chapter three

*Role of polymers in drug delivery**

Contents

* Adapted from Ranade, V.V., Drug delivery systems. 3A. Role of polymers in drug delivery, *J. Clin. Pharmacol.*, 30, 10, 1990; and 3B. Role of polymers in drug delivery, *J. Clin. Pharmacol.*, 30, 107, 1990. With permission of *J. Clin. Pharmacol.* and J.B. Lippincott Publishing Company, Philadelphia, PA.

I. Introduction

The usefulness of polymers in drug delivery systems is well established. Continued improvement and accelerating research and development in polymeric materials has played a vital role in the progress of most controlled-release technologies. In the past 25 years, there has been a considerable increase in interest in this technology, as is shown by the increasing number of publications and patents in the area of controlled drug-release systems using synthetic as well as naturally occurring polymeric materials.[1–5]

II. Currently available polymers

Currently available polymers for controlled release can be classified into four major categories: (1) diffusion-controlled systems, (2) solvent-activated systems, (3) chemically controlled systems, and (4) magnetically controlled systems.

A. Diffusion-controlled systems

Diffusion-controlled systems involve two types: reservoir and matrix. A reservoir is generally spherical, cylindrical, or disc-like in shape and consists of a drug core in powdered or liquid form. A layer of nonbiodegradable polymeric material, through which the drug slowly diffuses, surrounds the core. The properties of the drug and the polymer govern the diffusion rate of the drug and its release rate into the bloodstream. In order to maintain uniformity of drug delivery, the thickness of the polymer must be consistent. One of the problems with the reservoir system is that such a system must be removed from the body after the drug is depleted because the polymer remains intact. Another potential problem is that if the reservoir membrane accidentally ruptures, a large amount of drug may be suddenly released into the bloodstream (known as "drug dumping").

In the matrix type of diffusion-control system, the drug is uniformly distributed throughout the polymer matrix and is released from the matrix at a uniform rate as drug particles dislodge from the polymer network. In such a system, unlike the reservoir, there is no danger of drug dumping in case of an accidental rupture of the membrane.

B. Solvent-activated systems

Solvent-activated systems are also of two types: osmotically controlled systems and swelling-controlled systems. In the osmotically controlled system, an external fluid containing a low concentration of a drug moves across a semipermeable membrane to a region inside the device, where the drug is in high concentration. Osmotic pressure tends to decrease the concentration gradient between one side of the membrane and the other. The inward movement of fluid forces the dissolved drug out of the device through a small orifice.

In the swelling-controlled systems, the polymer holds a large quantity of water without dissolving. The system consists of hydrophilic macromolecules cross-linked to form a three-dimensional network. A characteristic of such systems is their permeability, for low molecular weight solutes, at a controlled rate as the polymer swells.

C. *Chemically controlled systems*

Chemically controlled systems also have two classes: the "pendant-chain" system and the bioerodible, or biodegradable, system. A "pendant chain system" is one in which the drug molecule is chemically linked to the backbone of the polymer. In the body, in the presence of enzymes and biological fluids, chemical hydrolysis, or enzymatic cleavage, occurs with concomitant release of the drug at a controlled rate. The drug may be linked directly to the polymer or via a "spacer group."

In the bioerodible system, the controlled release of the drug involves polymers that gradually decompose. The drug is dispersed uniformly throughout the polymer and is slowly released as the polymer disintegrates. Two major advantages of erodible systems are (1) polymers do not have to be removed from the body after the drug supply is exhausted, and (2) the drug does not have to be water-soluble. In fact, because of these factors, future use of bioerodible polymers is likely to increase more than any other type of polymer in the future.

D. *Magnetically controlled systems*

Selective targeting of antitumor agents, while minimizing toxic effects, has been a major goal in cancer chemotherapy. Conventionally used systemic antineoplastic agents are unable to achieve ideal tumor specificity. Magnetically responsive drug carrier systems, composed of albumin and magnetic microspheres, have been developed for use in cancer chemotherapy. Because of their magnetic characteristics, these microspheres are theoretically capable of enhanced area-specific localization. This carrier system is capable of accommodating a wide variety of drugs. Two major advantages of the magnetically responsive carrier system over other drug delivery systems are its high efficiency for *in vivo* targeting and its controllable release of a drug at the microvascular level.

Due to rapid advances in recent years, the application of polymers to drug delivery has grown considerably. In order to provide a better understanding of the relationships and factors affecting various polymers, we have divided research and development into the following areas:

1. Soluble polymers
2. Biodegradable or bioerodible polymers
3. Mucoadhesive polymers

III. Soluble polymers as drug carriers

A. Pinocytosis

Soluble synthetic polymers are emerging as drug delivery vehicles of great promise. They appear to be more versatile than microparticulate carriers because of a greater number of potential target sites in the body.[6]

Biological membranes are effective barriers to macromolecules. The plasma membrane of the cell prevents the loss of enzymes from the cytoplasm, while intracellular membranes delineate functionally distinct subcellular compartments. Mechanisms for translocation of macromolecules across membranes exist, but these are often specific and sophisticated (e.g., pinocytosis).

Ideal characteristics for a macromolecular drug carrier include adequate drug-loading capacity; retention of water solubility when drug-loaded; molecular weight high enough to permit glomerular filtration, but low enough to reach all cell types; unmodified carrier not captured by adsorptive pinocytosis; a stable carrier-drug linkage in body fluids, but degradable in lysosomes; a slowly biodegradable carrier in the extracellular compartment or degraded in lysosomes; nontoxic; nonimmunogenic; and generally biocompatible.

During pinocytosis, the cell membrane invaginates to form a membrane-bound vesicle that contains extracellular fluid, solutes, and sometimes substances adhering to the cell surface. After "pinching off" from the plasma membrane, the pinocytotic vesicle migrates into the cytoplasm, fusing with other incoming vesicles and ultimately fusing with lysosomes to form what is known as a secondary lysosome. Normally, all macromolecules entering the secondary lysosome are susceptible to the organelles' degradative activity. The monomeric constituents liberated during hydrolysis can usually pass through the lysosomal membrane for reutilization in anabolic metabolism or, alternatively, are lost from the cell.

Large macromolecule-drug conjugates normally do not pass through cell membranes, but usually enter by pinocytosis. Drug conjugates that accumulate in lysosomes are termed "lysosomotropic." Coupling to a macromolecule automatically alters drug distribution. If the conjugate is passively captured solely as a solute, body distribution will depend on the rate of pinocytosis of individual cell types, as well as accessibility of the conjugate to each cell type. However, in those instances in which the conjugate has affinity for cell-surface receptors, and is therefore captured by adsorptive pinocytosis, the rate of uptake is dependent upon binding capacity. It is the latter carrier-mediated uptake that holds promise for targeting drug-carriers. To date, a number of cell-specific, receptor-mediated uptake processes have been identified. Many of these depend upon the interaction of specific carbohydrate moieties of a polymer with unique membrane receptors. If this type of approach, or other possible targeting systems (e.g., cell-specific antibodies), can be incorporated as a homing device into the carrier vehicle, there is a real possibility of achieving selective targeting (see Figure 3.1).

Although pinocytosis of polymers is somewhat affected by the molecular weight of the polymer-conjugate, its rate of penetration into a cell may be

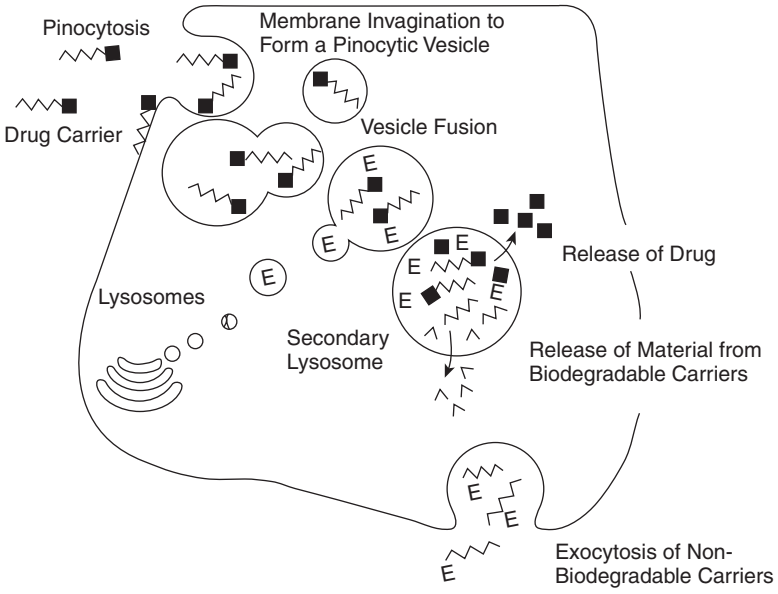

Figure 3.1 Intracellular fate of macromolecular drug conjugates. (From Anderson, J.M. and Kim, S.W., Eds., *Recent Advances in Drug Delivery Systems*, Plenum Publ. Corp., NY, 1984, 10. With permission.)

increased to some extent by the incorporation of hydrophobic units, (e.g., binding tyramine or tyrosinamide to water-soluble polymers). Both approaches, however, lack specificity. The targeting of polymers requires either binding of specific antibodies or binding of saccharide units able to interact with receptors on the surface of certain cells. The binding of saccharide units on synthetic polymers is based on the fact that a small change in the structure of glycoproteins leads to changes in the fate of modified glycoproteins in the organism. It is possible to facilitate the transport of both natural and synthetic polymers into liver hepatocytes, Kupffer cells, fibroblasts, or macrophages.

B. Ideal soluble polymers

According to Duncan and Lloyd,[6] the ideal drug carrier should possess the following features: polymer-drug linkages that display controlled biodegradability, a suitable molecular weight range, possibility for incorporation of residues that will facilitate direction to and efficient pinocytotic capture by the target cells, absence of any deleterious toxic effects, and nonpersistence in the body.

With the exception of biodegradability, synthetic polymers have advantages over their natural counterparts. Perhaps the most exciting feature of synthetic polymers is the wide choice that is available. In addition to homo-polymers, which consist of chains of identical repeating units, there are

many types of copolymers. Two or three different monomers may be copolymerized in a defined ratio. The resultant copolymer may have its component monomers arranged randomly or as regularly repeating dimers or trimers. Block copolymers consist of pieces of two homopolymers joined end-to-end. There is also the possibility of attaching several polymer chains together by cross-links, although this process frequently leads to loss of water solubility.

A useful polymer is one that adheres specifically to cells. Many authors have reported that polymers with a high density of positive charges, such as polylysine and polyornithine, bind tightly to cell membranes. Even a small change in charge density has profound effects. For example, a copolymer composed of 93% vinylpyrrolidone units and 7% (cationic) vinylamine adheres to mammalian cell surfaces, whereas the homopolymer polyvinylpyrrolidone does not. Conversely, a synthetic polyanion, pyran copolymer, has been found to adsorb to rat peritoneal macrophages and to enter these cells by pinocytosis 100 times more rapidly than polyvinylpyrrolidone.[7] Polyhydroxypropylmethacrylamide (polyHPMA) does not adsorb to cell membranes, but its rate of pinocytosis increases dramatically if 10 to 20% of the monomer residues are substituted with a phenolic residue.[8,9] Similarly, the incorporation of 10 to 20% phenolic side-chains greatly increases the cell-binding of another polymer, polyhydroxyethyl-aspartamide.[10]

Polymers that bind to cell surfaces are also likely to bind to plasma proteins. This fact will inevitably alter their interactions with cells and, *in vivo*, may lead to intravascular aggregate formation. A block copolymer composed of a hydrophilic portion, polyethyleneoxide, and a hydrophobic polylysine, whose ε-amino group was substituted to 50% with palmitoyl residues, has been synthesized.[11] Its rate of pinocytosis by rat peritoneal macrophages is similar to that of the homopolymer polyethyleneoxide, indicating that the major hydrophobic domain was without significant effect. This appears to be due to the fact that in an aqueous environment the copolymer forms a unimolecular micelle, and that the cell sees only its hydrophilic portion.

Thus far, the best molecules that have been developed are polyvinylpyrrolidone and polyHPMA, with the latter preferred because of the ease of adding substituent groups. Derivatization of polyHPMA with low percentages of oligopeptides or phenolic residues is possible without causing adherence to cells.[12] Both polymers are water-soluble, even at high degrees of polymerization, but nonspecific cell adherence is seen with both at high molecular weights, thereby offering an advantage.[13,14] Another advantage of these two polymers is their biocompatibility. Both homopolymers polyVP and polyHPMA may be potential plasma expanders.

Using polyHPMA, investigators have been able to demonstrate both targeting and intracellular drug delivery. Targeting has been accomplished by derivatizing polyHPMA with glycylglycylgalactosamine.[15,16] This moiety appears to be recognized by the asialoglycoprotein receptor on hepatocytes. The polymer, when injected into the rat bloodstream, is efficiently removed by the liver's parenchymal cells and taken into their lysosomes.

It has been reported that an enzyme mix from rat liver lysosomes can, under appropriate circumstances, cleave p-nitroaniline from polyHPMA conjugates. The crucial factor is the size and nature of the spacer moiety linking the ligand to the polymer. p-Nitroaniline conjugated directly by an amide-linkage to methacryloyl moieties is not released, while interposition of a suitable oligopeptide renders the distal amide-linkage susceptible to cleavage.[17–19]

Oligopeptides can also be used as lysosomally digestible components of cross-links between polymer chains. Short lengths of polyHPMA can be linked by di(oligopeptidyl)diamines to yield a larger macromolecule. If such cross-linked molecules were used for targeted delivery of a cytotoxic drug, intralysosomal processing would not only release the drug, but also degrade the cross-links. The polymer fragments released from the target cell, upon its demise, would be small enough to enter the glomerular filtrate, thus preventing the accumulation of nondegradable polymer within the body. Degradation of oligopeptide-containing cross-links by lysosomal enzymes has been demonstrated.[14,20] A drug carrier must not release its drug prematurely. This means that the drug-spacer linkage must not be susceptible to degradation in body fluids. Although amidases are active in the bloodstream, it is possible to design oligopeptide spacers that retain the drug during transit through the bloodstream, but release it under the influence of the lysosomal enzymes.[21]

IV. Biodegradable or bioerodible polymers

Pioneering studies in the field of controlled subdermal drug delivery began in the 1960s and used biostable commercial polymers, such as polyethylene and silicon rubber.[22–24] The rate of release of the drug from the polymeric matrix, or reservoir device, was determined solely by diffusion. Biodegradation of the polymer was thought to represent a less well-defined and unnecessary experimental variable. Subsequently, interest in biodegradable polymers developed for two reasons. First, as the field expanded from research to application, it was recognized that surgical removal of a drug-depleted delivery system was difficult, leaving nondegradable foreign materials in the body for an indefinite time period, which constituted an undesirable toxicological hazard. Second, while diffusion-controlled release is an excellent means of achieving predefined rates of drug delivery, it is limited by polymer permeability and the characteristics of the drug.[25–27]

The development of polymers containing hydrolytically or enzymatically labile bonds has been an ongoing process, principally in connection with the search for improved absorbable sutures. Although absorbable sutures were originally derived almost exclusively from various forms of collagen, and evolved to the modern-day catgut, there has also been an increasing emphasis on developing synthetic materials that would hydrolyze to yield natural metabolites. As a result of these efforts, two materials have emerged: poly(lactic acid) and poly(glycolic acid).

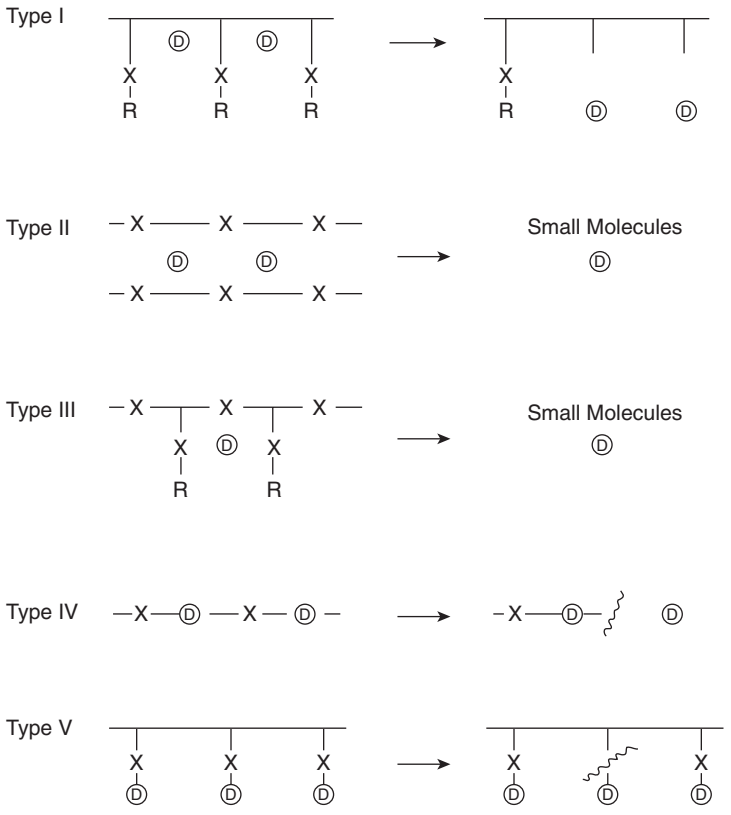

Figure 3.2 Different approaches to drug delivery systems based on biodegradable polymers (X is a bio-labile linkage; D is a drug molecule). (From Bruck, S.D., Ed., *Controlled Drug Delivery*, Vol. 1, CRC Press, Boca Raton, FL, 1983, 56.)

