Drug delivery and targeting

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When a pharmaceutical agent is encapsulated within, or attached to, a polymer or lipid, drug safety and efficacy can be greatly improved and new therapies are possible. This has provided the impetus for active study of the design of degradable materials, intelligent delivery systems and approaches for delivery through different portals in the body.

Although delivery systems that could target drugs to specific body sites or precisely control drug release rates for prolonged times have long been dreamed of, only in recent years has the development of such systems become practical. Yet in a short time, new drug-delivery systems have had an impact on nearly every branch of medicine including cardiology, ophthalmology, endocrinology, oncology, pulmonology, immunology and pain management. Annual sales in the United States of advanced drug-delivery systems exceed $10 billion (Table 1) and are rising rapidly. Many principles used in drug delivery, such as the application of materials for long-term controlled release of encapsulated agents, have also been used for the delivery of pesticides, fertilizers, herbicides, fragrances, flavours and other substances, making controlled release an area of remarkably widespread application.

Potential advantages of improved drug delivery include: (1) continuous maintenance of drug levels in a therapeutically desirable range; (2) reduction of harmful side effects due to targeted delivery to a particular cell type or tissue; (3) potentially decreased amount of drug needed; (4) decreased number of dosages and possibly less invasive dosing, leading to improved patient compliance with the prescribed drug regimen; and (5) facilitation of drug administration for pharmaceuticals with short *in vivo* half-lives (for example peptides and proteins). Advantages 1 to 3 are additionally important because up to 15% of all hospital admissions, some 100,000 deaths and $136 billion in health care costs in the US each year can be attributed to adverse drug events[1,2]. Another 10% of hospital admissions are due to a lack of patient compliance (advantage 4)[2,3]. The above advantages must be weighed against the following concerns in the development of each particular drug-delivery system: (1) toxicity of the materials (or their degradation products) from which the drug is released, or other safety issues such as unwanted rapid release of the drug (dose dumping); (2) discomfort caused by the system itself or the means of insertion; and (3) expense of the system due to the drug encapsulation materials or the manufacturing process.

Polymer-based drug-delivery systems

There are three general mechanisms by which drugs are delivered from polymer or lipid systems: (1) diffusion of the drug species from or through the system; (2) a chemical or enzymatic reaction leading to degradation of the system, or cleavage of the drug from the system; and (3) solvent activation, either through osmosis or swelling of the system[4]. Advantages and disadvantages of these systems have been discussed previously[5]. A combination of mechanisms is possible.

Polymer-based systems have had an enormous impact on drug therapies (Fig. 1). In one approach, the drug is physically entrapped inside a solid polymer that can then be injected or implanted in the body. Early forms of these systems involved non-degradable polymers (membrane-controlled diffusion) (Fig. 1a) such as silicone rubber, which could release low molecular mass lipophilic drugs for extremely long times[6]. This type of approach led to the development of Norplant, small silicone capsules containing contraceptives that are slowly released by diffusion through the polymer for 5 years. However, this approach does not permit the slow delivery of either ionic species or molecules with a relative molecular mass (M_r) over about 400 because they are not able to diffuse through such polymers. To address this problem, drugs were physically embedded in polymers at concentrations high enough to create a series of interconnecting pores through which the drug could subsequently slowly diffuse[7] (a type of matrix system, Fig. 1b). Early studies utilized ethylene–vinyl acetate copolymer or various hydrogels as model polymers. Subsequently, to develop biodegradable systems with such properties, lactic/glycolic acid copolymers were utilized. In this case, the combination of diffusion through pores as well as polymer matrix degradation allows control of release rates. This approach has provided the basis for injectable delivery systems lasting for 1 to 4 months for normally short-lived polypeptide hormones such as luteinizing hormone releasing hormone analogues[8] now used by about 300,000 patients annually for treating advanced prostate cancer, endometriosis or precocious puberty.

To permit the slow release of even larger molecules such as proteins, approaches for controlling release kinetics must also consider

Table 1 US sales of advanced drug-delivery systems (1996 and 1997)

Type of system	Sales (millions of $US) 1996	1997
Oral	6,066	7,178
Transdermal	1,525	1,701
Injectable/implantable polymeric systems	856	1,109
Ocular	12	17
Liposomes	107	208
Transmucosal (vaginal, buccal)	35	65
Lung delivery (nebulizers, metered-dose inhalers)	2,513	2,573
Nasal delivery	851	994
Total:	11,965	13,841

Sources: Cowen and Co., Boston, Massachusetts, USA; IMS America Plymouth Meeting, Pennsylvania, USA.

