degradation involves hydrolysis of the pendent ester bonds and the imino−carbonate bonds of the backbone.[110] Degradation rates are comparable to the degradation rate of poly(L-lactic acid), occurring over a period of months. Poly(iminocarbonates) are currently being investigated for use in small bone fixation devices as bone screws and pins.[111]

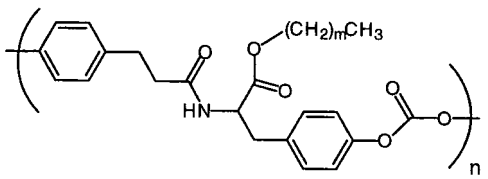


Figure 13. Degradable polymers derived from the polymerization of desaminotyrosyl tyrosine alkyl esters.

F. Phosphorus-Containing Polymers

1. Poly(phosphazenes)

Poly(phosphazenes) provide an interesting contrast to the development of poly(ester), poly(ortho ester), and poly(anhydride) systems because properties and biodegradation kinetics are generated by structural changes in the side-chain structure rather than the polymer backbone.[112] Biomedical poly(phosphazenes) are synthesized by molecular substitution of poly(dichlorophosphazene) as shown in Figure 14.

Generally, it is difficult to perform substitution reactions on polymers because of the lowered reactivity of the side groups. Yet due to the high reactivity of uncrosslinked poly(dichlorophosphazenes) side groups, these polymers can readily undergoes halogen replacement. Poly(phosphazenes) are of particular interest because of their unique inorganic phosphorus−nitrogen backbone and remarkable synthetic versatility. Comprehensive reviews for these polymers have recently been published by Scopelianos and Allcock.[112,113] The poly(phosphazenes) provide covalent and coordinate drug binding sites and breakdown into nontoxic products such as phosphate, ammonia, amino acids, and ethanol.

Biodegradable poly(phosphazenes) that are insoluble in water prior to hydrolysis have been employed in the temporal controlled release of many drug classes including nonsteroidal antiinflammatory agents and peptides.[8,114−116] For these types of applications, poly(organophosphazenes) have been synthesized that possess amino acid side groups. When these polymers degrade, they form amino acid, ethanol, phosphate, and ammonium salts. The mechanical properties and rates of degradation have been controlled by appropriate selection of amino acid side-chain structures.[117] The versatility of these polymers has been demonstrated by the formation of 200 nm diameter poly(organophosphazene) nanoparticles that present covalently coupled poly(ethylene glycol) (PEG) at their surfaces.[118] In a development that parallels the synthesis of the self-catalyzed poly(ortho esters) (section III.C), Schacht et al. incorporated hydrolysis-sensitive ester groups that generate pendant carboxylic acid groups which can catalyze the degradation of the inorganic backbone.[114]

A number of approaches have been proposed to generate cross-linked poly(phosphazene) for temporal controlled release. Poly[bis(carboxylatophenoxy)phosphazene] was cross-linked in the presence of Ca^{2+} ions[119,120] to produce an ionically stabilized system. This polymer allowed drug molecules to be encapsulated into poly(phosphazene) microspheres

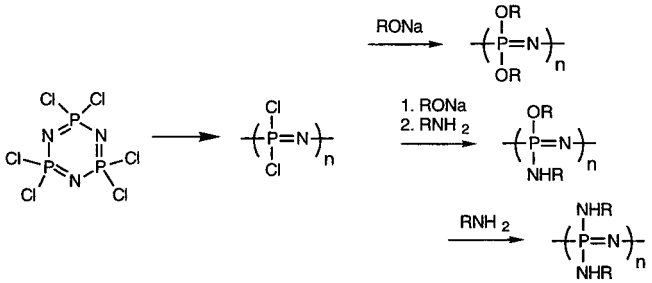


Figure 14. Formation of poly(phosphazenes) and examples of backbone modification.

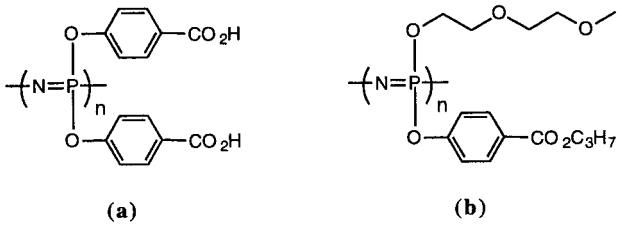


Figure 15. Structures of (a) poly[bis(carboxylatophenoxy)phosphazene] and (b) a poly(phosphazene) with oxybenzoate and methoxyethoxyethoxy side groups.

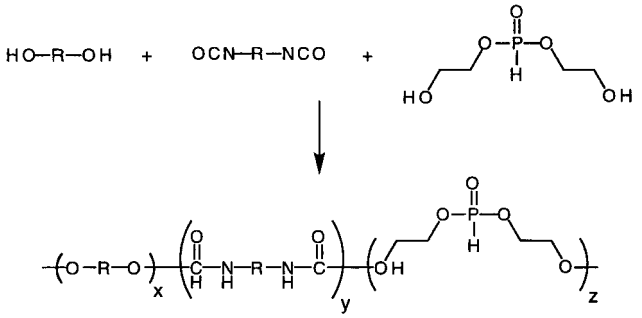


Figure 16. Formation of poly(phosphoester−urethanes).

under mild environmental conditions. pH-sensitive hydrogels have been synthesized by the formation of poly(phosphazenes) with oxybenzoate and methoxyethoxyethoxy side groups (Figure 15). Swelling at different pH values was controlled by varying the ratios of the two side groups.[121]

2. Poly(phosphoesters)

Leong et al. have incorporated phosphoester groups into poly(urethanes).[122] For years, poly(urethanes) have been used as blood-contacting biomaterials because of range of physical properties that can be obtained—from hard and brittle to soft and tacky. Poly(urethanes) were designed to be inert biomaterials, but for some applications controlled biodegradation is desirable. Leong introduced a phosphoester linkage into the poly(urethanes) to provide biodegradable materials that maintain the mechanical properties inherent in the poly(urethanes). Poly(phosphoester−urethanes) are obtained by reaction of diisocyanates and polyols (e.g., PEG) with phosphites added as chain extenders (Figure 16).

Hydrolysis of the poly(phosphoester−urethanes) yields phosphates, amines, alcohols, and carbon dioxide. Phosphoester bonds are readily cleaved under physiological conditions.

In addition, the pentavalency of the phosphorus provides a site for future functionalization. For example, Leong et al. observed that the release kinetics of poly(phosphoester−urethanes) were influenced by the side chains attached via the phosphoester of the polymer backbone.[123] The release mechanism was found to be a combination of diffusion, swelling, and degradation.

IV. Conclusions

This review has focused on some of the more widely studied synthetic biodegradable polymers considered or used for controlled release applications. Yet many of the future challenges we face, such as gene therapy delivery, may require degradable polymer systems

modeled with unique requirements for specific applications. At present, there remains a scarcity of materials that can be evaluated for biomaterial applications even though there are many research groups actively designing new materials. One unique approach to polymer design is the use of combinatorial methods to design arrays of new polymeric materials. For example, Kohn et al. created a permutationally designed library of over 100 copolymers.[124] For nonchemists needing polymers for biomedical applications, combinatorial methods provide a large selection of materials to evaluate for their required applications.

The ability to impart bioadhesivity, cell specificity, active transport, or other specific characteristics into a biocompatible polymer represents an important synthetic challenge. Biodegradable polymers have had a remarkable impact on the science of controlled drug delivery and promise to have an even greater impact in human health care.

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