The first disclosure of the use of a synthetic biodegradable polymer for the systemic delivery of a therapeutic agent was made in 1970 by Yolles and Sartori.[43] Since that time, a substantial body of literature on drug release from bioerodible polymers has been generated as attention turned to custom-synthesized biodegradable polymers. Three basic approaches have evolved:[28–35] (1) erosion of the polymer surface with concomitant release of physically entrapped drug; (2) cleavage of covalent bonds between the polymer and drug, occurring in the polymer bulk or at the surface, followed by drug diffusion; and (3) diffusion-controlled release of the physically entrapped drug, with bioabsorption of the polymer delayed until after drug depletion. The third approach avoids any irreproducibility of the bioerosion rate and the difficulty of trying to synchronize the diffusion and bioerosion processes to achieve a specified delivery rate (see Figure 3.2).

A polymer that is to be used in a biodegradable delivery system must be tailored to meet a number of requirements, the most important of which are permeability, biodegradability, biocompatibility, and tensile strength.

These properties are interdependent to some degree, and modification of a polymer to optimize one property will have an effect on the other three. Commercial polymers rarely meet all desired specifications, and custom synthesis is therefore advantageous.

A number of potentially biodegradable polymer systems are used based on the known susceptibility of their monomer analogues to undergo cleavage under mild hydrolytic conditions. These include activated carbon-carbon polymers; polyamides and polyurethanes; polyesters and polycarbonates; polyacetals, polyketals, and polyorthoesters; and inorganic polymers. To this list can be added natural polymers subject to enzymatic attack, examples of which are polypeptides and polysaccharides. Until recently, there have been no proven examples of synthetic polymers that undergo enzymatic degradation.

The preceding chemical classes cannot be ranked in order of susceptibility to hydrolytic or enzymatic attack because, in practice, the degree of substitution of the polymer morphology and the physical form (e.g., surface-to-volume ratio) of the implanted polymer all contribute to the observed degradation rate.

Specific physical properties that contribute to the rate of polymer degradation are as follows:

1. Water permeability and water solubility, a reflection of the free volume of the polymer and its hydrophilicity, will determine the rate of hydrolysis and whether bulk or surface hydrolytic degradation occurs. Autocatalysis of the degradation process is possible if acidic or basic groups are produced by the polymer breakdown, as in the case of polyesters and ortho-esters.
2. Crystallinity of the polymer; only the amorphous phase of the polymer is accessible to permeants (i.e., water, drug) and to enzymatic attack.
3. Glass-transition temperature; the glassy or rubbery nature of the polymer will be reflected in its permeability and molecular chain mobility. The chain mobility appears to be an important factor in determining the susceptibility to enzymatic attack. In addition, the inability of cleaved fragments to diffuse out of a glassy polymer will magnify an autocatalytic hydrolytic process. This may contribute to the rate of degradation of polymers such as polylactic and polyglycolic acid.
4. Physical dimensions (e.g., size and surface-to-volume ratio); these appear to become significant in the advanced stages of biodegradation, when phagocytosis may come into play.

Biodegradable polymers can be defined as polymers that are degradable *in vivo*, either enzymatically or nonenzymatically, to produce biocompatible or nontoxic by-products. These polymers can be metabolized and excreted via normal physiological pathways. They are classified into three groups, namely natural, semisynthetic, and synthetic, based on their sources. Examples of commonly used natural biodegradable polymers are gelatin, alginate,

Table 3.1 Biodegradable *in situ* solid-forming delivery systems

Delivery system	Common problems	Common components
Thermoplastic pastes	High temperature at the time of injection	PLA, PLGA, PCL; alcohols as initiator
In situ cross-linked systems; thermosets	Unacceptable level of heat released during reaction Burst in drug release Toxicity of unreacted monomers	Stannous octoate as catalyst; oligomers of PLA, PDLLA, PCL, polyols as initiator and peroxides as curing agent
Photo-cross-linked gels	Shrinkage and brittleness of the polymer due to high degree of cross-linking	PGA, PLA, PEG, initiators such as eosin dye, light source (e.g., UV or laser)
Ion-mediated gelatin	Low shelf life Burst in drug release Long degradation time	Alginate with Ca^{2+} as gelling agent
In situ polymer precipitation; solvent removal	Burst in drug release Burst in drug release	PDLLA, PCL, PLA, solvents such as DMSO or NMP
Precipitation	Application of organic solvents	
Thermally induced sol-gel transition	Stability of oils and purity of waxes	NIPAAM, PEG, PLA, PLGA, chitosan, pluronics
Organogels	Lack of toxicity data Phase separation	Oils, such as peanut oil and labrafil, waxes (e.g., beeswax and pericerol)

Source: From Elsevier, *J. Control Rel.*, 80, 9–28, 2002. With permission.

albumin, collagen, starch, dextran, chitosan, and chitin, whereas examples of synthetic biodegradable polymers are polylactic acid, polyglycoloc acid, poly(lactide-co-glycolide), poly(orthoester), polyhydroxybutyrate, polyhydroxyvalerate, and polyanhydride. Modifications can be made to naturally occurring biodegradable polymers, such as chitosan, alginate, and hyaluronic acid, to produce semisynthetic biodegradable polymers. These modifications can result in altered physicochemical properties, such as thermogelling properties, mechanical strength, and degradation rates. Synthetic polymers are composed of repeating monomeric units, which are linked together by covalent bonds in the main chain backbone. Polymerization can be achieved by addition and condensation reactions, and these contain monomeric units. Synthetic biodegradable polymers are preferable to the natural biodegradable polymers because they are presumed to be free of immunogenicity and their physicochemical properties are more predictable and reproducible. Polydioxanone, polyphosphazone, pseudopoly(amino acids), water-soluble SELPs protein polymers (based on silk-like and elastin-like amino acid blocks), diblock polymers, and multiblock copolymers are examples of synthetic biodegradable polymers. These have been prepared to afford a multi-

Table 3.2 Hydrogel material

Based on natural materials
Collagen
Starch
Chitosans
Gelatin
Alginates
Dextrans
Based on synthetic polymers
N-vinylpyrrolidone
Poly(vinyl alcohol)
Polyphosphazenes
Poly(ethylene oxide-b-poly(propylene oxide)
Copolymers
PL(G)A/PEO/PL(G)A copolymers
PVA-g-PLGA graft-polymers
PEGT-PBT copolymers (PolyActive)
MA-oligolactide-PEO-oligolactide-MA
Responsive polymers
Methacrylates (pH-dependent swelling)
Poly(N-isopropylacrylamide) (LCST)
PEO-PPO-PEO (Pluronics)
PEO-PPO-PAA graft-copolymer (LCST)
PLGA-PEO-PLGA (LCST)

Source: From Advanstar, *Pharm. Tech.,* March 2002, 144. With permission.

Table 3.3 Commercially available biodegradable drug delivery systems

Name of product	Dosage form	Active ingredient	Biodegradable polymer[a,b]
Lupron Depot	Microspheres	Leuprolide	PLGA
Sandostatin LAR	Microspheres	Octreotide	PLGA
Neutropin Depot	Microspheres	Somatropin	PLGA
Trelstar Depot	Microspheres	Triptorelin	PLGA
Gliadel	Waffer	Cumustin	Polyanhydride
Zoladex	Rod	Goserelin	PLGA
Atridox	Gel	Doxycycline	PLGA

[a] PLGA: poly(lactic-co-glycolic acid)

[b] Polyanhydride: poly[bis(p-carboxyphenoxy) propane: sebacic acid] in a 20:80 molar ratio

Source: From Russell Publ., *Am. Pharm. Rev.,* 4, 4, 25, 2001. With permission.

tude of polymers with diverse properties, such as degradation rates, mechanical strength, porosity, diffusivity, and inherent viscosity.

According to Sun and Watts,[178] the factors that affect the degradation rate of the polymer involve chemical properties such as structure of monomers, which can affect the lability of the cleavable bonds and composition

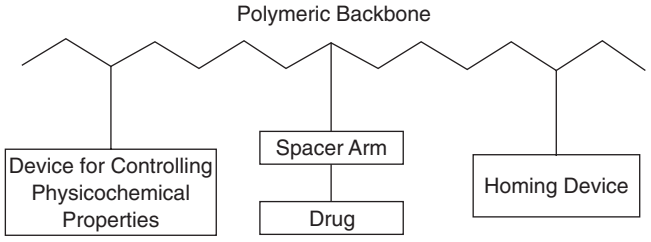

Figure 3.3 Ringsdorf's model of polymeric pro-drugs. (From Ringsdorf, H., in *Polymeric Delivery Systems*, Kostelnik, R.J., Ed., Gordon & Breach Publishers, New York, 1978, 197. With permission.)

of the monomers; physical properties, such as hydrophilicity and crystallinity, which are controlled by the chemical composition of the monomers and process conditions; molecular weight of the polymers; geometric factors of the polymer devices, such as size, shape, and surface area; and additives and environmental factors, such as pH and ionic strength. Biodegradation of polymer devices or drug delivery systems usually undergoes four steps: hydration, mechanical strength loss, integrity loss, and mass loss. The hydration step is critical and is determined by the hydrophilicity/hydrophobicity or crystallinity of the polymer.[179,180] Natural biodegradable polymers (see Figures 3.4 and 3.5), such as human serum albumin and collagen, are hydrophilic and undergo degradation by hydrolysis, whereas most of the synthetic biodegradable polymers are hydrophobic. Polymers are never 100% crystalline, and amorphous regions separate crystalline domains. The degradation of biodegradable polymers is sensitive to the pH of the environment (e.g., poly(lactide-co-glycolide) degrades faster in a highly alkaline buffer than in

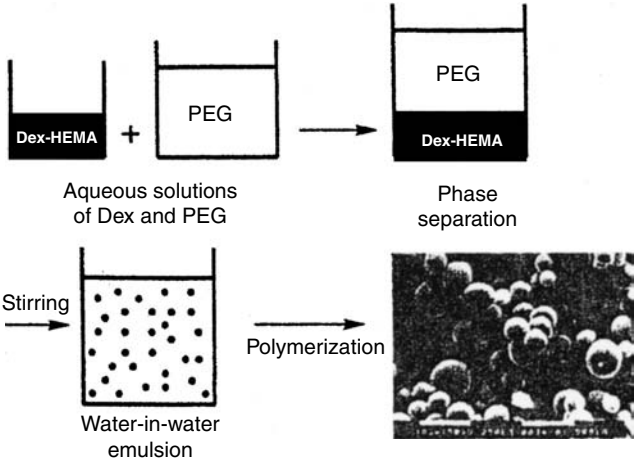

Figure 3.4 Schematic representation of the microsphere preparation process. (With permission, Advanstar, *Pharm. Tech.*, Oct. 2001, 110.)

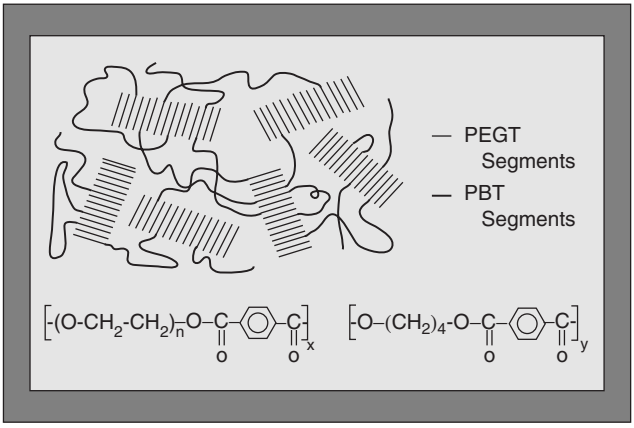

Figure 3.5 Schematic representation of the morphology of PEGT-PBT copolymers. The PBT segments form hydrophobic domains in the hydrophilic PEG matrix, thereby creating a physically cross-linked network. (With permission, Advanstar, *Pharm. Tech.*, Oct. 2001, 110.)

acidic and physiological buffers, polyanhydrides degrade faster in basic conditions, and hydrolysis of poly(orthoester) is catalyzed by acid).[181] Biodegradable polymers (see Figure 3.6) that are hydrophobic can undergo surface degradation (i.e., degradation occurs on the outer layer exposed to the aqueous body fluid). Environmentally catalyzed biodegradation normally involves naturally occurring biodegradable polymers, such as polysaccharides, proteins, and poly(beta-hydroxy acids). For synthetic biodegradable polymers, degradation involves enzymes only at certain stages of physical conditions. Insignificant enzyme involvement is expected in the early stages for polymers in the glassy state. However, as erosion or fragmentation occurs, enzymes can play an important role in the degradation of polymer (see Figures 3.7–3.9).[182–184]

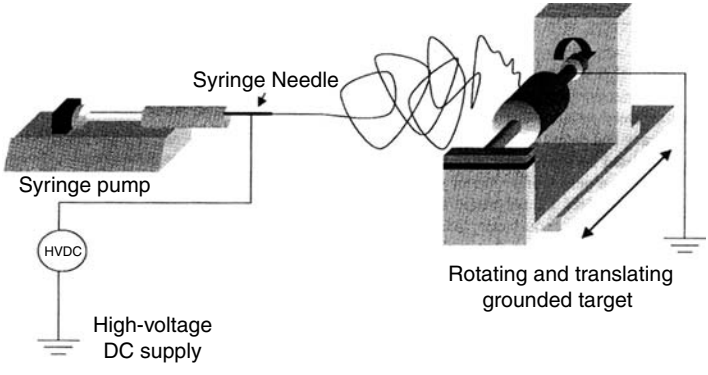

Figure 3.6 Schematic of electrospinning system. (With permission, Elsevier, *J. Control Rel.*, 81, 57–64, 2002.)

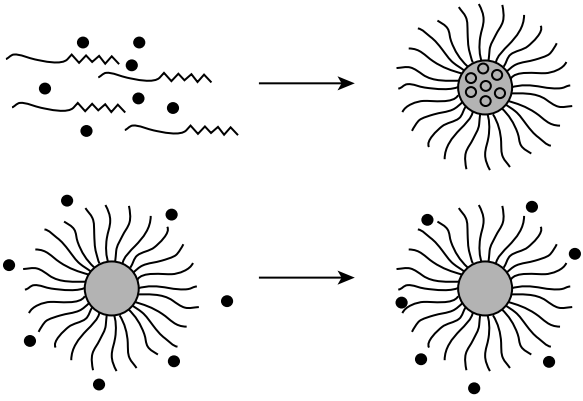

Figure 3.7 Process of drug incorporation to polymeric micelles. Preformed micelles have no ability to incorporate ADR. (With permission, Elsevier, *J. Control Rel.*, 78, 155–163, 2002.)

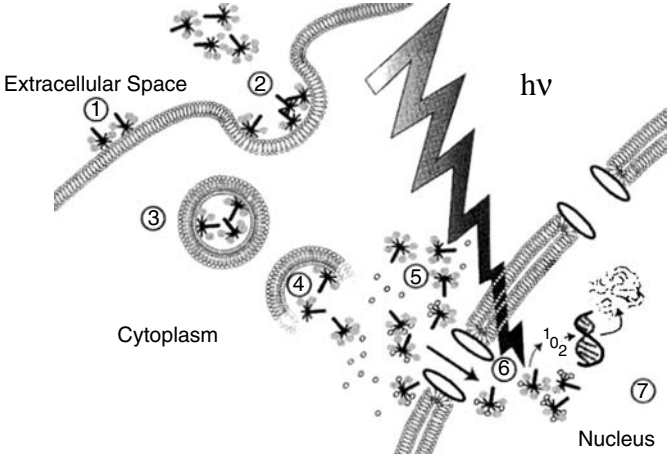

Figure 3.8 Proposed cellular import mechanism of Ce6-loligomer. Loligomers are represented as branched structures, and chlorine e_6 groups are represented as gray ovals. Ce6-loligomers bind to cell surfaces via their cationic CTS sequences (step 1). This triggers membrane invagination (step 2), followed by the internalization of the Ce6-loligomer molecules into vesicular compartments (step 3) in a process referred to as absorptive endocytosis. A fraction of the Ce6-loligomers escape from these vesicles (step 4), and their NLS sequences are recognized by cytosolic carrier proteins (small open ovals in the diagram) (step 5), enabling import into the nucleus (step 6). A light burst from outside the cell (hν), results in activation of the Ce6 molecules and production of singlet oxygen species ($^1O_2$) in the nucleus, leading to efficient DNA damage (step 7). This damage eventually results in apoptosis and cell death. (With permission, Elsevier, *J. Control Rel.*, 78, 115–123, 2002.)

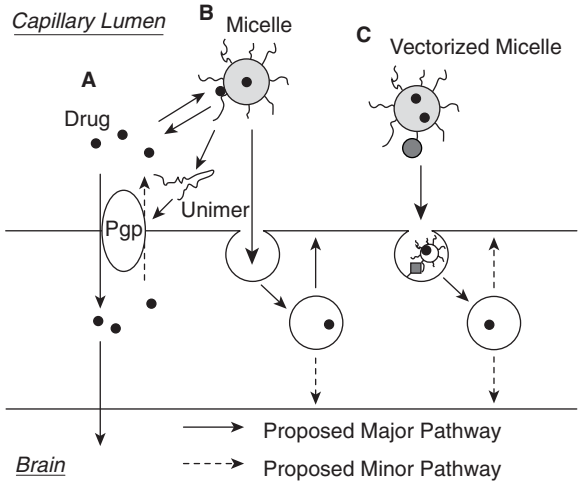

Figure 3.9 Proposed mechanism of drug transport in brain's microvessel endothelial cells with Pluronic® block copolymers: (A) inhibition of Pgp results in increased flux of drug from blood to brain, (B) solubilization of drugs in micelles decelerates drug transport across BBB, micelles undergo fluid phase endocytosis, and (C) conjugation of micelles with insulin vector enhances drug transport through adsorptive endocytosis. (With permission, Elsevier, *J. Control Rel.*, 82, 189–212, 2002.)

A. Drug release by matrix solubilization

Materials in this category include currently used enteric coatings, which can generally be classified as polyacids.[36] In their un-ionized form, they are water-insoluble, but upon ionization of their carboxylic acid groups, they become more water-soluble. Some of the most widely studied systems are partially esterified copolymers of methyl vinyl ether and maleic anhydride or partially esterified copolymers of ethylene and maleic anhydride.[37–39] In a constant pH environment, esterified polymers undergo a controlled dissolution process and are, therefore, useful materials for the controlled release of therapeutic agents dispersed within them.

