Advances in Biomaterials, Drug Delivery, and Bionanotechnology

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Biomaterials are widely used in numerous medical applications. Chemical engineering has played a central role in this research and development. Polymers as biomaterials, materials and approaches used in drug and protein delivery systems, materials used as scaffolds in tissue engineering, and nanotechnology and microfabrication techniques applied to biomaterials are reviewed.

Introduction

In the rapidly changing scientific world, contributions of scientists and engineers are leading to major new solutions of significant medical problems. No longer is the treatment of diabetes, osteoporosis, asthma, cardiac problems, cancer, and other diseases based only on conventional pharmaceutical formulations. Biology and medicine are beginning to reduce the problems of disease to problems of molecular science, and are creating new opportunities for treating and curing disease. Such advances are coupled closely with advances in biomaterials and are leading to a variety of approaches for relieving suffering and prolonging life.

Of particular interest is the central position that materials (especially polymers, ceramics and metals) have taken in the development of novel treatments over the last 30 years. Biomaterials are generally substances other than food or drugs contained in therapeutic or diagnostic systems that are in contact with tissue or biological fluids. They are used in many biomedical and pharmaceutical preparations, they play a central role in extracorporeal devices, from contact lenses to kidney dialyzers, and are essential components of implants, from vascular grafts to cardiac pacemakers. There are many current biomaterials applications, found in about 8,000 different kinds of medical devices, 2,500 separate diagnostic products, and 40,000 different pharmaceutical preparations. Although biomaterials already contribute greatly to the improvement of health, the need exists for better polymer, ceramic, and metal systems and improved methods of characterizing them (Peppas and Langer, 1994).

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In this article we discuss recent advances in the fields of: (i) polymers as biomaterials; (ii) materials in drug and protein delivery; (iii) materials for tissue engineering; and (iv) materials used in nanotechnology and microfabrication of medical devices. We analyze scientific progress in these fields over the last ten years, and we stress the impact of chemical engineering thinking on developments in this field.

Polymeric Materials as Biomaterials

The development of biomaterials has been an evolving process. Many biomaterials in clinical use were not originally designed as such, but were off-the-shelf materials that clinicians found useful in solving a problem. Thus, dialysis tubing was originally made of cellulose acetate, a commodity plastic. The polymers initially used in vascular grafts, such as Dacron, were derived from textiles. The materials used for artificial hearts were originally based on commercial-grade polyurethanes. These materials allowed serious medical problems to be addressed. Yet, they also introduced complications. Dialysis tubing may activate platelets and the complement system. Dacron-based vascular grafts can only be used if their diameter exceeds about 6 mm. Otherwise, occlusion can occur because of biological reactions at the blood-material and tissue-material interfaces. Blood-materials interactions can also lead to clot formation in an artificial heart, with the subsequent possibility of stroke and other complications (Peppas and Langer, 1994).

In the last few years, novel synthetic techniques have been used to impart desirable chemical, physical, and biological properties to biomaterials. Materials have either been syn-

thesized directly, so that desirable chain segments or functional groups (Bures et al., 2001) are built into the material, or indirectly, by chemical modification of existing structures to add desirable segments or functional groups.

Polymeric biomaterials can be produced by copolymerizations of conventional monomers to achieve nearly monodisperse polymers. It is possible to produce polymers containing specific hydrophilic or hydrophobic entities, biodegradable repeating units, or multifunctional structures that can become points for three-dimensional (3-D) expansion of networks (Peppas, 2000). Advanced computer techniques allow researchers to follow the kinetics of formation of 3-D structures of these biomaterials (Ward and Peppas, 2000).

Another synthetic approach involves genetic engineering for the preparation of artificial proteins of uniform structure (Tirrell et al., 1996, 1998). This enables the synthesis of periodic polypeptides that form well-defined lamellar crystals, polypeptides containing non-natural amino acids, and monodisperse helical rods. Important issues to be addressed include immunogenicity and purification from contaminants during large-scale production. If techniques were developed to produce polymers with the use of non-amide backbones, the versatility of this approach would be extended.

Efforts have also been made toward chemical modification of polymer surface or bulk properties, by treatments such as plasma modification. One surface treatment of biomaterials involves grafting inert substances such as PEO segments onto or within existing polymers such as polyurethanes to enhance biocompatibility or reduce protein adsorption (Peppas et al., 1999; Morishita et al., 2002). In addition, polymers have been synthesized that promote a desirable interaction between themselves and surrounding cells. Thus, peptide sequences, such as Arg-Glu-Asp-Val, that promote endothelial cell seeding have been synthesized into polymers for potential use as artificial blood vessels (vascular grafts) and copolymers of lactic acid and lysine have been synthesized, to which specific amino acid sequences that promote adhesion of hepatocytes or other cells can be attached for potential use in tissue engineering (Barrera et al., 1993; Vacanti and Langer 1999).

Other synthetic approaches have been used to develop environmentally responsive biomaterials (to surrounding pH, ionic strength, or temperature). For example, poly(acrylic acid) with ionizable side groups responds to changes in pH or ionic strength (Foss and Peppas, 2001). Research in certain specific biomaterials is now discussed.

Hydrogels

Hydrogels are water-swollen networks (crosslinked structures) composed of hydrophilic homopolymers or copolymers (Lowman and Peppas, 1999). They are rendered insoluble due to the presence of chemical (covalent or ionic) or physical crosslinks. The latter can be entanglements, crystallites, or hydrogen-bonded structures (Peppas, 1987). The crosslinks provide the network structure and physical integrity. Over the past 35 years, hydrogels have been extremely useful in biomedical and pharmaceutical applications mainly due to their high water content and rubbery nature which is similar to natural tissue, as well as their biocompatibility (Peppas et al., 2000). They can be neutral or ionic hydrogels based on the type of charges of their pendent groups. They can be also classified as amorphous, semicrystalline, hydrogen-bonded structures, supermolecular structures, and hydrocolloidal aggregates.

Hydrogels may exhibit swelling behavior dependent on the external environment. Thus, in the last thirty years there has been a major interest in the development and analysis of environmentally or physiologically responsive hydrogels (Peppas, 1993). These hydrogels show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature of the swelling agent, and electromagnetic radiation. Hydrogels which exhibit pH-dependent swelling behavior contain either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendent groups can ionize, developing fixed charges on the gel. Some advantages to using ionic materials, as they exhibit pH and ionic strength sensitivity, are relevant in drug delivery applications.

An additional advantage of hydrogels, which is only now being realized, is that they may provide desirable protection of drugs, peptides, and especially proteins from the potentially harsh environment in the vicinity of the release site (Lee et al., 1995; Peppas et al., 2000). Thus, such carriers may be used in the future for the oral delivery of proteins or peptides. Finally, hydrogels may be excellent candidates as biorecognizable biomaterials (Kopecek et al., 1996). As such, they can be used as targetable carriers of bioactive agents, as bioadhesive systems, or as conjugates with desirable biological properties.

Hydrophobic carriers and Molecular Design

Initial studies in our laboratories focused on materials that were commercially available and had some useful properties such as being reasonably biocompatible, although the properties may not have always been optimal for a particular application. In the 1970s ethylene-vinyl acetate copolymer was a polymer that was particularly useful. It had already been approved in certain medical devices; even though it's original applications were in commodity objects such as coatings. Nonetheless, to try to make it useful as a biomaterial, it was important that certain types of antioxidants be extracted from it. Procedures such as ethanol extraction were developed for this purpose (Langer et al., 1985).

In the 1980s, it became increasingly clear that polymers should be more rationally designed for medical purposes. A particular example is polyanhydrides. We and others had suggested that, rather than using materials in commodity objects, the biomaterial could be chemically synthesized from first principles to possess precisely the correct chemical, engineering, and biological properties for the exact medical application. In the case of synthetic degradable polymers for drug delivery, most polymers displayed bulk erosion (Figure 1), in which the polymer matrix becomes highly porous as time progresses and fell eventually apart. Thus, if a drug were originally distributed uniformly throughout the matrix, the drug could potentially "dump" out as the matrix erodes. From an engineering standpoint, it would be better if polymers degraded by surface erosion (Figure 2). To achieve this goal, the following engineering design questions were asked:

(i) What should cause polymer degradation - enzymes or water? Water was chosen because enzyme levels differ be-

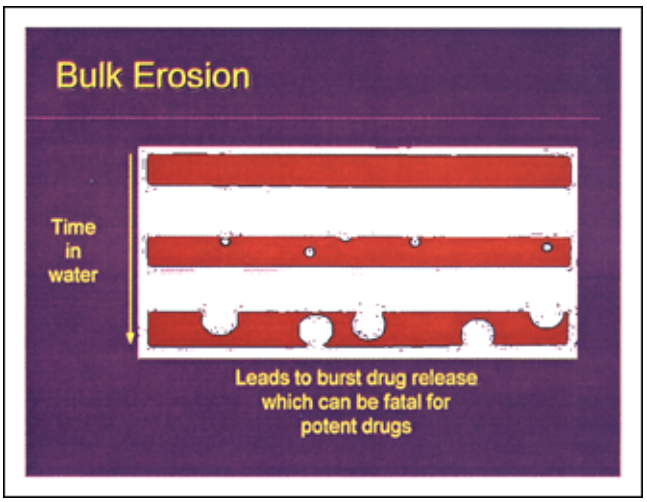

Figure 1. Bulk eroding polymer matrix.

tween individuals and the cellular response (cells contain different enzymes) surrounding a material changes over time. However, everyone has excess water.

