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REVIEW ARTICLE

# Polymeric Controlled Drug-Delivery Systems: Perspective Issues and Opportunities

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## ABSTRACT

*Although, the drug-delivery system (DDS) concept is not new, great progress has been made recently in the treatment of a variety of diseases. Targeting delivery of drugs to the diseased lesions is one of the most important aspects of DDS. To convey a sufficient dose of drug to the lesion, suitable carriers of drugs are needed. Polymers, which swell and contract in response to external pH levels, are being explored. The research in this area is being carried out all over the world at a great pace. Not only that new developments are emerging in the existing technologies, but also various new technologies are being developed and tested. Consequently, a huge amount of new information is available, which should be compiled and presented in a comprehensive way to benefit large numbers of users in this area as well as to help active research workers in the field. The purpose of this review is to discuss some recent advances and future prospects in controlled drug-delivery technology. The article serves as a useful tool for the beginners as well as for the researchers actively involved in this fascinating area of applied polymer science.*

**KEY WORDS:** Drug delivery; Drug targeting; Films; Hydrogels; Tablets; Transdermal devices.

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‡This paper is dedicated to Dr. K.G. Ramachandran Nair, Principal Scientist, Central Institute of Fisheries Technology, Indian Council of Agricultural Research, Matsyapuri PO, Kochi, Kerala, India, who has inspired me with his scientific approach, his honesty, and his human warmth.

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## INTRODUCTION

Of the several possible routes of introducing controlled-release medication into the body, the oral administration of single-dose medicinals is one of the simplest and safest because it does not pose the sterility problem, and the risk of damage at the site of administration is also minimal. However, an oral controlled-release formulation is subjected to frequently changing environments during transit through the gastrointestinal tract as it passes from the strongly acidic to the weakly alkaline medium in the lower part of the small intestine. The variable absorbing surfaces over the length of the GI tract adds additional constraint to the design of oral dosage forms. Moreover, the stomach-emptying period varies from person to person. These factors collectively introduce considerable variability in the performance of oral controlled-delivery systems. Several approaches have been taken in the past to prolong the retention of the dosage form in the stomach (1).

The polymeric controlled-delivery systems are being used for a wide range of reagents in various environments. The most popular application is the drug delivery, in which the main objective is to achieve an effective therapeutic administration for an extended period. The technique is also called sustained release. In spite of pharmaceutical applications, these techniques have been used in the agricultural area for creating a continued environment of soil nutrients, insecticides, herbicides, and other agro-expedient agents (2). The purpose of this review is to take a closer look at the polymeric controlled drug-release formulations such as hydrogels, films, and tablets. Based on the current research and existing products, some new and futuristic approaches, in the development of novel drug-delivery systems have been thoroughly discussed. Relevant patents for the review are included in the Appendix.

### Urgent Need for Controlled-Release Systems

Controlled drug-delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human health care. These delivery systems offer numerous advantages compared with conventional dosage forms, which include improved efficacy, reduced toxicity, and improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. By doing so, treatments that would not otherwise be possible are now in conventional use. Although the introduction of the first clinical controlled-release systems occurred two decades ago, the sales of advanced drug-delivery systems in the United States alone were approximately $14 billion (3). The review critically examines the current developments in polymeric controlled-release systems and opportunities. Before considering the variety and evolution of these polymeric structures, it is necessary to examine the motivation for achieving controlled release. This field of pharmaceutical technology has grown and diversified rapidly in recent years. Understanding the derivation of the methods of controlled release and the range of new polymers can be a barrier to involvement by the nonspecialist. All controlled-release systems aim to improve the effectiveness of drug therapies (4,5). This improvement can take the form of increasing therapeutic activity compared with the intensity of the side effects, reducing the number of drug administration required during treatment, or eliminating the need for specialized drug administration (e.g., repeated injections). Two types of control over drug release can be achieved: temporal and distribution control.

### An Understanding of Controlled-Release Systems

In temporal control, drug-delivery systems aim to deliver the drug over an extended period or at a specific time during treatment. Controlled release over an extended period is highly beneficial for drugs that are rapidly metabolized and eliminated from the body after administration. An example of this benefit is shown schematically in Figure 1, in which the concentration of drug at the site of activity within the body is compared after immediate release from four injections administered at 6 hourly intervals and after extended release from a controlled-release system. Drug concentrations may fluctuate widely during the 24-hr period when the drug is administered via bolus injection and for only a portion of the treatment period when the drug concentration in the therapeutic window (i.e., the drug concentration that produces beneficial effects without harmful side effects). With the controlled-release systems, the rate of drug release matches the rate of drug elimination, and therefore the drug concentration is within the therapeutic window for the vast majority of the 24-hr period. Clinically, the temporal control can produce a significant improvement in drug therapy. For example, when an opiod painkiller is administered to a patient with terminal cancer, any time that the drug concentration is below therapeutic concentrations, the patient experiences pain. A temporally controlled-release system would ensure that the maximum possible benefit is derived from the drug.

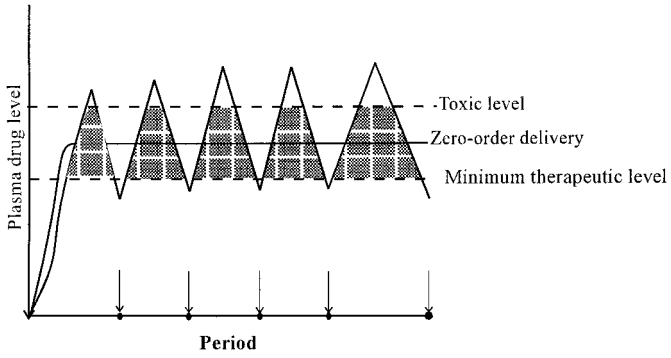



**Figure 1.** Controlled drug delivery versus immediate release.

In distribution control, drug-delivery systems aim to target the release of the drug to the precise site of activity within the body, in which drug concentrations at the site of activity and side effect production are compared. There are two principle situations in which distribution control can be beneficial. The first is when the natural distribution causes drug molecules to encounter tissues and cause major side effects that prohibit further treatment. This situation is often the cause of chemotherapy failure when bone marrow cell death prevents the patient undergoing a complete drug treatment. The second situation is when the natural distribution of the drug does not allow drug molecules to reach their molecular site of action. For example, a drug molecule that acts on a receptor in the brain will not be active if it is distributed by the patient's blood system but cannot cross the blood-brain barrier. A large number of classes of drugs can benefit from temporal or distribution controlled release, and the mechanisms are discussed in detail elsewhere (3).

## Scope of Polymeric Systems

Polymers are the youngest members of the materials family, and the recent progress in this fascinating area of applied polymer science is quite noteworthy. Pharmaceutical uses of biodegradable polymers are well established, e.g., resorbable sutures, hard and soft tissue implants, and controlled drug-release systems, mainly because the unique properties of the materials override the costs involved. Drug-release system incorporates the active substance into a patient. A diffusion mechanism produces maintained drug release followed by bulk hydrolysis of the polymer, which is ideal for the drug delivery of relatively small molecules. However, modern techniques require the incorporation of drugs, which vary in nature and molecular size, and a diffusion mechanism is too slow for the release of large molecules. Thus, an erosion release mechanism must be used. The range of degradation profiles available is limited in terms of both degradation time and character. The balance between abiotic and biotic degradation both in vivo and is not fully understood, even for the most studied biodegradable polymers such as poly($\alpha$-esters) and poly(hydroxyalkanoates). More pure or blended materials with surface erosion characteristics are required for drug delivery.

The blending of biodegradable polymers is a method of reducing the overall cost of the material and offers a method of modifying both the properties and the degradation rates of the materials. Miscibility is usually characterized by a single glass transition in the blend, which varies with composition and can be measured using mechanical or thermal testing. The advantages of producing miscible blends include single-phase morphology in the melt and reproducible mechanical properties. However, forming a miscible blend, particularly with a nonbiodegradable component. Immiscible blends have the advantage of including properties that are dependent on the blend morphology produced by processing, and these are often not reproducible. However, some can show higher biodegradation rates than the unblended biodegradable homopolymers(s).

The development of two and three component blends represents an area of considerable interest. Several groups have studied the use of natural polymers and biodegradable polyesters, but there is still considerable potential, especially if compatible blends can be made using materials with relatively low glass transition temperature. The use of low-molecular-weight plasticizers and photoactive materials in tertiary blends of biodegradable and nonbiodegradable synthetic and natural polymers is another field of study.

## HYDROGELS

Hydrogels are highly swollen, hydrophilic polymer networks that can adsorb large amounts of water and drastically increase in volume. It is well known that the physicochemical properties of the hydrogel depend not only on the molecular structure, the gel structure, and the degree of cross-linking, but also on the content and state of water in hydrogel. Hydrogels have been widely used is controlled-release systems (6,7).

Hydrogels, which swell and contract in response to external pH levels (8), are being explored. The pH-sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of the GI tract and have been prepared for low-molecular-weight and protein drug delivery (9). It is known that the release of drugs from the hydrogels depends on their structure or their chemical properties in response to environmental pH levels (10). These polymers, in certain cases, are expected to reside in the body for a long time and to respond to local environmental stimuli to modulate drug release (11,12). Thus, to be able to design hydrogels for particular application, it is important to know the varieties of systems in the environmental conditions to design them in proper situations. Some recent advances in controlled-release formulations using hydrogels are discussed here.

### Crosslinked Poly(Ethylene Glycol) Networks for Protein Delivery

Biocompatibility of poly(ethylene glycol) (PEG) makes it the polymer of choice for numerous biomedical applications (13). Graham and co-workers (14) pioneered the field of PEG networks cross-linked by diisocyanates as reservoirs for drug delivery. They explored loading of low-molecular-weight compounds into and release from PEG hydrogels. Recently, PEG networks are challenged as reservoirs for delivery of macromolecules, such as proteins, via a transdermal route (15). Poly(ethylene glycol)s are cross-linked by *tris*(6-isocyanatohexyl) isocyanurate via urethane/allophanate bond formation to obtain polymeric networks capable of swelling in phosphate buffered saline (PBS) or ethanol, resulting in gels. Swelling of the networks in PBS and ethanol is governed by parameters of the initial mixture of PEG and isocyanate, such as the molecular weight of PEG and the ratio of eqivalents of isocyano and hydroxyl groups. Protein and ethanol release from PEG gels through phospholipid-impregnated membranes mimics that from the biphasic transdermal systems. Spectroscopic data and retention of enzymatic activity of the released proteins indicate that they remain in their native state on release (15).

### Poly($\varepsilon$-Caprolactone)/Poly(Ethylene Glycol) Macromer

Drug release from biodegradable or bioerodible polymer matrices has been intensively investigated for the last decade (2–5). The most thoroughly investigated and used bioerodible polymers are the poly($\alpha$-hydroxy esters) such as poly(lactic acid) (PLA); poly(glycolic acid) (PGA), and poly(LA-*co*-GA) that would degrade into naturally occurring substances (3). Recently, poly(ethylene glycol) PEG macromers terminated with acrylate groups and semi-interpenetrating polymer networks (SIPNs) composed of poly($\varepsilon$-caprolactone) PCL and PEG macromer were synthesized and characterized with the aim of obtaining a bioerodible hydrogel that could be used to release tetracycline HCl for local antibiotic therapy administered preoperatively (16). Polymerization of PEG macromer resulted in the formation of cross-linked gels owing to the multifunctionality of macromer. Noncross-linked PCL chains were interpenetrated into the cross-linked three-dimensional networks of PEG. Glass transition temperature ($T_g$) and melting temperature ($T_m$) of PCL in the SIPNs were inner-shifted, indicating interpenetration of PCL and PEG chains. It was found that water content increased with increasing PEG weight fraction owing to the hydrophilicity of PEG. Drug release is expected to be controlled by weight fraction of PEG in the PCL/PEG SIPNs, concentration of PEG macromer in the SIPNs preparation, and the nature of PEG (16). The results obtained from their investigations indicated the hydrophilic nature of PEG that increases the accessibility of water to the polymer matrix. Also, PCL has been known to degrade very slowly because of its hydrophobic structure that does not allow fast water penetration (16). From SEM photographs, the morphology of the SIPNs after 50 days in vitro demonstrate that the degradation is attributable to bulk bioerosion rather than to surface hydrolysis (16).

