BIOMATERIALS
Polymers in Controlled Drug Delivery

Lisa Brannon-Peppas

New materials are enhancing innovative systems currently under development.

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Other advantages of using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored: the possible toxicity or nonbiocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

Micrograph of particles used to carry drugs to the lung. (Photo courtesy of R. Langer, Massachusetts Institute of Technology, Cambridge, MA).

Providing control over the drug delivery can be the most important factor at times when traditional oral or injectable drug formulations cannot be used. These include situations requiring the slow release of water-soluble drugs, the fast release of low-solubility drugs, drug delivery to specific sites, drug delivery using nanoparticulate systems, delivery of two or more agents with the same formulation, and systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in Figure 1a, in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Figure 1b, remaining constant, between the desired maximum and minimum, for an extended period of time. Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to 1 month (Lupron Depot) to 5 years (Norplant).
In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled-release systems can respond to changes in the biological environment and deliver—or cease to deliver—drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered. While much of this work is still in its early stages, emerging technologies offer possibilities that scientists have only begun to explore.

**BIOMATERIALS FOR DELIVERY SYSTEMS**

A range of materials have been employed to control the release of drugs and other active agents. The earliest of these polymers were originally intended for other, nonbiological uses, and were selected because of their desirable physical properties, for example:

- Poly(urethanes) for elasticity.
- Poly(siloxanes) or silicones for insulating ability.
- Poly(methyl methacrylate) for physical strength and transparency.
- Poly(vinyl alcohol) for hydrophilicity and strength.
- Poly(ethylene) for toughness and lack of swelling.
- Poly(vinyl pyrrolidone) for suspension capabilities.

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. Some of the materials that are currently being used or studied for controlled drug delivery include:

- Poly(2-hydroxy ethyl methacrylate).
- Poly(N-vinyl pyrrolidone).
- Poly(methyl methacrylate).
- Poly(vinyl alcohol).
- Poly(acrylic acid).
- Polyacrylamide.
- Poly(ethylene-co-vinyl acetate).
- Poly(ethylene glycol).
- Poly(methacrylic acid).

However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body, among them

- Polylactides (PLA).
- Polyglycolides (PGA).
- Poly(lactide-co-glycolides) (PLGA).
- Polyanhydrides.
- Polyorthoesters.

Originally, polylactides and polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products—both desirable and potentially nondesirable—must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials. The most important of these factors are shown in the box below—a list that is by no means complete, but does provide an indication of the breadth of structural, chemical, and processing properties that can affect biodegradable drug delivery systems.¹

<table>
<thead>
<tr>
<th>Factors Affecting Biodegradation of Polymers</th>
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<tbody>
<tr>
<td>- Chemical structure.</td>
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<tr>
<td>- Chemical composition.</td>
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<tr>
<td>- Distribution of repeat units in multimers.</td>
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<tr>
<td>- Presents of ionic groups.</td>
</tr>
<tr>
<td>- Presence of unexpected units or chain defects.</td>
</tr>
<tr>
<td>- Configuration structure.</td>
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<tr>
<td>- Molecular weight.</td>
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<tr>
<td>- Molecular-weight distribution.</td>
</tr>
<tr>
<td>- Morphology (amorphous/semicrystalline, microstructures, residual stresses).</td>
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<tr>
<td>- Presence of low-molecular-weight compounds.</td>
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<tr>
<td>- Processing conditions.</td>
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<tr>
<td>- Annealing.</td>
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<td>- Sterilization process.</td>
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<tr>
<td>- Storage history.</td>
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<tr>
<td>- Shape.</td>
</tr>
<tr>
<td>- Site of implantation.</td>
</tr>
<tr>
<td>- Adsorbed and absorbed compounds (water, lipids, ions, etc.).</td>
</tr>
<tr>
<td>- Physicochemical factors (ion exchange, ionic strength, pH).</td>
</tr>
<tr>
<td>- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.).</td>
</tr>
<tr>
<td>- Mechanism of hydrolysis (enzymes versus water).</td>
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</tbody>
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CONTROLLED-RELEASE MECHANISMS

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the polymer matrix—or on a molecular level, by passing between polymer chains. Examples of diffusion-release systems are shown in Figures 2 and 3.

In Figure 2, a polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

Figure 2. Drug delivery from a typical matrix drug delivery system.

For the reservoir systems shown in Figures 3a and 3b, the drug delivery rate can remain fairly constant. In this design, a reservoir—whether solid drug, dilute solution, or highly concentrated drug solution within a polymer matrix—is surrounded by a film or membrane of a rate-controlling material. The only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Since this polymer coating is essentially uniform and of a nonchanging thickness, the diffusion rate of the active agent can be kept fairly stable throughout the lifetime of the delivery system. The system shown in Figure 3a is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 3b illustrates a transdermal drug delivery system, in which only one side of the device will actually be delivering the drug.
Figure 3. Drug delivery from typical reservoir devices: (a) implantable or oral systems, and (b) transdermal systems. Once the active agent has been released into the external environment, one might assume that any structural control over drug delivery has been relinquished. However, this is not always the case. For transdermal drug delivery, the penetration of the drug through the skin constitutes an additional series of diffusional and active transport steps, as shown schematically in Figure 4.²(A thorough analysis of transdermal drug delivery may be found in a review by Cleary³ or in other sources listed in the bibliography.)