(ii) What should be the nature of the monomers? To achieve surface erosion, the monomers should be hydrophobic to keep water out of the polymer matrix interior.

(iii) What should the chemical bonds connecting the monomers be? Here it is important that the bonds be hydrolytically labile. The anhydride bond was chosen.

(iv) What should be the precise chemical structure of the monomers connecting the anhydride bonds? This was examined from both a toxicological and polymer chemistry standpoint; several monomers such as carboxyphenoxypropane and sebacic acid were selected on this basis.

The polymers were then synthesized, formed into microspheres or discs, and drugs could be placed inside them (Tamada and Langer, 1992). One of the advantages of polyanhydrides is that they can be made by procedures such as bulk polycondensation (Leong et al., 1985) that do not have

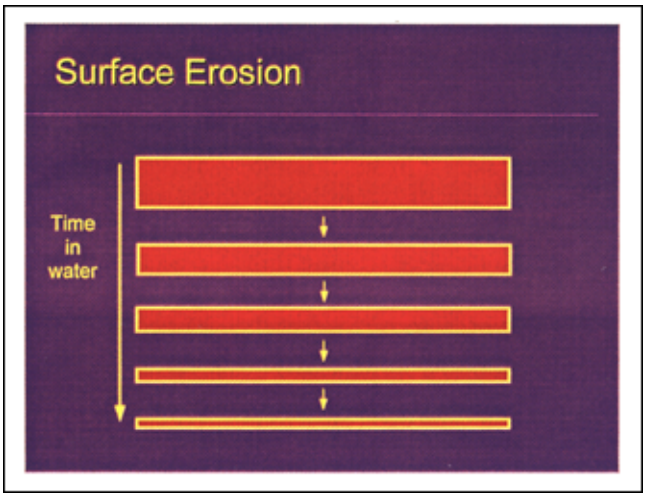

Figure 2. Surface eroding polymer matrix.

initiators or other types of impurities. As such, they ended up being relatively biocompatible (Leong et al., 1986). A variety of methods for polyanhydride synthesis were then developed (Leong et al., 1987). Today, polyanhydrides have been used in combination with drugs to treat thousands of patients with brain cancer through localized controlled release.

Most recently, high throughput polymer synthesis has been employed to rapidly synthesize new polymers and screen them for different applications (Brocchini et al., 1997, 1998; Belu et al., 2000). For example, recently in trying to design polymers for gene therapy delivery, a parallel synthesis approach was developed for creating polyβamino esters. Some of the properties of these polymers that make them amenable to this type of approach are:

(i) The monomers, in particular, the diamine and diacrylate monomers, are inexpensive, commercially available starting materials;

(ii) The polymerization can be achieved in a single synthetic step;

(iii) Purification steps are generally not necessary because byproducts are not produced during the polymerization procedure.

In one study, approaches were developed to synthesize these polymers (Lynn and Langer, 2000). A library of 140 such polymers were synthesized by starting with seven different diacrylates and 20 diamines. Through this synthetic approach, two polymers showed higher transfection efficacies than existing polymers or other non-viral reagents currently used for DNA transfection (Lynn et al., 2001) Most recently, methods were developed to automate these approaches and over 2000 such polymers in a single day were synthesized (Anderson et al., 2003).

Materials in Drug and Protein Delivery

There are several different goals in drug delivery. One goal —controlled drug delivery—is to control the duration of action of the drug and the drug's level in the human body. A second is to target the drug to particular places or cells in the body. A third is to overcome certain tissue barriers such as the lung, skin, or intestine. A fourth is to overcome certain cellular barriers as may be important in applications such as gene therapy.

Controlled drug delivery

Numerous controlled release systems exist today ranging from implants that release contraceptive drugs for up to 5 years to novel osmotically driven pills that deliver drugs at constant rates (Langer, 1998). One recent area of great importance has been the development of polymer-coated stents, which have shown remarkable results in reducing restenosis following angioplasty. Various scientists have developed approaches where they can coat metal, stents using drugs such as paclitaxel (Heldman et al., 2001), sirolimus (Oberhoff et al., 2002), and other drugs. Clinical trials have shown remarkable results in keeping blood vessels open and enhancing patient survival (Morice et al., 2002).

In controlled drug delivery, drug release generally occurs by one of three main mechanisms: (i) diffusion, (ii) chemical reaction; and (iii) solvent activation and transport. In the case

of diffusion control, there are two main drug distribution geometries that are used—either a reservoir where the drug is surrounded by a polymer barrier or a matrix where the drug is generally uniformly distributed through the polymer. In either case, diffusion through the polymer is the rate-limiting step (Narasimhan et al., 1999). In the case of chemical control, the polymer can be either degraded by water or a chemical reaction to release the drug. Alternatively, the drug can be attached to the polymer by a covalent bond that can be cleaved by water or an enzyme and release the drug. A third mechanism is solvent activation. The drug can be released either by swelling of the polymer in which the drug was previously locked into place within the polymer matrix in a glassy state or by an osmotic effect, which can be accomplished by external water entering the drug delivery system because of an osmotic driving force and subsequently driving the drug out of the system (Langer and Peppas, 1983). We now discuss research in different hydrogel polymers as they pertain to controlled release as examples of ongoing research.

Novel Hydrogels for Drug Delivery. The development of "conventional" controlled release devices based on hydrogels or hydrophilic carriers that can swell in the presence of a biological fluid has been described in several reviews (Peppas, 1997). Swelling-controlled release systems have found many applications for the solution of a wide range of medical problems. Recent developments concentrate on the novel use of the solute diffusional process to achieve desirable release rates and "dissolution profiles." For example, new phase erosion controlled release systems have been reported (Mallapragada and Peppas, 1997; Peppas and Colombo, 1997) that exhibit an unusual molecular control of the drug or protein delivery by simple dissolution of the carrier. Hydrophilic carriers pass through a process of chain unfolding from the semicrystalline phase to the amorphous one, eventually leading to complete chain disentanglement. It has been shown that poly(vinyl alcohol) (PVA) and poly(ethylene glycol) (PEG) are useful systems for such release behavior, and that such devices have the potential to be used for a wide range of bioactive agent release processes.

Environmentally Responsive Hydrogels. Several factors affect the swelling/deswelling of environmentally responsive hydrogels. They include the degree of ionization in the network, the ionization equilibrium and the nature of the counterions. As the ionic content of a hydrogel is increased in response to an environmental stimulus, increased repulsive forces develop and the network becomes more hydrophilic. Because of the Donnan equilibrium, the chemical potential of the ions inside the gel must be equal to the chemical potential of the ions in the solvent outside of the gel. An ionization equilibrium is established in the form of a double layer of fixed charges on the pendant groups and counterions in the gel. The nature of counterions in the dissolution medium also affects the swelling of the gel. Work on environmentally responsive hydrogels has taken several directions over the past several years, concentrating predominantly on ingeniously designed systems that utilize the pH- and temperature-sensitivity characteristics of certain hydrogel structures.

For example, various types of poly(N-isopropyl acrylamide) (PNIPAAm) have been used both as expanding (swelling) and squeezing hydrogels (Brazel and Peppas, 1996, 1999). Such systems have been shown to exhibit an "on/off" mechanism of control of the drug or protein release/delivery rate. Podual et al. (2000a) have shown how such systems can be employed for auto-feedback drug delivery, whereby the hydrogel will be connected to a biosensor and will respond to fast changes in the external biological conditions. This type of idea has been used to develop novel insulin delivery systems (Doyle et al., 1996). Another novel use of these systems is for the release of human calcitonin (Serres et al., 1996). The physicochemical understanding of such hydrogels under the conditions of application is neither simple nor well developed. Considering that all these carriers are ionic hydrogels, and that several ionic and macromolecular components are involved, with associated thermodynamically non-ideal interactions, it is evident that analysis and prediction of the swelling and drug delivery behavior is rather complex.