B. Erodible diffusional systems

Erodible diffusional systems combine the attributes of a rate-controlling polymer membrane, which provides a constant rate of drug release from a reservoir-type device, with erodibility, which results in bioerosion and makes surgical removal of the drug-depleted device unnecessary. Because consistency of drug release requires that the bioerodible polymer membrane remain essentially unchanged during the delivery regimen, significant bioerosion must not occur until after drug delivery has been completed. Major emphasis for the development of erodible diffusional systems has centered on devices that release contraceptive steroids or narcotic antagonists. The polymer systems most extensively investigated in the form of subdermal

capsules for the release of levonorgestrel are various aliphatic polysters, in particular, poly(ε-caprolactone).[40]

C. *Monolithic systems*

In monolithic systems, the drug is physically incorporated into a polymer matrix and is released to the surrounding environment as the polymer bioerodes. In describing drug release from such systems, it is necessary to consider both polymer erosion and drug diffusion. If mobility of the drug in the matrix is such that rapid diffusional release is possible, its release kinetics will be first order. Zero-order release requires that the erosion process be confined to the surface of the solid device and that the drug be highly immobilized in the matrix. Although surface erosion is difficult to achieve, such systems have several significant advantages. Among these are the ability to control drug delivery rate by simply varying drug loading within the matrix, controlling lifetime of the device, varying the physical dimension of the device, and the ability of one matrix to deliver a variety of therapeutic agents.

Narcotic antagonists have been incorporated into poly(L (+) lactic acid) in the form of films implanted in rats.[41–43] The release of narcotic antagonists from composites in particle form has also been investigated *in vitro* and *in vivo*. For cyclazocine and naltrexone, *in vitro* release rates were faster than *in vivo* release rates, whereas for naloxone, both the rates were similar.[44,45] The large difference in the *in vitro* release rates was ascribed to the excess of extractant present.

Poly(L+-lactic acid) has also been used for the controlled release of progesterone, β-estradiol, and dexamethasone. Devices have been fabricated by dissolving the drug and the polymer in dichloromethane. The solvent is evaporated under reduced pressure and the solid residue melt-pressed.[43,46] The release of d-norgestrel from cylindrical implants fabricated from various homopolymers and copolymer of L(+) lactic acid, DL-lactic acid, and glycolic acid has also been studied. Because poly(L+ lactic acid) is highly crystalline, chain segments have restricted mobility and release of d-norgestrel is low. However, the introduction of either DL-lactic acid or glycolic acid into a poly(L+ lactic acid) chain disrupts the crystalline nature of the polymer, and chain mobility is increased.[47–49] Because crystalline regions are highly hydrophobic and prevent access of water to the labile ester linkages, a decrease of crystallinity will also result in increased rates of matrix hydrolysis.

The release of cyclophosphamide, doxorubicin, and cis-dichloro diamine platinum from poly(L+ lactic acid) has been evaluated.[50] Although *in vitro* and *in vivo* release of these agents has been poorly characterized, this methodology may offer advantages in lowering drug toxicity while increasing the number of "cures" relative to single-dose administration. Poly(L+ lactic acid) or copolymers of lactic and glycolic acids have also been evaluated as injectable controlled-release systems for the antimalarial drugs quinazoline derivative (WR-158122) and sulfadiazine. Using WR-158122 and a copolymer

prepared from 25 wt% DL-lactic acid and 75 wt% glycolic acid, sustained release through 14 weeks was demonstrated by means of radioactivity measurements of excreted urine.[51] Using the rodent malaria *Plasmodium berghei*, no parasitemia was detected for several weeks, and some animals survived through 14 weeks. Copolymers of gluconic acid and (γ-ethyl-L-glutamate have also been used in the development of bioerodible monolithic devices. Unlike poly(lactic acid) and poly(glycolic acid), which were originally developed as biodegradable surgical sutures and were not intended to be used as bioerodible monolithic devices for controlled drug release, poly(orthoesters) were specifically designed as monolithic matrixes capable of undergoing a surface-erosion process.

In recent years, there have been major advances in genetic engineering and, consequently, the production of many interesting and pharmacologically active polypeptides.[52] There have also been concurrent improvements in procedures for total chemical synthesis of lower molecular weight peptides, such as Zoladex (ICI-118630), which is a highly potent, synthetic analog of luteinizing hormone-releasing hormone (LHRH). However, the therapeutic and commercial potential of this and other polypeptide drugs will only be fully realized if these advances are accompanied by improvements in the design of dosage forms, leading to practical and effective formulations.

Polypeptides are ineffective by the oral route since they are rapidly degraded and deactivated by the acidic pH and proteolytic enzymes in the alimentary tract. Even if stable to enzymatic digestion, their relatively high molecular weights prevent facile translocation through the intestinal wall. Other routes of administration, including intranasal, buccal, intravaginal, and rectal, have been used, but these are associated with low and variable bioavailability, and none of these rates offers a general solution applicable to all polypeptides. Consequently, polypeptides and proteins are best administered parenterally. Since these drugs have short elimination half-lives, frequent injections are required to produce an effective therapy.

For polypeptide hormones, in which the pharmacology of the agent is compatible with sustained release, the most appropriate dosage form is one that is capable of releasing a drug continuously at a controlled rate over a period of weeks or even months. If such release is from a polymer, then it is preferred that the polymer be biodegradable. Experience with homo- and copolymers of lactic and glycolic acids has shown that these materials are inert and biocompatible in the physiological environment of the body and degrade to toxicologically acceptable products. Consequently, these polymers are invariably the materials of choice in the initial design of parenteral sustained-delivery systems using a biodegradable carrier, particularly when release over many weeks is required.[53–59]

V. Mucoadhesive polymers

Bioadhesive polymers have been employed in both surgery and dentistry for many years.[60] Such polymers include the well-documented "super

glues," the esters of cyanoacrylates, which have found applications ranging from repair of osteochondral fractures to capping extraction wounds in dentistry. Other synthetic bone-glue candidates have included polyurethanes, epoxy resins, acrylate, and polystyrene. Often, the mechanism of bonding for these bioadhesive polymers involves the formation of covalent bonds with the target tissue in order to provide a permanent or semipermanent linkage.[61,62]

In the development of oral controlled-release dosage forms, considerable benefits may ensue from the use of bioadhesive polymers providing relatively short-term adhesion between the drug delivery system and the mucus or epithelial cell surface of the gastrointestinal tract.[63,64] Binding will therefore involve secondary forces, such as hydrogen bonds or van der Waals forces. Mucoadhesives may, therefore, be regarded as a specific class of bioadhesives. Polymer candidates need to be nontoxic and nonabsorbable, adhere rapidly to wet tissues, and release the incorporated drug in a controlled manner.

The ability to localize a drug delivery system in a selected region of the GI tract could conceivably lead to improved bioavailability, especially for drugs exhibiting narrow windows of absorption or instability in certain sectors of the tract. Intimate contact with the target absorption membrane should lead to optimization of both the extent and rate of drug absorption. Alternative mechanisms for the control of GI transit of the dosage form, for example, through manipulation of particle size and density, together with the use of fibrous materials, have not, in general, been successful.[65]

A material may adhere to a mucosal surface in two ways: by binding to the tissue itself or by associating with the mucus coat that is ultimately associated with the tissue surface. The gastric mucosa is the primary target in the development of a mucoadhesive-based sustained release action since gastric retention will be the main mechanism in delaying the rapid absorption that occurs once the formulation reaches the specialized absorptive areas of the small intestine.[66,67]

Throughout the GI tract, the mucosal surface is comprised of columnar epithelial cells, the morphology of which changes as the tract is descended. In the stomach, specific mucus-secreting glands are in the cardiac and pyloric region, which serve to coat incoming food boli and hence reduce possible abrasive action. Mucus-secreting cells are also found in the necks and depths of the acid-secreting gastric pits, where they form a protective buffer zone around the stream of acid. The surface columnar epithelial cells maintain the mucus coating over the rest of the stomach surface, and secretion is stimulated by mechanical and chemical irritation. The mucus layer also serves to protect the gastric epithelium from the action of secreted acid and proteolytic enzymes. The layer is usually continuous, but can be disrupted under the action of certain irritant substances, and an ineffective mucus layer is usually associated with conditions of gastric ulceration.[68,69]

Particles that are small enough to be buried in the surface of the mucus will be securely held due to the relatively high storage capacity of the gel.

However, as mucus is continually secreted, such particles will be pushed farther from the mucosal surface to a point where they are sheared away, either under the weight of the gel itself, or due to mechanical abrasion of the luminal contents. Larger particles, for which there is a favorable interface interaction with the mucus gel, may, nevertheless, be pulled from the mucosal surface due to their weight or because they are more easily dislodged by the peristaltic action of the stomach. One method of prolonging mucosal association can be to use a hydrophilic polymer in a dry powder or granule, from which, after embedding in the mucus, will slowly hydrate and take up water at the expense of the mucus gel. This will compensate for the continued gel secretion by increasing the elasticity or storage capacity of the gel, thereby enabling a more substantial erosion of the polymer surface.[70–76]

Although the mucus gel presents only a limited barrier to small molecules, due to the low microviscosity of the interstices, the diffusion of macromolecules is more severely restricted because of physical obstruction.[77] Thus, molecularly dispersed polymers can interact with the mucus gel at the surface via a combination of secondary bonds. Diffusional resistance of the mucus gel can prevent a total mixing of mucin and polymer on the mucosa and lead to a stiffening of the mucus gel, such as that observed under selected *in vitro* conditions. However, a limited degree of chain presence at the adhesive-mucus interface will be essential for effective mucoadhesion.

The most effective mucoadhesives are linear or lightly cross-linked polymers, which differ considerably in structure to mucus glycoproteins. Consequently, it is unlikely that they adhere to the gel through interactions similar to the mucin–mucin interaction that is so important to inherent gel structure. Interestingly, one common factor in effective mucoadhesives is the presence of carboxylate groups that have no significant role in the purely mucin–mucin interaction. Likely points of interaction for these polymers are the oligosaccharide side-chains on the mucin that are aligned normal to the linear axis of the protein backbone of the glucosylated subunit. If penetration of this glycosylated coat is a prerequisite to the formation of a viable interaction, then the "free ends" of the interacting polymers need be no more than several monomer units long. However, as there seems to be a relation between the molecular weight of a polymer and its supposed mucoadhesive properties, it could be that interdigitation between the whole mucin subunits is of greater relevance in the polymer–mucin interaction. The polymers considered to date lack characteristics that promote an interaction with hydrophobic regions of the glycoprotein, such as the globular protein unit or the numerous esterified fatty acid residues.[78–81]

The development of mucoadhesive polymers may be traced back as far as 1947, when gum tragacanth and dental adhesive powders were combined to form a vehicle for applying penicillin to the oral mucosa. An improvement in this system resulted when carboxymethyl cellulose and petrolatum were combined to form the vehicle. The development of Orahesive® followed, leading to trials of Orabase® in 1959. Orahesive is a mixture of finely ground sodium carboxymethyl cellulose (SCMC), pectin, and gelatin, while Orabase

is a blend of these in a polymethylene/mineral oil base. After several trials, it was found that dry polymer powders would form better mucoadhesive agents since such formulations would be capable of absorbing a greater amount of water and, hence, adhere more strongly to the tissue substrate than when blended with the polymer carrier. A further development was the blending of SCMC with poly(isobutylene) (PIB) and laminating this mixture onto a polyethylene sheet. This system benefited from both wet-surface and dry-surface adhesion, with the added bonus of being protected from physical interference (e.g., from the tongue, by the polyethylene-sheet backing).[82–84]

An extensive range of such systems, whereby a water-soluble polymer and PIB are blended together and laminated with a polyethylene film, was tested by Chen and Cyr.[85] The polymers identified as exhibiting the best adhesion were sodium alginate, SCMC, guar gum, hydroxyethylcellulose (HEC), Karya gum, methylcellulose (MeC), polyethylene glycol, Retene, and Tragacanth. Acrylic polymers were soon recognized as useful mucoadhesive materials, and the early 1980s saw a plethora of patents in which hydroxypropylcellulose, or MeC and poly(acrylic acid), were blended together to form mucoadhesive preparations. By far the most-studied mucoadhesive polymers through the 1980s have been poly(acrylic acid), hydroxypropylcellulose, and SCMC. Some polymers used have been standard pharmaceutical materials, such as MeC, HEC, and sodium alginate, and others have been specifically synthesized to achieve optimal results, such as 2-ethyl hexyl acrylate-lauryl methacrylate-vinyl stearate copolymer and isooctyl acrylate-methoxy poly (ethylene oxide) acrylate-acrylic acid polymer.

The work of Chen and Cyr,[85] together with Park[64] and Smart et al.,[80] involved the investigation of a range of polymers of varying molecular character. These studies appeared to arrive at similar conclusions as to the molecular characteristics required for mucoadhesion. The properties exhibited by such a molecule, described by Peppas and Buri,[79] may be summarized as follows: (1) strong H-bonding groups (-- OH; -- COOH); (2) strong anionic charges; (3) sufficient flexibility to penetrate the mucus network or tissue crevices; (4) surface tension characteristics suitable for wetting mucus/mucosal tissue surfaces; and (5) high molecular weight.

In accordance with the theory that secondary bond formation is the principal source of mucoadhesion, those polymers with carboxyl groups present are, without exception, all mucoadhesive. The carboxyl group in its un-ionized form is capable of strong H-bond formation and in its ionized form can interact electrostatically. However, the functional groups on the polymer backbone should not be in such proximity that they interfere with each other (e.g., by intramolecular H-bonding). As the carboxyl concentration along a polymer chain decreases, for example, in moving from sodium alginate to Karya gum to gelatin, the mucoadhesive strength also decreases.

The effect of other secondary bond-forming groups (e.g., hydroxyl, ether, oxygen, amine) on the mucoadhesive properties of the polymers previously mentioned is not as clearly defined as that for the carboxyl group.

The cellulosic polymers have an abundance of hydroxyl and ether groups along their length, yet their mucoadhesion exhibits little relationship to this characteristic.

Another important feature of a mucoadhesive molecule is believed to be the ability to form physical bonds, principally by entanglement with the substrate molecules. This is illustrated by polyethylene oxide (PEO), a linear, flexible molecule with minimal secondary bond-forming capacity. At high molecular weights, this molecule exhibits a mucoadhesive strength comparable to MeC and sodium alginate, whose secondary bond-formation is far greater. This may be due to the fact that the segmental mobility of PEO is extremely high since ether linkages make for a flexible backbone and, hence, penetration into substrate networks is deep and relatively rapid. The effective depth is, however, affected by molecular chain length (i.e., molecular weight) since a short-chain molecule can form fewer entanglements and penetrate to a lesser degree than a larger molecule. The interaction between the polymer adhesive and mucus or mucosal tissue is primarily a surface-tension phenomenon. Therefore, the lower the contact angle between the adhesive and the mucus/mucosa, the better the chances of interaction.

The ideal mucoadhesive polymer is composed of a combination of various carefully balanced properties. It must be a polymer of high molecular weight to maximize adhesion through entanglements and van der Waal's forces. The segmental mobility of the polymer chain should be high to facilitate rapid and deep penetration into the substrate. The repeating unit of the polymer should contain carboxyl groups and other secondary bond-forming groups, principally primary hydroxyl groups and short-chain ethers. This would ensure the potential for adhesion via as many modes as possible. For further discussion of structural features of mucoadhesive polymers, see Hunt et al.[60]

VI. Polymers containing pendant bioactive substituents

A major approach to increasing the therapeutic efficiency of bioactive agents while decreasing their toxicity has involved their bonding to synthetic or naturally occurring macromolecules.[86] Thus, various agents have been bound via degradable linkages to many different polymeric systems. The original rationale behind this approach was that systems could be designed that would undergo hydrolysis or enzyme-catalyzed cleavages when placed in the body in order to release the agent at a predetermined rate. Since the rate of excretion of high-molecular weight polymers is extremely slow, it was felt that agent/polymer adducts could function as depots for extended periods of time. Early work in this area led to the hope that perhaps polymeric systems could also be modified (e.g., by the attachment of a tumor-specific antibody) in order to display high specificity for target organisms, such as tumors. In this case, the modified polymer was to carry the active agent to a specific site of action and then release it. In effect, the systems were to function as target-seeking guided missiles.[87–89]

With the exception of some substituted polyethyleneglycols, large macromolecules cannot readily enter the body via the GI tract or by cutaneous absorption. In fact, a molecular weight of 5,000 to 10,000 is considered high enough to prevent any appreciable absorption through skin or mucosal tissues. Thus, adducts that are taken orally or administered topically can only function as depots. However, such systems can still offer considerable advantages for localized treatments of the GI tract or the eye, mouth, skin, vagina, etc. In these cases, a high molecular weight, biostable polymeric carrier is preferred. Since topically administered systems experience such mild conditions, the agent should be attached to the polymer via a linkage that is extremely susceptible to hydrolysis. For treatment of the GI tract, it is likely that the system would have to be protected with an enteric coating to prevent premature hydrolysis from occurring in the stomach.[90,91]

A dextromethorphan-polymer complex (dextromethorphan is an antitussive) can be coated with a semipermeable outer coating of varying thickness. The drug is released only when ions in the GI tract cross the outer coating and displace the active drug. Since ion concentration in the GI tract is quite stable, drug release is precise, controlled, and unaffected by variations in pH, temperature, or volume of contents in the stomach or intestine. The system releases its active agent at an effective level for 12 h.[90]

Since most synthetic polymers with molecular weights above 60,000 to 80,000 cannot be excreted via renal glomerular filtration, biodegradable systems are usually preferred for implantation of parenteral administration. It has been claimed that the body can eliminate high-molecular weight, biostable polymers via the liver and its biliary system into the intestine. However, the rate of excretion by this route is normally quite slow. The main result of an uptake of a biostable polymer is lysosome and cellular overloading, which can lead to toxic effects. Large macromolecules can cause erythrocyte aggregation and changes in platelet or leukocyte distribution. Since these high molecular weight species can be present in polymers with relatively low average molecular weights, samples may require fractionation to remove high molecular weight species. Unfortunately, physiological interactions can even result in the complete retention of polymers with molecular weights below the limit of glomerular filtration. Biostable polymers are, in general, more likely to function as antigens than are biodegradable systems. Olefin polymers have produced immunological responses in rabbits at levels of 10 g per animal. A notable exception is a series of biostable, sulfoxide-containing polymers with molecular weights as high as 172,000 that are claimed to be nontoxic and excretable. Of course, if an injected polymeric adduct is expected to reach a specific target via the bloodstream, it should be water-soluble. Regardless of the method of administration, both the polymer and the adduct must not produce any toxic or immunogenic response.[92–94]

Trout has divided the potential sites of action of targeted systems into three major areas:[89] extracellular, pericellular (i.e., cell surfaces), and intracellular. Active agents that might be directed toward extracellular targets include antibiotics acting on extracellular bacteria or parasites; inhibitors

that block the deleterious effects of enzymes released by inflammation, shock, or rheumatoid arthritis; enzymes like asparginase and urease; and anticoagulants. In the preceding cases, a form of targeting can be achieved if the active agent is maintained in the extracellular space at a desired level and for an extended period of time. Thus, a system might be targeted by manipulating its molecular weight so that it is high enough to retard the permeation of the adduct through membrane capillaries but low enough to minimize its uptake by the endocytizing cells of the RES system. Cations might also be distributed along the backbone to maximize the interaction of the adduct with negatively charged blood proteins. The carrier could also be designed to shield the bound agent in order to decrease its immunogenicity and decrease its reactivity with free or cell-bound antibodies. However, the primary function of the retained adduct polymer complex would be to act as a drug depot.