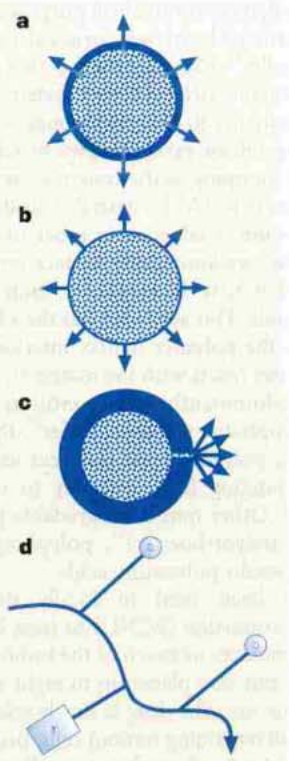

Figure 1 Examples of polymer-based delivery systems. In **a**–**c**, small dots represent drug, and arrows show the direction in which drug is released. **a**, Reservoir system in which drug diffuses through a polymer membrane (blue rim). This is the design for Norplant, Ocusert and a number of other systems. **b**, Matrix system in which the drug is evenly distributed through a polymer system. The drug can be released by diffusion through the polymer. Alternatively, drug release can occur by a combination of drug diffusion and polymer erosion. **c**, Osmotic system in which drug is pumped out through a laser-drilled hole. Water is attracted through the blue semipermeable membrane (the membrane is permeable to water but impermeable to drug) by osmosis due to the drug or a coencapsulated salt in the system. **d**, Polymeric drug conjugates. The curved line represents polymer. The bonds connecting drug (D) and polymer are cleavable inside the body. The targeting moiety, T, is optional.

the stability of proteins in the solid state (the state in which they generally exist in polymer matrices)[9]. Enhancement of stability is important because exposure to moisture in the body can lead to significant protein aggregation. Approaches are being developed to stabilize important molecules such as human growth hormone so that they can be released for a month from injectable microcapsules[10].

Although much effort has been focused on utilizing polymers that have a history of medical use and then adapting their microstructures to provide desired delivery rates, another approach is the intentional design of materials that solve specific drug-delivery problems. In fact, most biomedical research in the 1960s and 1970s focused on utilizing 'off-the-shelf' polymers designed for consumer applications and adapting these polymers for medical purposes. For example, materials used in the artificial heart were originally components used to make women's girdles[11]. Consider the fact that most degradable polymers used in injectable drug-delivery systems display bulk erosion that causes the polymer to dissolve throughout the entire matrix. This makes constant release rates complex to achieve and creates the possibility of dose dumping as the system eventually hydrolyses. To address these issues it would be desirable to design polymers that display surface erosion, analogous to a bar of soap dissolving. One strategy to achieve predominantly surface erosion involves synthesizing polymers that have hydrophobic monomer units connected by water-labile bonds. This approach has the advantage of keeping water away from the polymer matrix interior but allows controlled erosion when water reacts with the matrix surface. Polymer matrices that display predominantly surface erosion have been created by synthesizing hydrophobic polyanhydrides[12]. By the appropriate choice of monomers, polyanhydride matrices can be made to degrade over periods ranging from one day to many months or any time in between[13]. Other new biodegradable polymers being synthesized include polyorthoesters[14], polyphosphoesters[15], polyphosphazenes[16] and pseudo-polyamino acids[17].

Polyanhydride matrices have been used to locally deliver chemotherapeutic drugs such as carmustine (BCNU) to treat brain cancer[18]. In this case, the surgeon removes as much of the tumour as possible at the time of operation, but also places up to eight small polymer–drug wafers at the tumour site. The drug is slowly released from the polymer for 1 month to kill remaining tumour cells. Because the drug is delivered locally, harmful side effects that normally occur from systemic chemotherapy are minimized. One recent clinical trial showed that after 2 years, 31% of the treated patients were alive whereas only 6% in the control group survived[19]. In 1996, the United States Food and Drug Administration approved this treatment for patients with recurrent glioblastoma, the first new brain cancer therapy approved in over 20 years. A similar approach also in clinical trials has been used to locally release gentamycin to treat osteomyelitis[20].