Recently, there has been significant interest in the synthesis of PNIPAAm-based hydrogels that contain increased amounts (domains) of the temperature-sensitive component NIPAAm. Major new methods of preparation of such systems (graft, block or comb-like copolymers) have been reported. NIPAAm-rich hydrogels can be prepared by simple methods (Vakkalanka and Peppas, 1996). Such systems show promise for rapid and abrupt or oscillatory release of drugs, peptides, or proteins, because their swelling/syneresis process can occur relatively fast. Conjugates of PNIPAAm with various enzymes have also been reported (Podual et al., 2000a). The details of the molecular mechanism of solute transport through ionic networks are not fully understood. Recent studies (Peppas and Wright, 1996) shed light on the special interactions between an ionic drug and an ionic network (polymer carrier). ATR-FTIR spectroscopy seems to be a promising technique for the analysis of drug binding on hydrogels as well as for visualization of drug distribution (am Ende and Peppas, 1995). Certain hydrogels may exhibit environmental sensitivity due to the formation of interpolymer complexes. These complexes, which have been shown in homo- and copolymer networks, are formed by non-covalent association between two or more complimentary polymers. The stability of the associations is dependent on such factors as the nature of the swelling agent, temperature, type of dissolution medium, pH and ionic strength, network composition and structure, and length of the interacting polymer chains. The incorporation of poly(ethylene glycol) (PEG) in pH- or temperature-sensitive materials seems to provide desirable characteristics of protein stability and biological stealth behavior. Hydrogen-bonded, complexation networks of poly(methacrylic acid-g-ethylene glycol) hydrogels (Bell and Peppas, 1996; Vakkalanka et al., 1996) exhibit abrupt expansion and contraction which is based on hydrogen bonding between the carboxyl group of MAA and the etheric group of EG. There is a rather abrupt change in the gel swelling ratio q, and mesh size ξ (which is a linear measure of the diffusional space available in a hydrogel) due to pH changes. Modulation of drug permeation is thus possible for delivery of a number of drugs, including streptokinase (Vakkalanka et al., 1996) for clot dissolution.

Neutral Hydrogels. Significant efforts have been undertaken to further develop and characterize the structure of predominantly neutral hydrogels used in drug delivery. Acrylamide-based hydrogels have been used for a wide range of applications in the past 15 years. Work by the group of Kopecek and

associates have provided synthetic roots for improved application of such systems. For example, hydroxypropyl methacrylamide-based copolymers and hydrogels have been developed for use in photodynamic crosslinking (Shen et al., 1996). Such polymers could potentially be used in photodynamic therapy of tumors.

Hydrogels of PEO have received significant attention in the last few years, especially because of their associated stealth characteristics in certain biological drug delivery applications. Radiation-crosslinked PEO hydrogels have been prepared and their mesh size and drug diffusional behavior have been analyzed in detail (Stringer and Peppas, 1996). Micelles of PEO with various other comonomers are promising systems for release of drugs because of the stealth nature of particles prepared from these polymers. Poly(vinyl alcohol) (PVA) has also received significant attention in recent studies. For example, PVA hydrogels (Peppas and Mongia, 1997) have been well characterized and various studies have been performed on drug transport through these structures. Of particular promise are PVA hydrogels prepared by a freezing/thawing process that creates crystallites and forms a physically-crosslinked 3-D network.

Bioadhesive Hydrogels. An alternative method of targeting drugs to specific sites is by the use of bioadhesive and mucoadhesive hydrogels (Peppas and Sahlin, 1996). Such systems usually consist of hydrogen-bonded structures such as poly(acrylic acid) (PAA)-based hydrogels which adhere to the mucosa due to hydrogen bonding and/or polymer chain penetration into the mucosa or tissue. In one study Sahlin and Peppas indicated that linear PEG chains could be added to PAA-based mucoadhesives either as free chains or as tethered structures to serve as mucoadhesion promoters (Sahlin and Peppas, 1997). Such systems, especially those prepared from PVA, can be promising for wound healing applications (Mongia et al., 1996).

Glucose-Sensitive Hydrogels. Research has also been conducted in the utilization of environmentally responsive hydrogels as glucose-sensitive systems. Typically, this is achieved by incorporation of glucose oxidase (Podual et al., 2000a) during or after the polymerization for the production of pH- or temperature-sensitive hydrogels.

Other Hydrogels. Environmentally-sensitive hydrogels have been reported as excellent agents for the release of fibrinolytic enzymes or heparin (Brazel and Peppas, 1996). Streptokinase can be released from P(NIPAAm-co-MAA) hydrogels by a simple change of temperature and pH in a narrow range.

New methods of delivery of chemotherapeutic agents using hydrogels have been recently reported. For example, biorecognition of various sugar-containing copolymers (Putnam et al., 1996) can be used for the release of chemotherapeutic agents. Kopecek and associates have used poly(N-2-hydroxypropyl methacrylamide) carriers for release of a wide range of such agents.

In the last few years there have been new methods of preparation of hydrophilic polymers and hydrogels that may be used in the future in drug delivery applications. For example, novel biodegradable polymers include polyrotaxanes, which are considered potentially useful for molecular assemblies for drug delivery (Ooya and Yui, 1997). Dendrimers and star polymers are new materials that enable a large number of functional groups to be available in a very small volume. Merrill has offered a useful review of PEO star polymers and their applications in the biomedical and pharmaceutical fields (Merrill, 1993). Griffith and Lopina (1995) prepared gels of controlled structure and large biological functionality by irradiation of PEO star polymers. Such gels may be promising materials as carriers for drug delivery if combined with techniques of molecular imprinting. Indeed, there have been several reports of the use of crosslinked polymers as templates for drug imprinting and subsequent release (Cheong et al., 1997). Still, this field is relatively new and its applications may not be immediately forthcoming.

Thus, new synthetic methods have been used to prepare homo- and copolymeric hydrogels for a wide range of drug, peptide, and protein delivery applications. Random copolymers with balanced hydrophobicity/hydrophilicity can offer desirable release rates and dissolution profiles, but graft, block, and comb-like copolymers offer additional advantages, especially when they contain temperature- or pH-sensitive pendent groups. Several interesting applications of such systems in the treatment of diabetes, osteoporosis, cancer or thrombosis have been discussed. Other hydrogels with promise as drug delivery vehicles include neutral gels of PEO or PVA, and gels of star molecules and other complex structures (Keys at al., 1998).

Controlling drug pharmacokinetics and targeting

One approach for altering the drug's pharmacokinetics and duration of action is to covalently couple polymers such as polyethylene glycol (PEG) to it. This has been used to lengthen the lifetime of proteins such as interferon (Burnham, 1994) that can now last up to one week in humans.

For tissue targeting, water-soluble non-immunogenic biocompatible polymers, which will either degrade or be eliminated by the body, are chemically linked to drugs, ideally through bonds that are cleaved once they reach their target (for example, a tumor). By changing the drug from a small to a large molecule, the biodistribution of the drug is altered (Duncan et al., 1996; Putnam et al., 1995). This approach has been used in cancer chemotherapy. The concept is that low molecular weight anticancer drugs when given intravenously will penetrate most tissues because they pass rapidly through cell membranes. Thus, the drug is quickly distributed throughout the body, with no tumor selectivity. However, if the polymer-drug linkages are designed so that they are stable in blood, the polymer-drug conjugate circulates for a longer time than just the drug itself because the high molecular weight polymer-drug can generally only gain entry to cells by endocytosis. Because most normal tissues have intact non-leaky microvasculature, the polymer-drug accumulates more in the tumor that has a leaky vascular bed (Duncan et al., 1996; Putnam and Kopecek, 1995). One approach involves *N*-(2-hydroxypropyl) methacrylamide (HPMA copolymer) coupled to doxorubicin. The conjugates can be cleaved by thiol-dependent proteases in lysosomes. Nearly seventy times more doxorubicin accumulates in mouse melanoma tumors than in normal tissues. Furthermore, the maximum tolerated dose of the polymer-drug is 5–10 times greater than the free drug (Duncan et al., 1996; Murakami et al., 1997). The injection of a styrene-maleic anhydride copolymer cou-

pled to neocarzinostatin (SMANCS) into the hepatic artery to treat liver cancer is another example of a polymer drug targeting strategy (Maeda, 1991).

Specific targeting to specific tissues can be achieved by coupling the polymer-drug with a molecule (such as antibody or a carbohydrate) recognized by tissue cell surface receptors. One challenge has been discovering appropriate targeting molecules. Galactose which is recognized by the hepatocyte cell surface asialoglycoprotein receptor is one example where successful targeting has been achieved (Duncan, 2003).

Liposomes have been used both for targeting and to create safer intravenous drug formulations for drugs such as doxorubicin for treating HIV-associated Kaposi's sarcoma and liposomal amphotericin B for fungal infections in cancer (Park et al., 1997; Torchilin, 1994). Liposomes provide a way of altering a drugs pharmacokinetics and can make them less toxic by changing their biodistribution in the body.

Noninvasive delivery of proteins

A significant opportunity has appeared in the pharmaceutical sciences over the past 35 years with the development of advanced drug delivery formulations. These formulations do not simply release the drug, peptide, or protein at some characteristic rate, but do so in a way that the pharmaceutical scientist and molecular designer wants (Peppas et al., 2000). For example, insulin may be delivered only when needed, calcitonin may be directed to bypass the stomach and be delivered only in the upper small intestine, and large molecular weight, genetically-engineered molecules are delivered across tissues at acceptable rates (Peppas and Huang, 2002).