The targeting of agents that have pericellular and intracellular receptor sites is somewhat similar because, for an adduct to reach the latter, absorption must also occur on the cell surface. In the first case, it would be highly desirable for the complex to release the drug upon contact with the cell surface. This could be achieved if the drug-polymer linkage was susceptible to hydrolysis induced by enzymes in the plasma membrane or by an enzyme secreted by the target cell and having a short range of action. For example, Trout[89] suggests that systems might be designed to release anti-inflammatory or antirheumatoid agents upon contact with the neutral proteases or collagenases secreted by cells involved in the initiation and development of inflammation (e.g., rheumatoid arthritis).

Agents released as previously described, could be directed against targets located inside the cell. As mentioned, intracellular sites can also be reached via endocytosis of pinocytotic vesicles. Since endocytosis occurs at different rates with different polymer types and different cells, adducts can be prepared that will be preferentially taken up by certain cells. However, attempts to prepare systems that are only endocytized by specific cells other than those of the RES system are plagued by the high endocytic activity of the latter. A side benefit of this approach is that some agents that are normally unable to penetrate the plasma membrane may enter the cell via the endocytic route.

Although a level of selectivity for intracellular sites is provided by the fact that cells differ in their endocytic activity, a much higher degree of selectivity can be attained, at least *in vitro*, by attaching "homing molecules" to the adduct that interact with specific cell types. For example, considerable work has been done with antibodies that interact with specific tumor-associated antigens.[95–97] Other targeting moieties that have been used to target proteins to specific cell receptors include peptide hormones, viral components, and carbohydrates, such as galactose, mannose, fucose, and N-acetylglucosamine. Acetylation of the side chains of proteins can also dramatically change their cellular-uptake patterns. For example, acetylation of low-density lipoprotein with acetic anhydride stops its uptake by fibroblasts while

stimulating its uptake by peritoneal macrophages. Several polymers can function as both the carrier and the homing molecule. Antibodies and abrin, ricin, and diphtheria toxins have been investigated as inherent targeting carriers. Lectin carriers, such as concanavalin A, also give evidence of tumor-specific association.[98–101]

Although there have been many reports of successful agent targeting *in vitro*, there have been few successes *in vivo*. Goldberg et al.[102] have listed the following problems that occur with antibody-targeting systems:

1. Circulatory antigen and antigen–antibody complexes
2. Metabolic/biochemical changes in adducts with loss of activity
3. Transport kinetics to tumor tissue versus competitive binding and metabolism
4. Changing and cross-reactive antigenicity
5. Masking or interiorization of tumor-cell-specific antigens

Various approaches to overcoming these problems include:

1. Complexing or removing
2. Use of (Fab′) portion of the immunoglobulin to avoid F-complement binding and reduce molecular size
3. Therapy with intratumor and IV injections of antibody adducts
4. Surgical or radiation reduction of primary lesion tumor burden coupled with systemic administration of the antibody adducts for elimination of metastasis

Another approach to targeting agent polymer adducts involves the direct injection and retention of soluble or insoluble systems into a specific site, such as a tumor. Insoluble adducts will, of course, be retained by physical immobilization. Various approaches to retaining soluble systems include the use of targeting moieties, as discussed previously, and the introduction of pendant functional groups along the polymer backbone that can form covalent bonds with tissue carbonyl groups. Nonspecific electrostatic bonding between negatively charged cells and cationic adducts has also been used.[102]

Rowland et al.[103] have successfully attached a p-phenylene-diamine mustard (PDM) and an immunoglobulin (I) from a rabbit antiserum against mouse lymphoma cells (EL4) to polyglutamic acid (PGA). Goldberg and coworkers have investigated the use of lectin adducts in intratumor immunochemotherapy. For example, mitomycin C (MC) and adriamycin (AD) have been attached to the lectin concanavalin A (Con A). Goldberg points out that several processes may explain the favorable intratumor activity of these adducts.[102] These include cell-surface binding via lectin receptors, antimetabolic and cytotoxic activity of intact adduct, capping of endocytic receptors favoring cell uptake and lysosomal cleavage, and release of free MC locally.

VII. Matrix systems

Within the scope of this general term, there are a variety of controlled-release devices.[104] Included among these are dissolved systems that are prepared from a matrix containing a drug at or below the saturation solubility of the drug in the polymer and dispersed systems that contain the drug within a matrix at a concentration that greatly exceeds the saturation solubility of the drug in the polymer. In this case, it is assumed that the drug is present as discrete solid particles. This implies that upon leaching of the drug, macroscopic channels or pores within the polymer matrix do not exist. Other controlled-release devices include reservoir-dispersed matrix systems, which are analogous to the dispersed system except that a barrier layer is present at the surface of the device that is of lower permeability to a drug than the bulk polymer matrix, and porous matrix systems, which are prepared from a dispersion of drug particles and preformed polymer. In porous matrix systems, it is assumed that upon leaching of the drug, continuous macroscopic pores or channels arise from the displacement of drug by solvent.

One of the major advantages of matrix devices relative to other types of controlled-release drug delivery systems (e.g., reservoir devices) is the ease of manufacture. In general, matrix devices can be prepared by mixing the drug as a finely divided powder with the prepolymer. This mixture is then placed in an appropriate mold and allowed to cure. This technique is especially useful for dispersed-type matrix devices, provided that the initial drug load is below the saturation solubility of the drug in the cured polymer. The preparation of reservoir-matrix devices is more complicated due to the need to incorporate the barrier layer onto the matrix.

Most often, dispersed-type matrix devices have been prepared from polydimethyl siloxane. This polymer has a number of advantages for controlled-release systems, including: (1) it is an elastomer with good mechanical properties; (2) it is highly permeable to hydrophobic solutes; (3) it is nontoxic; (4) it is molded into a wide variety of shapes and is polymerized with simple techniques; and (5) its permeability is not affected via prolonged contact with biological fluids. Its major disadvantages are (1) it is not permeable to highly water-soluble solutes, especially charged species; (2) it evokes a moderate foreign-tissue response upon subdermal implantation; and (3) the permeability of the polymer is not easily varied by alterations in polymer composition.[105–110]

Because of the disadvantages associated with polydimethyl siloxane, a number of investigators have utilized polymers prepared from various derivatives of hydroxyalkyl methacrylates. These polymers offer a number of advantages, including: (1) they are not toxic; (2) they evoke a minimal foreign-tissue response; (3) they are highly permeable to both hydrophobic and water-soluble solutes, including charged species; and (4) they are of variable permeability to drugs, depending upon copolymer composition and cross-link density. Copolymers of the hydroxyalkyl methacrylates and methyl methacrylate have also been utilized. Such copolymers offer the

advantage of increased mechanical strength and may offer some advantage relative to blood and tissue compatibility. Other authors have utilized a variety of polymers, including ethylene vinyl acetate, polyacrylamide, polyvinyl acetate, polyethylene, and polyether urethanes.[111–118]

The release of drugs from matrix devices is governed by the diffusion of solute within the matrix phase. The development of the appropriate form of the release-rate equation is generated via Ficks' first or second laws of diffusion. In general, three limiting factors exist. First, when the initial drug load is equal to or less than the saturation solubility of the drug, the rate of release is dependent upon the diffusion coefficient of the drug in the polymer and upon the initial drug load. The diffusion coefficient, in turn, is dependent upon the properties of the drug and the polymer matrix. Such systems can be described as a homogeneous matrix. Second, when the initial drug load is greater than the saturation point, but small relative to the total volume of the polymer (e.g., less than 10% w/w), drug-release rates will also be dependent upon the diffusion coefficient of the drug within the polymer matrix and the initial drug load. However, in such systems, an additional variable becomes important, namely, the saturation solubility of the drug in the polymer. Such systems should be described as a heterogeneous matrix. Third, when the initial drug load is increased beyond 10% w/w, a point is reached when the solid drug particles begin to form continuous pores or channels within the matrix. Under these circumstances, the path of least resistance for the drug is diffusion within channels formed where the drug has previously leached from the matrix. In this case, the rate of release is governed by diffusion within these channels, the diffusional characteristics of which are governed by the elution medium. Such systems are termed "porous" or "granular" matrices.

The previous classifications must be taken to represent general guidelines. It is apparent, for example, that as the initial drug load is increased, the matrix will become more porous as drug is leached from the polymer. In effect, the free volume for diffusion increases as a result of the voids created by the leached drug. This increase in void volume will be reflected by changes in the "effective" diffusion coefficient of drug in the matrix phase.

In addition to effects arising from the initial drug load, the release characteristics of a polymer matrix are also a function of the geometry of the matrix. This fact arises due to variations in the nature of the concentration gradient within the drug depletion zone of the matrix. For example, in a heterogeneous polymer matrix containing dispersed drug, a zone of depletion is formed as the drug is released from the matrix. For devices (e.g., cylinders or spheres) in which the area of the receding drug boundary decreases with time, the flux of the drug will again follow a path that is perpendicular to the receding boundary. However, the volume of the depletion zone will increase radially from the surface, and the concentration gradient is nonlinear within the zone of depletion. As a consequence, release-rate equations are dependent upon the geometry of the device.[119–121]

VIII. Heparin-releasing polymers

The pioneering work in heparin-controlled release materials was accidentally initiated by Gott et al.[122] At that time, these investigators were evaluating numerous materials for thromboresistance by venous implantation, and colloidal graphite gave the best results. These investigators first thought the thromboresistance was due to the extreme smoothness imparted to surfaces following graphite coating and the chemically inert nature of the colloidal graphite. These materials were sterilized by soaking in a benzalkonium-sulfate solution. Further studies showed that these graphite-benzalkonium-heparin (GBH) surfaces retained significant quantities of heparin even after three months of implantation in the venous system.[123]

A major disadvantage of the GBH surfaces is that the graphite can only be coated to rigid materials because any flexing would result in a disruption in the integrity of the graphite coating with possible "flaking off" of the GBH coating. To circumvent this problem, Leininger et al.[124] chemically modified numerous polymer surfaces by forming permanent surface-associated quaternary ammonium groups, thus eliminating the need for prior adsorption of a cationic surfactant onto a hydrophobic surface, such as graphite. Depending upon the polymer, three surface treatments were used: (1) chloromethylation of styrene followed by quaternization with dimethyl aniline; (2) radiation grafting of vinyl pyridine to numerous polymers followed by quaternization with methyl iodide or benzyl chloride; and (3) incorporation of quaternizable monomers, such as vinyl pyridine, into copolymer formulations.

After quaternization, the surfaces were placed in a heparin solution and heparin was ionically bound to the ammonium groups. Following contact with fibrinogen, γ-globulin, and albumin solutions, Zeta potential measurements indicated that the surfaces were progressively becoming less negatively charged, which can be attributed to plasma protein adsorption. From these studies, the authors attributed the nonthrombogenic nature of the heparinized surfaces to alterations in the plasma protein adsorption properties of the heparinized materials relative to the starting materials, rather than to heparin release.

In an attempt to provide heparinized cellulose membranes that could be utilized in kidney dialysis applications, Merrill et al.[125] ionically bound heparin to cellulose membranes via an ethyleneimine intermediate. Various procedures were used to couple ethyleneimine to the hydroxyl groups on cellulose. Of those procedures, pretreatment with ethylene oxide vapor to convert secondary cellulose hydroxyl groups into primary hydroxyl groups was followed by reacting ethyleneimine in toluene-produced aminated surfaces, which could then ionically bind heparin to the greatest extent. Plasma exposed to these materials demonstrated prolonged clotting times.

Hufnagel et al.[126] were first to incorporate heparin into either silicone rubber or a combination of silicone rubber plus colloidal graphite. A novel approach to the controlled release of heparin from polymer matrixes has

been provided by Ebert et al.[127,128] It is known that heparin can adversely interact with platelets, thereby resulting in aggregation and potentiation of aggregation and release reactions caused by exogenous agents. Prostaglandins (e.g., PGE_1, PGI_2, PGD_2), on the other hand, are agents known to prevent platelet aggregation and degranulation by stimulating membrane-bound adenylate cyclase, resulting in increased intracellular cAMP levels. By combining both heparin and prostaglandin into controlled-release polymer matrixes, both intrinsic coagulation and adverse platelet interactions may be controlled.

A disadvantage of ionically bound and physically dispersed heparin/polymer systems is that heparin is continually depleted with time, thereby limiting the effective anticoagulant duration of such materials. Numerous investigators have covalently bound heparin to polymer surfaces to provide long-term heparinized materials. For example, a procedure for radiation-grafting polystyrene to various polymeric materials has been described. The resultant polystyrene surfaces are chloromethylated and subsequently treated with an ammonia/alcohol solution to form benzylamine groups. These polystyrene/benzyl-amine surfaces are then heparinized via a peratin/cyanuric chloride adduct.

Salyer and Weesner[129] have blended heparin into epoxy resins. Although these authors initially thought the nonthrombogenicity of these materials was due to the slow leaching out of heparin into the blood, later studies showed that when heparin was combined with epoxy resins and urethane monomers, polymerization resulted in covalent incorporation of heparin into the copolymer composition and heparin did not leach out. Epoxy and urethane polymers with chemically incorporated heparin demonstrated vastly increased whole-blood clotting times relative to control polymers. Merrill et al.[125] covalently coupled heparin to polyvinyl alcohol via glutaraldehyde cross-linking in the presence of an acid catalyst through hydroxyl groups on heparin and polyvinyl alcohol. Using S-labeled heparin covalently coupled to polyvinyl alcohol, numerous clotting tests were conducted, including thrombin time, partial thromboplastin time, activated partial thromboplastin time, prothrombin time, and whole-blood clotting time.[35]

IX. Ionic polymers

Ionic polymers used as drug carriers include soluble as well as insoluble (cross-linked) polymer systems.[130] However, of the different ionic macromolecules, ion-exchange resins have been investigated most extensively. Although constant rate (zero-order) kinetics is not necessarily achievable by these systems, it is likely that future developments in this field may utilize ionic polymers as drug carriers in controlled delivery.

The use of ion-exchange resins to prolong the effect of drugs is based on the principle that positively or negatively charged drugs combined with appropriate resins yield insoluble poly-salt resinates. The slow release of drugs from ion-exchange resins was recognized early by Saunders and

Srivastava as a suitable approach to the design of sustained-release preparations.[131] A major route of administration of such resinate formulations is via the oral route. Ion exchangers administered orally are likely to spend approximately two hours in the stomach in contact with an acidic pH (1–2). They will then pass to the intestine, where, for six hours or more, they will be in contact with a fluid of slightly basic pH and an ion strength equivalent to that of 0.1 N sodium chloride. The drug can then be slowly liberated by exchange with ions such as sodium or chloride present in the GI fluid.

Drugs to be used in prolonged-action dosage forms, and particularly in resinate formulations, must meet certain conditions. Obviously, only drugs having acidic or basic groups in their chemical structure can be considered. The biological half-life ($t_{1/2}$) of drugs to be formulated should be 2 to 6 h. There is probably no rational reason for preparing long-acting preparations for oral use of drugs having a $t_{1/2}$ of 8 or more hours. Active ingredients having a $t_{1/2}$ of 1 h or less are difficult to be formulated into this type of dosage form if their usual single dose is high (e.g., more than 100 mg). It is necessary to know whether the drug candidate is absorbed from all regions of the GI tract. In the case of a limited absorption zone, the bioavailability of such a drug will be insufficient. The drug should also be sufficiently stable in the gastric juice; otherwise its therapeutic effectiveness will decrease drastically.

Ion-exchange materials are basically insoluble ionic materials possessing acidic or basic groups, covalently bound, and placed in repeating positions on the resin chain. These charged groups are associated with other ions of opposite charge. Depending on whether the mobile counter ion is a cation or anion, it is possible to distinguish between cationic and anionic ion-exchange resins. The matrix carries ionic groups, such as $-SO_3^{\theta}$, $-COO^{\theta}$, and $-PO_3^{2-}$ (in cationic exchangers), and $-NH_3^{\oplus}$, $-NH_2^{\oplus}$, and $-N-^{\oplus}$ (in anionic exchangers). The resin matrix determines its physical properties, its behavior toward biological substances, and, to a certain extent, its capacity. The matrix may be based on inorganic compounds, polysaccharides, or organic synthetic resins. The most important ion exchangers are the synthetic organic-ion exchangers. Carboxylic acid-type exchangers are prepared mostly by polymerization of organic acids, such as acrylic or methacrylic acid in the presence of a cross-linking agent (e.g., a diacrylate or divinyl benzene [DVB] to yield cross-linked networks).