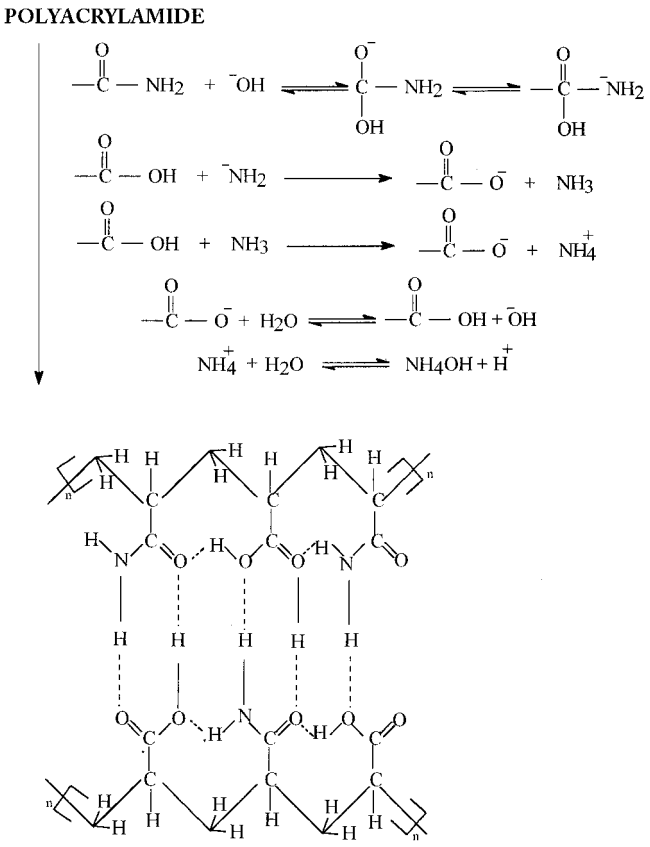
### Gelatin-Polyacrylamide

Ramaraj and Radhakrishnan (17) prepared an interpenetrating hydrogel network from gelatin and polyacrylamide by cross-linking. The swelling behavior of the interpenetrating polymer network system was analyzed in water and in citric acid-phosphate buffer solution at various pH levels. The effect of temperature on swelling behavior of the gels has been analyzed by variation from

25 to 60°C at physiological pH levels. The drug (Bromothymol blue) release behavior of the gels was also analyzed by varying temperature at physiological pH levels. An increase in temperature beyond 37°C showed a decrease in drug release followed by erratic change. At physiological pH levels, the increase in temperature has accelerated the hydrolysis of acrylamide groups. The polymer matrix with acid and amide groups and the possible interaction between acid and amide groups lead to a formation of complex structures through hydrogen bonding (Scheme 1). Such a tight structure of the complex restricts the mobility of the polymer segments resulting in lower release of the drug. This may be the reason for the slow drug release beyond 37°C. The swelling of GleX-PAam is more than that of Gel-PAamX, whereas the drug release for the former is lower, for the reasons noted above. It has been established that the gelatin and polyacrylamide IPN systems have a higher drug-release rate at physiological temperature (37°C) and at physiological pH levels.

## Hydroxypropyl Cellulose Gels

Cellulose ethers are common components of pharmaceutical preparations, whether for topical use (18–20) or for oral administration (21,22). In solid and semisolid dosage forms of this type, the rate of diffusion of the drug through the gel formed on hydration of the polymer is the key factor to determine the release rate (19,21,23). As a result, the effects of formulation variables on drug diffusion rates are of considerable practical relevance (22,24–26). Recently, investigations focusing on the influence of the rheological properties of hydroxypropylcellulose (HPC) gels on the in vitro release of theophylline were carried out by Alvarez-Lorenzo et al. (27). They performed the experiments with six HPC varieties (mean molecular weight between $5 \times 10^5$ and $1.2 \times 10^6$; nominal viscosity between 100 and 4000 mPa) at concentration of 0 to 2% (w/w). The theophylline diffusion coefficient declined exponentially with HPC concentration in the case of the lowest-molecular-weight HPC; however, the diffusion coefficient




**Scheme 1.**

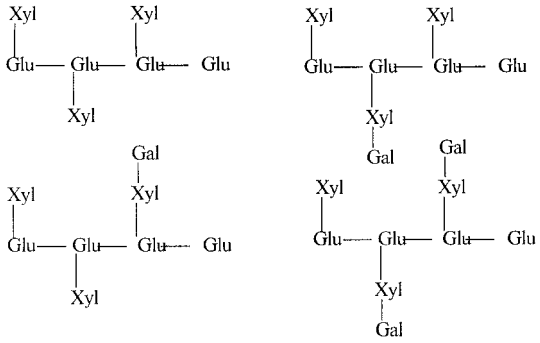
remained constant to HPC concentrations of up to 0.8%, probably because of the weight entanglement concentration of the HPC. Gel microviscosities as determined by dynamic light scattering (DLS) with latex microspheres (162 nm) were considerably lower than the macroviscosities determined by capillary viscometry and were similar to microviscosities estimated on the basis of theophylline diffusion.

## Thermally Reversible Xyloglucan Gels

Materials that exhibit sol to gel transition in aqueous solution in between ambient and body temperature are of interest in the development of sustained-release vehicles with in situ gelation properties. A compound that has received considerable attention is polyoxyethylene/polyoxypropylene/polyoxyethylene triblock copolymer Pluronic F127 (poloxomer 407), the thermoreversible gelation. However, there are inherent problems associated with triblock copolymers of polyoxyethylene and polyoxypropylene; commercial samples are subject to batch-to-batch variability (28), and laboratory synthesis is complicated by the so-called transfer reactions, which result in the presence of diblock impurities (29). These problems may be avoided through the use of block copolymers in which oxybutylene is substituted for oxypropylene as the hydrophobe, which can be tailor-made to have the necessary sol-gel transition between ambient and body temperatures to confer in situ gelation characteristics (30). Yuguchi et al., (31) suggested the polysaccharide xyloglucan, which also exhibits sol-to-gel transition in the required temperature region and which has the additional advantage of recognized nontoxicity and lower gelation concentration as an alternative polymer.

Xyloglucan polysaccharide derived from tamarind seeds is composed of a (1-4)-$\beta$-D-glucan backbone chain which has (1-6)-$\alpha$-D-xylose branches that are partially substituted by (1-2)-$\beta$-D-galactoxylose. The tamarind seed xyloglucan is composed of three units of xyloglucan oligomers with heptasaccharide, octasaccharide, and nanosaccharide, which differ in the number of galactose side chains (Scheme 2). When xyloglucan derived from tamarind seed is partially degraded by $\beta$-galactosidase, the resultant product exhibits thermally reversible gelation, with the sol-gel transition temperature varying with the degree of galactose elimination (31). Such gelation does not occur with native xyloglucan. The potential use of xyloglucan gels for rectal (32) and intraperitoneal (33) drug delivery has been reported.

Recently, sustained-release vehicles of gels formed in situ after the oral administration of dilute aqueous solutions of a xyloglucan has been assessed by in vitro and in vivo studies (34). Aqueous solution of xyloglucan that had been partially degraded by $\beta$-galactosidase to eliminate 44% of galactose residues, formed rigid gels at concentrations of 1.0 and 1.5% w/w at 37°C according to Kawasaki et al. (34). The in vitro release of indomethacin and diltiazem from the enzyme-degraded xyloglucan gels followed root-time kinetics over a 5-hr period at 37°C at a pH level of 6.8. Plasma concentrations of indomethacin and diltiazem after oral administration to rats of chilled 1% w/w aqueous solutions of the enzyme-degraded xyloglucan containing dissolved drug and a suspension of indomethacin of the same concentration were compared. Constant indomethacin plasma concentrations were noted from both formulations after 2 hr and were maintained over a period of at least 7 hr. Bioavailability of indomethacin from xyloglucan gels formed in situ was increased approximately three-fold compared with that from the suspension (34). From these studies, it appears that enzyme-degraded xyloglucan gels can be used as prominent vehicles for oral delivery of drugs.

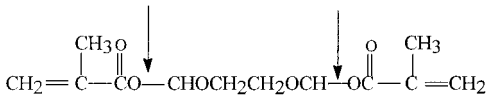



**Scheme 2.**

## Novel Star-Shaped Gel Polymers

Divinyl cross-linking reagents have often been used for the preparation of star-shaped (co)polymers. A linear living polymer was first prepared using a living polymerization technique, and this was subsequently followed by the reaction of its living end with a small amount of divinyl compound. Just adding a bifunctional monomer to a completed living polymerization system could easily carry out this synthetic technique. However, the number of the resulting (co)polymers could hardly be controlled.

Ruckenstein and Zhang (35) prepared a novel breakable cross-linker and pH-responsive star-shaped and gel polymer. A bifunctional methacrylate monomer, such as ethylene glycol di(1-methacryloyloxy)ethyl ether (1), was




**Scheme 3.**

prepared through the addition reaction between ethylene glycol divinyl ether and methacrylic acid. 1 was used as a cross-linker in the preparation of a star-shaped poly(methylmethacrylate) [poly(MMA)], a branched soluble poly(MMA), and a polymer gel. The addition of 1 to an anionically prepared living poly(MMA) solution generated a star-shaped polymer with a central poly(1) gel core and several poly(MMA) arms. On the other hand, when MMA and 1 were simultaneously added to a tetrahydrofuran (THF) solution of an anionic initiator, a branched soluble poly(MMA) and a polymer gel was obtained, depending on the amount of 1. The cross-linking points in the above polymers could be easily broken by hydrolysis under acidic conditions (Scheme 3), leading to linear polymers. These polymer gels could be broken into soluble polymers in an acid medium differing with the common polymer gels. However, it was just swollen in basic or a neutral medium. The hydrolyzed products from the star-shaped polymer was a block copolymer consisting of poly(MMA) and poly(methacrylic acid) segments, and those hydrolyzed from the branched polymers and polymer gels were random copolymers of MMA and methacrylic acid. All the hydrolyzed polymers possessed quite different solubilities than those of their precursors. Ruckenstein and Zhang claimed that these properties might be favorably used for controlled drug-release systems and is relevant to the environment protection (35).

## Superporous Hydrogels

Porous hydrogels can be prepared using a variety of methods, such as the porosigen technique, phase separation technique, cross-linking of individual hydrogel particles, and gas-blowing (or foaming) technique. In the porosigen technique, porous hydrogels are made by preparing hydrogels in the presence of dispersed water-soluble porosigens such as micronized sucrose (36), sodium chloride (37), and PEG (38), which can be removed later by washing with water to leave a meshwork (36,39). Water itself can be used as a porosigen if a polymer network is formed in the frozen state (36,40). The pore size of hydrogels prepared by the porosigen technique depends on the size of the porosigens used. The phase separation technique is based on a decrease in solvent quality for polymers (41,42). The major limitations of the phase separation method are that only very limited types of porous hydrogels (such as HEMA and NIPAM) can be prepared and that there is not much control over the porosity of the macroporous hydrogels. Porous hydrogels can also be prepared by cross-linking individual hydrogel particles to form cross-linked agregates of particles (43). Pores in such structures are present between hydrogel particles, and the size of pores is smaller than the sizes of the particles. This approach is limited to the absorbent particles that have chemically active functional groups on the surface.