The increased availability of large molecular weight protein- and peptide-based drugs with the recent advances in the field of molecular biology has given new ways to treat a number of diseases (Silbart and Keren, 1989). The structure, physicochemical properties, stability, pharmacodynamics, and pharmacokinetics of these new biopharmaceuticals place stringent demands on the way they are delivered into the body (Lee, 1991). More specifically, peptides and proteins must retain their structural integrity until they reach their delivery site and cannot be degraded upon enzymatic interactions. In addition, the mucosal lining that usually protects organs from mechanical and abrasive damage poses a main obstacle for the successful penetration of such drugs to the appropriate delivery site. Thus, each peptide and protein should be administered in an optimal temporal pattern that would account for the drug's unique pharmacodynamics and pharmacokinetics.

Alternative delivery methods to the traditional intravenous route are a subject of continuous intensive research efforts in both industry and academia. Prominent among these are the nasal, transdermal, pulmonary, buccal, ocular, vaginal, rectal and oral delivery routes with oral administration being considered the most convenient (Lehr, 1994).

The oral delivery route is the most challenging for complex drugs such as peptides or proteins from a technical perspective due to the extremely low bioavailability associated with the instability and low permeability of these drugs. Enzyme activity in the intestine or stomach also contributes significantly to the overall instability of such drugs. With the significant advances in the creation of protein and peptide therapeutics, it is vital that novel technologies be developed to formulate and deliver these drugs. Important challenges relate to the problems of stability, low bioavailability, the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity and short half-life of proteins and peptides (Peppas et al., 2001; Torres-Lugo et al., 2002b).

For example, the bioavailability of leuprolide, a luteinizing hormone-releasing hormone (LHRH) analog, is only 0.05% through the oral route, 3% for the nasal route, 8% for the rectal route, 38% for the vaginal route, and 65% for the subcutaneous injection (Okada et al., 1982). Emphasis has been placed on increasing the bioavailability of peptides and proteins for various administration routes by designing novel drug delivery systems tailored specifically for a specific application (Lowman et al., 1999; Kim and Peppas, 2002; Peppas, 2003).

Typically, the selection of the route of administration depends on

- Intended therapeutic use of a peptide or protein
- Desired duration of service-life
- Physicochemical properties of the protein or peptide.

For example, oral delivery of peptides and proteins is attractive due to its ease of application. However, there are many problems that need to be addressed, such as the harsh gastric environment, permeability through the lipophilic epithelial cellular membrane and/or the tight junction in the upper small intestine, as well as first pass metabolism by the liver.

Recently, there also has been much attention on chronopharmacological drug delivery systems. These drug delivery systems are intended to match the delivery of the therapeutic agents with the biological rhythm. These systems are important especially in the area of endocrinology and in delivery of vaccines. For example, it has been shown that the treatment of hypopituitary dwarfism by administration of human growth hormone releasing hormone (GHRH) is more effective when the GHRH is administered in a pulsatile manner (Chappel, 1999).

Clearly, the distinct properties of each individual peptide and protein combined with the physiological peculiarities of each delivery route prevent the design of a generic controlled-release system for even a general subset of peptides or proteins. Furthermore, the complexity involved in the design of a controlled-release device is very interdisciplinary and often involves teams of polymer chemists, chemical engineers, pharmacokineticists, pharmacologists, clinicians, and pharmaceutical scientists (Robinson, 1997).

In the oral route, Peppas and co-workers (Lowman et al., 1999a,b; Torres-Lugo et al., 2002a,b) have used bioadhesives that can respond to a pH change and, at the same time, protect protein drugs such as insulin and calcitonin from the acidic pH of the stomach and then release it into the more alkaline pH of the intestine (Figure 3). One of the novelties of these particular bioadhesive polymers is that they are also able to protect the protein from degradation in the small intestine and temporarily open connections between intestinal cells to allow proteins to penetrate into the intestine (Morishita et al., 2002). Figure 4 shows the main cellular barriers to drug or protein transport. Several mechanisms are involved in protein cellular transport including paracellular, transcellular and transcytotic transport (Figure 5). As

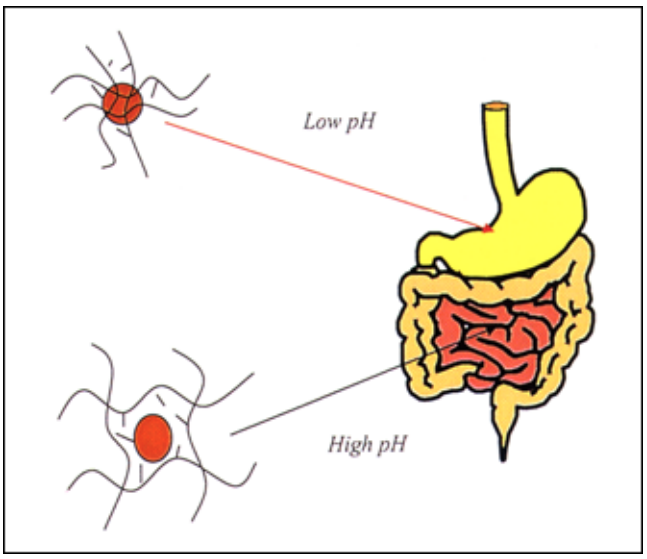

Figure 3. Swelling behavior of poly(methacrylic acid-g-ethylene glycol) hydrogels P(MAA-g-EG) as a function of the pH of the gastrointestinal tract.

Torres-Lugo et al. (2002a) pointed out, it is possible using Caco-2 cell lines to identify the main mechanisms of solute transport across tissues and, therefore, improve the solute bioavailability. Mathiowitz and co-workers have used certain types of polyanhydrides that have bioadhesive properties. By

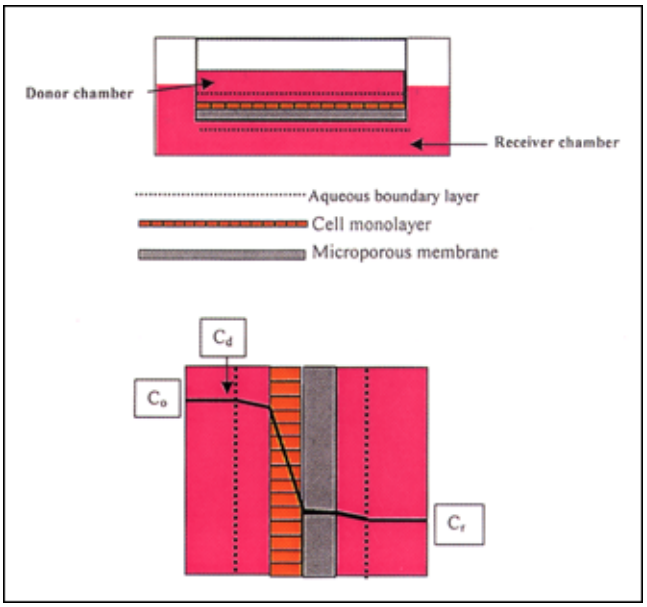

Figure 4. Potential barriers to solute transport in a cell culture system.

(A) Cell monolayer system grown onto a microporous system; (B) concentration profile system for the solute with the largest concentration drop within the cell monolayer. C_o, original concentration of the solute, C_d, concentration of the solute in the donor chamber, C_r, concentration of the solute in the receiver chamber.

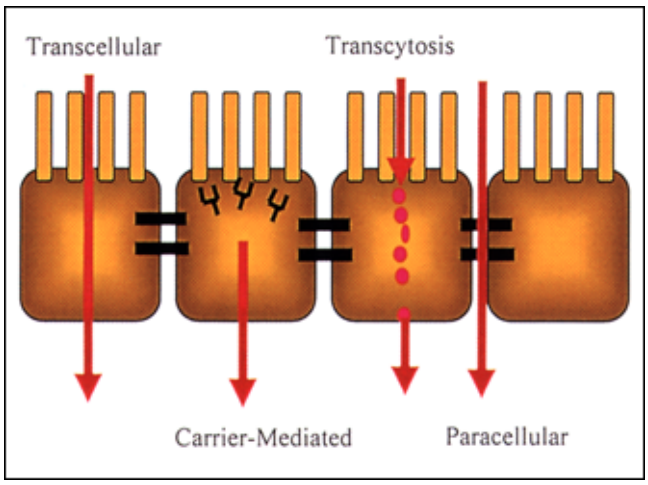

Figure 5. Protein or drug transport pathways through the cell monolayer (courtesy: J. Lopez).

exposing carboxylic groups on the polymer's exterior surface, they are able to bind to the gut. In particular, polyfumaric sebacic acid anhydride exhibits strong adhesive forces. Nanospheres made of these polymers were able to deliver drugs like insulin in diabetic rats (Mathiowitz et al., 1997). This type of approach has also been used to deliver genes in rats. Another approach has been to combine protein drugs with small molecules that are molecular carriers that appear to make the protein smaller and enable them to cross the intestine. This approach is being used to deliver insulin and heparin in animals (Leone-Bay et al., 1996; Milstein et al., 1998). Another method has been to couple proteins to molecules that target receptors in the gastrointestinal tract. For example, Russell-Jones et al. (2000) have coupled proteins to vitamin B-12 , which has receptors in the intestine. By doing this, protein along with the vitamin, is transported into the intestine where subsequent cleavage takes place, releasing the intact protein (Alsenz et al., 2000).

