

Polymer-Controlled Drug Delivery Systems

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Research in the area of controlled drug delivery systems has become increasingly important,¹ due to the advantages in safety, efficacy, and patient convenience that these long-acting systems provide. Furthermore, many new complex drugs, e.g., peptides, are often very difficult to deliver in a convenient way by any other means. Controlled release systems exist in many forms, including specially-designed tablets that can be taken orally, injectable microspheres or implants, and transdermal patches. In this paper we discuss mechanisms of controlled drug delivery systems and examine progress in the area of transdermal, oral, and injectable/implantable systems.

Mechanisms of Drug Release

We define a controlled release system as an entity which delivers a drug at a predetermined rate (constant if desired) for a long time (at least 12 h). Controlled release systems can be constructed from either polymers or pumps. Because of their small size and lower cost, polymers have been the most widely-used controlled release vehicles.

There are three fundamental mechanisms by which polymers release drugs.² The first of these is diffusion. In some cases (reservoir systems), the drug is surrounded by a polymer membrane, such as a capsule or microcapsule. In other cases (matrix systems), the drug is uniformly distributed through the system. In both cases, diffusion of the drug through the polymer backbone or pores in the polymer membrane is the rate-limiting mechanism. Release rates from membranes are determined by the steady-state Fick's Law diffusion equation:

$$J^* = -D \, dc/dx \quad (1)$$

Here D is the concentration-independent drug diffusion coefficient in the membrane, J^* is the drug molar flux, and dc/dx is the drug concentration gradient within the membrane. For a concentration-independent dif-

fusion coefficient and constant membrane thickness, eq 1 can be rewritten as

$$J^* = D\Delta c/l \quad (2)$$

where l is the membrane thickness. To maintain a constant flux, the transmembrane concentration difference, Δc , must be constant. This can be achieved by maintaining a constant, high drug concentration at the membrane's inner wall. To accomplish this, powdered drug can be loaded at a level much higher than the drug solubility. As long as powdered drug is available, the drug concentration at the inner wall will be the drug saturation concentration, and constant release will occur.

The most commonly used membranes for controlled release systems are nonporous homogeneous polymeric films. For these systems it is convenient to rewrite eq 2 as follows:

$$J^* = DK\Delta c/l = dM/A \, dt \quad (3)$$

Here the drug partition coefficient, K , describes the equilibrium ratio of the saturation concentration of the drug in the membrane to that in the surrounding release medium (e.g., water), and Δc represents the drug concentration difference of the solutions on either side of the membrane. The steady-state flux, J^* , per unit area of exposure, A , can be also expressed as $dM/A \, dt$, where M is the quantity of drug released at time t .

Microporous membranes are also used in controlled release polymer systems. In this case the drug does not pass through the polymer phase, but diffuses through the water-filled pores. For these systems, eq 2 may be written as

$$J^* = (D_w \epsilon / \tau) (\Delta c / l) = dM/A \, dt \quad (4)$$

where D_w and c are the diffusion coefficient and concentration, respectively, of the drug in the pore-filling liquid phase and ϵ and τ are the porosity and tortuosity of the membrane, respectively.

In matrix systems the drug is uniformly distributed throughout a solid polymer. There are four general categories describing release rates. For each, there is an equation which can be used to predict initial release rates, i.e., up to 40% release. For example, for matrices in the form of a slab of thickness, l , neglecting any edge effects, in the first case, the drug is molecularly dissolved in the polymer matrix and drug diffusion occurs via a solution-diffusion mechanism. Then

$$dM/A \, dt = 2c_s(D/\pi)^{1/2}(t^{-1/2}) \quad (5)$$

In the second case, the drug is dispersed in the polymer matrix (i.e., it is loaded above its solubility), and

