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New Methods of Drug Delivery

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Conventional forms of drug administration generally rely on pills, eye drops, ointments, and intravenous solutions. Recently, a number of novel drug delivery approaches have been developed. These approaches include drug modification by chemical means, drug entrapment in small vesicles that are injected into the bloodstream, and drug entrapment within pumps or polymeric materials that are placed in desired bodily compartments (for example, the eye or beneath the skin). These techniques have already led to delivery systems that improve human health, and continued research may revolutionize the way many drugs are delivered.

IN THE LAST FEW YEARS, WE HAVE WITNESSED AN EXPLOSION in research aimed at creating new drug delivery systems. This research has been fueled by several developments. (i) Many drugs, both old pharmaceutical products and new molecular entities, can be administered in ways that not only improve safety and efficacy but, in some cases, permit new therapies. (ii) Newer and complex drugs such as proteins are becoming available through genetic engineering; the delivery of these drugs is often more complicated than that of more conventional drugs, necessitating novel delivery systems. (iii) There is an increasing awareness that drug release patterns (continuous versus pulsatile) significantly affect therapeutic responses. (iv) The overall expense to create a pharmaceutical that is a new molecular entity is at least $150 million; the lower cost to improve the delivery of an existing drug is sometimes seen as a better investment. This issue is exacerbated because drug patents expire after 17 years, and a new drug delivery system may permit continued benefits for the company producing it.

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(v) Advances in materials science and biotechnology are permitting the development of new physical and chemical methods of drug delivery. In this article, some of the methods being studied to deliver drugs are discussed.

Chemical Modification

A drug may be chemically modified to selectively alter such properties as biodistribution, pharmacokinetics, solubility, or antigenicity. One example is drugs that are designed to cross a normally impermeable barrier. The blood brain barrier, which contains tight endothelial cell junctions and prevents most molecules from entering the central nervous system, has been the target of considerable research. Several experimental approaches have been developed, in which drugs are complexed to agents that enable them to cross this barrier (for example, by rendering the drug more lipophilic or coupling it to a molecule that has a specific transport mechanism) (*1*).

Drugs have also been attached to soluble macromolecules such as proteins, polysaccharides, or synthetic polymers via degradable linkages. This process alters the drug's size and other properties, resulting in different pharmacokinetics and biodistribution. One example involves coupling the antitumor agent neocarzinostatin to styrene–maleic acid copolymers (*2*). When this complex was injected intra-arterially into patients with hepatocellular carcinoma, decreases in α-fetoprotein levels and tumor size were observed. In animals, antitumor agents such as doxorubicin coupled to *N*-(2-hydroxypropyl) methacrylamide copolymers showed radically altered pharmacokinetics, resulting in reduced toxicity. The half-life of the drug in plasma and the drug levels in the tumor were increased while the concentrations in the periphery decreased (*3*).

An exciting approach for "targeting" drugs to specific cells involves linkage of a bioactive agent (drug, radioisotope, or toxin) to a monoclonal antibody. Antibody conjugates are now being studied in the treatment of cancer, septic shock, and acquired immunodeficiency syndrome (AIDS). There are several critical issues in the use of antibodies. With mouse antibodies, anaphylactic reactions frequently occur with repeated administration. Thus, ongoing research is directed toward producing human monoclonal

antibodies or toward making mouse antibodies more human-like through the use of genetic engineering. This problem may be exacerbated for immunotoxins (antibody-toxins) because of the proteinaceous character of the toxin. Thus far, clinical usefulness of immunotoxins has been demonstrated in therapy regimens characterized by rapid pharmacokinetics, such as treatments for lymphoma and graft versus host disease, and extracorporeal treatments such as bone marrow purgings. The powerful killer potential of certain toxins, such as ricin or diphtheria toxin, makes immunotoxins an attractive approach if an appropriate antibody is available that can be internalized by desired cells (*4*). Antibody-radioisotopes act over a greater distance than immunotoxins. One requirement with such complexes is the availability of a suitable chelator that allows a kinetically stable binding of the radioisotope. The degradation of the linker structure between the chelator and antibody is also critical, since nondegradable structures may cause kidney and liver toxicity. Initial clinical results with certain beta-emitters have shown regression of lymphomas. Other critical issues in the use of an antibody are its affinity, specificity, size, and large-scale production; for cancer chemotherapy, tumor characteristics and blood flow are important considerations (*5*).