Transdermal patch technology represents an important area of biomaterials. The rate limiting barrier for transdermal patches are made up of substances such as ethylene vinyl-acetate or other polymers. These patches can deliver drugs from one to seven days. Currently, 11 drugs or drug combinations are delivered through the body via this method. Scientists are also exploring various physical forces to enhance the transport of drugs through the skin to expand the number of drugs being delivered. Approaches involve electricity such as iontophoresis (Merino et al., 1997) or electroporation (Prausnitz et al., 1993; Langer, 1998). Ultrasound is also being studied. In the latter case, the permeability of some drugs can be increased several thousand fold (Mitragotri et al., 1995). In addition, it is not only possible to deliver drugs using electrical or ultrasonic approaches, but also to extract intestinal fluid and actually sense particular analytes such as glucose in that fluid (Kost et al., 2000).

A variety of strategies have been used to deliver drugs into the lung. However, it has been difficult to get significant amounts of drug from an inhaler into the lung. 10% is often an upper limit. One of the reasons for this has been the ag-

gregation of aerosols following their delivery from an inhaler. A variety of groups are developing improved inhalers (Schuster et al., 1997). At the same time, new materials designs are being used to develop better aerosols. One widely used approach involves lowering the density of the aerosol particles while increasing their porosity and size (Figure 6). By doing this, aerosol aggregation is greatly reduced. In addition because these particles are larger than conventional aerosols, they are less likely to be taken up by lung macrophages and as such are able to prolong the release of drugs such as insulin in animal models for up to four days (Edwards et al., 1997).

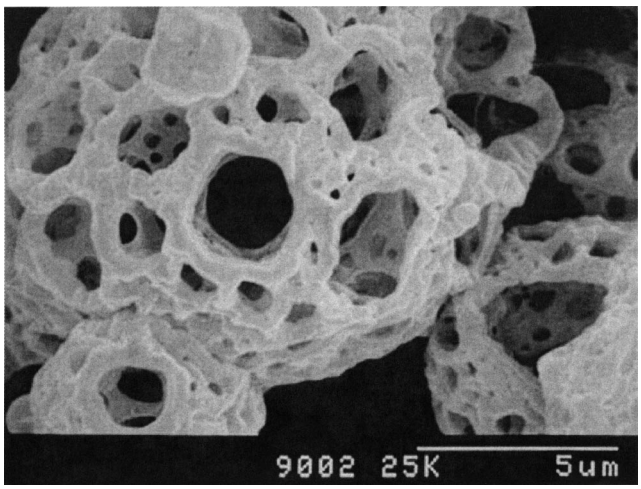

Figure 6. Scanning electron micrograph of a large porous aerosol particle.

Overcoming cellular barriers

Gene therapy represents an area where polymers can be used to help drugs overcome cellular barriers. To achieve successful gene therapy, the delivery system must overcome a variety of different barriers, as follows:

(1) It is important to be able to condense DNA to a reasonably small particle.

(2) The particle must be endocytosed or taken up by a cell.

(3) It must then be taken up by the cells endosome.

(4) It must release the DNA in active form.

(5) It must be transferred to the cell's nucleus.

There have been a number of classical materials that have been used for gene therapy. Some examples are lipids, such as lipofectamine, liposomes, and various polymers, like polyethylenenimine. An interesting new type of system that has been developed by Davis and co-workers is cationic cyclodextrins. These have been shown to complex with DNA to form small particles that have shown to be useful in a variety of *in vivo* and *in vitro* studies (Davis, 2001). Another example is the work of Putnam and co-workers who have modified polylysine to form novel polycationic polymers by precisely balancing the structure of side-chain termini to the polymer (Putnam et al., 2001).

Materials for Tissue Engineering

There are three ways in which materials have been shown to be useful in tissue engineering:

(1) The materials are able to induce cellular migration or tissue regeneration.

(2) The materials are used to encapsulate cells and act as an immunoisolation barrier.

(3) The materials are used as a matrix to support cell growth and cell organization.

An example of the first approach involves the use of glycosaminoglycan/collagen constructs that stimulates healing and act as an artificial skin. This type of approach has also been used in nerve regeneration and cartilage regeneration (Yannas et al., 1982). In the second case, cells are encapsulated in a polymer which acts an immunoisolation barrier. This has taken place in one of three forms. The first is (a) hollow fiber membranes where the cells are connected to the body. Some of the materials used are polysulfone membranes. This type of approach is in clinical trials for treating patients with liver failure by using porcine hepatocytes in the hollow fibers. These types of systems are being explored as a "bridge to transplant," for patients dying of liver failure who are urgently waiting for a transplant (Hubbell and Langer, 1995). This type of approach has also been explored for implantable systems containing beta cells for treating diabetes (Sullivan et al., 1991). The second form is (b) macrocapsules that can be implanted in the body. The macrocapsules also act as an immunoisolation barrier to prevent immune cells from entering the cellular transplant, but can allow medium or small sized molecules to penetrate through. One of the materials that has often been used for these applications are polyacrylonitrile-polyvinylchloride (PAN-PVC) membranes. These systems have been in clinical trials for treating certain brain diseases, for example, for releasing pain medication into the brain (Aebischer et al., 1991). The third are (c) microcapsules can keep the cells viable. The most widely studied system has been alginates which have the advantage of being able to encapsulate cells because the encapsulation is water based and the alginates can be ionically cross-linked by divalent ions such as calcium ions. This type of approach was originally pioneered by Lim and Sun in the treatment of diabetes in animal studies (Lim and Sun, 1980). Synthetic polymers have also been explored. For example, novel polyphosphazenes have been synthesized that can be ionically crosslinked in the presence of cells and water (Cohen et al., 1990). Interestingly, Sefton and co-workers have shown that they can even encapsulate mammalian cells in viable form using polymers in organic solvents (Uludag and Sefton, 1993; Lahooti and Sefton, 2000).

The third type of approach involves using a polymer matrix to act as a scaffold to enable cellular proliferation and reorganization. One of the most widely used scaffolds has been lactic/glycolic acid copolymers. In this case the lactic/glycolic acid copolymers are formed into fibrous systems or foams in desired anatomical shapes (Mikos et al., 1993; Mooney et al., 1995; Shastri et al., 2000) (Figure 7 and Figure 8). The cells are placed on them and are allowed to grow and organize to form appropriate cellular constructs. This type of approach has already been used in the creation of artificial skin (Hansbrough et al., 1992) and is in clinical trials for the cre-

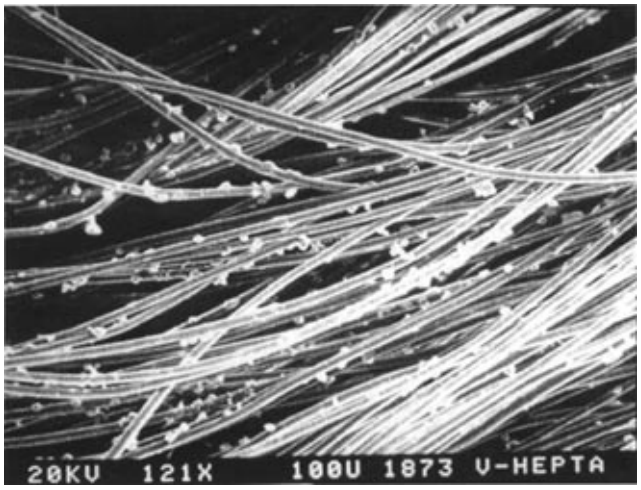

Figure 7. Scanning electron micrograph of lactic glycolic acid copolymer fibers.

ation of cartilage. The approach has been widely studied to create a variety of tissues in animal studies such as blood vessels, bone, and urologic structures (Vacanti and Langer, 1999). A number of new polymers are being synthesized for the purposes of improving cellular specificity. An example is the synthesis of polylactic acid-co-lysine polymers. These enable the attachment of specific amino acid sequences through the carboxyl group of the lysine via a carbodiimide (Barrera et al., 1993).

Nanotechnology and Microfabrication

In recent years we have seen an explosion in the field of novel microfabricated and nanofabricated devices for drug delivery. Such devices seek to develop a platform of well controlled functions in the micro- or nanolevel. They include: (i) Recognitive molecular systems; and (ii) Microfabrication and microelectronic devices.