Copolymers of styrene and maleic anhydride cross-linked with DVB, as well as cross-linked methacrylate terpolymers, have been described for specific therapeutic purposes. The majority of cationic resins used for preparing drug resinates are sulfonic acid exchangers. They are, in general, cross-linked polystyrenes with sulfonic acid groups that have been introduced after polymerization by treatment with sulfuric acid or chlorosulfonic acid.

As a rule, DVB is used as a cross-linker.[132] Ion-exchange resins should be insoluble and able to swell to a limited extent. Swelling is attained by the substitution of ionic groups on the hydrophobic hydrocarbon chain. The extent of swelling depends on the degree of cross-linking. By varying the

DVB content, cross-linking and swelling can be adjusted. The DVB content is used to indicate the degree of cross-linking. Commercial products usually contain 40 to 55% DVB-isomers and 45 to 60% ethylstyrene.

The major anion-exchange resins are made from cross-linked polystyrene "pearl" polymers.[133,134] The basic groups can be introduced by a number of different procedures. Most anion exchangers are produced by chloromethylation of polystyrene beads with subsequent treatment with ammonia, or primary, secondary, or tertiary amines.

Ion exchangers based on polysaccharides (e.g., sephadex, sepharose, or cellulose) have found only a limited use in therapeutic applications. The capacity of an ion exchanger is a quantitative measure of its ability to take up exchangeable counter-ions and is, therefore, of major importance. In general, commercial exchangers specify the total capacity. The actual capacity obtainable under specific experimental conditions depends on the accessibility of the functional groups for the drug of interest. The so-called "available capacity" will be related to the drug properties and, as a rule, will be inferior to the total capacity.[135,136]

Another fundamental property is the type of the charged groups which, in turn, determines the type and the strength of the ion exchanger. The acid or base strength of an exchanger is dependent on the various ionogenic groups incorporated into the resin. Resins containing sulfonic, phosphoric, or carboxylic acid-exchange groups have approximate pK_A values of <1, 2–3, and 4–6, respectively. Anion exchangers with quaternary, tertiary, or secondary ammonium groups have apparent pK_A values of >13, 7–9, and 5–9, respectively. The pK_A value of the resin has a significant influence on the rate at which the drug is released from the resinate in gastric fluids.

A number of chemical and physical properties of ion-exchange resins can be varied by modifying particle size and cross-linkage. The rate of an ion-exchange reaction will depend on the size of the particles. Decreasing the size of a resin particle significantly decreases the time required for the reaction to reach equilibrium with a surrounding solution.[137,138]

Rates of ion-exchange reactions and the limiting size of ions that can penetrate into a resin matrix depend strongly on its porosity. In the broadest sense, porosity is defined as the ratio of the volume of interstices of the material to the volume of its mass. Various physical methods have been developed for measuring pore volume, pore diameter, and the internal surface. With the older ion-exchange resins, one was dealing with homogeneous single-phase gels. Later, macroporous resins were produced. They consist of conglomerations of quasispherical particles with interconnecting cavities. The active centers are located both on the surface of the microspherical particles and within them. In contrast to small organic ions, penetration of large organic ions in the resin phase is slow, and capacities are limited to those sites exposed to the macroporous cavities. The diameter of the resin pores through which a molecule must pass for exchange to take place markedly affects the uptake and release of large molecules for which the resin can exhibit a sieve effect. The porosity of an ion exchanger depends not only

on the amount of cross-linking substance used in polymerization, but also on the polymerization procedure.

The structural parameters discussed previously will significantly influence the swelling behavior of a resin and consequently have a marked effect on the release characteristics of drug resinates. The interaction between resins, solvents, solutes, and electrolytes has been discussed by Samsonov and Pasechnik.[139] Cation exchangers, in the salt form, brought in contact with acid were reported to shrink. A reduction of pore diameter can lead to the entrapment of large ions.

Since drug-resin combinations contain 60% or more of the resin, it is necessary to establish the toxicity of the ion-exchange resins themselves. Administration of large quantities of ion-exchange resin can disturb the ion strength in body fluids and cause harmful side effects. McChesney et al.[140] have found that administration of sulfonic and carboxylic acid anionic exchangers results in a reduced potassium level in the blood. Macaulay and Watson treated young children with Katonium®, a sulfonic acid exchanger.[141] After prolonged use, symptoms of tetany were manifested as a result of reduced calcium levels.

Synthetic as well as natural polysaccharide-based ion-exchange resins have been used with good results for diagnostic determinations (e.g., gastric acidity). They have also found applications as adsorbents of toxins, as antacids, and as bile-acid binding agents. Among other therapeutic applications, they have been successfully utilized for treatment of liver diseases, renal insufficiency, urolithic disease, and occupational skin diseases. However, with chronic use, the risk of disturbing the ionic strength in the GI fluids should be considered.[142] Despite the numerous positive results reported in the literature, the validity of drug resinates as prolonged-release dosage forms has been questioned. Berg and Ostrup,[143] for example, have made a critical study of the use of resinate formulations.

It should also be recognized that the duration of action of a resinate administered orally may vary considerably from one patient to another. The transport of a solid dosage form through the GI tract is not a standardized process. It depends on many variables, including stomach-emptying time, composition of the alimentary fluid, and peristaltic effects. The constituents of gastric and intestinal secretions in diseased patients may also vary from that of healthy persons. Furthermore, the acid content in the stomach differs with age.

Soluble polyelectrolytes, such as polyacrylic and methacrylic acids, sulfonated or phosphorylated poly(vinyl alcohol), or polysaccharides and polyuronic derivatives, are frequently used as additives in drug formulations (e.g., as suspending agents or tablet disintegrants). Their viscosity-enhancing effect, due to swelling in GI fluids, in addition to their ability to form poorly soluble salts with appropriate drugs, has been utilized in novel drug delivery systems to change the release profile of a drug.

According to Miller and Holland, different salts of the same drug rarely differ pharmacologically.[144] Variations are usually based on their physical properties. Although the nature of the biological response may not differ

appreciably, the intensities of the responses may differ markedly. The salt form, in general, and the poly-salt, in particular, are known to influence a number of physiochemical properties of the parent drug, including stability, hygroscopy, solubility, and dissolution rate. These properties, in turn, affect the bioavailability of the drug.

The release process of a drug from a polymeric salt after oral administration can be divided in various stages: (1) penetration of the dissolving medium in the dosage form with simultaneous liberation of a small quantity of drug; (2) swelling of the polymer with formation of a gel barrier; (3) release of the drug ion by exchange with penetrating ions and subsequent diffusion through the gel matrix; and (4) eventual dissolution of the polymeric matrix with liberation of the drug by an ion-exchange process between the polymeric salt and the surrounding medium. If a slow dissolution of the drug-polymer system occurs in the gastric juice as well as in the intestinal fluids, the final result will be a prolonged release. However, ionic polymers having weak acid ionic groups are poorly soluble in gastric juice, and a major release of the drug will occur in the intestine. Delivery systems of this type act as delayed-action dosage forms.

The first long-acting preparations were based on the formation of macromolecular salts. They were combinations of antibiotics with polyacids, such as poly(acrylic acid), sulfonic or phosphorylated polysaccharides, carboxymethyl starch, and poly(uronic acids). Malek et al.[145] showed that parenteral administration of these compounds produced low blood levels of the antibiotics for long periods, while high concentration levels were attained in lymph. In comparison, drug sulfates gave high blood levels but low levels in lymph. The high uptake of the poly-salt in lymph, attributed to the high affinity of the lymphatic system for macromolecules, caused a prolonged passage through the body since the lymphatic circulation is quite slow.

Streptomycin alginates have been prepared by El-Shibini et al. and shown to be effective in prolonged-release preparations.[146] Ozawa et al. report that streptomycin dextran sulfate injected in rabbits gradually releases the antibiotic over a period of approximately 48 h.[147] This prolonged effect may, nevertheless, be due to storage of the poly-salt in the lymphatic system. This phenomenon, first reported by Malek et al., demonstrates the ability of poly-salts to alter the transport of drugs in the body and, hence, modify the intensity and duration of the therapeutic response.[145]

Cavallito and Jewell[148] prepared polygalacturonates of several therapeutic amines in which the polygalacturonates served as agents for influencing the rate of release of the amines. Dialysis experiments showed that poly-galacturonates can reduce the rate of release of therapeutically effective amines. This finding has applications for the preparation of oral repository drug formulations. Poly(galacturonic acid) has also been used to prepare poorly soluble quinidine salts, which have been reported to be four times less toxic orally than the sulfate salts. This reduction in toxicity is attributed to slow release of quinidine from the polygalacturonate.

A remarkable example of a long-acting polymer-drug salt is pilocarpine alginate. When dispersed in sterile water and dried to a solid gel, this preparation was found to possess long duration of action for ophthalmic application. While liquid preparations of alginate or hydrochloride salts had a similar miotic activity, the solid pilocarpine alginate preparations were found to significantly increase the duration of miosis. In contrast to eye drops, which release pilocarpine immediately to the conjunctival fluid, the solid dose of pilocarpine diffuses slowly through the gel matrix and is available more uniformly.

Klaudianos has prepared long-acting preparations based on alginic acid according to a simple and economical method.[149] Sodium alginate was mixed with calcium phosphate and a therapeutic amine and compounded into tablets. Upon oral administration, GI fluids diffuse into the tablet, and the soluble sodium alginate is transformed by cation exchange into an insoluble but swellable calcium alginate. The resulting hydrogel acts as a depot from which the drug slowly diffuses. In the approach of Klaudianos, it is not the drug, but a polyvalent metal ion that causes cross-linking of the polyacid. Salib et al.[150] used an analogous procedure to obtain long-acting chloramphenicol dosage forms based on carboxymethylcellulose to which aluminum sulfate was added as the gel-forming agent.

It has been shown that on precipitation of polyacids by the addition of cationic drugs, considerable amounts of drug are physically entrapped. Goodman and Banker[151] developed a system of molecular-scale drug entrapment by flocculation of highly concentrated colloidal dispersions of acrylic copolymers in the presence of cationic drugs (e.g., methapyrilene). Studies of effectiveness in rats indicated a significantly increased duration of action and reduced acute toxicity of methapyrilene in the entrapped form.

Drug entrapment by polymeric flocculation as an approach to slow-release dosage forms was further studied by Rhodes et al.[152] and Elgindy.[153] It was shown that polymer–drug interactions in flocculates are complex processes that cannot be explained by ionic effects. Hydrogen bonding, as well as hydrophobic drug–drug and drug–polymer interactions, may be involved. This confirmed earlier reports of Kennon and Higuchi,[154] who studied the interaction of cationic drugs with the sodium salt of anionic polyelectrolytes and concluded that drug entrapment appeared to take place by coacervation of oppositely charged ions, additional intermolecular force phenomenon, or replacement of bound sodium by organic cations.

In summary, combining drugs with appropriate ionic polymers is a relatively simple means of altering their physiochemical and biological characteristics. Polymers can contribute to improved drug therapy, particularly in reducing drug toxicity, and influencing the release profile of novel dosage forms. Several sympathomimetics, antitussives, antihistamines, anticholinergics, anthelmintics, antibacterials, and miscellaneous compounds, such as morphine, gentisic acid, and salycylic acid, have been developed by utilizing the drug–resin combination approach.

X. Oligomers

The use of oligomeric instead of high molecular weight matrices to prepare derivatives of drugs can lead to products with considerably prolonged pharmacological activity.[155] In the case of oral, and possibly intradermal administration, the oligomeric matrix is often able to transfer the active principles across physiological barriers, thus facilitating absorption and increasing bioavailability.

Broadly speaking, the preparation of oligomeric or polymeric derivatives of drugs may be achieved in two ways: the preparation of a polymerizable derivative of the drug and the preparation of oligomeric or polymeric matrices carrying chemical functions able to react selectively with some constituent present in the drug molecule. The latter is more convenient, as a rule, since a single matrix can be used to prepare derivatives of a number of drugs. Furthermore, in many cases, drug moieties contain chemical functions that can interfere with the polymerization processes. An interesting variation to these techniques is to use the drugs themselves, leading to polymeric or oligomeric products that are degradable in body fluids reverting to the parent monomers.[156,157] Ferruti et al. have reported on the various possible oligomers and polymers as drug carriers.[155]

XI. Miscellaneous

The following polymers or polymeric materials have been investigated for their use in sustained-release medications:

1. Ethylcellulose and methyl stearate mixtures
2. Hydrated hydroxyalkyl cellulose
3. Salts of polymeric carboxylates
4. Chelated hydrogels
5. Water-insoluble hydrophilic copolymers
6. Cellulose ether compositions
7. Partial esters of acrylate-unsaturated anhydride copolymer
8. Water-soluble coating resins
9. Polymers with oxacycloalkane units
10. Polymers and copolymers of arylene-substitutes orthoesters
11. Polymers with alkoxy or oxacycloalkane substituents
12. Polyglycolic acid polyester condensates
13. Partial esters of polycarboxylic acids
14. Ionene-modified polymeric beads
15. Ethylene-vinyl acetate copolymers
16. Silicone polymer matrix having microsealed compartments
17. Gelatin nanoparticles
18. Serum albumin spherules
19. Phospholipid dispersion
20. Polyglycolic acid sutures and films

21. Polylactides
22. Dacron sutures
23. Caprolactone polymers and copolymers
24. Polysiloxane with N-vinylpyrrolidone
25. Hydrophilic acrylates or methacrylate polymers
26. Siloxane rubbers
27. Hydrocolloids
28. Amine-modified polyanhydrides
29. Polyelectrolytes or gelatin
30. Hydrophobic polycarboxylic acids
31. Metal cation cross-linked polyelectrolytes
32. Polymer–prostaglandin anticoagulant
33. Propranolol spheroids
34. Polymeric macrolides
35. Aspirin–polysiloxane-cellulose derivative matrix
36. Aspirin–pectin combinations
37. Iron compounds with natural resins
38. Polyacrylic alkali metal salts
39. Iron preparation with carboxylic polymers
40. Micronized insoluble cellulose
41. Furosemide–polystyrene
42. Glassy hydrophobic hydrogels
43. Beads containing acetaminophen
44. Acetaminophen using microcrystalline cellulose/wax formulations
45. Polyethylene glycol-derivatized superoxide dismutase
46. Poly(β-hydroxybutyrate), a copolymer with hydroxy valearate
47. Ibuprofen with acrylic polymers
48. Catecholamines using poly-(DL-Lactide-CO-glycolide)
49. Fenvalerate-poly-urea
50. Caffeine release using polyacrylate-methacrylate
51. Release of niclosamide and pituitary hormones using polymers
52. Theophylline and cimetidine using bioadhesive polymers
53. N-(2-hydroxypropyl) methacrylate copolymers
54. Alloys of hydrophilic-balanced coploymers
55. Collagen-poly hydroxyethylmethacrylate hydrogels
56. Ethylene vinyl acetate matrices
57. Hydroxyproline polyesters
58. Indomethacin in biodegradable polymers
59. Pluronic F-127, polaxamer
60. Pesticide chlordimeform in polymeric systems
61. Silicone–cellulose dispersions
62. Progesterone, testosterone, propranolol, and indomethacin from silicone matrices
63. Biodegradable fibers and tetracycline
64. Polymeric-pellet delivery systems for aquatic herbicides (e.g., fluridone)

65. Ethyl cellulose and ranitidine hydrochloride
66. Cyclodextrins for controlled release of insecticides, microbiocides, fungicides, pesticides, and polyorthoesters
67. Cellulose acetate trimellitate and phthalate
68. Hydropropyl methyl cellulose phthalate
69. N-(2-hydroxypropyl) methacrylamide
70. Ethylene-CO vinyl acetate
71. Glucoside monomers
72. Maleic anhydride/mono-methoxyoligoethylene glycol vinyl ether copolymers
73. Oligo(N-isopropylacrylamide)
74. N,N-dimethyl acrylamide

In veterinary products:

1. Enteric-coated swine vaccines
2. Rumen stable pellets (e.g., terpolymers of alkanolamine acrylates) polyamides of piperizine derivatives, and imidazoline-modified styrene-acrylonitrile copolymers

XII. Recent advances

Aqueous polymeric dispersions for controlled drug delivery have been prepared by the Wurster process. Methods of producing sustained-release products from small-coated particles have been reported. The feasibility of obtaining aqueous polymer-coated bead formulations using Aquacoat® and Surelease® dispersions of propranolol as the model drug have been investigated.[158,159]

A delivery system using "Medisorb" bioresorbable polymers has been created by microencapsulating a drug in a polymer. These microcapsules are usually about 50 microns in diameter, which is small enough to be injected through a syringe. Microcapsules can be created in two configurations. As the polymer of a monolithic delivery system breaks down, minute doses of drug are continuously released into the body. The second form delivers a burst of medication in the body. Combining the two capsule forms in one injection creates a comprehensive treatment profile that is particularly useful in the administration of antibiotics. The speed at which the polymer dissolves is regulated by choosing lactide, glycolide, or a copolymer of the two. Copolymer blends can be formulated in varying ratios to yield drug-release times ranging from 7 days to 1 year.[160]

Biodegradable and bioabsorbable polymers have been synthesized, which may be used as a temporary scaffold for tissue regeneration, as a transient barrier, or in controlled drug delivery systems. The copolymers consist of polyester segments creating hard, crystalline blocks of the copolymer and flexible polyether glycols forming the soft blocks of the segmented chains.[161]

A biodegradable polymer has been developed by the Massachusetts Institute of Technology. It is implanted at tumor sites in the brain following

Table 3.4 Commercial preparation of drug–polymer combinations

Corporation	Drug	Polymer as a matrix
Scios Nova & MIT	Gentamicin and carmustine	BIODEL delivery system (Polifeprosan)
DynaGen	Vaccine, immunogens	Sleeper system
KabiPharmacia & Berol Nobel	Drugs for blood disorders	Bioadhesive thermogel
Fidia	Antibiotics, antiseptics, and anti-inflammatories	HYAFF series (modified hyaluronic acids)
TheraTech	Systemic drug administration	BHHA, biodegradable hydrogel
	Wide variety of drugs	HIPN (heterogeneous interpenetrating polymer network)
Verex	Propranolol	POLiM (polymers liquid hydrogel matrix)
Searle/Monsanto	Misoprostol	OLipHEX and pHEMS Polymer delivery system
Advanced Polymer Systems & Rhone-Poulenc Rorer	5-FU 2,4, (1H, 3H)-Pyrimidine-delivery system dione-5-fluoro	Microsponge-based
Biosearch	Piloplex, a derivative of pilocarpine	Polymeric complex
Allelix & Glaxo	Corticosteroids	ALX 25 corticosteroid binding globulin (CBG)
(Alkermes)Enzytech	Therapeutic proteins OraLease, ProLease	Polymer-based delivery system

surgery. Once in place, it slowly releases drug or antibodies, thereby enabling delivery of drug doses hundreds of times greater than is normally possible. Eventually, the polymer implant dissolves. Alza Laboratories manufactures a "bioerodible" polymer called Alzamer that releases drugs at a controlled rate. Possible applications include delivery of drugs or hormones to treat chronic diseases, to provide contraception, or for topical therapy.[162]

Proteins — such as antibodies and lipoproteins, liposomes, synthetic polymers — and polysaccharides — such as dextran and insulin — are various types of macromolecules used as drug delivery systems. Polymers have been used extensively in these systems, including nanoparticles, microcapsules, laminates, matrices, and microporous powders. In all these delivery systems, the drug is merely dispersed or incorporated into the system without the formation of a covalent bond between the drug and polymer. Because the molecular weight of a polymeric drug delivery system is so high, such systems are often referred to as macromolecular carrier systems. Although the majority of polymer-drug conjugate systems have no biological activity, all such systems release the conjugated drug *in vivo*. A schematic diagram of Ringsdorf's model is given in Figure 3.3.