Figure 4. Transport processes in transdermal drug delivery. (Diagram courtesy of G. Cleary, Cygnus Inc., Redwood City, CA.)

For the diffusion-controlled systems described thus far, the drug delivery device is fundamentally stable in the biological environment and does not change its size either through swelling or degradation. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Hydrogel</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Acidic or basic hydrogel</td>
<td>Change in pH — swelling — release of drug</td>
</tr>
<tr>
<td>Ionic strength</td>
<td>Ionic hydrogel</td>
<td>Change in ionic strength — change in concentration of ions inside gel — change in swelling — release of drug</td>
</tr>
<tr>
<td>Chemical species</td>
<td>Hydrogel containing electron-accepting groups</td>
<td>Electron-donating compounds — formation of charge/transfer complex — change in swelling — release of drug</td>
</tr>
<tr>
<td>Enzyme-substrate</td>
<td>Hydrogel containing immobilized enzymes</td>
<td>Substrate present — enzymatic conversion — product changes swelling of gel — release of drug</td>
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</tr>
<tr>
<td>Magnetic</td>
<td>Magnetic particles dispersed in alginate microspheres</td>
<td>Applied magnetic field — change in pores in gel — change in swelling — release of drug</td>
</tr>
<tr>
<td>Thermal</td>
<td>Thermoresponsive hydrogel poly(N-isopropylacrylamide)</td>
<td>Change in temperature — change in polymer-polymer and water-polymer interactions — change in swelling — release of drug</td>
</tr>
<tr>
<td>Electrical</td>
<td>Polyelectrolyte hydrogel</td>
<td>Applied electric field — membrane charging — electrophoresis of charged drug — change in swelling — release of drug</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Ethylene-vinyl alcohol hydrogel</td>
<td>Ultrasound irradiation — temperature increase — release of drug</td>
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Table I. Environmentally sensitive polymers for drug delivery.

ENVIRONMENTALLY RESPONSIVE SYSTEMS

It is also possible for a drug delivery system to be designed so that it is incapable of releasing its agent or agents until it is placed in an appropriate biological environment. Swelling-controlled release systems are initially dry and, when placed in the body, will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. Examples of these types of devices are shown in Figures 5a and 5b for reservoir and matrix systems, respectively. Most of the materials used in swelling-controlled release systems are based on hydrogels, which are polymers that will swell without dissolving when placed in water or other biological fluids. These hydrogels can absorb a great deal of fluid and, at equilibrium, typically comprise 60–90% fluid and only 10–30% polymer.

Figure 5. Drug delivery from (a) reservoir and (b) matrix swelling-controlled release systems.

One of the most remarkable, and useful, features of a polymer’s swelling ability manifests itself when that swelling can be triggered by a change in the environment surrounding the delivery system. Depending upon the polymer, the environmental change can involve pH, temperature, or ionic strength, and the system can either shrink or swell upon a change in any of these environmental factors. A number of these environmentally sensitive or "intelligent" hydrogel materials are listed in Table I. For most of these polymers, the structural changes are reversible and repeatable upon additional changes in the external environment. The diagrams in Figure 6 illustrate the basic changes in structure of these sensitive systems. Once again, for this type of system, the drug release is accomplished only when the polymer swells. Because many of the potentially most useful pH-sensitive polymers swell at high pH values and collapse at low pH values, the triggered drug delivery occurs upon an increase in the pH of the environment. Such materials are ideal for systems such as oral delivery, in which the drug is not released at low pH values in the stomach but rather at high pH values in the upper small intestine.
All of the previously described systems are based on polymers that do not change their chemical structure beyond what occurs during swelling. However, a great deal of attention and research effort are being concentrated on biodegradable polymers. These materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable, and progressively smaller, compounds. In some cases—as, for example, polylactides, polyglycolides, and their copolymers—the polymers will eventually break down to lactic acid and glycolic acid, enter the Kreb’s cycle, and be further broken down into carbon dioxide and water and excreted through normal processes. Degradation may take place through bulk hydrolysis, in which the polymer degrades in a fairly uniform manner throughout the matrix, as shown schematically in Figure 7a. For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system (see Figure 7b).

The most common formulation for these biodegradable materials is that of microparticles, which have been used in oral delivery systems and, even more often, in subcutaneously injected delivery systems. Given appropriate fabrication methods, microparticles of poly(lactide-co-glycolide) (PLGA) can be prepared in a fairly uniform manner to provide essentially nonporous microspheres, as shown in Figure 8. These particles will degrade through bulk hydrolysis in water or body fluids, yielding polymer fragments over time. The polymer fragments shown in Figure 9, for example, are of a 75:25 lactide:glycolide PLGA microparticle after 133 days of degradation in water.
Figure 8. Biodegradable microparticles of 60:40 lactide:glycolide PLGA. (Photo courtesy of T. Tice, Southern Research Institute, Birmingham, AL.)