In some situations, it would be useful to create materials that can be injected through an extremely small needle. Recent work has involved the synthesis of a thermosensitive biodegradable hydrogel consisting of blocks of poly(ethylene oxide) and poly(lactic acid)[21]. A bioactive agent is dissolved in the aqueous polymer phase at 45 °C (where the system is liquid) and the solution is injected at 37 °C (body temperature) whereupon it quickly solidifies. Another approach to achieve solidification of a liquid polymer solution involves first dissolving polymers in non-toxic organic solvents. The polymer solution is then injected, where exposure to water causes precipitation[22].

Polymers that are bioadhesive to mucosa are being explored to prolong drug residence time in the vagina, gastrointestinal tract and other body sites[23]. Materials containing functional groups that exhibit hydrogen bonding, such as certain hydrogels or polymers containing free carboxyl groups, are useful materials for this application[24]. Another goal is to design pharmacological activity into a polymer as well. One example is the incorporation of immune adjuvants, such as tyrosine derivatives, into polymers so that when the polymer degrades and a vaccine is slowly released an adjuvant is also released that stimulates the immune response further[25].

The concept of chemically binding (as opposed to physically entrapping) drugs to water-soluble polymers can confer new properties upon the drug such as decreased immunogenicity or tissue targeting. For example, the biological half-life of high molecular mass substances such as adenosine deaminase (ADA) and asparaginase has been lengthened and their immunogenicities reduced by binding these molecules to polyethylene glycol (PEG)[26]. This has led to new treatments for severe combined immunodeficiency disease associated with ADA deficiency and acute lymphoblastic leukaemia.

For tissue targeting, water-soluble non-immunogenic biocompatible polymers, which will either degrade or be eliminated by the kidney, are chemically linked to drugs, ideally through bonds that are cleaved once they reach their target (for example a tumour) (Fig. 1d). By changing the drug from a small to a large molecule, the biodistribution of the drug following intravenous administration will be different[27,28]. This approach has been used in several cancer chemotherapy strategies. The concept is that low molecular mass anticancer drugs will penetrate most tissues because they pass rapidly through cell membranes. Thus, the drug is quickly distributed throughout the body, with no selectivity toward tumour tissue. However, if the polymer–drug linkages are selected so that they are stable in the bloodstream, the polymer–drug conjugate will circulate for a longer time than just the drug itself because the high molecular mass polymer–drug can generally only gain entry to cells by endocytosis. Because most normal tissues have intact non-leaky microvasculatures, the polymer–drug accumulates to a greater extent in tumour tissue which has a leaky capillary bed[27–29]. This approach is known as passive targeting. One example involves *N*-(2-hydroxypropyl) methacrylamide (HPMA copolymer) conjugated to doxorubicin through a peptidyl linker that is cleaved by thiol-dependent proteases in lysosomes. Up to 70 times more doxorubicin accumulates in mouse melanoma tumours *in vivo* than in normal tissues. In addition, the maximum tolerated dose of the polymer–drug conjugate is 5–10 times higher than that of the free drug in animals and humans[27]. Another example involves injecting a styrene–maleic anhydride copolymer coupled to neocarzinostatin (SMANCS) into the hepatic artery to treat liver cancer[30]. Passive targeting may also be useful for modulating drug distribution after direct delivery to tissues[31].

Active targeting to specific tissues can be achieved by complexing the polymer–drug conjugate with a molecule (such as antibody, carbohydrate) that will be recognized by cell surface receptors in that tissue. One difficulty with this approach has been finding highly specific non-immunogenic targeting molecules. Nonetheless, progress is being made. For example, the HPMA copolymer drug conjugate has been targeted to the liver by adding galactose which is recognized by the hepatocyte cell surface asialoglycoprotein receptor[27]. These systems as well as HPMA–taxol conjugates are in clinical trials. Another approach involving polymeric drugs utilizes a polymeric (poly[N^5-(2-hydroxyethyl)-L-glutamine]) immunoconjugate of adriamycin and a targeting antibody such as a human IgM antibody directed against tumour-associated antigen. These immunoconjugates were designed to allow selective release of adriamycin in the acidic environment of the tumour through a new acid-labile maleamic acid linker[32].

Liposome-based delivery systems

Small lipid vesicles known as liposomes have been widely explored as drug carriers[33–35]. Encapsulating drugs within a vesicle, as opposed to attaching them to a single polymer chain, has the potential advantage of providing a higher drug-carrying capacity. However, to use liposomes effectively, a number of issues had to be overcome including shelf-life, difficulty in targeting specific tissues and rapid clearance by the phagocytic cells of the reticuloendothelial system (RES). A strategy to address this latter issue was to alter the liposome surface by adding hydrophilic substituents, such as PEG, that reduce RES uptake thereby prolonging liposome circulation time[33].