Polymers, such as polyethylene glycol (PEG), can be attached to drugs to either lengthen their lifetime or alter their immunogenicity. The polymers physically prevent cells and enzymes from attacking the drug. PEG-uricase reduced serum urate levels in patients with hyperuricemia and gout; PEG-asparaginase has been used for patients with leukemia, and PEG–adenosine deaminase has been used for patients with a severe combined immunodeficiency (*6*). Drug longevity and immunogenicity may also be affected by biological approaches, including protein engineering and altering glycosylation patterns.

Vesicles

Vesicles are microparticulates or colloidal carriers composed of substances such as proteins, lipids (for example, liposomes), carbohydrates, or synthetic polymers. Vesicles share some of the advantages of drug-macromolecular conjugates (altered pharmacokinetics and biodistribution) and make possible a potentially higher drug payload. Liposomes, the most widely studied of these vesicles, can be formulated with a variety of lipid compositions and structures and are potentially nontoxic, degradable, and nonimmunogenic. However, many liposomes exhibit poor stability during storage and use. Liposome stability may be improved by increasing the liposomal cholesterol content or synthesizing polymerizable liposomes, but biodegradability may then be diminished (*7*). Engineering issues such as large-scale lipid production and manufacturing of liposomes are also critical to the more widespread use of these vesicles.

In clinical studies, liposomal doxorubicin reduces side effects such as alopecia and nausea associated with the administration of the free drug yet permits a higher maximal tolerated dose and a reduction in cardiac toxicity of 86% (*8*). Liposomal amphotericin B is more effective than the free drug in treating immunocompromised cancer patients with fungal infections (*9*). Methods are also being studied to create liposomes that release more drug in response to specific stimuli such as heat, enzymes, polycations, light, or pH (*10*).

Vesicles may be "targeted" either passively or actively. Passive targeting involves the natural uptake by cells that scavenge foreign microparticulates such as reticuloendothelial cells, which are concentrated in tissues such as the liver or spleen, or circulating monocytes. Thus, liposomes have been used for delivering toxic agents, such as arsenic, to treat liver-specific parasitic diseases (for example, schistosomiasis) in animal models (*11*) with doses 0.1% of those of conventional regimens. Similarly, immunostimulating agents encapsulated in liposomes are taken up by monocytes, which then leads to enhanced killer cell activity. This approach is being tested in certain cancer treatments (*12*). Liposomes can also be used to deliver vaccines (*13*).

Active targeting generally involves placing a charge or recognition sequence (for example, from an antibody) onto the vesicle such that it is more rapidly taken up by certain cell types (such as cancer cells) than others. One difficulty with this approach is that reticuloendothelial cells also scavenge these vesicles. However, recent approaches for altering vesicle compositions, by coating them with surfactants or altering lipid compositions, may reduce the magnitude of this problem (*14*). Vesicles that contain magnetic microparticles have also been used to target drugs to specific locations in animal models via external magnetic fields (*15*).

Controlled Release Systems

Controlled release systems deliver a drug at a predetermined rate for a definite time period. In general, release rates are determined by the design of the system and are nearly independent of environmental conditions, such as pH. These systems can also deliver drugs for long time periods (days to years). Although vesicles or drug macromolecule conjugates may prolong release, optimal control is afforded if the drug is placed in a polymeric material or pump. Controlled release systems differ from older "sustained release" or "slow release" preparations that include complexes (to salts or ion-exchange resins), suspensions, emulsions, slowly dissolving coatings that do not dissolve in the stomach yet do dissolve in the intestine (enteric coatings), and compressed tablets. Generally, sustained-release systems emit drugs in less than a day, and environmental conditions influence release rates, which leads to patient to patient variations.

Controlled release systems provide advantages over conventional drug therapies. For example, after ingestion or injection of standard dosage forms, the blood level of the drug rises, peaks, and then declines. Since each drug has a therapeutic range above which it is toxic and below which it is ineffective, oscillating drug levels may cause alternating periods of ineffectiveness and toxicity. Although sustained release preparations attenuate the peaks and valleys, they do not eliminate them. In contrast, a controlled release preparation maintains the drug in the desired therapeutic range by a single administration. Other potential advantages of controlled release systems include (i) localized delivery of the drug to a particular body compartment, thereby lowering the systemic drug level; (ii) preservation of medications that are rapidly destroyed by the body (this is particularly important for biologically sensitive molecules such as proteins); (iii) reduced need for follow-up care; (iv) increased comfort; and (v) improved compliance.

