

Korea Polymer Journal

Volume 8, Number 5 October 31, 2000

© Copyright 2000 by The Polymer Society of Korea

Review

Advances in Biodegradable Polymers for Drug Delivery Systems

Yong Kiel Sung*

Department of Chemistry, Dongguk University, Seoul 100-715, Korea

Sung Wan Kim

*Center for Controlled Chemical Delivery, Department of Pharmaceutics and Pharmaceutical Chemistry,
University of Utah, Salt Lake City, Utah 84112, U. S. A.*

Received September 20, 2000

Abstract : The recent development of biodegradable polymers for drug delivery system (DDS) has been investigated. The biodegradable polymers for DDS are mainly discussed in two categories: one category is natural biodegradable polymers such as polysaccharides, modified celluloses, poly(α -amino acid)s, modified proteins, and microbial biodegradable polymers; the other is synthetic biodegradable polymers such as poly(ester)s, poly(ortho ester)s, poly(phosphazene)s, poly(anhydride)s, poly(alkyl cyanoacrylate)s, and multiblock copolymers. The bioconjugate polymeric drug delivery systems have been also proposed for the design of biocompatible polymeric controlled drug delivery.

Introduction

The controlled drug delivery utilizes some of proper polymeric systems to provide the desired drug release profiles. Biodegradable polymers have been recently used to develop the advanced drug delivery systems.¹⁻⁵ The drug delivery systems have been extensively examined to over-

come the disadvantages of conventional drug therapy. In order to improve the conventional methods, the drug delivery systems have been introduced in the following ways⁶: One is the release system of drugs in a sustained method, keeping the plasma drug concentration between minimum effective level and minimum toxic level for the desired duration of time. The others are the controlled drug delivery systems, providing for the drug release at a controlled rate over the spec-

* e-mail: yksung@dgu.edu

ified period of time. A variety of advanced drug delivery systems have been recently made in several ways, using transdermal systems, self-regulating systems, drug targeting systems, stimuli-responsive modulating systems, and so forth.^{7,8} Those have been led to investigate the new polymeric systems for the drug delivery. There has been simultaneously a growing interest in biodegradable polymers for medical and pharmaceutical applications.⁹⁻¹³ A number of biodegradable polymers have been developed for the purpose of drug delivery systems. Those important biodegradable polymers are natural and synthetic nontoxic polymers, including polysaccharides, celluloses, proteins, poly(α -amino acid)s, poly(ester)s, poly(ortho ester)s, poly(phosphazene)s, poly(anhydride)s, poly(alkyl cyanoacrylate)s, and so on. The useful biodegradable polymers can be biodegraded into nontoxic intermediate monomers in the living body. The rate of biodegradation is one of the most important criteria for the useful applications of the biodegradable polymers. The degradation process of the biodegradable polymers should be examined either *in vivo* or *in vitro* tests. The *in vivo* biodegradation tests are usually carried out by introducing the biodegradable polymers into the particular site of the animals such as subdermal muscle peritoneal cavity, subcutaneous tissue, and blood stream.¹⁴ The *in vitro* biodegradation tests were carried out in pseudo extra cellular fluid, plasma solution, enzymes and buffer solutions.¹⁵ The researches on the polymeric drug delivery systems were also developed by using the water-insoluble polymers such as poly(glycolic acid) or poly(lactic acid) for the controlled delivery of a LHRH analogue from biodegradable injectable microspheres.^{16,17} Polymer-based drug delivery to the brain has been recently examined using biodegradable polymers of chemotherapy for recurrent gliomas.^{18,19} The biodegradable polymeric system of paclitaxel such as a novel antimicrotubule agent has been recently demonstrated that its significant activity shows in the clinical trials for a wide variety of tumors, including breast, non-small cell lung cancer, and AIDS-related Kaposi's sarcoma.²⁰ Biodegradable polymer-based cytokine gene delivery has been also recently developed for cancer treatment.²¹

Biodegradable Polymers for Drug Delivery Systems

The biodegradable polymers for drug delivery systems are mainly classified into the following two categories: one category is the natural and modified biodegradable polymers, and the other is the synthetic biodegradable polymers. The natural and modified biodegradable polymers will be discussed first in this section.