The system has a polymer backbone, which can be a homopolymer or a heteropolymer, depending on the constituents of the carrier polymer. Dextran and insulin are two polysaccharides that have been widely used. Sparer et al.[163] propose using glycosaminoglycans as drug carriers. Cellulose and polyarabogalactans have also been studied as possible drug carriers by these investigators Grolleman et al.[164] prepared a polymer pro-drug of naproxen with polyphosphazene, using a spacer molecule. Gros et al.[165] have synthesized a polymeric conjugate of poly(glutamic acid) and p-phenylenediamine, using immunoglobulin as a homing device. The polymer's immunogenicity, hemolytic activity, pyrogenicity, osmotic properties, and its interaction with plasma components must be studied before the polymer can be used in a drug delivery system. For example, even endogenous polymers, such as chondroitin sulfate, might show toxic effects after prolonged use at very high doses. Until recently, a polymeric pro-drug system has been used only in intravenous administration, but as in the case of phosphazene, such a system can now be used as a bioerodible implant. Localized effects, as in the case of gastrointestinal delivery, can be used effectively.[164,166]

Sustained-release tablets using an inert, compressed plastic matrix have become increasingly used clinically since their introduction several years ago. With these tablets, drug release is delayed because the dissolving drug must diffuse through a network of channels between the compacted polymer particles. The rate of release of a drug from a polymeric matrix can be controlled by altering the porosity or surface area of the matrix, thereby changing the solubility of the drug or its diffusion coefficient, or by adding other compounds that speed up or delay the release of the drug.

Rhodes et al.[152] have demonstrated that tablet matrices containing mixtures of two or more substances might be superior to the individual matrices currently available. The materials used in the study by Chang et al.[167] included polycaprolactone and cellulose propionate.

Because of cost, stringent environmental regulations, and the safety hazards associated with the use of organic solvents in coating processes, the pharmaceutical industry has been moving away from the use of organic solvent- based film-coating systems. Increasingly, the industry is relying on water-based coating formulations. New aqueous polymeric dispersions have also been developed, and intensive research is being conducted to maximize the use of water-dispersible colloidal particles in formulations for coating. Development of controlled-release dosage forms in which the mechanism of release is diffusion through a polymeric membrane formed via film coating requires the optimization of several processing and formulation variables to ensure reproducibility of the release rate.

When polymeric-coating systems composed of a latex or pseudo-latex are used to coat pellets or tablets, film deposition on the substrate must be followed by a curing stage in which the spherical submicron polymeric particles coalesce to form a continuous film. One procedure for curing involves storing the coated material at high temperatures for various periods of time, depending on the formulation. However, this procedure often leads

to problems with product handling because the film softens, causing tackiness. Although the tackiness eventually subsides after the temperature is lowered, the possibility of the film rupturing is always present, and this could have a detrimental effect on dissolution properties.[169]

Synthetic hydrogels are used in drug delivery systems primarily because their permeability can be controlled for aqueous solutes and they exhibit favorable swelling pressures and generally good biocompatibility. The hydrogels currently in use are based on covalently cross-linked hydrophilic polymers. This concept, which is more than 30 years old, has several inherent limitations. A new concept for hydrogels was developed over the past several years based on the use of multiblock copolymers containing hydrophilic and hydrophobic blocks. The hydrophobic blocks separate in the presence of water, and the hydrophobic domains formed in this manner can replace covalent cross-linking. The most advanced of these multiblock copolymers are the hydrogels with polyacrylonitrile blocks, which form crystalline domains of exceptional stability. This new concept allows processing by conventional methods and provides high degrees of strength even at a high level of water content.[170]

A wide variety of polymeric materials have been used in the fabrication and development of transdermal drug delivery systems. These materials have taken the form of components for devices, as well as polymeric materials that are mixed with drugs to slow down or enhance delivery. In reservoir-type transdermal devices, polymers have been used within the contents of the reservoir and in the rate-limiting membranes to regulate the passage of drug across the skin. In matrix transdermal systems, polymers have been used to form the device as well as to mediate drug absorption across the skin. In adhesive-type systems, polymers have been used as adhesives and have been mixed with the drug or used in the device.[171]

Amantadine has been modified by direct acylation with succinic and glutaric anhydrides and a covalent bond formed with substituted aspartamide (PHEA). The amount of amantadine in the copolymers was evaluated by hydrolysis of the conjugates. Binding of PHEA-succinylamantadine to surfactant micelles appeared to be stronger than that shown by PHEA-glutarylamantadine.[172]

A polymer carrier system has been developed to reduce the bitterness of erythromycin and its 6-O-methyl derivative, clarithromycin, by absorption to Carbopol.® The mechanism involves ionic bonding of the amine macrolide to high molecular weight polyacrylic acid, thereby removing the drug from the solution phase in an ion-free suspension. The macrolide-Carbopol complexes were prepared by dissolving or slurring predetermined ratios of drug and polymer in water or hydroalcoholic mixtures. Human bioavailability studies demonstrated that the microencapsulated Carbopol absorbates of erythromycin and clarithromycin give blood levels comparable to those from conventional solid formulations.[173]

Medical College of Ohio, Bowling Green State University, and Lilly have developed an azo cross-linked polymer coating for use in the delivery of

peptide drugs to the large intestine. The coating protects the peptides from stomach acid and digestive enzymes in the small intestine until bacteria in the large intestine break down the coating, releasing the peptides. Other potential applications are to deliver drugs such as heparin, peptide contraceptives, analgesics, anticancer, anti-inflammatory drugs, and the Sabin polio vaccine.

Biocompatible polymers have been tested as potential delivery systems for therapeutic antibodies and antibody fragments. The researchers incorporated antibodies and antibody fragments directed against a pregnancy hormone; human chorionic gonadotropin; into poly(ethylene-CO-vinyl) acetate, which is stable in biological environments; and a biodegradable polyanhydride copolymer of stearic acid dimer and sebacic acid. Saltzman and co-workers found that the antibodies released slowly from both polymers during 30 days of continuous immersion in buffered saline and retained their ability to bind antigens.[162]

The authors examined enantioselective release of controlled-delivery granules based on molecularly imprinted polymers (MIPs) for various racemic drugs (e.g., S-ibuprofen, S-ketoprofen, and R-propranolol). These were prepared using a multistep swelling and thermal polymerization method. The release profile of MIP granules exhibited differential release of enantiomers. The enantioselective release appeared to depend on polymer loading and medium pH. The drug/polymer ratio of 1:25 showed the best enantioselective release with initial enantiomeric excess of 100%.[185]

Polylactide-co-glycolide and polylactide polymer particles entrapping immunoreactive tetanus toxoid (TT) were prepared in order to study single-shot controlled-release vaccine formulation.[186] The results indicated the significance of protecting the immunoreactivity of TT during formation of polymer particles for sustained and improved antibody response.

Polyisobutylcyanoacrylate nanocapsules (PIBCA-NC) of pilocarpine were prepared by interfacial polymerization. Physicochemical characterization of the colloidal dispersion of pilocarpine was performed by measuring drug loading, particle-size analysis, and scanning electron microscopy.[187] It was found that Pluronic F127 gel delivery system increases the contact time of pilocarpine with the absorbing tissue in the eye, thereby improving ocular bioavailability of such hydrophobic drugs. Spray-dried powders of poly(D-L lactic acid) (PLA) or poly-epsilon-caprolactone (PepsilonC) from colloidal suspensions containing indomethacin using benzyl benzoate in nanocapsules or micelles were prepared by nanoprecipitation. After one month, the formulations with highest drug content (2.0mg/ml) showed a decline of total quantity of indomethacin.

Saito et al. investigated biodegradable poly-D-L-lactic acid-polyethylene glycol block copolymers as a bone morphogenetic protein (BMP) delivery system for inducing bone formation. According to the authors, in combination with biomaterials, these proteins can be used in a clinical setting as bone-graft substitutes to promote bone repair. Most recently, synthetic biodegradable polymers were tested as a delivery vehicle for osteoinductive

agents. In their earlier studies, these authors noted that polylactic acid homopolymers and poly-D-L-lactic acid polyethylene glycol block copolymers could be used as BMP delivery systems. These polymers were implanted into the dorsal muscle of mice to evaluate their capacity to elicit new bone formation.[188]

XIII. Conclusion

Recently, it has been stated that,[174] as in the past, when certain ages were characterized by the discovery of major materials (e.g., the Stone Age or the Bronze Age) the current period could be called the Polymer or Plastic Age. Most notably in the area of pharmaceutical applications, the rapid expansion of scientific work and intense interest in the development of new drug delivery systems have provided strong motivation for the creation of polymers and new polymeric materials.[167]

In state-of-the-art research and drug delivery system design, involving these entities in particular, the following topics have undergone extensive investigation: soluble synthetic polymers, oligomers, copolymers, bioerodible and biodegradable polymers, polymer-coated liposomes, encapsulated drugs for cancer, colloid carrier systems, albumin and gelatin microspheres, magnetic microspheres and magnetically modulated systems, microsealed drug delivery systems, matrix devices, swellable polymers and pseudo-latex dispersions, polymer-bioactive agent (or pro-drug) complexes, hydrogels, insulin delivery, and polymeric implants, liquid crystalline photoreactive, and performance polymers.

Currently, continuing significant advances in drug delivery devices composed of polymers and polymeric materials have occurred primarily with osmotic pumps, implants, and dermal and oral drug delivery systems. Exciting research in the area of polymers undoubtedly promises the development of new drug delivery systems. These systems will be designed for specific targeting and capable of providing precise and predictable systemic drug release with greater efficacy and minimal side effects. In the near future, the multidisciplinary efforts of leading researchers dealing with polymers will certainly result in the development of novel delivery systems in this rapidly expanding field.[175–177]

References

1. Wise, D.L., *Biopolymeric Controlled Release Systems*, Vol. 1, CRC Press, Inc., Boca Raton, FL, 1984.
2. Guiot, *Polymeric Nanoparticles and Microspheres*, CRC Press, Inc., Boca Raton, FL.
3. Langer, R.S., *Medical Applications of Controlled Release*, Vol. 1, CRC Press, Inc., Boca Raton, FL.
4. Tirrel, D.A., *Macromolecules as Drugs and as Carriers for Biologically Active Materials*, Vol. 446, The New York Academy of Sciences, New York, 1985.

5. Illum, L. and Davis, S.S., *Polymers in Controlled Drug Delivery*, Wright, Bristol, England, 1987.
6. Lloyd, J.B., Soluble polymers as targetable drug carriers. In *Drug Delivery Systems, Fundamentals and Techniques*, Horwood, E., Ed., VCH Publishers, England, 1987. Also see Duncan, R. and Lloyd, J.B., Biological evaluation of soluble synthetic polymers as drug carriers. In *Recent Advances in Drug Delivery Systems*, Anderson, J.M. and Kim, S.W., Eds., Plenum Press, New York, 1983, 9–22.
7. Prattern, M.K., Duncan, R., Cable, H.C., Schnee, R., et al., Pinocytotic uptake of divinyl ether-maleic anhydride (pyran copolymer) and its failure to stimulate pinocytosis, *Chem. Biol. Interactions*, 35, 319–330, 1981.
8. Duncan, R., Cable, H.C., Rejmanova, P., Kopecek, J., and Lloyd, J.B., Tyrosinamide residues enhance pinocytic capture of N-(2-hydroxypropyl)methacrylamide copolymers, *Biochem. Biophys. Acta*, 799, 1–8, 1984.
9. Duncan, R., Starling, D., Rypacek, F., Drobnik, J., and Lloyd, J.B., Pinocytosis of poly(α,β-(N-2-hydroxyethyl)-DL-aspartamide and a tyramine derivative by rat visceral yolk sacs cultured *in vitro*, ability of phenolic residues to enhance the rate of pincocytic capture of a macromolecule, *Biochem. Biophys. Acta*, 717, 248–254, 1982.
10. Duncan, R., Cable, H.C., Rypavek, F., Drobnik, J., and Lloyd, J.B., Characterization of the adsorptive pinocytic capture of a polyaspartamide modified by the incorporation of tyramine residues, *Biochem Biophys. Acta*, 840, 291–293, 1985.
11. Prattern, M.K., Lloyd, J.B., Horel, G,. and Ringsdorf, H., Micelle-forming block copolymers; pincocytosis by macrophages and interaction with model membranes, *Macromol. Chem*., 186, 725–733, 1985.
12. Duncan, R.D., Rejmanova, P., Kopacek, J., and Lloyd, J.B., Pinocytic uptake and intracellular degradation of N-(2-hydroxypropyl)methacrylamide copolymers, *Biochem. Biophys. Acta*, 678, 143–150, 1981.
13. Duncan, R., Pattern, M.K., Cable, H.C., Ringsdorf, H., and Lloyd, J.B., Effect of molecular size of I-labelled poly(vinylpyrrolidone) on its pinocytosis by rat visceral yolk sacs and rat peritoneal macrophages, *Biochem. J.*, 196, 49–55, 1981.
14. Cartlidge, S.A., Duncan, R., Lloyd, J.B., Rejmanova, P., and Kopacek, J., Soluble, cross-linked N-(2)hydroxypropyl methacrylamide copolymers as potential drug carriers, 1. Pincocytosis by rat visceral yolk sacs and rat intestine cultured *in vitro*, effect of molecular weight on uptake and intracellular degradation, *J. Controlled Release*, 3, 55–66, 1986.
15. Duncan, R., Kopacek, J., Rejmanova, P., and Lloyd, J.B., Targeting of N-(2-hydroxypropyl)methacrylamide copolymers to liver by incorporation of galactose residues, *Biochem. Biophys. Acta*, 755, 518–521, 1983.
16. Duncan, R., Seymour, L.C.W., Scarlett, L., Lloyd, J.B., et al., Fate of N-(2-hydroxypropyl)methacrylamide copolymers with pendent galactosamine residues after intravenous administration to rats, *Biochem. Biophys. Acta*, 880, 62–71, 1986.
17. Duncan, R., Lloyd, J.B., and Kopacek, J., Degradation of side chains of N-(2-hydroxypropyl)methacrylamide copolymers by lysosomal enzymes, *Biochem. Biophys. Res. Comm*., 94, 284–290, 1980.
18. Duncan, R., Cable, H.C., Lloyd, J.B., Rejmanova, P., and Kopacek, J., Degradation of side-chains of N-(2-hydroxypropyl)methacrylamide copolymers by lysosomal thiol-proteinases, *Bioscience Reports*, 2, 1041–1046, 1982.