Pumps are larger and more costly than polymeric systems and require surgery for implantation; however, they offer the advantage of very precise drug control and can release the drug directly into the bloodstream. In addition, some pumps are refillable. Both externally worn and implantable pumps have been developed. In both cases, the driving force is a pressure difference, which results in bulk flow of a drug solution through an orifice.

A common externally worn pressure-driven pump is the miniature syringe pump, in which the drug is delivered at a constant rate by a syringe barrel that moves at a constant velocity; the delivery rate is adjusted by altering either the drug concentration in the syringe or the barrel velocity. An implantable pressure-driven pump has been developed that uses a fluorocarbon propellant as a driving force. In this case, the pump controls a collapsible bellows, which divides the

pump interior into two chambers, one containing the propellant and the other containing the drug solution. At body temperature, the vapor pressure exerted by the propellant forces the drug solution through a filter and flow regulator at a constant rate. Other pressure-driven pumps use piezoelectric disk benders or valves. Release rates can be externally regulated by the use of approaches such as telemetry. Pumps have been used in cancer therapy where a catheter extending from a pump is selectively inserted into a blood vessel feeding an organ such as the liver or brain to increase the delivery rate to the diseased organ while sparing the rest of the body. Pumps have also been used to release insulin, heparin, morphine, and other drugs (*16*).

Polymeric materials generally release drugs by the following mechanisms: (i) diffusion, (ii) chemical reaction, or (iii) solvent activation. There are two types of diffusion-controlled systems: reservoirs (Fig. 1A) and matrices (Fig. 1B). Chemical control is accomplished either by polymer degradation (Fig. 1C) or chemical cleavage of the drug from a polymer (Fig. 1D). Solvent activation involves either swelling of the polymer (Fig. 1E) or osmotic effects (Fig. 1, F and G).

One of the first clinically used controlled release polymer systems was the Ocusert, a reservoir system designed to improve therapy for glaucoma, one of the world's leading causes of blindness. The conventional treatment involved the use of pilocarpine eye drops (which reduce intraocular pressure) four times a day. The eye drops often caused side effects, and patient compliance was sometimes poor. The Ocusert delivers pilocarpine (20 or 40 μg/hour) continuously for 1 week and controls intraocular pressure with less drug and fewer side effects. It is placed in the lower eyelid's conjunctival cul-de-sac, where it floats in the tear film. Despite its advantages, the Ocusert never achieved widespread use, initially because of its expense and poor acceptance by older patients who were reluctant to adjust to this system and later because of the introduction of timolol, a drug that requires only two applications per day.

The use of polymers to deliver contraceptive steroids has been widely studied. Four types of systems have been examined: (i) subdermal reservoir implants composed of nondegradable polymers that release drug for over 5 years (for example, the Norplant); these systems, based on a seminal study of diffusion through silicone rubber (*17*), are approved for use in 15 countries; (ii) subdermal implants or injectable microspheres composed of degradable materials, such as lactic acid–glycolic acid copolymers, polycaprolactones, or cholesterol; (iii) steroid-releasing intrauterine devices, such as the Progestasert, an ethylene–vinyl acetate copolymer reservoir that contains a 3-day supply (38 mg) of the amount of progesterone normally taken orally, but which, since it delivers progesterone to its