Park and co-workers (44–46) synthesized porous hydrogels with open channels using the gas-blowing (or foaming) technique. The capillary radius of the porous hydrogels is in the range of few hundred micrometers (46). Because this pore size is well beyond the pore sizes described as microporous (10 to 100 nm) and macroporous (100 nm to 10 $\mu$m) hydrogels (36), the hydrogels prepared by them were called superporous hydrogels (174). Superporous hydrogels prepared by the gas-blowing technique were also called hydrogel foams owing to the foaming process used in the preparation (44,45). Superporous hydrogels were synthesized by cross-linking polymerization of various vinyl monomers in the presence of gas bubbles formed by the chemical reaction of acid and $NaHCO_3$. The polymerization process was optimized to capture the gas bubbles inside the synthesized hydrogels. The use of the $NaHCO_3$/acid system allowed easy control of timing for gelation and foam formation. PF127 was found to be the best foam stabilizer for most of the monomer systems used in their studies (46). Scanning electron microscope pictures showed interconnected pores forming capillary channels. The capillary channels, which were critical for fast swelling, were preserved during drying by dehydrating water-swollen hydrogels with ethanol before drying. The ethanol-dehydrated superporous hydrogels reached equilibrium swelling within minutes. They have also reported that the equilibrium swelling time could be reduced to less than 1 min using a wetting agent (46). In the present case, water moisture was used a wetting agent because the amount of moisture content in the dried hydrogels could be easily controlled. Preparation of superporous hydrogels using the right blowing system, foam stabilizer, drying method, and wetting agent makes it possible to reduce the swelling time to less than 1 min, regardless the size of the dried gels. The superporous hydrogels can be used where fast swelling and superabsorbent properties are critical, especially in controlled drug-release formulations (46).

## Polyelectrolyte Complex Gel from Chitosan and *k*-Carrageenan

According to the literature, the interest in investigating chitin and chitosan and their derivatives for use in biology and medicine is rapidly increasing (47). Chitosan, the deacetylated form of chitin, is nontoxic and easily bioabsorbable with gel-forming ability at a low pH level. Moreover, chitosan has antacid and antiulcer activities that prevent or reduce drug irritation in stomach (48,49). Also, chitosan matrix formulations appear to float and gradually swell in acid medium (50–53). All these interesting properties of chitosan made this natural polymer an ideal candidate for controlled drug-delivery formulations (54,55).

When two oppositely charged polyelectrolytes are mixed in an aqueous solution, a polyelectrolyte complex is formed by the electrostatic attraction between the polyelectrolytes. Sakiyama et al. (56) reported a polyelectrolyte complex gel in cylindrical shape prepared from natural polysaccharide. *k*-Carregeen is used as a polyanion component, and chitosan is used as polycation component to afford a strong acid-weak base polyelectrolyte complex. The complex gel swelled in an isotropic manner at an ambient pH level of 10 to 12 and the swelling maxima were observed in an NaOH solution of pH 10.5. Thus, the swelling of the complex gel was revealed to be sensitive to a rather narrow pH range. The equilibrium swelling ratio was also affected by the kind of alkali used. However, in the presence of 4 or 6% NaCl, the complex gel contracted at any pH level (56). No reports were available on drug-release studies.

## Chitosan/Polyether

Yao et al. (57) reported a procedure for the preparation of cross-linked chitosan interpenetrating polyether network hydrogel. The pH sensitivity, swelling and release kinetics, and structural changes of the gel in different pH solutions have been investigated (58–60). It is well known that physicochemical properties of the hydrogel depend not only on the molecular structure, the gel structure, and the degree of cross-linking, but also on the content and state of water in the hydrogel. Because the inclusion of water significantly effects the performance of hydrogels, a study on the physical state of water in the hydrogels is of great importance because it offers useful suggestion on their microstructure and enables an understanding of the nature of the interaction between absorbed water and polymers. The dynamic water absorption characteristics, state of water correlation between water states, and swelling kinetics of chitosan-polyether hydrogels have been studied by applying some novel techniques such as positron annihilation life time spectroscopy and also by widely used techniques such as DSC (61).

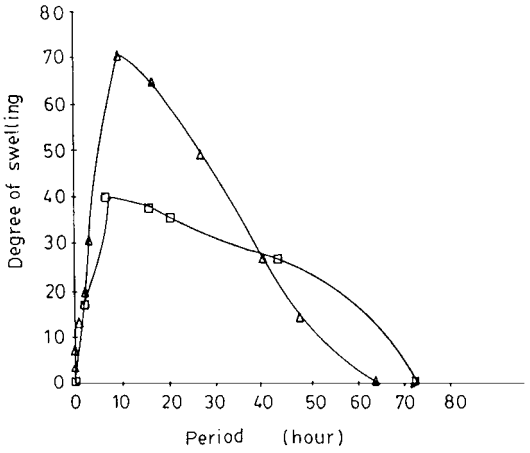



**Figure 2.** The effect of ionic strength ($I$) on the hydrolysis of sample 1 at pH 4.84 and 37°C (□); $I = 0.1$; ∇; $I = 0.03$.

The effect of ionic strength of solution on the hydrolysis rate of the gel has been studied and rapid hydrolysis of the gel with the decrease in the ionic strength of the solution was observed, i.e., a higher degree of swelling was seen in lower ionic strength solution (59) (Figure 2). It was concluded that the hydrolysis of the gel could be controlled by the amount of the cross-linker added and the effect of the cross-linker on the swelling behavior of gel has been studied (Fig. 3). From these studies, it is clear that the more cross-linker added, the higher the cross-link density of the SIPNs that results in a lower degree of swelling and difficulty of hydrolysis (59).

Chlorhexidini acetas and cimetidine were used as model drugs for drug-release studies. Fast swelling of gels resulting in more drug release at pH $<6$ in comparison with that at pH $>6$ was observed (57,58).

## $\beta$-Chitin/Poly(Ethylene Glycon) Macromer

SIPN hydrogels composed of $\beta$-chitin and poly(ethylene glycol) macromer were synthesized for biomedical applications (62). The thermal and mechanical properties of the hydrogels have been studied. The tensile strengths of SIPN in the swollen state from 1.35 to 2.41 Mpa, the highest reported values to date for cross-linked hydrogels. The hydrogels have been used as wound-covering materials and have also been studied in the drug-release behavior using silver dulfadiazine as a model drug (63).

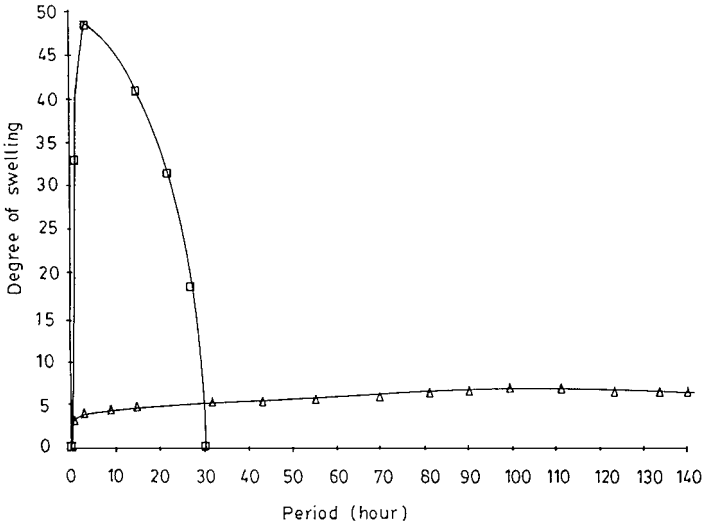



**Figure 3.** The effect cross-linker on the hydrolysis of the semi-IPN hydrogels at pH = 1.0 at 37°C; □ indicates sample 1; ∇ sample 3.

### β-Chitosan/Poly(Ethylene Glycol) Macromer

Lee and co-workers (64) reported a procedure for preparing SIPN polymer network hydrogels composed of β-chitosan and poly(ethylene glycol) diacrylate macromer. The crystallinity and thermal and mechanical properties of gels were reported (64). However, reports on drug-release behavior of the gels were not available.

### Chitosan-Amine Oxide Gel

A procedure for preparing homogeneous chitosan-amine oxide gel was reported (65). The procedure involves heating chitosan and *N*-methyl morpholine-*N*-oxide at 120°C to afford a geled mass. The swelling behavior and release characteristics of the gel were studied in buffer solution (pH 7.4) at room temperature (66–68). The homogeneous erosion of the matrix and near zero-order release of ampicilllin trihydrate (Fig. 4) were observed (64). Thermal studies of chitosan-amine oxide gel were also reported in additional studies (69).

### Poly(Ethylene Glycol)-*co*-Poly(Lactone) Diacrylate Macromer and β-Chitin

The synthesis and properties of poly(ester-ether-ester) block copolymers based on various lactones and poly(ethylene glycol)or poly(propylene glycol) have been reported in recent years (3). These polymers are generally used for biomedical materials, such as controlled release of drugs, bioabsorbable surgical sutures, and wound-covering materials. Among these polymers, copolymers of L-lactide, D,L-lactide, ε-caprolactone, and PEG have been noted by many workers. Such block copolymers have been obtained in bulk by a ring-opening polymerization mechanism. Poly(ester-ether-ester) triblock copolymers composed of PEG and lactones, D,L-lactide, or ε caprolactone were cross-linked with β-chitin to prepare SIPN hydrogels by the UV irradiation method (70). Triblock copolymers were synthesized using bulk polymerization with low toxic stannous octoate as catalyst or without catalyst. Photo-cross-linked hydrogels exhibited an equlibrium water content ranging from 60 to 77%. From differential

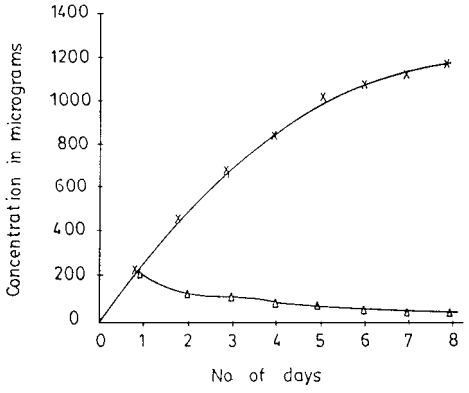



**Figure 4.** Release of ampicillin trihydrate from chitosan amine-oxide gel in phosphate buffer (pH 7.4).

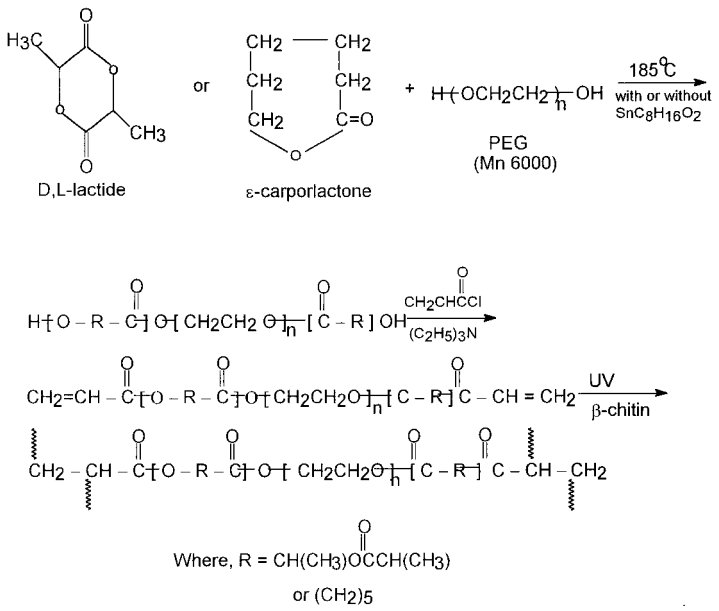



**Figure 5.** Synthetic scheme of PEGLM or PEGCM/$\beta$-chitin semi-IPNs.

scanning calorimetry (DSC) analysis, all the hydrogels revealed a drastic decrease in crystallinity after photo-crosslinking. In the swollen state, tensile strengths of the SIPN hydrogels ranked above 1 Mpa. In spite of their relatively high mechanical strength, elongation at break of swollen hydrogels ranged from 30 to 70%. Figure 5 shows the synthetic route of SIPNs composed of PEGLM or PEGCM and $\beta$-chitin. Vitamin A, vitamin E, and riboflavin were used as model drugs (71).