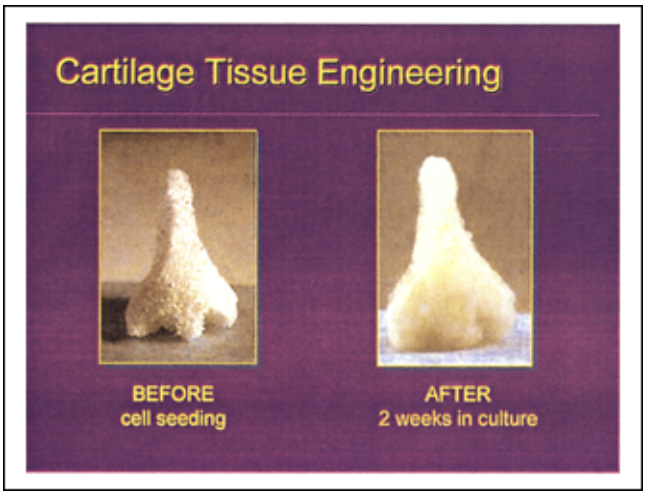

Figure 8. Polymer scaffold in the form of a human nose (courtesy, Prasad Shastri).

Recognitive molecular systems

Polymer surfaces in contact with biological fluids, cells, or cellular components can be tailored to provide specific recognition properties or to resist binding depending on the intended application and environment (Schakenraad et al., 1996). Engineering the molecular design of biomaterials by controlling recognition and specificity is the first step in coordinating and duplicating complex biological and physiological processes (Peppas and Langer, 1994). The design of surfaces for cellular recognition and adhesion, analyte recognition, and surface passivity encompasses a number of techniques such as surface grafting (ultraviolet radiation, ionizing radiation, and electron beam irradiation) (Ratner and Hoffman, 1996; Thom et al., 2000). Certain techniques can change the chemical nature of surfaces and produce areas of differing chemistry, as well as surfaces and polymer matrices with binding regimes for a given analyte. In recent years a novel technique of *configurational biomimesis* was developed (Byrne et al., 2002). The main characteristics of the technique are shown in Figure 9. Such techniques can generate novel biomimetic materials (mimicking biological recognition) for drug delivery, drug targeting, and tissue engineering devices. The synthesis and characterization of configurational biomimetic gels and molecularly imprinted drug release and protein delivery sys-

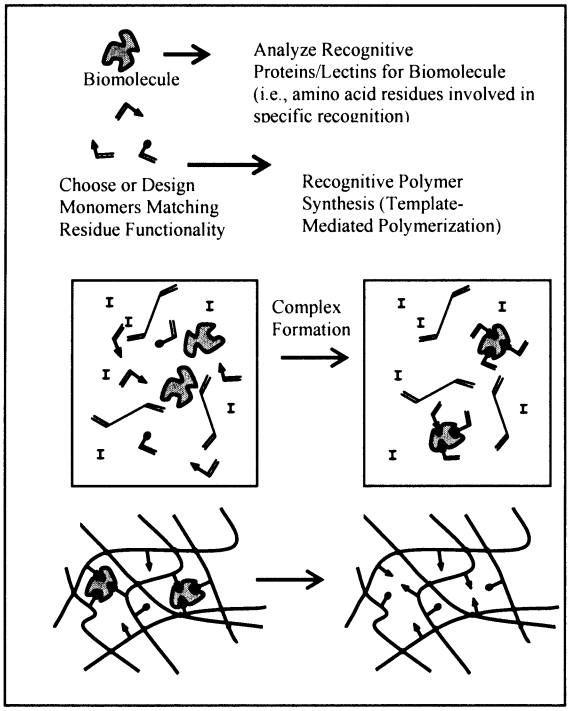

Figure 9. Configurational biomimetic imprinting process.

(A) Solution mixture of template, functional monomer(s) (triangles and circles), crosslinking monomer, solvent, and initiator (I). (B) The pre-polymerization complex is formed via non-covalent chemistry. (C) The formation of the network. (D) Wash step where original template is removed. (E) Rebinding of template. (F) In less crosslinked systems, movement of the macromolecular chains will produce areas of differing affinity and specificity (filled molecule is isomer of template) Courtesy: M. Byrne.

tems is a significant focus of recent research. Configurational biomimetic imprinting of an important analyte on an intelligent gel leads to preparation of new biomaterials that not only recognize the analyte, but also act therapeutically by locally or systemically releasing an appropriate drug.

The design of a precise macromolecular chemical architecture that can recognize target molecules from an ensemble of closely related molecules has a large number of potential applications. The main thrust of research in this field has included separation processes (chromatography, capillary electrophoresis, solid-phase extraction, membrane separations), immunoassays and antibody mimics, biosensor recognition elements, and catalysis and artificial enzymes (Takeuchi et al., 1999; Piletsky et al., 2001). Configurational biomimesis and nanoimprinting create stereo-specific 3-D binding cavities based on the template of interest. However, efforts for the imprinting of large molecules and proteins have focused upon 2-D surface imprinting (Shi and Ratner, 2000), a method of recognition at a surface rather than within a bulk polymer matrix. More recently, by using an epitope approach and imprinting a short peptide chain representing an exposed fragment of the total protein, 3-D imprinting of proteins within a bulk matrix has been successfully prepared (Rachkov and Minoura, 2001).

Configurational biomimetic imprinting (CBIP) techniques involve forming a pre-polymerization complex (Figure 9) between the template molecule and functional monomers or functional oligomers (or polymers) (Byrne et al., 2000; Wizeman and Kofinas, 2001; Byrne et al., 2002) with specific chemical structures designed to interact with the template either by covalent (Wulff, 1995; Mosbach and Ramstrom, 1996; Sellergren, 1997), or both (Whitcombe et al., 1995). Once the pre-polymerization complex is formed (Figure 9), the polymerization reaction occurs in the presence of a crosslinking monomer and an appropriate solvent, which controls the overall polymer morphology and macroporous structure. Once the template is removed, the product is a heteropolymer matrix with specific recognition elements for the template molecule. Several reviews exist describing the evolving field of molecular imprinting and designed molecular recognition (Ansell and Mosbach, 1996).

The CBIP network structure depends upon the type of monomer chemistry (anionic, cationic, neutral, and amphiphilic), the association interactions between monomers and pendent groups, the solvent (controls the overall polymer morphology), and the relative amounts of comonomers in the feed from which the structure is formed (Figure 10). Since recognition requires 3-D orientation, most techniques limit the movement of the memory site via macromolecular chain relaxation, swelling phenomena, and other processes, by using high ratios of crosslinking agent to functional monomers. As an increase in crosslinking monomer content leads to a decrease of the average molecular weight between crosslinks (see also Figure 11), the macromolecular chains become more rigid. In less crosslinked systems, movement of the macromolecular chains or, more specifically, of the spacing of functional groups will change as the network expands or contracts depending on the chosen rebinding solvent (thermodynamic interaction parameters characterizing the segment-solvent interaction) or application solution environment (Figures 9e and 9f). This process is reversible and transiently affects the binding behavior (Enoki et al., 2000) and leads to sites with varying affinity and decreased selectivity (Katz and Davis, 1999).

In biological applications, non-covalent techniques are the preferred synthesis routine since an easy binding non-binding template switching method is needed (that is, no harsh conditions to remove template). Imprinting success, that is, the ability to correlate high binding affinity and specificity, depends on the relative amount of cross interaction between the solvent and the intended non-covalent interactions (hydrogen bonding, hydrophobic interactions, π-π orbital interactions, ionic interactions, and van der Waals forces) employed during template-monomer complex formation (Mosbach and Haupt, 1998; Andersson et al., 1995). Proper tuning of non-covalent interactions such as increasing macromolecular chain hydrophobicity (Yu et al., 1997), including strong ionic directed recognition sites with hydrophobic domains (Haupt, 1998), has been shown to enhance binding and achieve selective recognition in aqueous solutions.

Biomimetic imprinted networks were first used as carriers for drug delivery (see also Figure 12) by Peppas and coworkers (Byrne et al., 2002). On the forefront of controlled drug

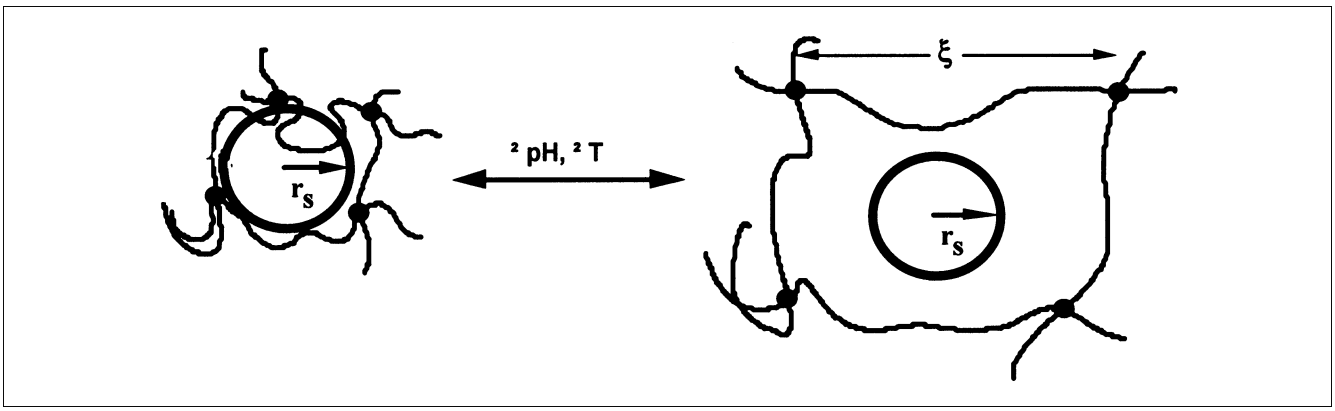

Figure 10. Hydrogels may expand or contract due to pH or temperature changes.