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diffusion occurs via a solution-diffusion mechanism. Then

$$dM/A dt = (1/2)[Dc_s(2c_d - c_s)]^{1/2}(t^{-1/2}) \quad (6)$$

In the third case, the drug is dissolved in the polymer matrix and diffusion occurs through water-filled pores in the matrix:

$$dM/A dt = 2c_d(D_w\epsilon/\tau\pi)^{1/2}(t^{-1/2}) \quad (7)$$

In the final case, the drug is dispersed in the polymer matrix and diffusion occurs through water-filled pores in the matrix

$$dM/A dt = (1/2)[(D\epsilon/t)c_{sw}(2c_d - \epsilon c_{sw})]^{1/2}(t^{-1/2}) \quad (8)$$

In these equations, $dM/A dt$ is the release rate of drug per unit area of exposure, c_s and c_{sw} are the drug solubility in the polymer and water, respectively, and c_d is the initial drug loading (soluble plus insoluble drug per unit volume) of the system. The differences between the cases where drug diffusion is through pores rather than through the polymer backbone involve corrections for the diffusion coefficient due to porosity, ϵ , and tortuosity, τ . In addition, c_{sw} , the solubility of drug in fluid, is used rather than c_s , the solubility in polymer.

The second mechanism involves a chemical reaction. In this case, water or enzymes cause degradation of a polymer which is used to encapsulate a drug (erodible or degradable system) or cleaves a bond between the drug and polymer, releasing the drug (pendant chain system).

From a chemical standpoint, bioerodible systems can be distinguished by three dissolution mechanisms: (1) water-soluble polymers insolubilized by degradable cross-links; (2) water-insoluble polymers solubilized by hydrolysis, ionization, or protonation of pendant side groups; and (3) water-insoluble polymers solubilized by backbone-chain cleavage to small water-soluble molecules. These mechanisms represent extreme cases, and erosion by a combination of mechanisms is possible. The most commonly used biodegradable polymer is poly(lactic acid) or lactic/glycolic copolymers (type 3). Others include poly(vinylpyrrolidone) (type 1), copolymers of methyl vinyl ether (*n*-butyl half-ester) and maleic anhydride (type 2), poly(anhydrides) (type 3), poly(ortho esters) (type 3), poly(ϵ -caprolactone) (type 3), and poly(amino acids) (type 3).

The third type of system is solvent-activated. In this case, the drug is entrapped in the polymer until either external solvent swells the polymer or water imbibement creates osmotic pressure. A particularly interesting form of osmotically controlled release system involves a tablet containing an osmotic agent (which could be the drug itself or an accompanying salt) surrounded by a semipermeable membrane (permeable to water but impermeable to salt or drug). The membrane contains a single laser-drilled hole. The external solvent, water, enters the tablet through the membrane at a constant rate and drives the drug out through the laser-drilled hole at a constant rate. An equation that describes release rates from these systems is

$$dM/A dt = KIIC/l \quad (9)$$

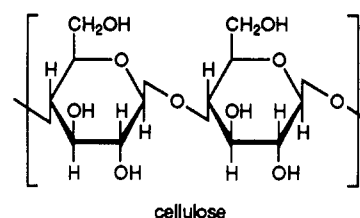
where K is a constant equal to the product of the membrane's hydraulic permeability and its reflection

coefficient, Π is the osmotic pressure of the osmotic agent of the core formulation, C is the drug concentration inside the osmotic tablet core, and l is the membrane thickness. This equation assumes that both the hydrostatic pressure inside the tablet and the osmotic pressure of the external aqueous medium are small compared to Π .

In addition to these general mechanisms, there are a number of ways by which drug release can be augmented by either chemical signals or external forces. For example, by placing magnetic beads in a matrix system and applying an external magnetic field, the beads can be made to "squeeze" drug out through the polymer.³ Alternatively, ultrasound can cause enhanced polymer matrix erosion, leading to increased drug delivery.⁴ Chemical signals have been also utilized to create self-regulated systems. In such cases, an external molecule such as glucose can diffuse into a polymer membrane and react with an enzyme that is immobilized in a standard membrane diffusion-controlled system. The enzymatic reaction with glucose may cause a pH shift which alters membrane permeability⁵ or drug solubility⁶ and thereby changes the release rate.