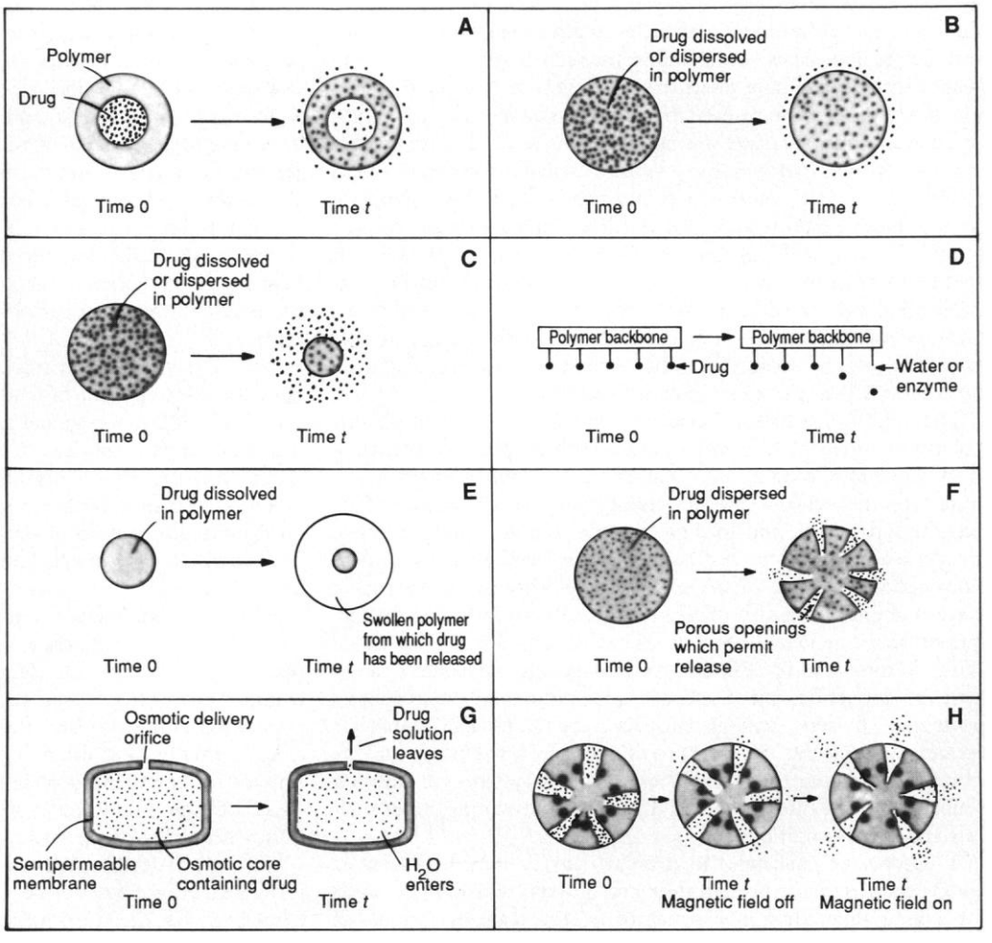

Fig. 1. Polymer release mechanisms. The most common release mechanism is diffusion, whereby the drug migrates from its initial position in the polymeric system to the polymer's outer surface and then to the body. Diffusion may occur through a reservoir (**A**), in which a drug core is surrounded by a polymer film, or in a matrix (**B**), where the drug is uniformly distributed through the polymeric system. Drugs can also be released by chemical mechanisms such as degradation of the polymer (**C**) or cleavage of the drug from a polymer backbone (**D**). Exposure to a solvent can also activate drug release. For example, the drug may be locked into place by polymer chains, and, upon exposure to environmental fluid, the outer polymer regions begin to swell, allowing the drug to move outward (**E**), or water may permeate a drug-polymer system as a result of osmotic pressure, causing pores to form and bringing about drug release (**F**). An attractive osmotic system that can provide constant release rates exists in the form of a pill that has a laser-drilled hole in the surface of a polymer coating (**G**). Some polymer systems can be externally activated to release more drug when needed, using forces such as magnetism (**H**). In this case, an external magnetic field causes polymer-embedded magnetic beads to "squeeze" drug-containing pores, forcing more drug out of a matrix. In all cases, dots represent drug, and in (H) the large dots represent magnetic beads. Combinations of the above mechanisms are possible. Release rates from polymer systems can be controlled by the nature of the polymeric material (for example, crystallinity or pore structure for diffusion-controlled systems; the lability of the bonds or the hydrophobicity of the monomers for chemically controlled systems) and the design of the system (for example, thickness and shape). The advantage of having systems with different release mechanisms is that each can accomplish different goals. For example, reservoir systems are able to produce near-constant release rates, whereas matrix systems are inexpensive to manufacture. Chemically controlled systems generally result in elimination of the polymer, whereas solvent-activated systems have release rates independent of pH (*50*).

target locally at a rate of approximately 65 μg/day, lasts for over 1 year; and (iv) vaginal rings, which are silicone reservoir systems used for 3 to 6 months; generally, for each monthly cycle they are inserted for 3 weeks and then are withdrawn for 1 week (*18*).

Tetracycline, incorporated into diffusion-controlled systems composed of ethylene–vinyl acetate copolymer or other substances, has been used to treat periodontal disease. When this controlled release system was placed in the periodontal pocket, significant reductions in bacterial counts and in the incidence of gingivitis were observed. Furthermore, because the systems are placed next to their target, treatment is accomplished with less than one-thousandth of the normal systemic dose (*19*).