Drug diffusion may be facilitated or impeded depending on the molecular radius of the drug r_s with respect to the mesh size ξ of the polymeric gel carrier.

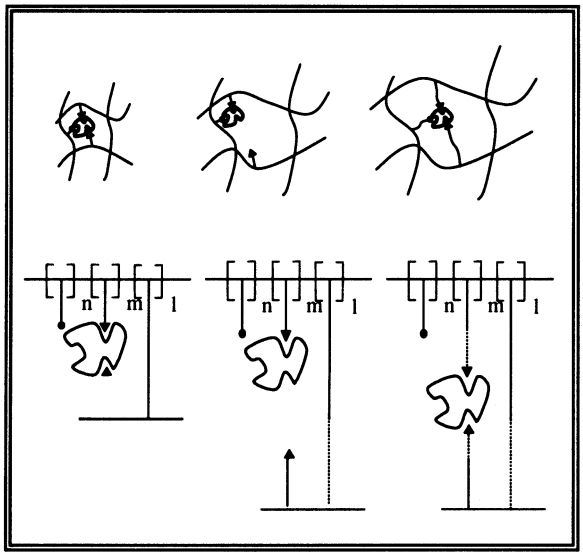

Figure 11. The heart of the configurational biomimetic process.

(A) Appropriate crosslinking to functional monomer size. (B) An increase in crosslinker molecular weight (linear size) without a change in functional monomer size. Note possible loss of effective recognition in some areas. (C) A corresponding increase in functional monomer molecular weight (linear size) compared to crosslinking monomer.

delivery are intelligent, stimuli-responsive gel systems that exhibit oscillatory swelling and, hence, modulate release in response to pH, temperature, ionic strength, electric fields, or specific analyte concentration differences (Byrne et al., 2002).

In these systems, release can be designed to occur via specific sites (adhesive or cell-receptor specific gels via tethered chains from the hydrogel surface). Currently, most analyte-sensitive gels are not entirely artificial and require a protein within the polymer matrix as the sensing/activation mechanism (Byrne et al., 2002). The inclusion of proteins, lectins, and other compounds (Figure 10) introduces immunogenic targets within these gels, as well as more constrained processing procedures. The use of imprinted highly crosslinked gels as the sensing/activation mechanism could lead to a variety of new, robust bimolecular sensing hydrogel networks for drug delivery (Peppas and Huang, 2002).

Since hydrogels swell significantly and contain large amounts of a hydrophilic solvent (within a thermodynamically favorable solvent, the macromolecular network will solvate and the network will expand), imprinting in hydrogels requires a different methodology. However, there are numerous examples of such systems in nature. Proteins are heteropolymers that contain both flexible and rigid areas, which have diverse dynamic binding functions. A protein can have side chain flexibility, amino acid segment mobility, and domain flexibility between various amino acid chain domains (Huber and Bennett, 1983). Since proteins are composed of a linear sequence (or sequences) of amino acids with each amino acid having a unique residue group (such as hydrophilic or hydrophobic, varying electrostatic properties, hydrogen bond donor or acceptor), it is this sequence that dictates the conformation of the final protein. The direct interactions of these groups with the water, with each other, and with other molecules (such as cofactors, chaperones, and so on) influence the folding of a protein into a stable 3-D arrangement. Theoretical analysis of protein folding and recognition by heteropolymers is the subject of a number of reviews (Jozefowicz and Jozefonvicz, 1997; Pande et al., 2000; Chakraborty, 2001; Shea and Brooks, 2001).

The macromolecular architecture is designed differently than more traditional dense networks and must include a spatially varying crosslinking density (micro- and macroporous regions). Density fluctuations in the polymer network create regions or microgels of localized higher crosslinking, which contain an effective imprinting structure and proper rigidity to produce adequate specificity (areas or patches of recognition). The binding kinetics and mass transfer of this design can be enhanced compared to known dense gels (mass transfer is slow and rebinding percentage is low as templates inherently are trapped within the matrix). However, analyte binding capacity is reduced on a per gel mass or volume basis (Peppas and Huang, 2002).

One promising alternative includes a post-crosslinking reaction, either between excess functional monomers on opposite macromolecular chains or via other monomers introduced into the network after the gel is formed and imprint is rebound. Since polymerization occurs within a solvent (as crosslinking in dilute polymer solutions minimizes physical entanglements and heterogeneity within the polymer network (Scott and Peppas, 1999), matching polymerization and rebinding solvents in terms of dielectric constant, polarity, protic nature, and so on (or keeping the original solvent when rebinding) will reduce differences in swelling behavior (Gibbs free energies associated with the elastic nature of the network and the energy of mixing). In these cases, the network can be designed in a less dense manner with recognition occurring between flexible functionalized chains (that is, longer and higher molecular weight) stabilized by additional post-crosslinking and post-stabilizing reactions either via opposite chains or within the functional monomer chain itself and a macromolecular chain. To date, little work has been completed on low crosslinked imprinted systems except for some recent work (Peppas and Huang, 2002; Byrne et al., 2002).

These methods (Peppas and Huang, 2002) have produced a new generation of low crosslinking recognition networks. In designing the macromolecular architecture with respect to monomer type and composition, as the molecular weight of the crosslinking monomer is increased, the length of the functional monomer or monomers increases accordingly to avoid loss of possible binding regimes irrespective of swelling or shrinking phenomena (Figure 13). This mainly deals with polymerization kinetics and the nature of the chains formed during polymerization, which influence the network morphology on a molecular level. With high crosslinking monomer ratios, the types of chains formed consist of primary copolymer chains of crosslinker and functional monomer and other secondary chains of crosslinking monomer that connect each macromer unit. This is a possible reason why investigators have seen marginal success in imprinting a given analyte by increasing the molecular weight of crosslinker without a corresponding increase in functional monomer molecular weight (linear size). Similarly, decreasing the crosslinker molecular size below a certain limit would produce a very restricted network for template diffusion and rebinding.

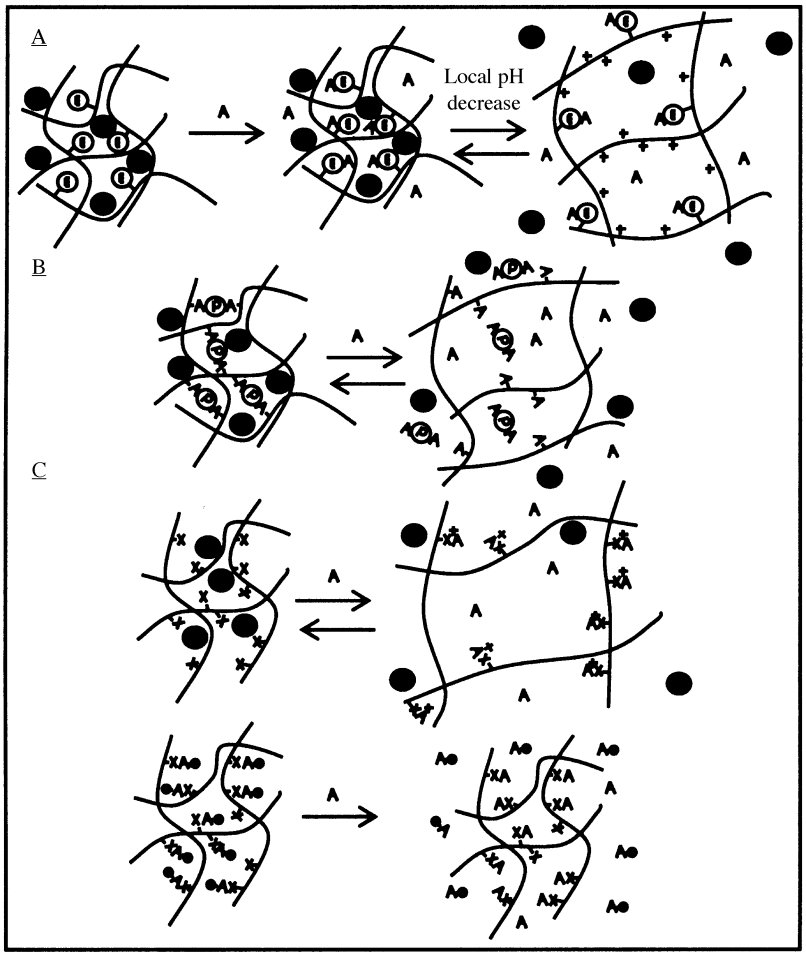

Figure 12. Intelligent analyte-sensitive CBIP hydrogel networks.