19. Duncan, R., Cable, H.C., Lloyd, J.B., Rejmanova, P., and Kopecek, J., Polymers containing enzymatically degradable bonds, 7, Design of oligopeptides side-chains in poly N-(2-hydroxypropyl)methacrylamide copolymers to promote efficient degradation by lysosomal enzymes, *Macromol. Chem.*, 184, 1997–2008, 1983.
20. Rejmanova, P., Kopacek, J., Pohl, J., Baudys, M., and Kostka, V., Polymers containing enzymatically degradable bonds, 8, Degradation of oligopeptide sequences in N-(2-hydroxypropyl)methacrylamide copolymers by bovine spleen cathepsin, *B. Macromol. Chem.*, 184, 2009–2020, 1983.
21. Rejmanova, P., Kopacek, J., Duncan, R., and Lloyd, J.B., Stability in rat plasma and serum of lysosomally degradable oligopeptide sequences in N-(2-hydroxy propyl)methacrylamide copolymers, *Biomaterials*, 6, 45–48, 1985.
22. Pitt, C.G. and Schindler, A., Biodegradation of polymers. In *Controlled Drug Delivery*, Vol. 1, Basic Concepts, CRC Press, Inc., Boca Raton, FL, 1983, 53-81.
23. Desai, S.J., Simonelli, A.P., and Higuchi, W.L., Investigation of factors influencing release of solid drug dispersed in inert matrices, *J. Pharm. Sci*, 54, 1459, 1965.
24. Folkman, J. and Long, D.M., The use of silicone rubber as a carrier for prolonged drug therapy, *J. Surg. Res.*, 4, 139, 1964.
25. Baker, R.W. and Lonsdale, H.K., *Controlled Release: Mechanism and Rates in Controlled Release of Biologically Active Agents*, Vol. 47, Tarquasy, A.C. and Lacey, R.E., Eds., Plenum Press, New York, 15, 1974.
26. Rogers, C.E., Solubility and diffusivity, In *Physics and Chemistry of the Organic Solid State*, Vol. 2, Fox, D., Labes, M.M., and Weissberger, A., Eds., Wiley Interscience, New York, 1965.
27. Crank, J. and Park, G.S., Eds., *Diffusion in Polymers*, Academic Press, London, 1968.
28. Langer, R.S. and Peppas, N.A., Present and future applications of biomaterials in controlled drug delivery, *Biomaterials*, 2, 201, 1981.
29. Heller, J., Controlled release of biologically active compounds from bioerodible polymers, *Biomaterials*, 1, 51, 1980.
30. Benagiano, G. and Gabelnick, H., Biodegradable systems for the sustained release of fertility-regulating agents, *J. Steroid Biochem.*, 11, 449, 1979.
31. Pitt, C.G. and Schindler, A., The design of controlled drug delivery systems based on biodegradable polymers. In *Biodegradables and Delivery Systems for Contraception*, Vol. 1, Hafez, E.S.E. and van Os, W.A.A., Eds., MTP Press, Ltd., Lancaster, U.K., 17, 1980.
32. Pitt, C.G., Marks, A., and Schindler, A., Biodegradable drug delivery systems based on aliphatic polyesters; application to contraceptives and narcotic antagonists. In *Controlled Release of Bioactive Materials*, Baker, R., Ed., Academic Press, New York, 19–43, 1980.
33. Graham, N.B., Polymeric inserts and implants for the controlled release of drugs, *Br. Polym. J.*, 10, 260, 1978.
34. Kim, S.W., Petersen, R.V., and Feijen, J., *Polymeric Drug Delivery Systems in Drug Design*, Vol. 10, Ariens, E.J., Ed., Academic Press, New York, 1980.
35. Schindler, A., Jeffcoat, R., Kimmel, G.L., Pitt, C.G., et al., Biodegradable polymers for sustained drug delivery. In *Contemporary Topics in Polymer Science*, Vol. 2, Pearce, E.M. and Schaefgen, J.R., Eds., Plenum Press, New York, 251, 1977.
36. Heller, J., Zero-order drug release from bioerodible polymers. In *Recent Advances in Drug Delivery Systems*, Anderson, J.M. and Kim, S.W., Eds., Plenum Press, New York, 101–121, 1983.

37. Lappas, L.C. and McKeehan, W., Synthetic polymers as potential enteric and sustained-release coatings, *J. Pharm. Sci*., 51, 808, 1962.
38. Lappas, L.C. and McKeehan, W., Polymeric pharmaceutical coatings materials, I. Preparation and properties, *J. Pharm. Sci*., 54, 176, 1965.
39. Lappas, L.C. and McKeehan, W., Polymeric pharmaceutical coating materials, II. *In vivo* evaluation as enteric coatings, *J. Pharm. Sci*., 56, 1257, 1967.
40. Heller, J., Baker, R.W., Gale, R.M., and Rodin, J.O., Controlled drug release by polymer dissolution, I. Partial esters of maleic anhydride copolymers, properties and theory, *J. Appl. Polymer Sci.*, 22, 1991, 1978.
41. Heller, J., *Bioerodible Systems 69–101 Medical Applications of Controlled Release*, Vol. 1, Langer, R.S. and Wise, D.L., Eds., CRC Press, Inc., Boca Raton, FL, 1984.
42. Woodland, J.H.R., Yolles, S., Blake, D.A., Helrich, M., and Meyer, F.J., Long-acting delivery systems for narcotic antagonists, *I. J. Med. Chem.,* 16, 897, 1973.
43. Yolles, S. and Sartori, M.F., Degradable polymers for sustained drug release. In *Drug Delivery Systems*, Juliano, R.L., Ed., Oxford University Press, New York, 1980.
44. Yolles, S., Eldridge, J., Leafe, T., Woodland, J.H.R., et al., Long-acting delivery systems for narcotic antagonists. In *Controlled Release of Biologically Active Agents*, Tanquary, A.C. and Lacey, R.E., Eds., Plenum Press, New York, 1974.
45. Yolles, S., Controlled release of biologically active agents. In *Polymers in Medicine and Surgery*, Kronenthal, R.L., Oser, Z., and Martin, E., Eds., Plenum Press, New York, 1975.
46. Yolles, S., Leafe, T., Sartori, M., Torkelson, M., et al., Controlled release of biologically active agents. In *Controlled Release Polymeric Formulations*, Paul, D.R. and Harris, F.W., Eds., American Chemical Society, Washington, D.C., 1976.
47. Gresser, J.D., Wise, D.L., Beck, L.R., and Howes, J.F., Larger animal testing of an injectable sustained-release fertility control system, *Contraception*, 17, 253, 1978.
48. Wise, D.L., Gregory, J.B., Newberne, D.M., Bartholow, L.C., and Stanbury, J.B., Results on biodegradable cylindrical subdermal implants for fertility control. In *Polymeric Delivery Systems*, Kostelink, R.J., Ed., Gordon & Breach, New York, 1978.
49. Kulkarni, R.K., Moore, E.G., Hegyeli, A.F., and Leonard, F., Biodegradable poly-(lactic acid) polymers, *J. Biomed. Mater. Res*., 5, 169, 1971.
50. Yolles, S., Leafe, T.D., and Myer, F.J., Timed-release depot for anticancer agent, *J. Pharm. Sci*., 64, 115, 1975.
51. Wise, D.L., McCormick, G.L., Willet, G.P., and Anderson, L.C., Sustained release of an antimalarial drug using a copolymer of glycolic/lactic acid, *Life Sci*., 19, 867, 1976.
52. Hutchinson, F.G. and Furr, B.J.A., Design of biodegradable polymers for controlled release. In *Drug Delivery Systems, Fundamentals and Techniques*, Johnson, P. and Lloyd-Jones, J.G., Eds., VCH Publishers, Ellis Horwood, U.K., 106–119, 1987.
53. Anik, S.T., Sanders, L.M., Chaplin, M.D., Kushinsky, S., and Nerenberg, C., Delivery systems of LHRH and analogs. In *LHRH and Its Analogs: Contraceptive and Therapeutic Applications*, Vickery, B.H., Nestor, Jr., J.J., and Hafez, E.S.E., Eds., MTP Press, Ltd., Boston, MA, 421–435, 1984.
54. Petri, W., Seidel, R., and Sandow, J., Pharmaceutical approach to long-term therapy with peptides, *Int. Cong. Series — Excerpta Medica*, 656, 63–76, 1984.

55. Anders, R., Merkle, H.P., Schurr, W., and Ziegler, R., Buccal absorption of protirelin: An effective way to stimulate thyrotropin and prolactin, *J. Pharm. Sci*., 72, 1481–1483, 1983.
56. Okado, H., Zamazaki, I., Ogava, Y., Hirai, S., et al., Vaginal absorption of a potent leutenizing hormone-releasing hormone analog (Leuprolide) in rats, I. Absorption by various routes and absorption enhancement, *J. Phar. Sci*., 71, 1367–1371, 1982.
57. Okado, H., Zamazaki, I., Yashiki, T., and Mima, H., Vaginal absorption of a potent leutenizing hormone-releasing hormone analog (Leuprolide) in rats, II. Mechanism of absorption enhancement with organic acids, *J. Pharm. Sci*., 72, 75–78, 1983.
58. Okado, H., Yashiki, T., and Mima, H., Vaginal absorption of a potent leutenizing hormone-releasing hormone analog (Leuprolide) in rats, III. Effect of estrous cycle on vaginal absorption of hydrophilic model compounds, *J. Pharm. Sci*., 72, 173–176, 1983.
59. Okado, H., Zamazaki, I., Yashiki, T., Shimamoto, T., and Mima, H., Vaginal absorption of a potent leutenizing hormone-releasing hormone analog (Leuprolide) in rats, IV. Evaluation of the vaginal absorption and gonadotrophin responses by radioimmunoassay, *J. Pharm. Sci*., 73, 298–302, 1982.
60. Hunt, G., Kearney, P., and Kellaway, I.W., Mucoadhesive polymers in drug delivery systems. In *Drug Delivery Systems, Fundamentals and Techniques*, Johnson, P. and Lloyd-Jones, J.G., Eds., VCH Publishers, Ellis Horwood, U.K., 180–199, 1987.
61. Mungiu, C., Gogalniceanu, D., Leibovici, M., and Negulescu, I., On the medical use of cyanoacrylate esters:tonicity of pure n-butyl-cyanoacrylate, *J. Polym. Sci. Polym. Symp*., 66, 189–193, 1979.
62. Vezin, W.R. and Florence, A.T., *In vitro* heterogeneous degradation of poly(n-alkyl-cyanoacrylates), *J. Biomed. Mater. Res*., 14, 93–106, 1980.
63. Meyer, G., Muster, D., Schmitt, D., Jung, P., and Jaeger, J.H., Bone bonding through bioadhesives: present status, *Biomat. Med. Dev. Art. Org*. 7, 55–71, 1979.
64. Park, J.B., Acrylic bone cement: *in vitro* and *in vivo* property-structural relationship: a selective review, *Ann. Biomed. Eng*., 11, 297–312, 1983.
65. Bechgaard, H. and Ladefoged, K., Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. *J. Pharm. Pharmacol*., 30, 690-692, 1978.
66. Florey, H., Mucin and the protectin of the body, *Proc. R. Soc. B*., 143, 147–155, 1955.
67. Davenport, H.W., *Physiology of the Digestive Tract*, Year Book Publishers, Inc., Chicago, IL, 1977.
68. Allen, A., Bell, A., Mantle, M., and Pearson, J.P., The structure and physiology of gastrointestinal mucus. In *Mucus in Health and Disease*, Vol. 2, Chantler, E.N., Elder, J.B., and Elstein, M., Eds., Plenum Press, New York, 115–133, 1982.
69. Parke, D.V., Pharmacology of mucus, *Brit. Med. Bull*., 34, 89–94, 1978.
70. Kulenkampff, H., The structural basis of intestinal absorption. In *Pharmacology of Intestinal Absorption: Gastrointestinal Absorption of Drugs*, Forth, W. and Rummel, W., Eds., Pergamon Press, London, 1–70, 1975.
71. Neutra, M.R., Grand, R.J., and Trier, J.S., Glycoprotein synthesis, transport and secretion by epithelial cells of human rectal mucosa: normal and cystic fibrosis, *Lab. Invest*., 36, 535–536, 1977.

72. Silberberg, A. and Meyer, F.A., Structure and function of mucus. In *Mucus in Health and Disease*, Vol. 2, Chantler, E.N., Elder, J.B., and Elstein, M., Eds, Plenum Press, NY, 35–74, 1982.
73. Bickel, M. and Kauffman, G.L., Gastric gel mucus thickness: Effect of distension 16, 16-dimethyl prostaglandin E_2 and carbenoxolone, *Gastroenterology,* 80, 770–775, 1981.
74. Allen, A., The structure of gastrointestinal mucus glycoproteins and the viscous and gel-formimg properties of mucus, *Brit. Med. Bull*., 34, 28–33, 1978.
75. Allen, A., Pain, R.H., and Roberts, T.R., Model for the structure of gastric mucus gel, *Nature*, 264, 88–89, 1976.
76. Meyer, F.A., King, M., and Gelman, R.A., On the role of sialic acid in the rheological properties of mucus, *Biochim. Biophys. Acta*., 392, 223–232, 1975.
77. Kearney, P., Kellaway, I.W., Evans, J.C., and Rowlands, C., Probing the mucus barrier with spin labels, J. *Pharm. Pharmacol*., 36, 26, 1984.
78. Allen, A., Foster, S.N.E., and Pearson, J.P., Interaction of polyacrylate, carbomer, with gastric mucus and pepsin, *Brit. J. Pharmacol*., 87, 126, 1986.
79. Peppas, N.A. and Buri, P.A., Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues, *J. Cont. Rel*., 2, 257–275, 1985.
80. Smart, J.D., Kellaway, I.W., and Worthington, H.E.C., An *in vitro* investigation of mucosa-adhesive materials for use in controlled drug delivery, *J. Pharm. Pharmacol*., 36, 295–299, 1984.
81. Slomiany, A., Slomiany, B.L., Witas, H., Aono, M., and Newman, L.J., Isolation of fatty acids covalently bound to the gastric mucus glycoprotein of normal and cystic fibrosis patients, *Biochim. Biophys. Res. Commun*., 113, 286–293, 1983.
82. Scrivener, C.A. and Schantz, C.W., Penicillin: new methods for its use in dentistry, *J. Am. Dental Assoc*., 35, 644–647, 1947.
83. Rothner, J.T., Cobe, H.M., Rosenthal, S.L., and Bailin, J., Adhesive penicillin ointment for topical application, *J. Dent. Res*., 28, 544–548, 1949.
84. Keutscher, A.H., Zegarelli, E.V., Beube, F.E., Chiton, N.W., et al., A new vehicle (Orabase) for the application of drugs to the oral mucus membranes, *Oral Surg., Oral Med., Oral Pathol*., 12, 1080–1089, 1959.
85. Chen, J.L. and Cyr, G.N., Compositions producing adhesion through hydration. In *Adhesion in Biological Systems*, Manly, R.S., Ed., Academic Press, New York, 163–167, 1970.
86. Harris, F.W., Controlled release from polymers containing pendent bioactive substituents. In *Medical Applications of Controlled Release*, Vol. 1, Langer, R.S. and Wise, D.L., Eds., CRC Press, Inc., Boca Raton, FL, 103–128, 1984.
87. Ringsdorf, H., Structure and properties of pharmacologically active polymers, *J. Polym. Sci. Polym. Symp*., 51, 135, 1975.
88. Ringsdorf, H., Synthetic polymeric drugs. In *Polymeric Delivery Systems*, *Midl. Macromol. Monogr.,* No. 5, Kostelnik, R.J., Ed., Gordon & Breach, New York, 197, 1978.
89. Trout, A., Carriers for bioactive materials. In *Polymeric Delivery Systems*, *Midl. Macromol. Monogr.,* No. 5, Kostelnik, R.J., Ed., Gordon & Breach, New York, 157, 1978.
90. Goldberg, E.P., Polymeric affinity drugs. In *Polymeric Delivery Systems*, *Midl. Macromol. Monogr.,* No. 5, Kostelnik, R.J., Ed., Gordon & Breach, New York, 197, 1978.
91. deDuve, C., deBarsy, T., Poole, B., Trout, A., et al., Lysosomotropic agents, *Biochem. Pharmacol*., 23, 2495, 1974.

92. Zaffaroni, A. and Bonsen, P., Controlled chemotherapy through macromolecules. In *Polymeric Drugs*, Donaruma, L.G. and Vogl, O., Eds., Academic Press, Inc., New York, 1978.
93. Regelson, W., Thrombocyclopenic and related physiological effects of heparin and heparinoids: Macromolecular-induced syndrome, *Hematol. Rev.*, 193, 1968.
94. Kalal, J., Drobnik, J., Kopecek, J., and Exner, J., Synthetic polymers in chemotherapy: general problems. In *Polymeric Drugs*, Donaruma, L.G. and Vogl, O., Eds., Academic Press, New York, 1978.
95. Ghose, T. and Blair, A.H., Antibody-linked cytotoxic agents in the treatment of cancer: Current status and future prospects, *J. Natl. Cancer Inst.*, 61, 657, 1978.
96. Sinkula, A.A., Methods to achieve sustained drug delivery: The chemical approach. In *Sustained and Controlled Release Drug Delivery Systems,* Robinson, J.R., Ed., Mercel Dekker, New York, 1978.
97. Thorpe, P.E., Edwards, D.C., Davies, A.J.S., and Ross, W.C.J., Monoclonal antibody-toxin conjugates: Aiming the magic bullet. In *Monoclonal Antibodies in Clinical Medicine*, Fabre, J.W. and McMichael, A.J., Eds., Academic Press, New York, 1982.
98. Goldstein, J.L., Ho, Y.K., Basu, S.K., and Brown, M.S., Binding site on macrophages that mediates uptake and degradation of acylated low-density lipoprotein producing massive cholesterol deposition, *Proc. Natl. Acad. Sci.* (USA), 76, 333, 1979.
99. Mahley, R.W., Weisgraber, K.H., Innerarity, T.L., and Windmueller, H.G., Accelerated clearance of low-density and high-density lipoproteins and retarded clearance of E apoprotein-containing lipoproteins from the plasma of rats after modification of lysine residues, *Proc. Natl. Acad. Sci.* (USA), 76, 1746, 1979.
100. Bradley, S.G., Marecki, N.M., Bond, J.S., Munson, A.E., and John, D.T., Enhanced cytotoxicity in mice of combinations of concanavalin A and selected antitumor drugs, *Adv. Exp. Med. Biol.*, 55, 291, 1975.
101. Lin, J.Y., Li, J.S., and Tung, T.C., Lectin derivatives of methotroxate and chlorambucil as chemotherapeutic agents, *J. Natl. Cancer Inst.*, 66, 523, 1981.
102. Goldberg, E.P., Iwata, H., Terry, R.N., Longo, W.E., et al., Polymeric-affinity drugs for targeted chemotherapy: Use of specific and non-specific cell-binding ligands. In *Affinity Chromatography and Related Techniques*, Gribnau, T.C.J., Vesser, J., and Nivard, R.J.F., Eds., Elsevier/North-Holland, Amsterdam, 375, 1982.
103. Rowland, G.F., O'Neill, G.J., and Davies, D.A., Suppression of tumor growth in mice by a drug-antibody conjugate using a novel approach to linkage, *Nature* (London), 255, 487, 1975.
104. Cardinal, J.R., *Matrix Systems Medical Applications of Controlled Release,* Vol. 1, Langer, R.S. and Wise, D.L., Eds., CRC Press Inc., Boca Raton, FL, 41–67, 1984.
105. Roseman, T.J., Monolithic polymer devices. In *Controlled Release Technologies: Methods, Theory and Applications*, Vol. 1, Kydonieus, A.F., Ed., CRC Press, Inc., Boca Raton, FL, 1980.
106. Leininger, R.I., Polymers as surgical implants. In *CRC Crit. Rev. Bio.*, Fleming, D.G., Ed., CRC Press, Boca Raton, FL, 333, 1972.
107. Zentner, G.M., Cardinal, J.R., and Kim, S.W., Progestin permeation through polymer membranes, I. Diffusion studies on plasma-soaked membranes, *J. Pharm. Sci.*, 67, 1347, 1978.