A number of other controlled release systems are under study. These include localized release of diphosphonates (calcium chelators) to prevent heart valve calcification, dopamine or bromocriptine for potential treatment of Parkinson's disease, and bethanecol for potential treatment of Alzheimer's disease (*20*).

Controlled Release Systems for Peptides and Proteins

For many years, controlled-release systems were capable of slowly releasing drugs of only low molecular weight (<600). Large molecules such as proteins were not considered feasible candidates, because polypeptides were considered too large to slowly diffuse through most polymeric materials, even after swelling of the polymer. Large molecules could diffuse through highly porous membranes such as Millipore filters or certain gels such as polyacrylamide; however, in these cases, diffusion was generally too rapid to be of value and tissue damage was usually observed. The discovery that matrices of solid hydrophobic polymers containing powdered macromolecules enabled molecules of nearly any size to be released for over 100 days permitted controlled delivery of a variety of proteins, polysaccharides, and polynucleotides (*21*). Examples of polymers that perform in this way are nondegradable ethylene–vinyl acetate copolymer and degradable lactic acid–glycolic acid copolymers. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly (vinylalcohol) also work effectively but release proteins for shorter time periods than the above polymer systems.

The release mechanism generally involves movement of the polypeptide through a complex porous path in the polymer matrix. If the polymer erodes, this will affect the pore structure and accelerate the release. Factors influencing release rates include protein particle size and loading, protein solubility and molecular weight, polymer composition and molecular weight, and the dimensions and shape of the matrix (*22*). Polymer systems are now being used in animal studies to release many proteins, including insulin, growth factors, and angiogenesis inhibitors (*23*). The first Food and Drug Administration (FDA)–approved system for controlled release of a peptide, the Lupron Depot (injectable microspheres composed of lactic acid–glycolic acid copolymer and leuprolide acetate, and lasting 30 days) was recently introduced for the treatment of prostate cancer. Other polymeric systems for releasing similar drugs (*24*) are also under evaluation for treating endometriosis and other conditions.

A number of challenges in protein delivery remain. Foremost among these is that, when encapsulated proteins remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C. This can cause a loss of biological activity and possible changes in immunogenicity. Stabilization approaches being developed in protein chemistry (*25*) will be important for the success of some of these delivery systems. In one study that used solid proteins as a model, small amounts of added water induced aggregation of albumin, ovalbumin, glucose oxidase, and β-lactoglobulin. The aggregation as a function of added water went through a maximum with just 3 μl of water, causing 97% aggregation of 10 mg of albumin in 24 hours. At lower and higher water concentrations, aggregation was reduced. The aggregation mechanism was discovered to be intermolecular S–S bond formation through thiol-disulfide interchange. This, in turn, suggested rational strategies for protein stabilization, including modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions (*26*). In a study of ribonuclease, oxygen was responsible for protein aggregation (*27*).

Transdermal Controlled Release Systems

The skin is often considered a barrier that keeps all agents, including drugs, out of the body. However, a few drugs have just the right properties to penetrate the skin at appreciable rates and are potent enough so that only low doses are required. Furthermore, compared to the oral route, losses due to liver metabolism are reduced. The rate-limiting barrier to drug entry through the skin is the outermost skin layer, the stratum corneum, which is composed primarily of keratin and lipids. For a drug to penetrate the skin significantly, it should have a low molecular weight and appreciable solubility in both water and oil.

The first transdermal delivery system introduced clinically released scopolamine from patches (reservoir systems) to prevent nausea associated with motion sickness. After the patch has been applied, a 4- to 6-hour lag period is required for the drug to reach therapeutic concentrations. Because of the small amount of drug required (7 μg/hour over 3 days) and the high skin permeability of scopolamine, this system can be designed so that the device rather than the skin is rate-controlling. This minimizes patient to patient variations. The device is placed behind the ear because the permeability of the stratum corneum there is comparatively high, which further enables the device, rather than the skin, to provide the principal diffusion barrier.

The most widely used transdermal systems release nitroglycerin daily for the treatment of heart disease. These systems, first introduced in 1982, have annual sales of approximately $500 million. The amount of nitroglycerin absorbed is determined by the skin rather than the device; nitroglycerin patches of different sizes are available so that patients can select the desired dosages. However, the continuous delivery of nitroglycerin may create drug tolerance. The possibility of controlled intermittent delivery of nitroglycerin is being explored.