## Chitosan/Gelatin

Yao and co-workers (72) reported a novel hydrogel based on crosslinked chitosan/gelatin with glutaraldehyde hybrid polymer network. The pH-dependent swelling behavior and drug release performance of the polymer network were studied. Drastic swelling behavior of the gels in acidic solution is shown in Figure 6.

Levamisole, cimetidine, and chloramphenicol were used as model drugs. In a comparative study of the pH-dependent release of cimetidine (Fig. 7), levamisole and chloramphenicol from the gel was reported (72). The results reveal that the drug delivery is controlled by diffusion and relaxation processes, whereas the diffusion coefficient and relaxation time are highly dependent on the pH level of the medium. Moreover, the drug solubility in water obviously has an influence on the release (72).

## Chitosan and D,L-Lactic Acid

Graft copolymerization is one of the best methods to bring together synthetic and natural polymers to retain the favorable properties of natural polymers such as biodegradation and bioactivity. Qu and co-workers (73) used lactic acid and water-soluble chitosan with a degree of deacetylation (DD) of 88% to synthesize the graft copolymers with hydrophobic synthetic side chains and hydrophilic natural main chains by direct polycondensation without using catalysts. The formation of hydrogels is explained with

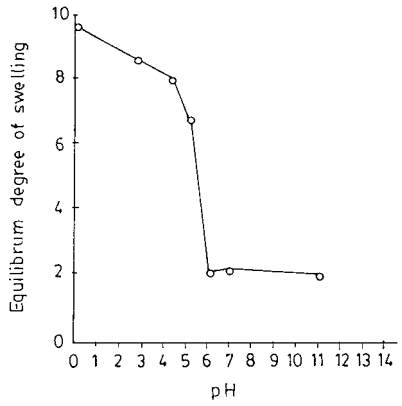



**Figure 6.** Swelling behavior of gel at different pH levels, ionic strength, $I = 0.1$ M; temp. 37°C.

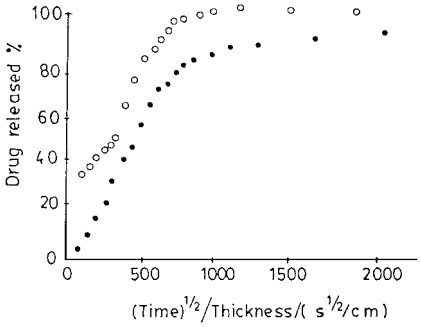



**Figure 7.** Cimetidine release performance from drug-loaded matrix of chitosan/gelatin hydrogel in different pH buffers at 37°C. ○ indicates pH 1.0; ● pH 7.8.

hydrophobic polyester side chains interactions serving as pseudocross-links, which stabilize hydrogel-forming molecules against permanent deformation in buffer. The specific solution content of hydrogels decreased when the pH values of buffers were increased, and this change in swellability is reversible. These pH-sensitive hydrogels have potential use in biomedical application such as controlled-release systems (73).

### Monolithic Gels

Diffusion through polymers is influenced not only by polymer structure, but also by the molecular structure of the solute. Solute structure may also influence the rate of partitioning into the elution medium. However, there is little relationship among the interrelationship of these factors. The influence of gel structure on the diffusion characteristics of solutes through poly(2-hydroxyethyl methacrylate) (poly HEMA) hydrogels has been reported (74). The nature of the water within the gel and the average pore size of the network influenced the diffusion mechanism. Sorption of solutes was reported to have marked affect on network structure (75). Wood and co-workers (76) investigated the in vitro and in vitro release kinetics of some structurally related benzoic acids from both monolithic and laminated poly HEMA gels. The influence of the physical structure of the polymer network, solubility, concentration, molecular weight of the solute, and presence of a rate-controlling barrier at the surface of the matrix have been investigated (76). Zero-order rates of release were achieved by lamination of a rate-controlling barrier to the polymer and the release rate modified through changes in the cross-linking density of the barrier layer (76).

### Starch-Based Thermoplastic

A potential alternative to the currently used materials is starch-based polymers, which are well known biodegradable materials (77). Recently, these materials have been proposed for possible use as biomaterials (78,79). Their good mechanical properties and appropriate degradation behavior (78) make them strong candidates for future biomedical applications. The development of new biodegradable hydrogels, based on corn starch/cellulose acetate blends, produced by free-radical polymerization with methyl methacrylate monomer (MMA) and/or acrylic acid monomer (AA), is reported (77). The polymerization was initiated by a redox system consisting of a benzoyl peroxide and 4-dimethylaminobenzyl alcohol at low temperature. Swelling studies were carried out, as a function of pH and temperature, in buffered solutions. Tensile and compression tests and dynamic mechanical thermal analysis were used to assess the mechanical performance of the developed materials. The developed materials are pH-sensitive, showing a clear reversible transition in a relatively narrow interval of pH, which is just in the range of physiological conditions. Fickian-type diffusion is the mechanism predominant in these systems, except for the composition with a higher concentration of AA that corresponds to the most desirable kinetical behavior for controlled release (case II-transport mechanism). Furthermore, the results obtained in the mechanical tests are is the range of those reported for typical PMMA bone cements, showing that it is possible to develop partially degradable cements with an adequate mechanical behavior (77).

## FILMS AND MEMBRANES

The choice of polymers suitable for forming the carrier film matrix and the barrier film were dictated by several factors as follows:

1. Compatibility with the gastric environment
2. Polymer stability during the time of complete drug delivery
3. Appropriate mechanical properties, i.e., capability of forming self-supporting films when containing the drug at high loading
4. Nonappreciable swelling in water and having a softening point above 37°C
5. Ease of fabrication
6. Cost

Several polymers were found to fit all or most of the above criteria and were used to prepare the carrier films. Polymers, such as ethyl cellulose, poly($\gamma$-benzylglutamate),

poly(vinylacetate), cellulose acetate phthalate, and copolymer of methylvinylether with maliecanhydride, were used. In addition to the base polymers, plasticizers were often needed to impart a suitable degree of flexibility. Platicizers, which were found to be compatible with the polymeric materials, include acetylated monoglycerides, esters of phthalic acid such as dibutylphthalates and dioctyllphthalate, D-sorbitol, diacetin, triacetin, dibutyltartarate, and others. An excipient was usually incorporated into the matrix of the carrier films. The excipients used were water-soluble materials that, as they dissolved, created channels in the polymer matrix and facilitated diffusion of the drug. Polyethylene glycol (PEG) of different molecular weights was used for this purpose.

The barrier or rate-controlling films were in general somewhat more permeable to water than were the carrier films. The materials used for this purpose consists of a base film-forming, water-soluble polymer in combination with at least one hydrophilic component such as hydroxypropylmethylcellulose or polyvinylpyrrolidone. The polymers used were the same as those for the carrier films. Some recent developments are discussed below.

**Cross-Linked Gelatin Films**

Bioadhesive materials that can adhere to soft tissues have potential medical applications. For instance, controlled drug delivery through mucous membranes, such as buccal, rectal, and vaginal mucus, requires such bioadhesive materials. Some transmucons drug-delivery systems have been commercialized using a mixture of hydroxypropyl cellulose and carbopol 934 (80) and carboxy vinyl polymer (81), which are reported to be adhesive to natural tissue. When damaged, abdominal, tendon, and pericardial tissues tend to form adhesions with the surrounding tissue, causing impairment of their function. In these cases, to prevent tissue adhesion we need biomaterials that can temporarily cover the wound site until tissue healing is complete. An antiadhesive material was recently commercialized as Seprafilm®. It is made of a mixture of hyaluronic acid and carboxymethyl cellulose, and it is claimed that it will adhere well to tissue and moist surfaces without suturing (82). Most of the biomaterials used for these purposes contain many ionizable groups, mainly carboxyl groups, which are able to adhere to soft tissues without sutures and adhesives, probably through hydrogen bonding between the carboxyl group of the biomaterials and the amino or hydroxyl group of the micous molecules. However, it has been recognized that the bonding strength is low and becomes lower when the biomaterials are swollen with water (83).

More recently, Matsuda et al. (84) reported a procedure for preparing strong bioadhesive gelatin films by introducing free aldehyde groups that can form covalent bonding through a Schiff's base formation with amino groups of biological soft tissues. Gelatin was selected because of its high biodegradability and its long history as a biomaterial. The free aldehydes originated from the dangling aldehyde group of the glutaradehyde (GA) used for the cross-linking of gelatin film. It is highly possible that some of the GA molecules used for the cross-linking of gelatin make use of one of the two aldehyde groups for a Schiff's base formation with an amino group of gelatin and leave the other aldehyde group unreacted because of steric hindrance.

In the procedure, gelatin films were treated with 0.5 M of GA solution at 60°C, and free aldehyde groups (up to 150 mmol/g) were introduced in the film. The bonding strength of GA-cross-linked gelatin films with biological tissue was assessed using porcine skin. It was found that bonding strength increased with increasing aldehyde content in the film. The GA-gelatin films had a bonding strength as high as 250 gf/cm$^2$, whereas the native gelatin film showed bonding strength of 40 gf/cm$^2$. When the aldehyde groups introduced in the gelatin films were quenched with glycine or reduced by $NaBH_4$, the films no longer demonstrated such high bonding strength (84). These facts suggest that a Schiff's base was formed between the free dangling aldehyde in the GA gelatin films and the amino groups of the natural tissue, which contributed strongly to a marked bioadhesion (84).

**Polymer Film Composites**

One of the earlier reports describes a flexible, sustained-release polymer drug-delivery composite film device for oral administration, which could be dispensed and administered in a compact form that extends in the stomach to remain buoyant (85). The author claimed that the film was suitably marked for facile measurement of prescribed medical dosage according to length (85). The drug-delivery system described was a multilayered polymeric composite film consisting of two essential components. The first of these was a carrier film containing the active agent dispersed or dissolved in the matrix. The drug could be dispersed homogeneously in the matrix, but a better control rate was obtained when the concentration of the medicament was increased from the outer wall to the interior of the film. The second essential component was the barrier film(s), which was placed on one or both surfaces of the carrier film. Ordinarily, it did not contain any drug but served to control the rate of release of the

active agent. In addition, the barrier film provided buoyancy of the drug-delivery system by entrapping air in small pockets or bubbles between it and the carrier film. Antiasthmatic agents theophylline and guinidine gluconate were used as model drugs (85). The films were cut to $2.1 \times 14$ cm$^2$, pleated or rolled, and inserted into hard gelatin capsules. In vitro measurement of release rate profile was performed using the USP-2 dissolution system with 900 mL 0.1 N HCl. In vivo gastric residence time determinations were performed on beagle dogs. The results indicated that the sustained-release device did open up or unfold in the stomach of beagles and that gastric residence time (mean, 6.5 hr) was considerably longer than that of controls (mean, 2.5 hr). Pharmacokinetic studies showed that the bioavailability of these drugs in vivo was constant during the release period (85).