As the above liposome development problems began to be solved, the ability of liposomes to alter drug biodistribution, thereby leading

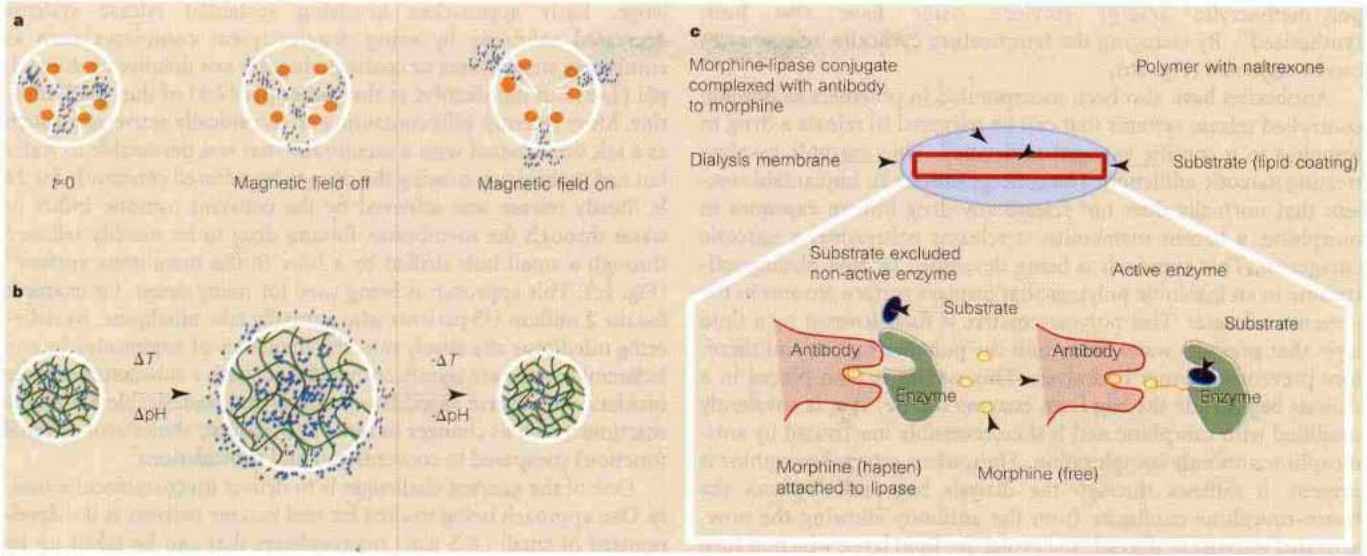

Figure 2 Examples of intelligent polymer delivery systems. See the main text for explanations of how these systems function. **a**, Magnetically controlled system. Large dots are magnetic beads. Small dots represent drug. **b**, pH- or temperature-controlled system (adapted from ref. 51). Small dots represent drugs. Lines represent polymer chains. **c**, Antibody-regulated system (adapted from ref. 56). Top panel, overall system; bottom panel, close-up of enzyme–antibody complex.

to decreases in drug toxicity, was utilized to create safer intravenous drug formulations. Liposomes loaded with duanorubicin and doxorubicin have now been approved by regulatory authorities for the treatment of HIV-associated Kaposi's sarcoma as has liposomal amphotericin B for fungal infections in cancer. The ability to achieve effective cellular targeting may depend on the ability to produce highly specific antibodies. For example, new antibodies coupled to liposomes such as those against the Her2 proto-oncogene, which plays an important role in the progression of breast and other cancers, are being explored for tumour targeting[36]. Liposomes that contain antibodies that recognize E-selectin, an endothelial-specific surface molecule, are being used to target vascular endothelial cells to achieve site-selective delivery in the cardiovascular system[37].

In some cases, polymeric drugs can be encapsulated within liposomes to beneficial effect. For example, *cis*-4-hydroxyproline (Chyp) prevents collagen accumulation when administered to animals and has been considered as a potential treatment for lung fibrosis. However, Chyp rapidly diffuses to many body sites causing toxicity by interfering with non-collagen protein synthesis. By coupling Chyp to a PEG–lysine copolymer, which prevents rapid diffusion and slowly releases Chyp, and encapsulating it into liposomes with amylopectin on their surface, which helps in lung targeting, collagen accumulation was prevented in the pulmonary arteries of hypoxic rats for over 1 week[38].