A weekly clonidine patch and a twice weekly estradiol patch are used to treat hypertension and estradiol deficiency (for postmenopausal females), respectively. There have been reports of local irritation with these systems, perhaps because of their longer application periods or because of the combined effects of bioadhesives, chemicals, and drugs used in the formulations. Transdermal systems for the delivery of testosterone, fentanyl, isosorbide dinitrate, nicotine, timolol, and antihistamines, although not yet clinically available, are under study.

The biggest challenge in transdermal delivery is to increase the variety of drugs that can be administered. Four approaches have been explored. Electrical means such as iontophoresis, which can drive charged molecules through the skin, have received considerable attention. It has been proposed that iontophoresis might allow the transdermal delivery of larger molecular weight drugs, such as insulin. Animal studies with insulin have not led to conclusive results; insulin permeation depends on the animal model, the type of

current, and whether the stratum corneum has been removed (*28*). Nonetheless, clinical studies have shown that smaller peptides such as luteinizing hormone–releasing hormone (LHRH) can be delivered at increased rates (*29*). A second approach uses ultrasound to enhance transdermal drug permeation. Ultrasound also eliminates the lag times associated with transdermal drug delivery in animal models (*30*). Chemical modification provides a third approach: a lipophilic drug could be synthesized that penetrates the skin and is subsequently converted by epidermal enzymes into the original drug. Finally, penetration enhancers such as Azone, dimethyl sulfoxide, and dimethyl formamide have been used. However, extensive testing must be done to establish safety. It may be more useful to utilize agents used in FDA-approved topical formulations (for example, ethanol is used in the estradiol system to enhance penetration).

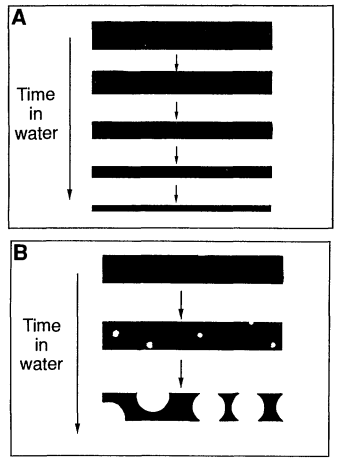

Fig. 2. Idealized diagram of polymer matrices displaying surface erosion (**A**) or bulk erosion (**B**).

Novel Degradable Polymers

Most materials used in medicine today were not designed for biomedical applications. For example, the polymers used in the artificial heart and dialysis tubing were originally used in ladies' girdles and sausage casings, respectively. These materials were chosen because they appeared, to some extent, to resemble the organs they were intended to replace. A significant challenge is to develop more rational approaches for creating improved materials for humans. This may be particularly important in the development of degradable polymers.

For such polymers, to maximize control over release, it is often desirable for a system to degrade only from its surface (Fig. 2A). [The only degradable polymers in common use, polyesters such as lactic acid–glycolic acid copolymers, display bulk (homogeneous) erosion (Fig. 2B), resulting in significant degradation in the matrix interior.] For surface-eroding systems, the drug release rate is proportional to the polymer erosion rate. This eliminates the possibility of dose dumping, improving device safety; release rates can be controlled by changes in system thickness and total drug content, facilitating device design. Achieving surface erosion requires that the degradation rate on the polymer matrix surface be much faster than the rate of water penetration into the matrix bulk. Efforts have begun to design such ideal polymers. Theoretically, the polymer should be hydrophobic but should have water-labile linkages connecting monomers.

It was proposed that, because of the lability of anhydride linkages, polyanhydrides would be a promising class of polymers. By varying the monomer ratios in polyanhydride copolymers, surface-eroding polymers lasting from 1 week to several years were designed and synthesized (*31*).

The possibility of implanting polyanhydride disks containing nitrosoureas for treating brain cancer after surgery is being explored. Normally, nitrosoureas are given intravenously (they have a half-life of 12 to 15 min and cause serious toxicity to several organs). By placing nitrosoureas in polyanhydrides, the drug is protected and its efficacy lasts approximately for the duration of the polymer lifetime (in this case, nearly 1 month). The polymer disks also deliver the drug locally to the brain, significantly reducing systemic toxicity. Surface erosion is desirable, for, if bulk erosion were to occur, uncontrolled amounts of this potentially toxic drug could be released during breakup of the matrix. These polymers have been shown to be safe in numerous animal models (*32*). Institutional Review Board approval was then obtained to conduct clinical trials with polyanhydrides at five U.S. hospitals. In 1987, the FDA approved these polyanhydrides for clinical trials. In an initial study of 21 patients, safety was demonstrated and patient lifetime was extended significantly beyond that afforded by conventional treatments (*33*). A phase-3 trial involving 32 hospitals is currently under way; over 100 patients have been treated.