### Cross-Linked Chitosan/Poly(Vinyl Alcohol) Membranes

The ability of chitosan to swell in water into a soft rubbery consistency resembling body tissue may enhance its biocompatibility (86) and makes it a good matrix for hydrophilic pharmaceuticals, which permeate only poorly in silicone matrices popularly used for drug delivery (3).

Nakatsuka and Andrady (87) proposed a mechanism for small-molecule transport across chitosan matrices and also determined the effect of cross-linking and blending with compatible synthetic polymers on the permeation characteristics. Vitamin B-12 was used as a model drug. Variation of the diffusion coefficient, the partition coefficient, and the swelling ratio with cross-linking and blending of chitosan with poly(vinyl alcohol) were the highlights of their investigations (87).

### Acrylic Acid Grafted Poly(Vinylidene Fluoride) Membranes

Lee and Shim (88) reported on the grafting of acrylic monomers onto porous polyurethane and polyamide membranes for pH- and temperature-sensitive membranes prepared by chemical UV and plasma initiation methods. However, no reports were available to determine the size of the graft chain, which may affect the permeability of the solute on changing pH or ionic strength of the solution for the following reason: the porous base membrane was not soluble in polar aprotic solvent such as dimethyl formamide (DMF), which is essential for determining the content of functional groups.

In their modified procedure, Lee and Shim (89) grafted acrylic acid onto the surface of commercial poly (vinylidene fluoride) (PVDF) membrane using plasma polymerization techniques. The effects of graft density or degree of polymerization (DP) of the graft chain on the pH-dependent permeability of riboflavin as a model drug through poly(acrylic acid) (PAA)-$\gamma$-PVDF membrane were examined Graft reaction was confirmed by x-ray photoelectron spectroscopy (XPS) spectra and attenuated total reflectance Fourier transform infrared spectra. Grafting rate was found to depend on plasma exposure time. For organ plasma at 30 w, grafting rate decreased after maximum rate was observed at 30 sec exposure. PVDF membrane with 30-sec plasma exposure and subsequently grafted with acrylic acid (AA-3) showed the greatest $O_{18}/F_{18}$ area ratio in XPS spectra. Thus its graft density and degree of polymerization were the largest among the graft membranes. Permeation of riboflavin through all poly(acrylic acid)-g-PVDF membranes showed a decrease in permeability of riboflavin at a pH level of 4 to 5 (89).

### Polyelectrolyte Complex Films of Chitosan and Gelatin

Polyelectrolyte complexes (PECs) are formed by the reaction of a polyelectrolyte with an oppositely charged polyelectrolyte in an aqueous solution (discussed in the section "Polyelectrolyte Complex Gel from Chitosan and *k*-Carrageenan"). Polysaccharides, which have bulky pyranose rings and a highly stereoregular configuration in their linear back bone chains, have frequently been studied. PECs have numerous applications, such as membranes and medical prosthetic materials, etc., and are discussed in previous sections of this article.

Yin et al. (90) prepared a series of chitosan-gelatin complexes by varying the ratio of constituents. IR and x-ray results demonstrate those optimum interactions between chitosan and gelatin to exist over a certain ratio range. The results indicate that the water uptake of a chitosan-gelatin complex is depressed by strong interactions within the networks. The authors claimed that chitosan can improve the tensile strength of complex films and that even with high water content, it can keep appropriate tensile strength and higher elongation (90). The application of these membranes is not reported in their studies.

### Transdermal Devices

The transdermal route has been recognized as one of the primary routes of systemic drug delivery. Extensive studies have been carried out to provide drugs through this route (91). Transdermal drug-delivery systems (TDS) are polymeric patches containing dissolved or dispersed drugs

that deliver therapeutic agents at a constant rate to the human body. The simplest type of such systems contains a drug dissolved in an adhesive that is applied to an impermeable backing membrane. This composite matrix is attached to a release liner. Although this type of delivery device is structurally simple, it places multiple requirements on the adhesive with respect to adhesion, drug storage, and release. Several incidences of crystallization of drugs have been reported during typical storage periods of these devices (92,93). The presence of crystals can pose several problems in the performance of transdermal systems. The release of the drug form the patch will be affected by the relative rates of dissolution of the crystals into the solution phase of the drug and diffusion of the dissolved drug through the adhesive (94). Furthermore, the possibility of the existence of a modified chemical form of the drug leads to concerns about the effectiveness of the transdermal device in delivering the correct therapeutic agent.

The only study in the literature that addresses the question of identifying the chemical structure of the crystals in transdermal systems was the Raman spectroscopic study on an estrogen patch, which was concerned primarily with mapping the distribution of the drug inside the adhesive (95). This mapping was carried out on a certain area of a patch, and no effect was taken to analyze the distribution of crystals along the thickness of the patch, which could be critical in terms of delivery kinetics. The researchers were able to identify a few crystals as those of a modified form of estradiol. Several techniques have been used to identify and characterize crystals in other drug-delivery systems. For example, x-ray diffraction was used to quantify the presence of drug in an amorphous matrix (96), and NMR (97) and IR spectroscopy (98) have been used to characterize oral dosage forms and drug dissolved in patches, respectively. However, NMR has limitations in terms of sampling problems, and the latter technique is not sensitive to crystallinity.

During the final stages of developing a synthetic formulation for a new drug entity, great emphasis is placed on obtaining material of high purity and reproducibility of its physical, chemical, and biological properties. If the dosage form is for oral delivery (i.e., tablets), every effort is made to ensure a high degree of crystallinity wherein the molecules have regular and well defined molecular packing. In contrast to oral delivery, transdermal delivery requires that the active substance (drug) be in the amorphous solid-state solution in transdermal patches. Typically, amorphous solids exhibit a short-range order over a few molecular dimensions and exhibit a physical property quite different from that in the crystalline state. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability (99), which are desirable characteristics in transdermal patches. This gives credence to the efforts taken to preserve drugs in the amorphous/dissolved state in adhesives used in transdermal systems.

Molecules in the amorphous state are thermodynamically metastable relative to the crystalline phase. This property creates an opportunity for crystallization during storage and handling of the pharmaceutical product, the occurrence of which has been observed in postcompression hardening of tablets (100), particle aggregation in dry powder inhalers (101) and transdermal patches, etc. Thus it would appear important to anticipate conditions that gives rise to crystallization and to be able to inhibit it if so desired.

The coexistence of two thermodynamically different states (crystal/amorphous) in a TDS may result in (1) significant structural heterogeneitics and (2) batch-to-batch variation is physical properties. This heterogeneity could result in one of these phases acting as a focal point for spontaneous phase transitions, such as crystallization (102). Furthermore, the presence drugs in polymers in either the dissolved or the precipitated state could significantly affect the properties of the polymer, such as glass transition. This has been observed in salicylic acid and chlorpheniramine maleate (CPM) dispersed in a polymethacrylate amino ester copolymer (103); in lidocaine, ketoprofen, and aminopyrine in acrylic and acrylic/rubber (polyisobutylene) copolymers (104); and in polyvinylpyrrolidone and adsorbed water (105).

More recently, Variankaval and co-workers (106) used a variety of characterization tools to determine the physical and chemical nature of the precipitates formed in situ in estradiol patches. Optical microscopy revealed that crystals were formed in a single layer inside the adhesive matrix and that there were two distinctly different morphologies: needle-like crystals and aggregates around the needles. From IR measurements, it was evident that estradiol probably was present in more than one crystal form in these patches. Raman microscopy showed that the needle-like crystals contain the adhesive component and the aggregates some modified crystal form of estradiol, indicating that in addition to the drug, the polymeric adhesive also crystallize during storage (106).

Thacharodi and Rao reported permeation-controlled transdermal drug-delivery systems using chitosan (107–109). Studies on propranolol hydrochloride (Prop-HCl) delivery systems using various chitosan membranes with different cross-link densities as drug release-controlling membranes and chitosan gel as the drug reservoir were performed. The physicochemical properties of the

membranes have been characterized, and the permeability characteristics of these membranes to both lipophilic and hydrophilic drugs have been reported (107,108). In vitro evaluations of the TDS device while supported on rabbit pinna skin was carried out in modified Franz diffusion cells (108). The in vitro drug-release profiles showed that all devices released prop-HCl in a reliable, reproducible manner. The drug release was significantly reduced when cross-linked chitosan membranes were used to regulate drug release in the devices. Moreover, the drug-release rate was found to depend on the cross-link density within the membranes. The device constructed with chitosan membrane with high cross-link density released a minimum amount of drug. This is attributable to the decreased permeability coefficient of the cross-linked membranes resulting from the cross-link point. Apart from these reported studies, the following points should be taken into consideration while fabricating a TDS.

The major limitations of this TDS route are difficulty of permeation of drug through human skin and skin irritation (91). Studies have been carried out to find safe permeation enhances to improve the transdermal flux of drugs (110).

Rajendran et al. (111) investigated a modified matrix system for the in vitro delivery of terbutaline sulfate through excised guinea pig skin, using non-ionic surfactants as permeation enhancers. Eight non-ionic surfactants were used as permeation enhancers. The flux of terbutaline sulfate from transdermal patches containing any of the selected non-ionic surfactants or without surfactants was determined using Keshary-Chein cells. Among the spans used, span 80 produced the highest permeation of the drug. Of the Tweens used, Tween 80 produced the highest permeation of the drug. Adequate levels of transdermal permeation were observed by them (111).

## TABLETS

Many direct-compression diluents have been reported, but every diluent has some disadvantages (112). Crystalline cellulose (MCC) has been widely used as a tablet diluent in Japan. For their versatility, chitin and chitosan were reported to be useful diluents for pharmaceutical preparations (113,114).

### Chitosan Tablets

Sawayanagi and co-workers (115) reported the fluidity and compressibility of combined powders of lactose with chitin (lactose/chitin) and with chitosan (lactose/chitosan) and of potato starch with chitin (potato starch/chitin) and with chitosan (potato starch/chitosan). To develop direct-compression diluents, the disintegration properties of tablets made from these powders were studied in comparison with those of combined powders of lactose with MCC (lactose/MCC) and potato starch with MCC (potato starch/MCC).

From their investigations, it appears that the fluidity of combined powders with chitin and chitosan was greater than that of the powder with crystalline cellulose. The reported hardness of the tablets follows the order chitosan tablets > MCC > chitin. In the disintegration studies, tablets containing <70% chitin or chitosan have passed the test. Moreover, the ejection force of the tablets of lactose/chitin and lactose/chitosan was significantly smaller than that of lactose/crystalline cellulose tablets (115). However, no reports were available on CDR formulations using these tablets.

Recently, Mi et al. (116) reported chitosan tablets for controlled release of theophylline. To control the swelling and erosion rate of the chitosan tablets in acid medium, alginate was used as an anionic polyelecrolyte. Nuclear magnetic resonance imaging microscopy was also introduced to examine the swelling/diffusion mechanism of various tablets (116).

### Ethylcellulose Matrix Tablets

Ethylcellulose (EC) is an inert hydrophobic polymer that has been studied substantially for its application as a matrix-forming material in direct compression tablets. Direct compression is the preferred method of manufacture for producing tablets intended for immediate or sustained release. There have been reports on the compressibility and compatibility of EC (117) and on its use as a matrix-forming material in direct compression tablets for delivery of soluble and poorly soluble drugs (118).

Tablet hardeners (117,118), particle size of the polymer (117–119), and viscosity grade (118) were observed to directly affect the drug-release rate. It was noted that tablet hardness affected the dissolution half-life more profoundly than did the viscosity grade (118). Lower viscosity grades were more compressible and allowed a wider range of tablets hardness, and thus dissolution rates, for theophylline and indomethacin (118). It was found that there is apparently a limit to the tablet hardness that could be obtained by an increase in compression force when a particular viscosity grade is used (117). A major problem associated with hydrophobic matrix tablets is the reduction in the terminal release rate. The erosion of the EC matrix over time can serve to reduce this problem (118).