(A) Induced Swelling - as analyte (A) binds, the enzymatic reaction (E denotes covalently attached enzyme) produces a local pH decrease. For the cationic hydrogel, which is weakly basic, the result is ionization, swelling, and release of drug, peptide, or protein (filled circle). When (A) decreases in the bulk concentration, the gel shrinks. (B) Loss of Effective Crosslinks - Analyte competes for binding positions with the protein (P). As free analyte binds to the protein, effective crosslinks are reversibly lost and release occurs. Picture not to scale, binding protein is much larger than released drug, peptide, or protein. (C) Artificial system: bound analyte induced swelling - when analyte binds to a pendant functional group, an ionized complex forms which swells the network and release occurs. (D) Artificial system: analyte binding switch - analyte binding groups are randomly introduced into the network during polymerization. Then, chemically modified (analyte (A) attached) drug, peptide, or protein is bound. As analyte from solution competes for binding sites, release occurs. Courtesy: M. Byrne.

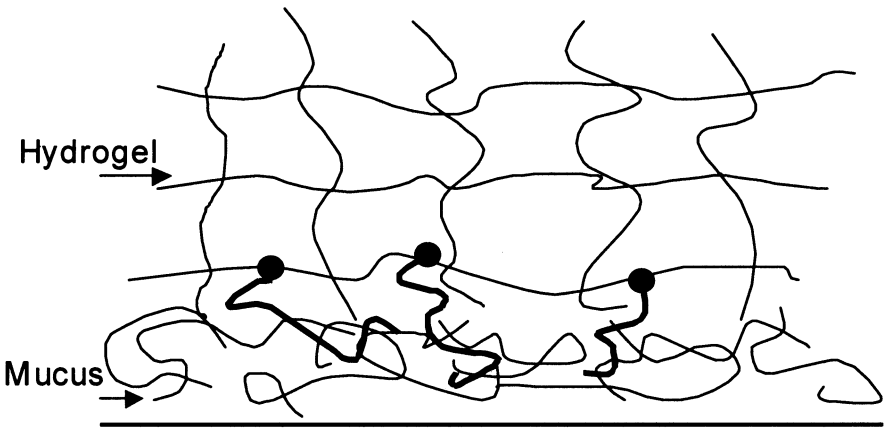

Figure 13. Hydrogels containing tethered chains may be rendered mucoadhesive due to the adhesion promoting capabilities of such tethered chains.

Therefore, there is an optimum crosslinking to functional monomer molecular weight ratio, which directly depends on the size of the template. For multifunctional crosslinking agents, the corresponding linear portions of the vinyl chains are expected to follow the same relationship, albeit on a different length scale depending on the physical molecular nature of the crosslinker. Although it is important to consider that as the macromolecular chains increase in size, the flexibility of the chains also increases.

Analyte sensitive polymer networks have been designed in a number of ways (Figure 12). They include enzymes, which, as a result of reaction, invoke a local pH change, modulating the swelling of the network and thus release (Albin et al., 1985; Goldreich and Kost, 1993; Podual et al., 2000a,b,c; Peppas and Colombo, 1997). They can include crosslink dependent systems where pendent (attached to the copolymer) chains and free analyte compete for binding positions within protein sites. As analyte replaces pendent analyte groups within the protein, the network loses effective crosslinks, opens the network mesh size, and regulates release (Lee and Park, 1996; Obaidat and Park, 1996, 1997, Miyata et al., 1999; Nakamae et al., 1994: Kokufata et al., 1991). As the analyte decreases in concentration within the bulk phase, the protein binds again with the pendent analyte groups closing the network structure. Similarly, systems have been designed that have a specific antigen and corresponding antibody grafted to a semi-interpenetrating network, which swells in response to binding of the antigen due to a loss of effective crosslinks (Miyata et al., 1999).

The design and implementation of imprinted recognition release systems is not simple, but one envisions imprinted gel particles or particles with thin coatings of imprinted films taking the place of the proteins within the above-mentioned gels. In particular, low crosslinked gels have been formed consisting of a functionalized network (with template not bound) and then an interpenetrating procedure where another network is formed in the presence of template (with additional crosslinks imposed by pendant analyte group interaction) (Zhang and Peppas, 2000). When in a solution of analyte, the gel loses effective imprints (or complexation) and release occurs. The releasable drug loading scheme involves imbibition (equilibrium partitioning) or entrapment during polymerization (if the drug does not interfere with the network formation and the template complex itself).

Microfabrication and microeclectronic devices

There are a variety of microelectronic devices that are being studied for controlled drug delivery systems. One example has been the creation of microchips with nano-sized wells that can house literally hundreds of different drugs or chemicals or, alternatively, hundreds of different doses of such substances (Figure 14). The original types of systems were made out of silicon and coated with gold. Gold has the advantages of having unique electro-chemical properties. It is easily deposited and patterned, has a low reactivity compared to other substances, and resists spontaneous corrosion generally in aqueous based solutions over a wide pH range. It also appears to be highly biocompatible. By applying a small voltage (such as 1 volt) in the presence of a small amount of chloride ion, however, the gold can be made to corrode and whatever drug is underneath it can be released. In proof of principle experiments, both single and multiple drugs have been released on demand from tiny microchips both *in vivo* and *in vitro* (Santini et al., 1999). More recently, polymer based microchips have been designed as well (Richards-Grayson et al., 2003).

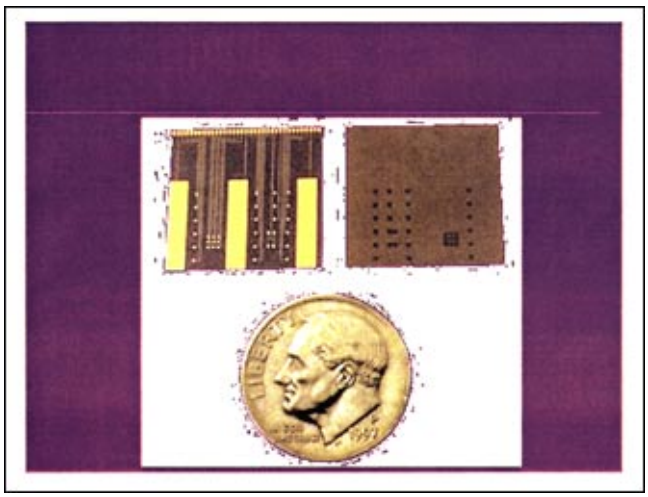

Figure 14. Photograph of top and bottom views of a drug delivery microchip and a U.S. coin.

Although 34 wells are shown, it is possible to put in at least 400 wells in a similar sized chip

Sensors represent another area where microfabrication can be important. For example, scientists are building capacitor-based sensors which have been tested *in vitro* in model blood vessels. One concept is to implant such systems in small animals to measure blood pressure during cardiovascular studies (Ziaie and Najafi, 2001). In another case, small sensors are being used to measure intraocular pressure for glaucoma patients (Stangel et al., 2001). For *in vivo* sensors, issues of biocompatibility will be important, and, as such, packaging issues may become significant. To address such issues, in one case an electrochemical sensor array was developed to put inside a biocompatible tube which can be monitored by telemetry (Madou, 2002; Kim et al., 1993). This sensor was designed so that it could monitor such substances as pH, carbon dioxide and oxygen.

Other sensors are being developed to replace lost perception of different senses. For example, scientists are studying approaches for retinal stimulation to compensate for photoreceptor regeneration in the back of the eye. A silicon microsimulator has been developed which can be controlled by telemetry (Schwarz et al., 2000).

Another interesting approach involves the development of microfabricated microneedles. This type of approach can have a remarkable effect in enhancing the delivery of drugs without causing significant pain to the patient. Microneedles are able to do this without pain because they don't penetrate deep enough into the skin layers that contain nerves, but are able to penetrate far enough into the skin for the therapeutic compounds to enter the circulation (Kaushik et al., 2001). In addition, injectable micromodules have been used to deliver electronic devices such as neuromuscular stimulators to peo-

ple. Some of these systems are small enough to be implanted by intracutaneous injection by a large gauge hypodermic needle, thereby eliminating the need for surgical implantation (Troyk, 1999).

Conclusions

The above examples represent only some of the approaches where chemical engineers are employing materials to address medical problems. Nonetheless, materials based systems are now being used in the treatment of cancer, heart disease, the creation of new tissues such as skin, and many other treatments. With continuing advances in chemical engineering, materials science, and biology, we expect continuing and even greater progress in biomaterials research and application in the future.

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