Several different surface-eroding polyorthoester systems have been synthesized. In this case, additives are placed inside the polymer matrix, which causes the surface to degrade at a different rate than the rest of the matrix. Such a degradation pattern can occur because these polymers erode at very different rates, depending on pH, and the additives maintain the matrix bulk at a pH different from that of the surface. By varying the type and amount of additive, release rates can be controlled (*34*).

It may be desirable to have degradable polymers that consist of, and break down into, naturally occurring metabolites. Thus, new polyamino acids were synthesized in which L-amino acids or dipeptides were polymerized by nonamide bonds between functional groups (for example, esters) located on amino acid side chains. This approach permits the synthesis of biomaterials (for drug delivery systems, artificial organs, vascular grafts, or other prostheses) that are derived from nontoxic substances, which also have other desirable properties: (i) the incorporation of an anhydride linkage into the polymer backbone causes rapid degradability; (ii) an ester bond provides better film and fiber formation; and (iii) an imide or iminocarbonate bond improves mechanical strength (*35*).

One such polymer is being studied in vaccine delivery. Many adjuvants such as aluminum oxide or Freund's adjuvant rely on a simple "depot" effect, releasing antigen over a short period, from several hours to a few weeks. In earlier studies in mice and rabbits, prolonged release of small amounts of antigen from a nondegradable device resulted in sustained antibody production for over 6 months (*36*). Although these studies demonstrated the potential value of controlled release in immunization, it would be advantageous to use degradable systems to avoid implant retrieval. This concept is particularly attractive, because the polymer degradation products could be intentionally designed to have adjuvant properties, that is, an "engineered" polymer. This would permit the design of a system that could stimulate the immune response while simultaneously releasing antigen over long periods. Because of the adjuvanticity of L-tyrosine and its derivatives, a polymer consisting of tyrosine or a tyrosine derivative connected by hydrolyzable iminocarbonate bonds was synthesized. When this polymer was converted into small pellets, this system provided sustained adjuvanticity while simultaneously serving as an antigen repository. The release of antigen from a single tyrosine-based polyiminocarbonate pellet gave rise, in mice, to higher antibody titers than release of the same antigen dose from a control polyiminocarbonate pellet or from two injections of the antigen over 1 year (*37*).

Pulsatile Polymeric Controlled Release Systems

It would be desirable if polymeric systems could be designed to release increased levels of drug when needed; this would mimic the body's physiological processes. Both open-loop and closed-loop approaches are being studied. One open-loop system contains drug and small magnetic beads embedded in a polymer matrix (Fig. 1H). Release rates are enhanced when desired by an oscillating external magnetic field. Parameters that affect the release rate include the magnetic field frequency and strength, the polymer composition, and the strength and orientation of the polymer-embedded magnets. Application of the magnetic field causes up to 30-fold increases in release rates (*38*). Ultrasound can also be used to enhance drug release rates from polymers (*39*). Successful clinical implementation of the ultrasonic or magnetic systems will probably require the creation of small portable triggering devices (wristwatch size) that can be preprogrammed or activated manually when desired.

Several closed-loop polymeric systems are being developed. In one case intended for the increased release of insulin in the presence of excess glucose, glucose oxidase was immobilized within an insulin-containing polyamine membrane. Glucose oxidase converts glucose to gluconic acid; the acid protonates amine groups within the membrane. The electrostatic repulsion of the positively charged amine groups causes expansion of the membrane and increased delivery of insulin. As the physiologic glucose concentration decreases in response to the released insulin, the membrane contracts, decreasing the rate of insulin release (*40*). In another approach, glucose oxidase was immobilized to agarose beads contained within a polymer matrix. The acid formed when external glucose reacts with the immobilized enzyme lowers the pH, which changes the solubility of insulin and the diffusional driving force. Increased release rates to glucose challenges were observed in vitro and in diabetic rats (*41*). A third approach involves the synthesis of glycosylated insulin bound to concanavalin A (Con A). Con A is immobilized on Sepharose beads. The glycosylated insulin is displaced from Con A in response to glucose, which competes for the same binding sites. The rate of insulin release also depends on the binding affinity of the insulin derivative to Con A and can be influenced by the choice of saccharide group in glycosylated insulin. By encapsulating glycosylated insulin-bound Con A within a suitable polymer that is permeable to both glucose and insulin, it is possible to control glucose influx and insulin efflux (*42*). Critical issues with respect to each of these delivery systems are the stability of insulin and enzymes and the rapidity of movement (response time) of insulin from the polymer matrix to the circulation. Such systems may also benefit from ongoing research in biosensors (*43*).