The mechanism of drug release appeared to be simple diffusion from an EC matrix tablet, and the data could be adequately described by the Higuchi square root of time relationship for water-soluble pseudophedrine hydrochloride at 12.5 to 25% drug loading (120). Release of slightly soluble theophylline or practically insoluble indomethacin from such tablets at 50 or 25% drug loading, respectively, was described by diffusion with polymer relaxation and erosion contributions to the release mechanism (121).

More recently, investigations were carried out to analyze the release data from EC matrix tablets to determine which release equation provides the best fit to the data and to observe the effect of drug solubility on the release mechanisms (122). Tablets were prepared by direct compression of drug, EC, and lubricant is an appropriate mass ratio to achieve a high and lower drug loading. Theophylline, caffeine, and dyphylline were selected as nonelectrolyte xanthine derivatives with solubilities from 8.3 to 330 mg/mL at 25°C. Drug release studies were conducted in 37°C water with UV detection at 272 nm. Several equations to characterize release mechanisms were tested with respect to the release data. Drug diffusion, polymer relaxation, and tablet erosion were the mechanisms considered. The Akaike Information Criterion was also considered to ascertain the best-fit equation. At high drug loading, drug released by a diffusion mechanism with a rate constant that increased with an increase in aqueous stability. At low drug loading, polymer relaxation also became a component of the release mechanism; however, its contribution to drug release was less pronounced as solubility decreased, becoming negligible in the case of theophylline (122). At each drug loading, an increase in drug solubility resulted in an increase in the dissolution rate, but this did not change the best-fit release model (122).

### Hydroxypropylcellulose (HPC) Tablets

Cellulose ethers are hydrophilic polymers that are widely used as pharmaceutical exipients (123). They are generally considered to be stable in the solid state when kept in closed containers under normal environmental conditions (124), and the norms established by official pharmacopoeias for their storage are accordingly not particularly stringent. The United States pharmacopoeia (125) and British Pharmacopoeia (126) merely require that they can be stored in closed containers, without specifying additional measures for prevention of water uptake or microbiological contamination. The microorganisms most frequently isolated from pharmaceutical raw materials are those with very frugal nutrient requirements and good tolerance to dryness, notably *Bacillus*, *Streptococcus*, Gram-negative bacteria, yeasts, and molds (127). The risks they pose to the integrity of cellulose ethers have hitherto received little attention (128), even though cellulose ethers with a moderate degree of substitution are often used in culture media for cellulase-producing fungi and bacteria because they constitute a suitable source of carbon for these microorganisms (129). The importance of the risk of excipient contamination derives from the likelihood that it will significantly alter the properties of the dosage forms in which the excipient is subsequently incorporated (127,130).

Alvarez-Lorenzo and co-workers (131) studied the stability of several varieties of HPC during long-term storage, concentrating on the properties that are most important for their use as pharmaceutical excipients. Drug-release properties of direct compression tablets formulated with the affected HPC were also investigated. Theophylline was used as a model drug in their studies. The stability of several varieties of HPC was monitored during 3 years of storage under the conditions recommended by manufacturer and official pharmacopoeias (simple storage include containers) and at zero relative humidity. After 1 year, severe degradation of the varieties with lower initial pH levels and particle size stored at ambient relative humidity was shown by changes in their molecular weight and in pH level and apparent viscosity of 2% aqueous dispersions. Microbiological analysis showed the observed degradation to be attributable to the action of fungi of the genus *Rhizomucor*. The changes in apparent viscosity significantly affected the release of theophylline from direct compression tablets formulated with the degraded excipients (131).

## MISCELLANEOUS

### Chitosan-Lipid Emulsions

Positively charged systems are receiving more attention as novel colloidal drug carriers for various potential therapeutic applications. Groth et al. (132), and Cortesi et al. (133) reported a novel use of cationic liposomes to target DNA into the cell nucleus, and this allows the replacement of the defective gene product and thus restores the normal cell function. Furthermore, it is well known from emulsion and liposomal studies that the surface charge and the size of the colloidal carrier may effect the biofate of a drug in various organs of the body after i.v. administration. Moreover, in many papers Benita and co-workers (134,135) showed the possibility of producing stable positively charged submicron emulsions, which are assumed to display several advantages. Davis

et al. (136) suggested that positively charged emulsion droplets can behave differently when introduced into the bloodstream, to normal (negatively charged) fat emulsion droplets with respect to the uptake of plasma blood components and opsonic factors. Therefore, positively charged systems may alter the pharmacokinetic profile of the incorporated drugs, resulting in a possible drug targeting with enhanced local drug concentration in the organs (136).

It would also be interesting to explore the intrinsic effects of the positively charged emulsions in accessible organs such as skin cornea, which is known to carry a net negative charge (137,138). So far, all positively charged submicronized emulsions were based on a mixture of phospholipids with Poloxamer and stearylamine as a cationic emulsifier. Unfortunately, stearylamine showed a high toxicity against the tested cell systems in vitro (139). This cytolitic and cytotoxic activity limits the utilization of the advantages of these systems as drug-delivery carriers (139).

Jumma and Muller (140) reported physicochemical properties of chitosan-lipid emulsions and their stability during the autoclaving process. The intent of this investigation was to formulate a stable positively charged emulsion with a nontoxic cationic polymer (chitosan) resulting in improved emulsion systems for drug delivery. The experiments were carried out and optimized using an experimental design to estimate the appropriate concentrations of chitosan and the non-ionic surfactant F68 (ABA block copolymer). A mixed film consisting of the ABA block copolymer and chitosan molecules was formed at the o/w interface with an overall positive surface charge. Conversely, a combination of chitosan with phospholipids and/or with a mixture of phospholipids with ABA block copolymers showed a phase separation during autoclaving. A chitosan type with a low viscosity was used, which was intended for possible use in ocular and parenteral applications. An experimental factorial design $3^2$ was used to investigate the effect of chitosan and F68 concentration on the physicochemical properties of the system and consequently their influence on the stability of emulsions during autoclaving. Both size and surface charge of emulsions were significantly affected as a function of the chitosan concentration. They could achieve formulation with a mean particle size of 125 to 130 nm and with a positive surface charge of 20 to 23 mV. Moreover, the chitosan emulsions were autoclaved without a significant change in their particle size. It was concluded from their investigations that the increasing concentration of chitosan needs a higher amount of F68 to achieve stable emulsion during autoclaving because of the interaction between the positively charged chitosan and the negatively charged free fatty acids, which are contained in the oil phase (castrol oil) (140).

### Poly(DI-Lactide-*co*-Glycolide)-Methoxypoly(Ethyleneglycol) Copolymers

The application of block copolymers of biodegradable poly(lactide) (PLA) and poly(lactide-*co*-glycolide) (PLGA) with poly(ethylene glycol) (PEG) in controlled drug delivery and drug targeting has been proposed (3). Triblock copolymers PLA-PEG-PLA and PLGA-PEG-PLGA form more hydrophilic matrices than do PLA and PLGA and are considered more suitable for controlled delivery of proteins (141). Also, diblock PLA-MPEG and PLGA-mPEG copolymers (mPEG, methoxypolyethylene glycol) have been used in the preparation of nonoparticles, exhibiting prolonged residence in systemic circulation after intravenous administration and therefore having potential as targeted drug carriers (142). These polymers are not yet commercially available. The synthesis of PLA-PEG-PLA triblock copolymers has been studied (141), and a coordinate reaction mechanism has been proposed for the polymerization catalysed by stannous octoate (143). Relatively few reports appear to exist on the synthesis of PLGA-mPEG diblock coploymers (144). Moreover, of these studies deal in a systematic way with the effect of the conditions of preparation on the properties of the prepared PLGA-mPEG-copolymers.

Belesti et al., (145) reported a systematic study of the effect of certain preparative variables, such as the composition of the feed and the polymerization time and the polymerization temperature, on the yield of the polymerization and on the properties of the resulting PLGA-mPEG-copolymers. The results with regard the molecular weight and yield were discussed in relation to a polymerization mechanism proposed recently by Du et al. (143). It was found that the higher the PEG content of the feed, the lower the molecular weight of the copolymer and the yield of the reaction. The breadth of the molecular weight distribution decreased initially with time but appeared to stabilize later at low values. Both the ethylene oxide content and the lactide to glycolide molar ratio in the copolymer appear to depend on the reaction temperature and varied with reaction time. From their investigation, it is clear that PLGA and mPEG are partially miscible and that copolymers containing approximately 40% mol or higher ethylene oxide exhibit crystallinity (145).

**Polymer-Based Gene Delivery Systems**

The use of poly(2-dimethylamino)ethylmethacrylate (PDMAEMA) was reported as an efficient nonviral transfectant (146,147). This polymer is able to bind electrostatically to plasmids yielding polymer-plasmid complexes. It was found that the size of the complexes formed was a dominant factor for the transfection efficiency. The highest transfection efficiency was observed at a poymer/plasmid ratio of 3 (w/w) and average molecular weight of the polymer $>250$ KDa. Under these conditions, particles between 0.15 and 0.25 $\mu$m and a slightly positive $\xi$-potential were formed. However, the complexes have a limited stability in aqueous solution owing to possible chemical and physical degradation processes. In additional studies, to preserve the size and transfection potential of polymer-plasmid complexes, Cherng and co-workers (148) used freeze-drying and freeze-thawing for stabilization of the complexes. It was found that the concentration of the sugars is an important factor affecting both the size and the transfection capability of the complexes after freeze-drying and freeze-thawing. However, the type of lyoprotectant (sugar) used is of minor importance. In their studies, it was also shown that when damage to polymer-plasmid complexes occurs, it results from the drying process but is not caused by the freezing step (148).

**Polypeptides Containing $\gamma$-Benzylglutamic Acid**

Synthetic polypeptides continue to be of interest as drug-delivery platforms because of their capacity to be both biocompatible as well as biodegradable to naturally occurring biological products (149). The large number of amino acids along with their range of physical and chemical properties renders this class of polymers useful for the design of novel drug-delivery systems. By appropriate selection of amino acid residues and sequences, a variety of polypeptides can be designed to process varying degrees of hydrophobicity, structural attributes, and electrostatic properties. This feature offers the potential that those specific polypeptide polymers possessing the requisite physicochemical properties could ultimately be tailormade to yield optimum delivery for particular drugs. Two obstacles are commonly cited as limiting the suitability of polypeptides for drug-delivery applications: their biological degradation and their potential toxicity (149). A number of approaches have been reported addressing these potential pitfalls. Because of the stability of the amide backbone toward hydrolysis, the catalytic activity of native enzymes is usually relied on for polypeptide degradation (151). An alternative approach is to incorporate labile chemical bonds into polypeptide backbone, thereby introducing hydrolytic instability to the polymer chain. To this end; the synthesis of copolymers of amino acids with either $\alpha$-hydroxy acids (152) or anhydrides (153) has been described. The concerns over polypeptide toxicity are generally minimized by careful selection of amino acid residues and by limiting the number of different amino acids in the polypeptide backbone (149).