Natural and Modified Biodegradable Polymers. There are many useful natural biodegradable polymers such as polysaccharides, modified celluloses, poly(α -amino acid)s and modified proteins. However, the natural products are not able to apply directly themselves without purification or modification into drug delivery systems. Some examples developed for drug delivery systems will be described briefly in the followings:

Polysaccharides: The polysaccharides are naturally consisted of long chains having many monosaccharides. The monosaccharide consists of a single polyhydroxyketone or polyhydroxyaldehyde units. Oligosaccharides consist of several short chains of monosaccharide units joined by glycosidic linkage together. The polysaccharides can be divided into several groups based on their sources: microbial, algae, seaweeds, bacteria, fungi, plants, and animals.²² The grafting of natural polysaccharide has been of considerable interest in drug delivery. The enzymes hydrolyze either O-glycosyl, N-glycosyl or S-glycosyl bonds in the drug delivery systems. The enzymes hydrolyzing polysaccharides are mainly glycosidases in a polysaccharide chains.²³ Modified starch systems have been widely used as drug delivery systems.²⁴ Using glycidylacrylate, starch has been usually derivatized to introduce acryloyl groups that are necessary for polymerization into microspheres. If the contents of derivatization are low, the modified starch microspheres are readily biodegradable in biological fluids.^{25,26} The potentiality of injectable modified starch microsphere has been investigated for drug targeting to the reticulo-endothelial systems.²⁷⁻³⁰ Chemically modified polysaccharides for enzymatically controlled oral drug delivery had been examined for the release of low and high molecular weight drugs from the

calcium crosslinked starch matrix in stimulated gastric and intestinal solutions containing α -amylase.³¹

The modified dextrans have been also widely used as drug carrier or as prodrug. The derivatized dextrans are mainly investigated for their biodegradation by dextranases, which exist in the colon, intestinal mucosa, kidney, liver, and spleen.³²⁻³⁵ The natural chitin and chitosan often exist a copolymer of glycosamine and acetylated glycosamines. The degrees of acetylation and deacetylation are those of the most important structural parameters in chitin and chitosan. The application of partially deacetylated chitin had been made in self-regulated drug delivery systems.³⁶ It has been obtained that the release of high concentration cis-platinum under an implantation to mouse muscle during more than eight weeks. The additional studies were aimed at the development of drug delivery systems using chitin and chitosan derivatives.^{37,38} N-Acetylation in chitosan and the rate of its enzymatic hydrolysis by lysozyme and chitinase were mainly investigated.³⁹

Modified Celluloses: Modified celluloses have been widely used in a variety of formulations including microcapsulation and drug delivery matrix systems.⁴⁰ The oxidations of celluloses produce several kind of absorbable biomaterials. The oxidized cellulose materials can be used in medical applications such as absorbable hemostatic agents and absorbable adhesion barriers. Cellulose is rendered bioabsorbable using an oxidizing process. The oxidized celluloses can be also used as a vehicle for drug delivery system.⁴¹ Due to the bioavailability of many carboxyl groups, the oxidized celluloses have a low pH condition in aqueous solution. The oxidized regenerated celluloses produce antibacterial activities against a broad range of pathogens.⁴²⁻⁴⁴ The partially substituted oxidized celluloses by sodium salts are less acidic. They show their biocompatibility with acid sensitive biologics such as thrombin. Considering the drug delivery system, it has been focused on the chemical moiety that can be easily bound to the oxidized celluloses. The chemical moieties have been studied for the applications of adhesion prevention by heparin⁴⁵ and tissue plasminogen acti-

vator.⁴⁶ The binding with the moieties may be occurred through adsorption, absorption, ionic bond, and intermolecular interactions. Modified cellulose derivatives used in drug delivery systems are hydroxyethylmethylcellulose(HEMC), hydroxypropylmethylcellulose(HPMC), ethylhydroxyethylcellulose(EHEC), hydroxyethylcellulose(HEC), hydroxypropylcellulose(HPC), and methylcellulose(MC). Their physical properties of modified cellulose derivatives are depended upon the amounts of the substituent groups on the cellulose.^{47,48} The influences of surfactants on drug release from the hydroxypropyl methylcellulose (HPMC) matrices were also mainly investigated.⁴⁹