One area of intense investigation is the application of liposomes, particularly cationic liposomes, for gene therapy. Negatively charged DNA binds to positively charged liposomes, providing efficient transfection for many cell types[39]. For example, certain types of cationic liposomes can target endothelial cells in specific organs such as the lung[40]. Liposomes may also be useful for the delivery of DNA vaccines[41].

Polymer vesicles have also been investigated for their ability to achieve long circulation times and altered drug biodistribution. PEG has been conjugated to lactic/glycolic acid copolymers[42] or polyphosphazenes[43] and formed into nanospheres that circulate for long time periods. Albumin–heparin microspheres containing adriamycin have also shown improved biodistribution and reduced toxicity in animals[44]. In gene therapy, cationic nanospheres composed of chitosan[45], cationic polymer conjugates such as polyethyleneimine[46] or cationic starburst dendrimers made of poly(amido amine) polymers[47] may be useful in delivering DNA.

Intelligent delivery systems

In many cases, constant or decreasing drug release rates, as achieved with most drug-delivery systems, do not always mimic the body's natural pattern of providing chemicals. For example, for drugs such as insulin, pulsatile delivery is desirable.

An early approach to pulsatile delivery involved incorporating magnetic beads in an elastic polymer (Fig. 2a). When an oscillating magnetic field was applied (for example as may someday be achieved in a wristwatch-like device) more drug was released. This occurred reversibly and repeatedly over several months. The external magnetic field appears to cause alternative expansion and contraction of the drug-carrying pores. Key factors in terms of achieving pulsatile release are magnetic bead strength, magnetic field strength, polymer elasticity, magnetic bead size and polymer matrix structure[48].

Ultrasound also noticeably enhances transport of molecules entrapped within polymer release systems. The enhancing effect of ultrasound on drug release appears largely due to convection, generated by cavitation. Critical parameters are ultrasound frequency, molecular mass of the incorporated drug and polymer matrix structure (size of pores in the polymer network)[49].

Electric current has been used to control release rates from polymers. In one new approach, two water-soluble polymers, poly(ethyloxazoline) and either polymethacrylic acid or polyacrylic acid, form a solid because of intramolecular hydrogen bonding between the carboxylic and oxazoline groups. When an electric field is applied by attaching a cathode to the polymer matrix surface, hydroxyl ions are produced by electrolysis of water causing a local pH increase near the cathode surface, disrupting hydrogen bonding and causing disintegration of the polymer complex. If a drug such as insulin is placed in the insoluble complex it is released only when the electric field is applied[50].

Hydrogels are being widely studied for pulsatile delivery[51]. The electrostatic charge of a hydrogel (due for example to charged amino groups) can change in response to an environmental stimulus such as pH, leading to increased repulsive forces between polymer chains, which alters the diffusion rates of an entrapped molecule. One example involves a copolymer of polyhydroxylethyl methacrylate and *N*,*N*-dimethylaminoethyl methacrylate. Depending on the pH, the systems can either expand or squeeze tightly leading to an on–off mechanism to control the release rate of a drug encapsulated within the hydrogel (Fig. 2b). Such systems can also contain drugs such as insulin and biosensors such as glucose oxidase, which responds to changing external glucose concentrations by producing acidic byproducts. Thus, a change in glucose concentration is sensed by the hydrogel and insulin release is correspondingly altered[52]. Temperature-sensitive polymers such as poly-*N*-isopropylacrylamide[53,54] or

poly(methacrylic acid-*g*) ethylene oxide have also been synthesized[55]. By changing the temperature cyclically, release rates can be regulated (Fig. 2b).

Antibodies have also been incorporated in polymers to develop controlled release systems that can be triggered to release a drug in response to a specific external molecule[56]. One example involves treating narcotic addiction. The concept utilizes an implantable system that normally does not release any drug but on exposure to morphine, a heroin metabolite, it releases naltrexone, a narcotic antagonist. This approach is being developed by first placing naltrexone in an insoluble polymer that displays surface erosion in the presence of water. This polymer matrix is then covered by a lipid layer that prevents water entry into the polymer matrix and therefore prevents polymer hydrolysis. This system is then placed in a dialysis bag. Inside the bag is an enzyme (lipase) that is covalently modified with morphine and is then reversibly inactivated by anti-morphine antibody complexation. Thus, when external morphine is present, it diffuses through the dialysis bag and displaces the lipase–morphine conjugate from the antibody allowing the now-activated enzyme to degrade the protective lipid layer, which in turn permits polymer hydrolysis, thereby liberating the narcotic antagonist which subsequently diffuses out of the dialysis membrane into the body (Fig. 2c)

Delivery routes

Scientists have been studying how to get drugs into every part of the body with the goal of either local delivery to that site or non-invasive systemic delivery of drugs using that part of the body as a route to the systemic circulation.