Although sometimes regarded as a liability, the stability of the polypeptide backbone toward hydrolysis could serve certain useful purposes. The enhanced stability of polypeptides can influence the mechanisms and kinetics of drug release by affecting the time scales over which both drug diffusion and polymer degradation occur (154). Drug release from hydrolytically labile polymers such as poly(D,L-lactide-*co*-glycolide) (PLGA) can proceed by both a diffusion-controlled mechanism (155) and a degradation-controlled mechanism (156). Thus, variations in polymer degradation rates could lead to irreproducible drug-release patterns thereby affecting both the efficacy and the toxicity profile of the drug therapy. In addition, the onset of polymer degradation could cause structural deterioration of the implanted device. As a result, the risk of dose dumping is increased should the partially degraded system collapse or retrieval be required when unexpected reactions occur during treatment. For these reasons, uncoupling the mechanism of drug release from polymer degradation would be a desirable alternative. Polypeptide polymers, which are less prone to hydrolysis and can thus provide structural integrity over a long period during which drug release may proceed through a diffusion-controlled mechanism, appear to be on outstanding choice.

Yang and co-workers (157) have done considerable work on polypeptide as drug-delivery platforms. One of their earlier findings demonstrated that simple changes in the ratio of hydrophilic to hydrophobic amino acid residues within the polypeptide backbone could modify the diffusion-controlled drug-release properties of such a material (158).

The synthesis of three modified polypeptides containing $\gamma$-benzylglutamic acid as the common structural backbone has been reported (157,158). Poly($\gamma$-benzyl-L-glutamine acid) (PBLG) was chosen as the model polypeptide in their studies because it contains a highly helical structure in the solid state. The structural attributes of this polymer were modified by random copolymerization of D-and L-isomers of $\gamma$-benzyl glutamic acid to produce poly($\gamma$-benzyl-D-L-glutamic acid) (PBDLG). In addition, the bulk polymer hydrophibicity of PBLG was modified

by polymerization of PBLG block (A) with a hydrophilic prepolymer block of PEG (B) to form an ABA triblock copolymer (PBLG-PEG-PBLG). The physicochemical properties of these synthetic polypeptides were characterized, and drug-release studies were performed using two model hydrophilic drugs, procainamide hydrochloride and protamine sulfate (157). PBDLG displayed a significantly slower release of procianamide compared with PBLG, whereas ABA triblock copolymer exhibited much faster release rates for both procianamide and protamine than those demonstrated by the other two polymers. The results indicate that by using ABA, protamine release rate ranging from 2 weeks to approximately 2 months were obtained by simply the varying the polymer-processing conditions and protein particle size. A nearly complete release of protein was obtained from ABA, and this occured without reliance on degradation of the polymer backbone (157).

### Aliphatic Polyanhydrides

Aliphatic polyanhydrides derived from fatty acids have been used as carriers for controlling drug delivery (159). The common aliphatic diacids in medically used polyanhydrides were sebacic acid (SA) and dimer erucic acid (FAD), with little attention to other diacid monomers of this series. The elimination of biodegradable polymer implants from the body involves the degradation of the polymer into water-soluble degradation products, which are carried away and excreted. Polyanhydrides are composed, in general, of sparingly water-soluble diacid monomers and thus elimination via dissolution may be a slow process. The elimination of copolyanhydrides of sebacic acid with 1,3-*p*-carboxyphenoxy propane [P(CPP-SA)] or with erucic acid dimer [P(FAD-SA)] have been extensively investigated. P(CPP-SA) (160) wafers implanted in the brain of rats and rabbits showed that the relatively water-soluble comonomer, SA (solubility in water, 1 mg/mL$^{-1}$), was eliminated within 1 week, leaving the less soluble comonomer CPP (0.01 mg/ml$^{-1}$) to be excreated over 4 to 6 weeks. Similarly, SA was released from poly[FAD-SA] implanted in bone within 2 weeks, whereas the FAD component was eliminated over a 3-month period (161). These studies indicate that solubilization of the degradation products in body fluids is a key parameter for the elimination of a biodegradable implant; however, a systematic study on this issue has not been reported. The effect of hydrolytic enzymes on the degradation rate of implanted polymers is essential for understanding the in vivo behavior of an implanted polymer matrix. The degradation of poly(lactide) and poly(glycolide) in the presence of several hydrolytic enzymes found around implants has been studied (162,163). Under the conditions used, bromelain and enzymes with esterase activity significantly influenced the polymer degradation. The effect of enzymes on the degradation of polyanhydrides was not studied.

Apart from these, Albertsson and Lundmark (164) prepared poly(adipic anhydride) (PAA), poly(sebacic anhydride) (PSA), and poly(dodecanoic anhydrides) (PDA), from the mixed anhydrides of diacids and ketene [in tetrahydrofuran (THF) solution] with the mixed anhydrides being subjected to melt polycondensation. The polymerization was carried out in the presence of diethylzinc as a catalyst.

Domb and Nudelman (165) studied biopolyanhydrides using a polymer series of linear aliphatic diacids with the following objectives: (1) to study systematically the effect of monomer solubility on the degradation and in vivo elimination of polyanhydrides, (2) to evaluate the use of linear aliphatic natural diacids as components in drug-delivery implants with increasing degradation rates, and (3) to determine the effect of common body enzymes on the degradation process of polyanhydrides. The polymer series are expected to degrade into monomer counterparts at approximately the same rate but differ in the water solubility of their degradation product. Polymers based on natural diacids of the general structure -[OOC-$(CH_2)_x$-CO]$_n$-, where x is between 4 and 12, were implanted subcutaneously in rats and the elimination of the polymers from the implant site was observed. The in vivo hydrolysis of this polymer series was studied by monitoring the weight loss, release of monomer degradation products, and content of anhydride bonds in the polymers as a function of time. A dependence was found between the monomer solubility and the rate of polymer elimination both in vitro and in vivo. It was observed that the elimination time for polymers based on soluble monomers ($x = 4$ to 8) was 7 to 14 days, whereas the polymers based on low monomer solubility ($x = 10$ to 12) were eliminated only after 8 weeks. The in vitro degradation of polyanhydrides in the presence of several common hydrolytic enzymes found around implants did not affect polymer degradation. Domb and Nudelman found these polymers as biocompatible and useful carriers for drug delivery.

In a similar manner, Teomin and Domb (166) reported a systematic study on the synthesis, characterization, degradation, and drug release of fatty acid terminated-poly(sebacic acid) PSA. Frankly, this approach may fall under a different subsection of fatty acid-terminated polyanhydrides. But owning to the basic end product

polyanlydrides, we feel discussing here. A second class of fatty acid-based polyanhydrides synthesized from nonlinear hydrophobic fatty acid ester, based on vicinoleic, maleic acid, and sebacic acid (discussed in detail in the following section), possessed desired physicochemical properties such as low melting point, hydrophobicity, and flexibility in addition to biocompatibility and biodegradability. The polymers were synthesized by melt condensation to yield forming polymers with molecular weights exceeding 50,000. The drug-release rate from these fatty acid-containing polymers was significantly slower, and a constant drug release for months was achieved. Similarly, in their procedure, fatty acid-terminated sebacic acid polymers were synthesized by melt condensation of acetate anhydrides of linear fatty acids (C8–C18) and sebacic anhydride oligomers to yield waxy off-white materials. Polymers with molecular weights between 9000 and 5000 were obtained for the 10 and 30% (weight ratio) containing fatty terminals, respectively. In up to approximately 30% of fatty acid terminals, the final product is mainly fatty terminated polymer, with up to approximately 5% w/w of the symmetric fatty anhydride. It is observed that increasing amount of fatty acid acetate anhydride in the polymerization mixture had little effect on the polymer molecular weight up to a ratio of 40:60 (fatty acid acetate: sebacic acid oligomer), which remains in the range of 5000 to 8000. Above this ratio, the molecular weight dropped to a level of 2000 to 3000, and the percent of the symmetric anhydride increased to 10 to 40%. Also from the Teomin and Domb investigations, fatty terminals had little effect on PSA melting and crystallinity. However, the fatty terminals had a significant effect on the polymer degradation and released the incorporated drug for more than 4 weeks compared with 10 days for the acetate-terminated PSA (166).

**Ricinoleic Acid-Based Biopolymers**

It is clear from the section "Aliphatic Polyanhydrides" above that the delivery of drugs form polyanhydrides has been studied extensively. Fatty acids are good condidates for the preparation of biodegradable polymers because they are natural body components (167), and their hydrophobicity allows them to retain the encapsulated drug for longer periods when used as drug carriers. However, the monofunctionality of fatty acids restricted them to serve as monomers for polymerization. As discussed in the previous section, fatty acids are converted to monomers by dimerization of unsaturated fatty acids such as oleic acid and erucic acid. Their homopolymers are viscous liquids; copolymerization with increasing amounts of sebacic acid (SA) forms solid polymers with increasing melting points (30 to 70°C) as a function of SA content. The in vitro and in vivo drug-release characteristics, toxicity, and elimination of these polymers have been reported (168). Poly(FAD-SA), prepared by mixing the drug in the melted polymers, has shown promising results in treating brain tumors in laboratory animals (169). The same polymer has been used for the delivery of gentamicin sulfate for the treatment of osteomyelitis (170). Gentamicin was released for a few weeks both in vivo and in vitro. Continuous glutamic acid stimulation of trigeminal motoneurons, using poly(FAD-SA) microspheres, showed a pronounced effect on the developing skeleton of growing rats (171).

Although these polymers were found to be suitable for drug delivery applications, in vivo studies in dogs showed that when implanted in muscle, the polymer degraded to the semisynthetic FAD monomers, which slowly cleared (6 months) from the implant site. This erucic acid-based FAD is not easily metabolized in vivo, probably because of C-C linkage between the two fatty acids.

Castor oil is a mixture of triglycerides, predominantly of ricinoleic acid (85 to 90%), that has an unusual structure such as a double bond present in the 9 position and a hydroxyl group in the 12 position (cis-12-hydroxyoctadeca-9-enoic acid). It is one of the few commercially available glycerides that contain hydroxyl functionality in such a high percentage of one fatty acid. The biochemical origin of ricinoleic acid arises from enzymatic hydroxylation of oleoyl-COA in the presence of molecular oxygen. This structure of ricinoleic acid affects the solubility and physical properties of castor oil. Reports are available on copolyesters of citric acid and castor oil synthesized by standard polycondenstation under vacuum at an elevated temperature using anhydrous $FeCl_3$ as the catalyst (172,173). Release studies were conducted using sulfadiazine (172) and paracetamol (173) as model drugs, and zero-order release was observed.

Teomim et al. (174) reported synthesis of ricinoleic acid and hydrogenated ricinoleic acid (hydroxy stearic acid)-based monomers, which were synthesized from the attachment of a carboxylic acid side chain via a hydrolyzable ester bond to the hydroxyl group (succinic acid/maleic acid). These monomers were copolymerized with sebacic acid and tested for their suitability as drug carriers (174). In vitro studies showed that these polymers underwent rapid hydrolytic degradation in 10 days. Moreover, methotrexate release from the polymers was not affected by the initial polymer molecular weight in the range of 10,000 to 35,000. From their studies, it appears that the in vitro drug release correlated with the degradation of the polymers, and the fatty acid ester monomers were further degraded

to their counterparts, ricinoleic acid and succinic/maleic acid.

### Polysiloxanes

Silicone elastomers have long been known for their exceptional ability to exhibit and retain mechanical properties over a broad temperature range. The main interest in these materials stems from the fact that they possess unique properties, such as good low-temperature flexibility, excellent electrical properties, water repellency, and chemical and physiological interests combined with biocompatibility not common in hydrocarbon polymers (175). Owing to its outstanding properties, the poly(dimethylsiloxane) (PDMS) elastomer has established itself as a well known biomaterial, and it has had a long history of biomedical applications. Currently, silicone elastomers have become indispensable for many controlled drug-delivery systems. The suitability of this system for controlled-release coating is primarily dependent on the permeability of silicones to various drug molecules (176). PDMS is popularly used to manufacture marketable devices for long-term administration of steroidal drugs. In the past decade, much effort has been made to demonstrate that monolithic matrices based on this material are apt to release water-soluble drugs and proteins at controlled rates (176). The research was focused on prolonged release systems with a potential to be implanted or inserted into body cavities. In vitro release of number of drugs, chlorphenramine maleate, pseudopheradrine hydrochloride, dextromethorphan hydrochloride, papaverine hydrochloride, clonidinehydrochloride, and salicylamide have been studied for oral applications using PDMS as a matrix material. The reported literature suggested that controlled release-rate studies have been carried out using only PDMS as matrix materials.