Materials Used in Controlled Release Systems

There are a number of important requirements for all biomaterials used in controlled release systems. Among these are biocompatibility, processability, and reasonable mechanical strength. In addition, there are a number of criteria specific to the particular controlled release application intended. These include the permeability characteristics of the polymer to various molecules, as well as extent of degradability. Discussed briefly here are some characteristics of polymers widely used in controlled release systems. Among these are cellulose and its derivatives. Cellulose consists of glucose units linked by $\beta(1-4)$ bonds as shown:



The glucose chains are hydrogen bonded with each other and form sheets which impart a great deal of strength to the cellulose fibers. The presence of hydrogen bonds can render cellulose insoluble in water despite its hydrophilicity. Cellulose can be chemically treated or derivatized to change its properties. Ethylcellulose and (hydroxypropyl)cellulose are common derivatives used in pharmaceutical preparations.

The poly α -esters (ester polymers prepared from α -hydroxy acids), in particular poly(glycolic acid) and

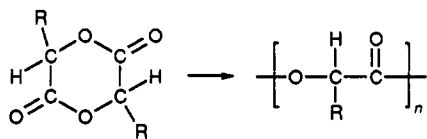
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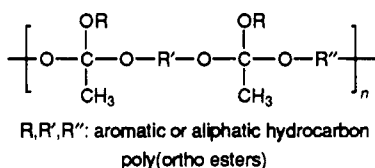
poly(lactic acid), are the most widely used implantable degradable polymers. They are usually produced by ring-opening polymerization of glycolide and lactide and are represented schematically below.



Poly(glycolic acid) (PGA) is a highly crystalline hydrophilic poly ethyl ester. Poly(lactic acid) (PLA) is more hydrophobic than PGA and therefore degrades at a slower rate. In both cases the mechanism is largely due to hydrolysis, and the eventual degradation products are water and carbon dioxide. Copolymers of lactic and glycolic acid, PLGA, are also widely used. By varying the ratio of these two monomers, different degradation and release rates can be achieved.⁷

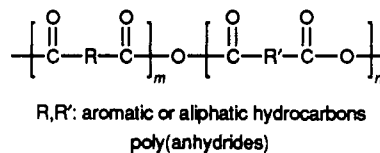
These polymers display bulk erosion characteristics—i.e., polymer mass is lost uniformly throughout the matrix, erosion rates are dependent on the volume of the matrix rather than its thickness, and the lifetimes of different thickness samples are the same.⁸ In contrast, surface eroding systems display material loss from the outside to the inside of matrix, erosion rate is dependent on the surface area rather than the volume of the polymer matrix, and thicker samples have longer lifetimes. Surface eroding systems offer the potential advantage of achieving zero-order degradation kinetics if the polymer system possesses a shape whose surface area does not change during erosion. A surface eroding system also minimizes the possibility of dose dumping.

There are several polymers that have been synthesized in attempts to achieve surface erosion. One of these polymer families is the poly(ortho esters):



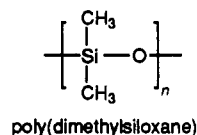
The rate of degradation of poly(ortho esters) is usually controlled by adding acid or basic compounds into the polymer matrix which can be used to control the hydrolysis rates.⁹ These excipients maintain the matrix bulk at a different pH than the matrix surface, enabling surface erosion to be obtained if the excipients do not diffuse out prior to polymer erosion.

To design an ideal surface eroding system—one that would inherently display the characteristics described above without the need for additives—it has been suggested that hydrophobic polyanhydrides might be a promising class of polymers due to lability of the anhydride bond.