Pulmonary. Local delivery to the lung has long been used in the treatment of respiratory diseases such as asthma and more recently for protein therapies such as DNase for cystic fibrosis. The deep part of the lung, which contains the alveoli, also has a number of potential advantages for systemic delivery of molecules including a large surface area, thin tissue lining and a limited number of proteolytic enzymes[57,58]. Most current lung delivery systems deliver drugs in liquid form and many incorporate chloroflurocarbon (CFC) propellants which may be environmentally dangerous. In addition, many of these systems do not deliver the drug reproducibly or efficiently; generally less than 10% of the drug is received by the lung from the device. Furthermore, repeated delivery every few hours is often necessary.

Recent advances in inhaler design involve non-CFC propellants and electronic breath actuation. New inhalers being designed control delivery by pushing liquid drug formulations through very tiny nozzles (2.5 μm diameter) at preprogrammed values of inspiratory flow rate and inhaled volume[59]. Approaches are also being developed to deliver fine dry-powder aerosols to the lung. An aerosol cloud is generated by compressing air into the drug powder inside the inhaler, thus breaking the powder into tiny (1–5 μm) particles that are capable of reaching the deep part of the lung. These newer inhalers reproducibly deliver 20–50% of the drug to the lung[60].

In spite of these advances, pulmonary drug delivery efficiency often remains relatively low and repeated administration continues to be necessary. To address these issues, the design of the aerosol particles themselves may be important. One recent approach has been to design large (5–20 μm) highly porous particles with extremely low densities. By lowering their density, the aerodynamics of the particles are altered making it possible for unusually large particles to enter the lungs through an airstream. Increasing particle size leads to decreased particle aggregation, creating greater inhalation efficiency, as well as decreased phagocytosis by alveolar macrophages. The decreased phagocytosis can result in sustained drug release. Insulin can be delivered in animals using these particles for over 4 days from a single inhaled dose[61].

Oral. Oral administration of small molecules is by far the most common approach for delivery of pharmaceuticals. However, maintaining a steady drug release rate for 12–24 h has long been a challenge. Early approaches involving sustained release systems decreased solubility by using drug/excipient complexes such as emulsions, suspensions or coatings that did not dissolve at stomach pH (1–5) but did dissolve at the higher pH (7.4) of the small intestine. More recently, pills containing an osmotically active agent such as a salt were coated with a membrane that was permeable to water but not to the drug, causing the drug to be released constantly for 24 h. Steady release was achieved by the constant osmotic influx of water through the membrane, forcing drug to be steadily released through a small hole drilled by a laser in the membrane surface[62] (Fig. 1c). This approach is being used for many drugs, for example for the 2 million US patients who annually take nifedipine. By delivering nifedipine at a steady rate, the frequency of angina attacks and ischaemic events are significantly reduced, with a substantially lower incidence of adverse vasodilatory effects and undesirable metabolic reactions (such as changes in serum potassium, cholesterol or renal function) compared to conventional oral formulations[2].

One of the greatest challenges is to deliver macromolecules orally. One approach being studied for oral vaccine delivery is the development of small (≤5 μm) microspheres that can be taken up by intestinal Peyer's patches and, to a lesser extent, enterocytes[63–66]. Although many materials such as poly(lactic/glycolic acid) have been studied as delivery vehicles there is usually a low uptake (less than 1%) by Peyer's patches. Lipophilic polymers led to higher uptake but most materials used to date are not degradable[63]. To develop lipophilic particles, liposomes were used orally, but were polymerized to prevent their destruction by bile acids. Over 3% uptake by Peyer's patches has been achieved using polymerized liposomes and this has been increased to 10% by covalently attaching ligands with an affinity for Peyer's patch M cells, such as ulex europaeus agglutinin, to the liposome surfaces[67].

One approach to achieving oral delivery of complex molecules, including genes, has been the development of polyanhydride microspheres, which display strong adhesive interactions with the intestinal mucosa and cellular lining. Low molecular mass drugs such as dicumarol, as well as larger molecules such as insulin and even genes, can be taken up in animals using this type of approach, presumably because the microspheres maintain contact with the intestinal epithelium for long times. Microscopic evidence has shown that the microspheres actually penetrate the epithelium, through and between cells[68].