Gupta and co-workers (177) reported the efficacy of polysiloxanes as matrix materials for slow release of PAM-Cl, an antidote against organophosphorous poisoning. The effect of viscosity of polysiloxiane matrices on in vitro release rate of PAM-Cl and the time taken for 80% PAM-Cl release was also studied. In their additional studies, they have synthesized a number of polysiloxanes and their copolymers by hydrolytic ploycondensation of dialky(ary) dichlorosilane or their mixtures in a saturated solution of NaCl in water at low temperature (0 to 5°C). These polysiloxanes were characterized by intrinsic viscosity and infrared and nuclear magnetic resonance spectroscopy. 2-Pyridine aldoxime-chloride (PAM-Cl) was incorporated into these polysiloxanes, followed by cross-linking with tetraethoxy-silane using dibutyltindilaurate as catalyst. The effect of pH level on in vitro release rates of PAM-Cl from polysiloxane matrices ultraviolet spectrophotometer. Transport parameters such as the order of release and diffusion coefficients for these systems (polysiloxane-PAM-Cl) were also reported (177).

### Water-Soluble Polyamides

Neuse and co-workers (178) have extensively studied water soluble polyamides as potential drug carriers. Some interesting features of their studies include the grafting of poly(ethylene oxide) (PEO) chains onto drug carrier-type polyaspartamides, with a view to increase the carriers hydrophilicity, reduce immunogenicity, and enhance resistance to both protein binding and to capture by reticutoendothetal system with concomitant prolongation of residence time in serum circulation. Such features have proved to be of biomedical importance. In addition to the PEO grafts, the polymer contained amine-functionalized side groups for drug conjugation. With these amine functions linked to the polymer backbone by very short (less than 10 atomic constituents) spacers, and attached drug species would reside in close proximity to the main chain and remain embedded in the protective layer of PEO "tentacles" surrounding the backbone. Although this spatial arrangement offers certain pharmacokinetic advantages, it also creates difficulties associated with poor accessibility of the biofissionable polymer-drug tether to proteolytic enzyme instrumental in the interacellular (lysosomal) release of the drug from the carrier (178).

### PTMC-PAA Blends

Blending provides a neat and smooth means of combining desirable properties of different polymers. Biodegradable matrices with new combinations of polymer properties and modification of drug-release profiles can thus obtained (153). The use of degradable polymers has been favored because they eliminate the need for surgical removal after depletion. Linear aliphatic polycarbonates such as poly(trimethyl carbonate) (PTMC) have shown to be suitable for these application by being biocompatible and degradable by simple hydrolysis, promoted in vivo by enzymatic activity. PTMC displays high elasticity at room temperature but degrades slowly in aqueous solution, showing little molecular weight loss, sample weight loss, or change in morphology after several months. Attempts have been made by changing the chemical composition by copolymerization of TMC with $\varepsilon$-caprotactone or

D,L-lactide or by blending PTMC with other degradable homopolymers (179). In additional studies, Edlund and Albertsson (180) described the copolymerization in bulk and solution of trimethylene carbonat (TMC) with adipic anhydride (AA) as well as the blending of homopolymers. Drug delivery from the blends were evaluated. They proposed a statistical factorial model to explore the influence of three important blend parameters and their interactions to predict the erosion and drug-release behavior of the blend matrices. It was found that the PAA:PTMC ratio and molecular weight of the polycarbonate component significantly influence the drug-release performance, mass loss, and degree of plasticization. The interaction among these factors is expected to influence the blend properties. Therefore, from their studies it is evident that blending offers a convenient alternative to copolymerization for the preparation of polymer matrices with predictable drug delivery (180).

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## APPENDIX

### Patents of Related Interest

| Authors/Organizations | Title | Reference | Year |
|---|---|---|---|
| *Sandoz SA* | Microcapsule and microspherule preparation for medicaments, etc.-by addition of phase separation agent to solution of polymer with solution or dispersion of active compound at −100 to −40°C | 15983B | 1979 |
| F.W. Fong, *Sandoz Inc.* | Microsphere production from particle dispersion in polymer solution-by adding phase separation agent at low temperature | 68042B | 1979 |
| J. Sandow & H.R. Seidel; *Hoechst AG* | Microcapsules for controlled release of regulatory peptides-containing poly(D-3-hydroxy butyric) acid as biodegradable carrier | 049030 | 1986 |
| R.L. Dunn & D.H. Lewis; *Stolle Res.& Dev.* | Slow release composition for treating aquatic plants-containing herbicides, etc., in strands of polymeric, e.g., poly(lactic acid), fiber | 301706 | 1984 |
| L.C. Dorman & P.A. Meyers; *Dow Chem. Co.* | New composite materials useful as hard tissue prosthetics-comprise synthetic biodegradable polymers and unstirred calcium phosphate biomaterials, and polymerized *in situ* | 226722 | 1986 |
| T. Miyaggawa, Y. Ogawa, H. Okada & M. Yamamoto; *Takeda Chem. Ind. Ltd., Wako Pure Chem. Ind. Ltd.* | Biodegradable polymer with low free acid content-and used in drug microencapsulation is e.g. hydroxy-acid ester or poly(cyano-acrylicester) | 306804 | 1986 |
| A.J. Domb | Poly(propylene glycol fumarate) composition for biomedical applications | 4888413 | 1989 |
| D. Lewis & J.D. Sherman; *Stolle Res. Dev. Corp.* | Polymer-encapsulated microsphere preparation by adding core materials to polymer solution in non-solvent for core, adding synthetic or vegetable oil and quenching with second non-solvent | 066688<br>150631 | 1989 |
| J.K. Sandow & R. Schmeidel; *Hoechst AG* | Microcapsule production containing soluble protein or peptide-using mixture of poly(hydroxybutyric acid) and poly(lactic-*co*-glycolide) | 146427 | 1989 |

**APPENDIX.** *Continued*

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| G. Spenlehauer, M. Veillard & T. Verrechia; *Rhone Poulenc Rorer SA* | Biocompatible microspheres for parenteral administration-containing biodegradable and biocompatible polymer and surfactant used for treating inflammation, infections and cancer | 324928 | 1991 |
| *Terumo Corp*. | Auxiliary material for fixing artificial joint or filling bone defects-composites biodegradable or bio-absorbable materials and leaves structure to allow formation of fresh bone | 060919 | 1992 |
| T. Canal, F. Carli, M. Lovrecich & M.L. Lourecich; *Vectorpharma Int. SPA* | Controlled release microparticles containing polysaccharide gelling agent etc.-comparising biodegradable polymer, interfacial agent, amphilic polymer and active substance, especially calcitonin, etc. | 176586 | 1992 |
| T. Fuse, H. Machino, K. Matuura, K. Niijima, S. Otani & S. Yanagisawa; *Mitsubishi Kasei Corp.; Res. Dev. Corp. Japan* | Synthetic bone-tooth filler for artificial limb and denture material-comprises water insoluble, biodegradable coating applied to substrate with porous surface layer | 391146 | 1992 |
| A.J. Domb | Lipospheres for controlled delivery of substances | 5188837 | 1993 |
| E. Buschmann, U. Kiessling, U. Neumann & G. Renz; *BASF AG* | Dispenser, especially for controlled release of sexual pheromones-used in plant protection, comprises pheromone-impermeable container sealed with pheromone-permeable foil | 153559 | 1993 |
| *Nippon Steel Chem. Co., Nippon Steel Corp.* | Slow release fertilizer-has multiple alternate coatings of a biodegradable polymer (I) and a water soluble polymer (II) | 164265 | 1993 |
| J. Clauss, N. Geroge, D.M. Horowitz, B.K. Hunter & J.K.M. Sanders; *Zeneca Ltd.*; *Monsanto Co.* | Particles of crystallizable polymer coated with surfactant of phospholipid to maintain amorphous state-for making shaped articles, e.g. fibres, for controlled release of pharmaceutical or agrochemical or for removal of solvent, etc. | 135521 | 1994 |
| S. Kino, H. Mizuta & T. Osajima; *Yoshimoto Pharm.Ind.KK* | Sustained release microspheres requiring no surgical implant-contain hydrophobic antipsychotic encapsulated in biodegradable polymer, allowing prolonged therapeutic effect by infrequent administration | 183125 | 1994 |
| S.S. Miettinen-Laehde & P.O. Toermaelae; *Orion-Yhtymae OY* | Preparation of drug releasing biodegradable compositions used for antibiotics etc.-by ultrasonically melting biodegradable polymer matrix and pharmaceutical substance | 193872 | 1994 |
| *Kirin Brewery KK* | Sustained release preparation of water-soluble peptide hormone-comprising fine tube with specified diameter made of water insoluble biodegradable, high-Mwt substance, containing core | 041205 | 1995 |
| E. Viherksoski | Biodegradable urethral stent-substantially shorter than the urethra in which it is totally installed | 044929 | 1995 |
| A.G. Coombes, S.S. Davis & E. Schacht; *Univ. Ghent; Univ. Nottingham* | Polymer microspheres useful for drug delivery and targeting etc.-prepared by mixing solution of water soluble polymer and solution of conjugate of poly(ethylene glycol) and evaporating first solvent | 351303 | 1995 |
| S.C. Arnold, E.P. Reilly & A.G. Scopelianos; *Ethicon Inc.; Johnson & Johnson* | Absorbable polymer composition for surgical and medical devices, e.g. sutures-comprises absorbable poly(ester anhydride), polylactone or poly(iminocarbonate) and polysuccinimide as bioabsorbable reinforcing filler | 122881 | 1995 |
| E.G. Joseph & D.R. Rutherford; *Minnesota Mining & MFG Co*. | Degradable multilayer melt-blown microfibre webs used for surgical dressings, etc.-comprise layers of polyolefin, PEL and degradable resins | 040269 | 1996 |

*(continued)*

**APPENDIX.** *Continued*

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| K. Pluder; *Buna GMBH* | Long-term fertilizer rods consist of a shell made of segments of polymer materials which biodegrade at different rates and are filled with plant nutrients | 201507 | 1996 |
| S.C. Arnold, E.P. Reilly & A.G. Scopelianos; *Ethicon Inc.* | Surgical device, e.g. staple or ligating clip-comprises absorbable and discrete filler material comprising polysuccinimide to increase stiffness of polymer, and device can withstand heavy loads | 267854 | 1996 |
| *Mitsubishi Gas Chem. Co. Ltd.* | Biodegradable resin composites used as containers for medical products-comprise poly(3-hydroxybutyric acid) and poly(caprolactone) with specified capillary size | 350294 | 1996 |
| M.S. Williams; *Advanced Cardiovascular Systems* | Expandable intra-luminal stent-made from sheet materials curled into cylinder having over lapping sdges, and incorporating external protrusions which engage apertures to hold the stent in the expanded condition | 044600 | 1997 |
| D. Hutmacher & A. Kirsch | Membrane for tissue or bone regeneration-contains at least three layers and is flexible and biocompatible | 459058 | 1997 |
| R.A. Mashelkar, G. Mohan & R.N. Karmalkar; *CSIR* | Polymer composition for controlled release of active ingredients in response to pH | 5851546 | 1998 |

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