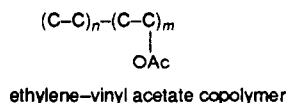


These polymers are generally synthesized by polycondensation¹⁰ and degrade hydrolytically. Among the most widely-used polyanhydrides are copolymers of sebacic acid (SA) and 1,3-bis(carboxyphenoxy)propane (CPP). By varying the ratio of these monomers, erosion times of several days to several years can be achieved for millimeter thick discs.¹¹ While polymers containing mostly CPP or mostly SA display nearly linear erosion (the aromatic PCPP degrades much more slowly than the aliphatic PSA), polymers containing nearly equimolar quantities of SA and CPP displayed two phases of erosion—a more rapid phase of erosion yielding principally SA monomers, and a slower phase of erosion of mostly CPP monomers. This is because PCPP-SA is a random copolymer containing a distribution of CPP-CPP, CPP-SA, and SA-CPP linkages. Erosion is more rapid as the SA-SA and SA-CPP bonds degrade, leaving slow-eroding polymer containing CPP-CPP bonds. To provide more linear release, polyanhydrides were prepared from aliphatic-aromatic dicarboxylic acid monomers—(carboxyphenoxy)alkanoic acids. These monomers possess an aromatic acid on one portion of the monomer and an aliphatic part on the other portion connected by a nonlabile bond. With this monomer construction, it is not possible for the polymer to be enriched in aromatic or aliphatic groups as erosion progresses; thus erosion is completely linear.¹² Polyanhydrides with unsaturated linkages, which offer the possibility of cross-linking,¹³ and polyanhydride co-amides, which display excellent mechanical and thermal qualities,¹⁴ have also been synthesized.

There are also several inert polymers that are frequently used in drug delivery systems. One of the most common is silicone rubber, the structure of which is shown below.



It can be prepared by polymerization of linear silanols and can be cross-linked by benzoyl peroxide or other agents. Silicone has a high permeability to various steroids; high molecular weight silicones have very good biocompatibility. Another widely used nondegradable polymer is ethylene-vinyl acetate copolymer.



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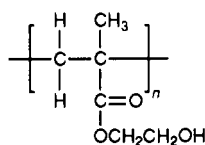
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This polymer also displays excellent biocompatibility, physical stability, biological inertness, and processability. Hydrogels, in particular, poly(2-hydroxyethyl methacrylate) (PHEMA), are also being widely studied.



poly(2-hydroxyethyl methacrylate)

These are prepared by polymerization of the monomer HEMA and can be cross-linked with small amounts of ethylene glycol diethylacrylate (EGDMA).

In addition to the above polymers which are being used clinically, there are many polymers that are still in the experimental stages which offer intriguing biomedical properties. One such polymer family is pseudopoly(amino acids), in which amino acids are polymerized through non-amino (e.g., ester, iminocarbonate) bonds, enabling the creation of poly(amino acids) with tailor-made physical and pharmacological properties.¹⁵ Another is ionically cross-linked polyphosphazenes, which can encapsulate very sensitive entities such as proteins and mammalian cells by simply using water and divalent ions at room temperatures.¹⁶

Transdermal Systems

Transdermal systems provide a novel way of delivering drugs that are difficult to take orally. When taken orally, some drugs may be destroyed by enzymatic degradation by passage through the liver. However, it is not easy to deliver drugs transdermally because the skin is generally an impenetrable barrier. This resistance is provided by the stratum corneum, the outermost layer of the skin, which is composed principally of lipids and keratin. To diffuse through the skin at an appreciable rate, the drug must have both appreciable water and oil solubility (generally at least 1 mg/mL) and a molecular weight of less than 1000. Even if all these requirements are met, a large dosage of drug should not be required. It is generally very difficult for more than 10 mg of a drug to pass through the skin per day through a reasonably-sized transdermal patch.

At present, six drugs have been developed into clinically useful transdermal delivery systems. These include scopolamine for motion sickness, estradiol for hormonal replacement for postmenopausal women, nicotine to achieve smoking cessation, nitroglycerin for angina pectoris, fentanyl for pain relief, and clonidine for hypertension. A number of other transdermal systems are being actively researched.