Research is being conducted on self-triggered release of drugs such as narcotic antagonists in multicomponent systems involving erodible polymers, antibodies, and enzymes (*44*). Pulsatile systems involving pH-sensitive or temperature-sensitive polymers are also being studied, as are polymer systems that can be activated by light or electricity (*45*).

Conclusions and Future Directions

The studies discussed here show that carriers can affect drug level, location, longevity, and antigenicity. Although this technology is at an early stage, it has already made a significant clinical and commercial impact. This technology is not limited to medicine. Controlled release has been used for pet flea collars, pesticides, anti-fouling agents, fertilizers, and fragrances. Liposomes are used in cosmetics.

There are numerous challenges ahead. One area is the creation of bioadhesive polymers that could alter a drug's location when given orally (*46*). This could be particularly important for drugs that are absorbed only in certain segments of the gastrointestinal tract. Even more tantalizing, but more difficult, is delivering large and complex molecules such as proteins orally. Research on novel anatomical delivery pathways such as the nose or lung may also permit the delivery of a wider spectrum of drugs. Furthermore, an understanding of cell transport mechanisms may aid in cellular targeting (*47*).

Although this article has focused principally on specific carriers for pharmaceuticals, ongoing research in cell transplantation could be used to provide desired agents (*48*). The possibility of inserting genes into cells to produce desired entities is being explored (*49*).

Furthermore, continuous advances in biotechnology will have at least several major effects on drug delivery. First, novel complex drugs will be created that will be difficult to administer by conventional means. Second, approaches being developed in genetic engineering may enable the creation of new molecular constructs (for example, deletion mutants, hybrid proteins, and ligated gene fusion hybrids) with increased ability to achieve site-specific delivery. Finally, advances in materials science and chemical engineering should permit improved polymers, lipids, antibodies, and other substances to be synthesized, better understood, manufactured, and effectively used in drug delivery.

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Molecular Targets for AIDS Therapy

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The development of antiretroviral therapy against acquired immunodeficiency syndrome (AIDS) has been an intense research effort since the discovery of the causative agent, human immunodeficiency virus (HIV). A large array of drugs and biologic substances can inhibit HIV replication in vitro. Nucleoside analogs—particularly those belonging to the dideoxynucleoside family—can inhibit reverse transcriptase after anabolic phosphorylation. 3′-Azido-2′,3′-dideoxythymidine (AZT) was the first such drug tested in individuals with AIDS, and considerable knowledge of structure-activity relations has emerged for this class of drugs. However, virtually every step in the replication of HIV could serve as a target for a new therapeutic intervention. In the future, non-nucleoside–type drugs will likely become more important in the experimental therapy of AIDS, and antiretroviral therapy will exert major effects against the morbidity and mortality caused by HIV.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) IS A PATHOgenic retrovirus and the causative agent of acquired immunodeficiency syndrome (AIDS) and its related disorders. One of the central questions after HIV was discovered was whether antiretroviral therapy would ever be feasible. Since that time, one drug, 3′-azido-2′,3′-dideoxythymidine (AZT or zidovudine) (*1*) has been shown to prolong the survival and improve the quality of life of individuals with advanced HIV infection (*2, 3*). More recently, the administration of AZT was shown to delay clinical progression in certain asymptomatic individuals with HIV infection (*4*). Thus, the central question now is no longer whether antiretroviral therapy will be feasible, but rather, how to use the emerging knowledge of the viral life cycle to create new opportunities for therapy.

The purpose of this review is to discuss some principles for the development of antiretroviral drugs in the therapy of HIV infection and to highlight some recent advances in this area. Successful antiviral drugs, in theory, exert their effects by interacting with viral receptors, virally encoded enzymes, viral structural components, viral genes or their transcripts, or cellular factors required for viral

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