Another approach involves designing low molecular mass carrier molecules that weakly bind to proteins and apparently carry them across the gastrointestinal epithelium. The carrier molecules, such as hydroxybenzylaminophenylbutyric acid[69] reversibly destabilize the native protein state favouring a partially unfolded conformation that can potentially diffuse more readily across the gastrointestinal epithelium into the systemic circulation. The unfolded form of the protein satisfies the definition of the protein's molten-globule state. The transport efficiency of these carriers for specific molecules correlates with their destabilizing potency which can be measured by techniques such as differential scanning calorimetry. Different carrier molecules appear to be specific for different proteins. This approach has been used for the oral delivery of interferon, calcitonin and human growth hormone in animals[70] and is currently in clinical trials with heparin.

The targeting of protein drugs to the colon, which has much lower levels of protease activity than other portions of the gastrointestinal tract, is also being studied. To achieve this, polymers that will not degrade in the intestine before entry into the colon are being synthesized. For example, by constructing polymers with enzymatically degradable azoaromatic crosslinks, azoreductases commonly found in high concentrations in the colon but much lower concentrations elsewhere can degrade the polymer, allowing the entrapped drug to escape. It may be necessary not only to protect the drug from proteolytic enzymes but also to coincorporate penetration enhancers into the oral formulation[71]. One of the chal-

lenges for this and all the above approaches to oral protein delivery will be achieving bioavailabilities high enough and reproducibilities consistent enough for practical use in humans.

Transdermal. The skin acts effectively as an impenetrable barrier for most drugs. However, small lipophilic drugs can cross the skin at low flux rates and this provides a means for delivering drugs that are destroyed by the liver when taken orally. Transdermal patches have been developed for seven different drugs lasting from 1 to 7 days (Table 2) and have been useful in producing new therapies and reducing adverse drug effects. For example, 2 years after being on transdermal nicotine patches for 12 weeks, 4 times as many patch users still do not smoke compared to patients who received placebos[72]. Over 700,000 US smokers have given up smoking because of these patches. Transdermal oestradiol patches are now being used annually for 1.3 million US patients; in contrast to oral formulations, these are not associated with liver damage. Transdermal clonidine, nitroglycerin and fentanyl patches also exhibited fewer adverse effects than conventional oral dosage forms[2].

To make transdermal delivery of other molecules practical, electrical approaches such as iontophoresis, which involves the usage of low-voltage pulses for long time periods, are being explored[73]. Iontophoresis can provide enhanced transport for some low molecular mass molecules such as pain medications and even decapeptides. To improve fluxes, high-voltage pulses for short time periods (milliseconds) have been used to induce pores temporarily in the skin (electroporation)[74], enabling the delivery of larger highly charged molecules including heparin[75] and oligonucleotides through human cadaver skin (the most commonly used model for human skin transport).

Ultrasound, particularly at low frequencies, can greatly enhance the flux of high molecular mass substances through the skin, presumably by temporarily disordering the lipid bilayers in the skin's outermost layer, the stratum corneum, which provides the principal barrier to diffusion. Using ultrasound, fluxes up to 5,000 times normal have been achieved and molecules the size of insulin or larger have been non-invasively transported through human skin models[76].

Other routes. The nose represents an additional portal for the delivery of large molecules. Using bioadhesive chitosan microspheres, the residence time of different macromolecules in the nose has been prolonged[77]. In addition, positively charged chitosan may interact with nasal epithelial cells, temporarily loosening up tight junctions in the nasal mucosa[78], causing enhanced permeability. This approach is in clinical trials for insulin.

Delivery to the brain has been a particularly difficult challenge because of the blood–brain barrier (BBB), which is composed of endothelial cells forming tight junctions that permit transport only of low molecular mass lipid-soluble molecules, with the exception of a few select peptides and nutrients that cross through specific transporting mechanisms. Although brain implants such as those discussed earlier permit localized delivery of encapsulated agents including proteins[79], it would also be useful to have less invasive means of delivering drugs, and of delivering them throughout the entire brain. Approaches to BBB transport include: BBB disruption using intracarotid administration of vasoactive molecules such as bradykinin or hypertonic solutions; the creation of prodrugs in which water-soluble drugs are attached by cleavable bonds to lipid-soluble carriers such as dihydropyridine; or attaching the drug to a vector that will transport across the BBB, such as the 83-14 murine monoclonal antibody to the human insulin receptor[80]. One approach that has moved to advanced clinical trials involves the use of a bradykinin agonist known as RMP-7 to aid in the delivery of anticancer agents such as carboplatin that normally do not cross the BBB[81].