The most critical issue in achieving effective transdermal drug delivery is that the great majority of drugs do not have the appropriate permeability characteristics to cross the skin at the dosage rate needed on a daily basis. Five procedures are being studied as approaches to enhance transdermal drug delivery. The first involves chemical enhancers. It is hoped that, by combining a chemical enhancer with the drug, the drug's

permeability through the skin can be increased. One example has been the use of ethanol as a transdermal enhancer for estradiol. By adding ethanol, the permeability of estradiol through the skin increased by a factor of 20, making the delivery of this drug practical. However, there is not a clear understanding of what kinds of enhancers are useful for which drugs. In addition, in some cases, when enhancers are combined with drugs in transdermal systems, skin irritation occurs. Future research must be aimed at better understanding how to develop appropriate chemical enhancers.

A second approach has been to chemically modify the drug to make it more lipophilic to enable it to pass through the skin. This type of approach, however, requires developing a new chemical entity, a costly procedure requiring extensive safety testing.

A third approach involves the use of therapeutic ultrasound. This method eliminates the lag times normally associated with transdermal delivery. It has also been shown to provide up to a 20-fold permeability enhancement of certain model drugs like mannitol.¹⁷

A widely studied approach involves iontophoresis. Iontophoresis involves several components including electrodiffusion, electroosmosis, and electrophoresis. It is believed that iontophoresis functions by driving drugs through hair follicles and pores in the stratum corneum. A number of studies have shown promising results using this approach for enhancing the delivery of peptides such as luteinizing hormone-releasing hormone, insulin, and other molecules.^{18,19} Further study will be needed to determine if this approach can be clinically useful in humans.

A final approach involves electroporation. In contrast to iontophoresis, electroporation affects the barrier (skin) by creating temporary pores in the stratum corneum through which drug can presumably penetrate. In addition, to achieve iontophoresis, relatively low voltages (single-digit voltages) over longer periods of time (hours) are used; electroporation involves extremely high voltages (hundreds of volts) for very short periods of time (microseconds). This approach has been shown to achieve up to 1000-fold reversible increases in skin permeability and is effective for molecules of at least 1000 molecular weight.²⁰ A critical feature in the ultimate success of iontophoretic or electroporation systems will be the development of small portable electronic triggering devices that are easy for a patient to apply and remove.

Oral Systems

There are a variety of novel oral drug delivery systems under study. One major goal is more constant release of the drug as it passes through the stomach and gastrointestinal tract. A second goal is to reduce the number of pills one needs to take and to enable the system to act longer.

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One novel approach that is being studied involves the use of the special osmotic tablet.²¹ This method has been shown to release a number of drugs effectively. The most noteworthy of these drugs is nifedipine, a calcium channel blocker used in treating heart disease. First introduced in the form of an osmotic tablet in 1989, its current sales approach one billion dollars per year.

Another novel approach for achieving long-acting constant release involves binding drugs to ion-exchange resins that can be coated with semipermeable membranes. As the drug passes through the gastrointestinal tract, salts in bodily fluids can displace the drug, enabling it to move through the membrane at a relatively constant rate. This approach is useful for charged drugs. Another approach involves using erodible polymers. For example, (hydroxypropyl)methylcellulose has been used to form tablets, the outer layer of which forms a gel acting as a diffusion barrier when exposed to water; over time, the system completely dissolves. Other approaches for oral delivery involve microencapsulating the drug, sometimes by itself or sometimes in combination with nonencapsulated drug, an approach successfully developed for constant-release theophylline systems for treating asthma patients.

Another major challenge in oral delivery is the development of bioadhesive systems which could be used to affect transit time of a drug traveling through the gastrointestinal tract. Several approaches involving cellulose derivatives and other polymers are under study to achieve bioadhesion.²²

In spite of the active research being pursued in oral delivery, controlled release systems may not be needed in some cases. For example, if a very large amount of drug is required, it would be difficult for all that drug to be encapsulated in a single tablet. Similarly, if the drug has a long *in vivo* half-life, such as digoxin, controlled release will probably not be needed. Furthermore, when there are significant first pass effects, e.g., destruction of the drug by the liver, controlled release may not be helpful. Finally, if there is a wide range between the maximum toxic dose and the minimal effective dose, controlled release systems are unlikely to be useful. In spite of these limitations the development of systems that can improve the bioavailability of drugs taken orally is among the most important challenges in drug delivery research.