108. Ermini, M., Carpino, F., Russo, M., and Nengiano, G., Studies on sustained contraceptive effects with subcutaneous polydimethylsiloxane implants, III. Factors affecting steroid diffusion *in vivo* and *in vitro*, *Acta Endocrinol.*, 73, 360, 1973.
109. Jeyaseelan, S., Tukkar, D., Bhuyan, U.N., Laumas, K.R., and Hingorani, V., Local tissue response to silastic implant containing norethindrone acetate in women, *Contraception*, 15, 39, 1977.
110. Anderson, J.M., Niven, H., Pelagalli, J., Olanoff, L.S., and Jones, R.D., The role of the fibrous capsule in the function of the implanted drug-polymer sustained release systems, *J. Biomed. Mater. Res.*, 15, 889, 1981.
111. Abrahams, R.A. and Ronel, S.H., Biocompatible implants for the sustained zero-order release of narcotic antagonists, *J. Biomed. Mater. Res.*, 9, 355, 1975.
112. Anderson, J.M., Koinis, T., Nelson, T., Horst, M., and Love, D.S., The slow release of hydrocortisone sodium succinate from poly(2-hydroxyethyl acrylate)membrabes. In *Hydrogels for Medical and Related Applications*, Andrade, J.D., Ed., American Chemical Society, Washington, D.C., 167, 1976.
113. Cowsar, D.R., Tarwater, O.R., and Tanquary, A.C., Controlled release of fluoride from hydrogels for dental applications. In *Hydrogels for Medical and Related Applications*, Andrade, J.D., Ed., American Chemical Society, Washington, D.C., 180, 1976.
114. Halpern, B.D., Solomon, O., Kopec, L., Korostoff, E., and Ackerman, J.L., Release of inorganic fluoride ion from rigid polymer matrices. In *Controlled Release Polymeric Formulations*, Paul, D.R. and Harris, F.W., Eds., American Chemical Society, Washington, D.C., 135, 1976.
115. Cardinal, J.R., Kim, S.W., Song, S.Z., Lee, E.S., and Kim, S.H., Controlled-release drug delivery systems from hydrogels: Progesterone release from monolithic reservoir, combined reservoir-monolithic and monolithic devices with rate controlling barriers. In *AIChE Symp. Series No. 206, Controlled Release Systems,* Vol. 77, Chandrasekaran, S.K., Ed., Am. Inst. Chem. Eng., New York, 52, 1981.
116. Wood, J.M., Attwood, D., and Collett, J.H., The swelling properties of poly(2-hydroxyethyl methacrylate) hydrogels polymerized by gamma-radiation and chemical initiation, *Int. J. Pharm.*, 7, 189, 1981.
117. Refojo, M.F., Natchair, G., Liu, H.S., Lahav, M., and Tolentino, R.I., New hydrophilic implant for scheral buckling, *Ann. Ophthalmol.*, 12, 88, 1980.
118. Tuttle, M.F., Baker, R.W., and Laufe, L.E., Slow-release aprotinin delivery for control of intrauterine-device-induced hemmorrhage, *Membr. Sci.*, 7, 351, 1980.
119. Kalkwarf, D.R., Sikov, M.R., Smith, L., and Gordon, R., Release of progesterone from polyethylene devices *in vitro* and in experimental animals, *Contraception*, 6, 423, 1972.
120. McRae, J.C. and Kim, S.W., Characterization of controlled release of prostaglandin from polymer matrixes for thrombus prevention, *Trans. Am. Soc. Artif. Intern. Organs*, 24, 746, 1978.
121. Baker, R.E., Tuttle, M.E., Longsdale, H.K., and Ayres, J.W., Development of an estradiol-releasing intrauterine device, *J. Pharm. Sci.*, 68, 20, 1979.
122. Gott, V.L., Whiffen, J.D., and Datton, R.C., Heparin bonding on colloidal graphite surfaces, *Science*, 142, 1297, 1963.
123. Whiffen, J.D. and Beeckler, D.C., The fate of the surface heparin of GBH-coated plastics after exposure to the bloodstream, *J. Thorac. Cardiovasc. Surg.*, 52, 121, 1966.

124. Leininger, R.I., Cooper, C.W., Falb, R.D., and Grode, G.A., Nonthrombogenic plastic surfaces, *Science*, 152, 1625, 1966.
125. Merrill, E.W., Salzman, E.W., Lipps, B.J., Gilliland, E.R., Austen, W.G., and Joison, J., Antithrombogenic cellulose membranes for blood dialysis, *Trans. Am. Soc. Artif. Intern. Organs*, 12, 139, 1966.
126. Hufnagel, C.A., Conrad, P.W., Gillespie, J.F., Pifarre, R., et al., Characteristics of materials for intravascular applications, *Ann. N.Y. Acad. Sci.*, 146, 262, 1968.
127. Ebert, C.D., McRea, J.C., and Kim, S.W., Controlled release of antithrombotic agents from polymer-matrices. In *Controlled Release of Bioactive Materials*, Baker, J., Ed., Academic Press, New York, 107, 1980.
128. Ebert, C.D. and Kim, S.W., Polymers for the prevention of thrombosis. In *Medical Applications of Controlled Release*, Vol. 2, CRC Press, Inc., Boca Raton, FL, 77–106, 1984.
129. Salyer, I.O. and Weesner, W.E., Materials and components for circulatory assist devices. In *Artificial Heart Program Conf. Proc.,* National Institute of Health, U.S. Department of Health, Education and Welfare, Washington, D.C., June 9–13, 59, 1969.
130. Schscht, E.H., Ionic polymers as drug carriers. In *Controlled Drug Delivery*, Vol. 1, Basic Concepts, Bruck, S.D., Ed., CRC Press, Inc., Boca Raton, FL, 149–173, 1983.
131. Saunders, L. and Srivastava, R., The absorption of quinine by a carboxylic acid ion-exchange resin, *J. Chem. Soc.*, 2915, 1950.
132. Hwa, J. and Loeffler, D., Therapeutic ion-exchange resins, *German Off.*, 1, 070, 381, 1959.
133. Mathur, N., Narang, C., and Williams, R., *Polymers as Aids in Organic Chemistry*, Academic Press, New York, 1980.
134. Hodge, P. and Sherrington, D., Polymer-Supported Reactions in Organic Synthesis, Wiley Interscience, New York, 1980.
135. Determann, H., Meyer, N., and Wieland, T., Ion exchanger from pearl-shaped cellulose gel, *Nature* (London), 223, 499, 1969.
136. James, K. and Stanworth, D., Chromatography of human serum proteins on diethylaminoethyl cellulose, *J. Chrom.*, 15, 324, 1964.
137. Helfferich, F., *Ion Exchange*, McGraw-Hill, New York, 87, 1962.
138. Boyd, G.E., Adamson, A.W., and Myers, L.S. Jr., The exchange adsorption of ions from aqueous solutions by organic zeolites, II. Kinetics, *J. Am. Chem. Soc.*, 69, 2836, 1947.
139. Samsonov, G.V. and Pasechnik, V.A., Ion exchange and the swelling of ion-exchangers, *Russ. Chem. Rev.*, 38(7), 547, 1969.
140. McChesney, E.W., Nachod, F.C., and Tainter, M.L., Aspects of cation-exchange resins as therapeutic agents for sodium removal, *Ann. N.Y. Acad. Sci.*, 57, 252, 1954.
141. Macaulay, D. and Watson, G.H., Tetany following cation-exchange resin therapy, *Lancet*, 2, 70, 1954.
142. Kamp, W., Application of ion-exchange resins in medicine, *Pharm. Weekblad.*, 97, 141, 1962.
143. Berg, P.R. and Ostrup, P., Ion-exchange resins as carriers for oral medications in order to achieve sustained release, parts I and II, *Dansk. Tidsskr. Farm.*, 40, 33, 55, 1966.
144. Miller, L.C. and Holland, A.H., Physical and chemical considerations in choice of drugs, *Mod. Med.*, 28, 312, 1960.

145. Malek, P., Kolc, J., Herold, M., and Hoffman, J., Problems of aimed penetration of antibiotics into the lymphatic system, III. Antibiolymphins and the lymphatic system. In *Antibiotics Annual* 1957–1958, Medical Encyclopedia, New York, 564, 1958.
146. El-Shibini, H.A.M., Abdel-Nasser, M., and Motawi, M.M., Streptomycin alginate as potential long-acting preparation, *Pharmazie*, 26(10), 630, 1971.
147. Ozawa, H., Ozeki, E., Shimizu, H., and Nishio, S., Gradually releasing drugs, *Japan Kokai*, 75, 24, 429; *Chem. Abstr.*, 83, 103292q, 1975.
148. Cavallito, C.J. and Jewell, R., Modification of rates of gastrointestinal absorption of drugs, I. Amines, *J. Am. Pharm. Assoc.*, 47, 165, 1958.
149. Klaudianos, S., Verfahren zur Herstellung von Retard-Tabletten auf Alginsaure Basis und Untersuchung der Wirkstoff-Freigabe, *Pharm. Ind.*, 33(5), 296, 1971.
150. Salib, N.N., El-Menshawy, M.E., and Ismail, A.A., Polysalt flocculates as a physicochemical approach in the development of controlled-release oral pharmaceuticals, *Pharmazie*, 31, 12, 1976.
151. Goodman, H. and Banker, G.S., Molecular-scale drug entrapment as a precise method of controlled drug release, I. Entrapment of cationic drugs by polymeric flocculation, *J. Pharm. Sci.*, 59(8), 1131, 1970.
152. Rhodes, C., Wai, K., and Banker, G.S., Molecular-scale drug entrapment as a precise method of controlled drug release, II. Facilated drug entrapment to polymeric colloidal dispersions, *J. Pharm. Sci.*, 59, 1578, 1581, 1970.
153. Elgindy, N.A., Molecular entrapment of cationic drugs by Carbopol 934, *Can. J. Pharm. Sci.*, 11(1), 32, 1976.
154. Kennon, L. and Higuchi, T., Interaction studies of cationic drugs with anionic polyelectrolytes, II. Polyacrylic and styrene polymers, *J. Am. Pharm. Assoc.*, 46, 21, 1957.
155. Ferruti, P., Angeloni, A.S., Scapini, G., and Tarisi, M.C., New oligomers and polymers as drug carriers. In *Recent Advances in Drug Delivery Systems*, Anderson, J.M. and Kim, S.W., Eds., Plenum Press, New York, 63–76, 1983.
156. Weiner, B.Z., Zilkha, A., Porah, G., and Grundfeld, Y., *Eur. J. Med. Chem.-Chim. Ther.*, 11, 525, 1976.
157. Pinazzi, C., Benoit, J.P., Rabadeux, J.C., and Pleurdeau, A., *Eur. Polym. J.*, 15, 1069, 1979.
158. Rekhi, G.S., Mendes, R.W., Porter, S.C., and Jambhekar, S.S., Aqueous polymeric dispersions for controlled drug delivery — Wurster process, *Pharm. Tech.*, 13(3), 112–125, 1989.
159. Harris, M.R., Ghebre-Sellasie, I., and Nesbitt, R.U., A water-based coating process for sustained release, *Pharm. Tech.*, 102, 1986.
160. Magda, A. et al., In *Polymeric Delivery Systems: Properties and Applications*, ACS Symposium Series Nos. 520, 408, 1993.
161. Tsuruta, T. et al., In *Biomedical Applications of Polymeric Materials*, CRC Press, Inc., Boca Raton, FL, 1993.
162. Saltzman et al., *Chem. Eng. News*, November 30, 1992 (Ref., *Bio/Technology*, 10, 1446, 1992).
163. Sparer, R.V., Ekwuribe, N., and Walton, A.G., Controlled release from glycosamino glycan drug complexes. In *Controlled Release Delivery Systems*, Roseman, T.J. and Mansdorf, S.Z., Eds., Marcel Dekker, New York, 107–119, 1983.

164. Grolleman, C.W.J., deVisser, A.C., Wolke, J.G.C., vanDer Goot, H., and Timmerman, H., Studies on a bioerodible drug carrier system based on a polyphosphazine, Part II, Experiments *in vitro*, *J. Controlled Release*, 4(2), 119–131, 1986.
165. Gros, L., Ringsdorf, H., and Schupp, H., Polymeric antitumor agents on a molecular and cellular basis, *Angew. Chem.*, 93(4), 311–332, 1981.
166. Friend, D.R. and Pangburn, S., Site-specific drug delivery, *Med. Res. Rev.*, 7(1), 53–106, 1987.
167. Chang, R., Price, J.C., and Whitworth, C.W., Control of drug-release rates through the use of mixtures of polycaprolactone and cellulose propionate polymers, *Pharm. Tech.*, 24, 1986.
168. Mollica, J.A., Technical considerations for advanced drug delivery systems. In *Recent Advances in Drug Delivery Systems*, Anderson, J.M. and Kim, S.W., Eds., Plenum Press, New York, 343–348, 1984.
169. Rosoff, M., *Controlled Release of Drugs*, VCH Publishers, New York, 1989.
170. Darby, T.D., Safety evaluation of polymeric materials, *Ann. Rev. Pharmacol. Toxicol.*, 27, 157–167, 1987.
171. Peppas, N.A., *Hydrogels in Medicine and Pharmacy*, Vol. 1, Fundamentals; Vol. 2; Vol. 3, Properties and applications, CRC Press, Inc., Boca Raton, FL, 1986.
172. Giammona, G., Carlisi, B., Pitarresi, G., Cavallaro, G., and Liveri, V.T., Water-soluble copolymers of an antiviral agent, synthesis and their interaction with a biomembrane model, *J. Control. Rel.*, 22, 197–204, 1992.
173. Fu Lu, M.-Y., Borodkin, S., Woodward, L., Li, P., et al., Polymer carrier system for taste masking of macrolide antibiotics, *Pharm. Res.*, 8, 706–712, 1991.
174. Lewin, M., Ed., *Polymers for Advanced Technologies*, VCH Publishers, New York, 1988.
175. Sheskey, P.J. and Cabelka, T.D., Reworkability of sustained-release tablet formulations containing HPMC polymers, *Pharm. Tech.*, 16, 60–74, 1992.
176. Dunn, R.L. and Ottenbrite, R.M., Eds., *Polymeric Drugs and Drug Delivery Systems*, ACS Symposium Series Nos. 469, 314, 1991.
177. Gebelein, C.G., Ed., *Biotechnological Polymers: Medical, Pharmaceutical and Industrial Applications (A Conference in Print)*, Technomic Publishing, Lancaster, PA, 224, 1993.
178. Sun, Y. and Watts, D.C., Biodegradable polymers and their degradation mechanisms, *Am. Pharm. Rev.*, 4, 8–18, 2001.
179. Kurita, K. et al., Nonnatural branch polysaccharides, synthesis and properties of chitin and chitosan having alpha mannoside branches, *Macromolecules*, 31, 4764–4769, 1998.
180. Denuziere, A. et al., Chitosan-chondroitin sulfate and chitosan hyaluronate polyelectrolyte complexes, biological properties, *Biomaterials*, 19, 1275–1285, 1998.
181. Wang, X. et al., Structural characterization of phosphorylated chitosan and their applications as effective additives of calcium phosphate cements, *Biomaterials*, 22, 2247–2255, 2001.
182. Bulpitt, P. and Aeschlmann, D., New strategy for chemical modification of hyaluronic acids: preparation of functionalized derivatives and their use in the formation of novel biocompatible hydrogels, *J. Biomed. Mater. Res.*, 47, 152–169, 1999.

183. Luo, Y. and Prestwich, G.D., Synthesis and selective cytotoxicity of a hyaluronic acid-antitumor bioconjugate, *Bioconjug. Chem.*, 10, 755–763, 1999.
184. Pelletier, S. et al., Amphiphilic derivatives of sodium alginate and hylauronate for cartilage repair, rheological properties, *Biomed. Mater. Res.*, 54, 102–108, 2001.
185. Suedee, R., Enantioselective release of controlled delivery granules based on molecularly imprinted polymers, *Drug Deliv.*, 9, 19–30, 2002.
186. Raghuvanshi, R.S. et al., Formulation and characterization of immunoreactive tetanus toxoid biodegradable polymer particles, *Drug Deliv.*, 8, 99–106, 2002.
187. Desai, S.D. and Blanchard, J., Pluronic F127-based ocular delivery system containing biodegradable polyisobutylcyanoacrylate nanocapsules of pilocarpine, *Drug Deliv.*, 7, 201–207, 2000.
188. Saito, N. et al., Biodegradable poly-D,L-lactic acid-polyethylene glycol block copolymers as a BMP delivery system for inducing bone, *J. Bone Joint Surg. Am.*, 83-A Suppl. 1(Pt. 2)S92–S98, 2001.