Figure 9. Biodegradable microparticle of 75:25 lactide:glycolide PLGA after 133 days of degradation in water. A very different erosion pattern is characteristic of polyorthoesters, which are surface-eroding polymers. Analysis of polyorthoester rods after 9 and 16 weeks of implantation in rabbits shows significant surface degradation, but the core of the drug delivery system remains intact (see Figure 10).

Figure 10. Biodegradable polyorthoester rods after (left) 9 and (right) 16 weeks of implantation in rabbits. (Photos courtesy of H. Heller, Advanced Polymer Systems, Redwood City, CA.)

DRUG DELIVERY AND THE TREATMENT OF DIABETES One disease that has received a great deal of attention because of the potential for therapies using controlled drug delivery is diabetes. For this disease, an optimal delivery system would be one that could deliver insulin upon detection of glucose in the bloodstream. Researchers have been working on this approach for more than a decade, and there are a few systems that show significant progress.

Most systems under study for insulin delivery base their delivery on the reaction of glucose in the blood with glucose oxidase, which can be immobilized on polymers within the drug delivery system. The glucose/glucose-oxidase reaction causes a lowering of the pH in the delivery system’s microenvironment. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin, for delivery systems that are based on copolymers containing N,N-dimethylaminoethyl methacrylate or polyacrylamide.
Figure 1. Molecular gates for the delivery of insulin triggered by the presence of glucose in the bloodstream.

Work with biodegradable polymers has also yielded polyorthoesters that are pH sensitive and that will degrade more quickly in acidic environments. Such polymers have been studied as the central core of a drug delivery system in which the polymer-insulin matrix is surrounded by a membrane containing grafted glucose oxidase, which provides the reaction substrate and the change in pH necessary to enhance biodegradation and subsequent insulin delivery. A recent inventive system that can deliver insulin in response to glucose uses polymers that will shrink rather than swell at low pH values. Depicted in Figure 1, this "molecular gates" system features an insulin-containing reservoir with a delivery-rate-controlling membrane of poly(methacrylic acid-g-poly(ethylene glycol)) copolymer in which glucose oxidase has been immobilized. This gel expands at high pH values (normal body pH of 7.4), closing the gates, and shrinks at low pH values (pH of approximately 4.0 due to interaction of glucose with immobilized glucose oxidase), opening the gates. Control of the insulin delivery depends on the size of the gates, the concentration of insulin, and the rate of the gates' opening or closing (response rate).

Until such time as these self-contained delivery systems become a reality, other researchers are investigating ways to monitor glucose levels without the need for blood samples and to administer insulin without injections. An imaginative first step in noninvasive glucose monitoring has been taken by Cygnus Inc. (Redwood City, CA), where researchers have essentially reversed the process of transdermal drug delivery and used iontophoresis to bring minute quantities of glucose in the blood to the surface of the skin, where it can then be measured. This system, known as the GlucoWatch for its resemblance to a wristwatch, could permit hourly monitoring of a diabetic's blood-glucose level and also track actions taken to manage the disease, such as insulin injections, eating, and exercise.

Providing insulin delivery by oral administration has been an elusive goal, one that a few researchers now appear to be nearing. Recent work by Lowman and Peppas indicates that dose-dependent oral delivery of insulin may be achievable using pH-sensitive systems. Early in vivo studies in rats have been promising, with additional work under way.

REFERENCES

FUTURE DIRECTIONS IN CONTROLLED DRUG DELIVERY
The most exciting opportunities in controlled drug delivery lie in the arena of responsive delivery systems, with which it will be possible to deliver drugs through implantable devices in response to a measured blood level or to deliver a drug precisely to a targeted site. Much of the development of novel materials in controlled drug delivery is focusing on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features. Such systems include:

- Copolymers with desirable hydrophilic/hydrophobic interactions.
- Block or graft copolymers.
- Complexation networks responding via hydrogen or ionic bonding.
• Dendrimers or star polymers as nanoparticles for immobilization of enzymes, drugs, peptides, or other biological agents.

• New biodegradable polymers.

• New blends of hydrocolloids and carbohydrate-based polymers.

These new biomaterials—tailor-made copolymers with desirable functional groups—are being created by researchers who envision their use not only for innovative drug delivery systems but also as potential linings for artificial organs, as substrates for cell growth or chemical reactors, as agents in drug targeting and immunology testing, as biomedical adhesives and bioseparation membranes, and as substances able to mimic biological systems. Successfully developing these novel formulations will obviously require assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials.

REFERENCES

BIBLIOGRAPHY
Lisa Brannon-Peppas, PhD, is president and founder of Biogel Technology, Inc. (Indianapolis, IN). The company, created in 1991, is a research-driven enterprise that specializes in applying the technologies of polymer science to controlled delivery, separations, biomaterials, bioadhesives, and other areas. The company is active in research, development, and preparation of polymeric materials in biotechnology, bioengineering, medical sciences, and industrial pharmacy.

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