Inserts, Implants, and Injectable Systems

A variety of polymer-based systems, either in clinical use or being actively studied, can be placed in certain bodily sites or implanted through the skin. One area in which polymer systems are being used is in the eye. In one controlled release system, the Ocuser, pilocarpine was placed between two ethylene-vinyl acetate copolymer membranes. By controlling the thickness of the membranes, release rates of 20 or 40 $\mu\text{g}/\text{hour}$ of pilocarpine can be achieved for a 1-week period. A patient could conveniently insert an Ocuser system once a week rather than take 28 eyedrops. In addition, by delivering the drug at a slow steady rate, many of the side effects associated with the eyedrops, such as

double vision, are significantly reduced. A second ocular system, the Lacrisert, is composed of an erodible polymer made of (hydroxypropyl)cellulose. This polymer dissolves in the eye and enables the cornea to hold onto moisture in the tear film. A new system is placed in the eye daily.

There has also been a considerable amount of research in the area of birth control. In one case, vaginal rings composed of silicone rubber have been designed to slowly release birth control drugs. These systems are generally used for a 6-month period. They are placed in the vagina for 3 weeks and then removed for 1 week to allow for bleeding.²³

In another approach, a reservoir system, composed of ethylene-vinyl acetate copolymer, slowly releases progesterone via diffusion for over a year. This system is placed in the uterus; because it delivers the drug locally to its target, a 3-day supply of the amount of drug normally taken orally can be used for over a year. This system also decreases menstrual bleeding.²³

A third system, the Norplant, involves the use of a silicone membrane reservoir system. Six tiny cylindrical reservoirs are implanted under the skin, slowly releasing birth control drugs for over 5 years. At the end of this time period, the system is surgically removed. Degradable versions of this type of system using lactic/glycolic acid copolymers, as well as other polymer systems, are under study.²³

A number of implants for other diseases are also being investigated. In one version, a biodegradable polymer system—composed of poly(anhydrides), a surface-eroding polymer²⁴—are used to encapsulate anticancer drugs such as carmustine. These systems are being used as adjuncts to surgery to treat normally fatal brain cancer. In these cases, the surgeon operates on the patient, removing as much of the tumor as possible. The poly(anhydride) implant is then placed at the site of the operation to kill any remaining tumor.²⁵ These systems release the drug over a 4-week period. This approach is currently being used in over 60 hospitals worldwide to treat patients with brain cancer.

Polymer-based systems are also under study for treating other brain diseases. In one case, ethylene-vinyl acetate copolymer discs releasing dopamine have been placed in the brain for treating Parkinsons' disease in animal models.²⁶ In another, bethanecol has been placed in poly(anhydride) microspheres that can be placed in the hippocampus (the memory area of the brain); this has been used to treat animal models of Alzheimer's disease.²⁷

Another use of polyanhydrides enables a new treatment of osteomyelitis. Loaded with gentamycin, polyanhydrides are placed in bone following surgery and slowly release the drug to prevent infections.²⁸ Nondegradable polymers composed of methyl meth-

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acrylate are also being used to slowly release gentamycin for this purpose. The use of a nondegradable polymer involves two operations, whereas with the degradable polymer only one operation is required, when the patient is normally operated on for the bone injury.