The vaginal route has also been widely used for drug delivery, most notably in the form of vaginal rings for contraception. Generally, these systems are used over 6 months and are periodically removed monthly for 1-week periods. The vagina is a primary infectious site for many sexually transmitted pathogens as well as the entry site for sperm. Recently, the possibility was explored that antibodies delivered directly to the vagina can provide significant protection against sexually transmitted diseases, as well as pregnancy. By designing a polymeric vaginal delivery device that delivers antibodies for long time periods, a continuous supply of antibodies to the vagina was provided[82].

Table 2 Currently marketed transdermal drug-delivery systems

Drug	Indication	Duration (days)
Scopolamine	Motion sickness	3
Nitroglycerin	Angina	1
Nicotine	Smoking cessation	1
Clonidine	Hypertension	7
Fentanyl	Pain	1
Oestradiol	Oestrogen replacement	3.5–7
Testosterone	Male hormone replacement	1

The eye is also an important site for continuous delivery[83]. One early example was the development of the Ocusert, an ethylene-vinyl acetate copolymer-controlled release system that slowly delivers pilocarpine for 1 week to treat glaucoma. The Ocusert is inserted into the conjuctiva. However, because many patients do not like to insert objects into their eye, eye drops that could gel in the eye because of a pH or temperature change might be a useful area of research. Many important ocular diseases, such as macular degeneration and diabetic retinopathy are located in the back of the eye; it would be of value to develop systems that could target this area. Although not directly placed in the back of the eye, the Vitrasert polymer system, which is placed in the vitreous and slowly delivers gangcyclovir, is useful in treating AIDS patients with cytomegalovirus retinitis[84].

Many diseases are confined to specific anatomic sites in the body. By physically applying polymer systems directly at these sites, these diseases can potentially be locally treated, increasing both safety and efficacy. For example, in vascular disease, the ability to locally deliver heparin[85] or antisense oligonucleotides[86] to blood vessels has been shown to prevent smooth muscle cell proliferation, leading to potentially new approaches to treat restenosis. Another application has been the delivery of tissue plasminogen activator or urokinase in biodegradable polymers to prevent post-surgical adhesions in rat models. The polymers used in this case are applied as a liquid and then photopolymerized in the presence of external light so that they not only solidify but adhere to the tissue surface to which they are applied[87]. Local polymeric delivery of calcium chelating agents such as bisphosphonates has been shown to be useful in preventing calcification of bioprosthetic heart valves[88]. The local delivery of antibiotics to the gums of patients with periodontal disease greatly reduces the systemic doses of these antibiotics and provides a new way of non-surgically treating this disease[89].

Discussion

Drug delivery is a remarkably interdisciplinary field. Important contributions have come from material scientists, engineers, biologists, pharmaceutical scientists and others who have developed important concepts and brought them to clinical application. Certainly one activity that will take place in the next 10 to 20 years is the clinical introduction and evaluation of many of the new delivery systems discussed above. At the same time, advances in many other scientific areas will aid in the development of new drug-delivery systems. Progress in immunology and human genomics should lead to a greater insight into the type of targeting molecules that can be used to achieve site-specific drug delivery. Advances in combinatorial chemistry are already being used to create new biomaterials and may enable large numbers of new biomaterials to be screened more rapidly[90]. Progress in microelectronics and nanotechnology may someday lead to tiny robots that may be able to travel through the bloodstream and perform both physical and chemical functions. The understanding of transport phenomena through various portals in the body such as the intestine, lung and skin may lead to new drug-delivery strategies. Delivery to sites that are not easily accessi-

ble such as the sinuses or nerves may also be important. In addition, the development of mathematical models that can predict delivery performance[91] will facilitate the design of various delivery systems.

Finally, the design of ideal carriers for applications such as gene therapy will be extremely important. The possibility of designing materials that can simultaneously avoid the RES, target specific cell types, be taken up by those cell types in such a way as not to destroy their DNA, and then made to release the DNA unharmed so that the DNA can travel to the nucleus will be an important challenge. Nonetheless, with the progress being made in biology, chemistry, biomaterials, engineering and pharmaceutical sciences, this field should have a bright and rapidly evolving future. □

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Acknowledgements. I would like to thank J. Kost, G. Cowley, H. Rosen, S. Mitragotri, D. Putnam, L. Niklason, I. Sanderson, J. Hrkach and S. Cannizzaro for their assistance. R.L.'s research in drug delivery is supported by the NIH.