A number of controlled release polymer systems for slowly releasing insulin are also under study. In animal studies, these systems delivered insulin for several months from a single implant.²⁹

An area of increasing importance involves vaccine delivery. By encapsulating a vaccine in degradable polymers such as lactic/glycolic acid copolymers,³⁰ or degradable polymers containing adjuvants such as tyrosine,³¹ antigen can slowly be released for over a year from a single injection. Such approaches could decrease the number of injections one might need and sometimes provide higher antibody titers. Variations of the injectable approach are also under study whereby microcapsules 5–10 μm in size administered orally become entrapped in the Peyer's patches, where they release antigen and stimulate the production of secretory immunoglobulin A2. This, in turn, can destroy specific antigens if they are taken up in the gastrointestinal tract in the future.³²

A variety of polymers are also under study to treat gum diseases such as periodontitis. In these cases, tetracycline is placed in fibers composed of matrix systems of ethylene-vinyl acetate copolymer or other polymers. These fibers can be wrapped around a tooth. Because the drug is delivered locally to its target, less than 1/1000th the amount of tetracycline required systemically is needed.³³

In another example of local release, polymer-based systems containing diphosphonates (calcium chelators) were placed adjacent to biomaterials such as heart valves; not only was calcification prevented but side effects normally observed with diphosphonates of the required systemic concentration were not observed.³⁴

A number of systems to release peptides and proteins are under study. In early studies, certain relatively hydrophobic polymers as well as hydrogels, such as poly(hydroxymethyl acrylate), were demonstrated to slowly release large molecules.³⁵ The mechanism generally involved diffusion through a complex porous matrix. If the polymer was degradable (e.g., lactic/glycolic acid copolymers), release rates would accelerate due to increased pore formation over time. Several systems for releasing peptides are now in use clinically. In one case, the Lupron Depot, lactic/glycolic acid copolymer microcapsules containing luteinizing hormone-releasing hormone analog, is

being used in similar treatments. Both systems release drug for 1 month.

A major challenge in the development of peptide and protein delivery systems is devising approaches to stabilize these molecules after they have been injected or implanted in the body. When proteins are exposed to conditions of moisture at 37 °C (body temperature), the protein may aggregate or become inactivated. Studies have therefore been directed at defining the mechanisms by which this inactivation occurs. For example, in the case of albumin, a thiol-disulfide exchange mechanism has been implicated as causing aggregation and can be prevented by modifying albumin, e.g., blocking the thiol groups using S-alkylation. Alternatively, the presence of the active species, the thiolate ion, can be minimized by freeze-drying albumin from an acidic solution.³⁶ In another example, the aggregation of insulin in solution under mixing conditions and in the presence of hydrophobic surfaces has been studied. The mechanism of aggregation involved monomers becoming partially denatured when they were exposed to hydrophobic surfaces. This subsequently led to a nucleation mechanism, causing insulin to precipitate out of solution. By choosing additives such as nonionic surfactants that preferentially occupy sites that insulin would normally occupy at the hydrophobic surface, insulin aggregation was prevented. Over a 1000-fold increase in insulin stability was achieved.³⁷ In a third example, bovine growth hormone was stabilized by controlling moisture content inside the polymers. This was achieved by using polymers—poly(anhydride)—of increasing hydrophobicity.³⁸

Polymer-based systems can release small molecules, peptides, and proteins, but also newer, complex molecules such as antisense oligonucleotides. In a recent study examining the prevention of restenosis, which occurs following 40% of balloon angioplasties (a common method to treat vascular occlusions occurring in heart disease), polymer gels composed of pluronics—poly(ethylene oxide), poly(propylene oxide) block copolymers—were used to slowly release oligonucleotides directed against the oncogene C-myc. This approach prevented smooth muscle cell proliferation and restenosis in animal models.³⁹

There are many important future challenges in drug delivery. Among the most important are the development of approaches where drugs can be targeted to specific cells, for example, to deliver anticancer drugs. Another challenge is to develop ways to target genes or transcription factors to specific cells. In addition, the design of drug delivery systems able to cross complex barriers such as the gastrointestinal tract or brain is of great importance. Finally, increased research in materials science to understand how to improve implant biocompatibility and to achieve desired drug delivery patterns must be conducted to administer drugs optimally.

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