Poly(α -amino acid)s: Poly(α -amino acid) has been used as a model compound to study the physicochemical properties of natural high molecular-weight polymer such as protein. The poly(α -amino acid) is composed of α -amino acids as natural molecules which exist in the living organism. Poly(α -amino acid) linked by peptide bonds had been synthesized by a ring-opening polymerization of N-carboxy- α -amino acid anhydrides initiated with a base.⁵⁰ The characterized poly(α -amino acid) has been recently used as a drug carrier.⁶ The water soluble poly(α -amino acid) has been applied as a carrier for drug delivery system. This idea has been extended to the drug delivery systems such as norethindrone, naltrexone, and antihypertensive drugs coupled to the poly(α -amino acid) backbones.⁵¹⁻⁵⁶

Several series of the polymers have been synthesized and investigated: poly(N-acyl hydroxyproline ester)s, poly(L-lysine ester)s, poly(glutamylalanine anhydride)s, and poly(iminocarbonate)s with tyrosine dipeptides.⁵⁷⁻⁶⁰ The copolymers of α -amino acids and α -hydroxy carboxylic acids have been prepared to produce the polydepsipeptides. The copolymers contain both ester and amide linkages on the backbones.⁶¹⁻⁶³ The degradation of polydepsipeptide has been investigated *in vivo* as well as *in vitro*.⁶⁴ The biodegradation of polydepsipeptide was also revealed that both proteases and esterases were responsible to degrade the polymers.⁶⁵

Modified Proteins: Protein biopolymers are sequential polypeptides with complex structural repeat units. Gelatin is also a protein obtained by

partial hydrolysis of collagen. The collagen is a main component of skin, bones, hides, and connective tissues. Collagen proteins have been identified at least nineteen different molecular forms.⁶⁶⁻⁶⁸ The biopolymers can be also produced using gene template directed synthesis. The development of new protein biopolymer involves the polymerization of a gene template that encodes the amino acid sequence of the desired protein.⁶⁹ Albumin microspheres have been widely used as carriers for studying active as well as passive drug targeting systems.⁷⁰⁻⁷² The influencing factors on the release of drugs from the microspheres have been investigated precisely.⁷³⁻⁷⁵ Gelatin has been known to be a natural, nontoxic, biodegradable polymer with low antigenicity. The modified gelatin microspheres have been usually prepared with a crosslinker such as glutaraldehyde or formaldehyde.^{76,77} The preparation and evaluation of modified gelatin microspheres and beadlets for drug delivery systems have been deeply investigated for controlled sustained release, anti-angiogenic agent TNP-470, streptomycin sulphate, mitoxantrone, targeting interferon, sulfonamides, phenytoin sodium microspheres.⁷⁸⁻⁸¹ Collagenous proteins form the structural framework of all mammalian extracellular matrices. Collagen has been applied as a biodegradable polymeric system for release of drugs such as 5-fluorouracil, antibiotics, insulin, hormone, dexamethasone, cyclosporine, and bone morphogenetic protein.⁸²⁻⁸⁷

Microbial Biodegradable Polymers: The site-specific drug delivery to colon can be achieved by exploiting the microbial enzymes predominantly present in the colon. The oral drug deliveries are unstable in the upper gastrointestinal tract due to the activities of proteolytic enzymes. That might be delivered to produce the local therapeutic effects in the colon. Among these drug delivery systems, the low and high molecular weights drug bioconjugates containing bonds susceptible to biodegradation by glycosidase or others have been recently examined.^{88,89} Insulin and vasopressin deliveries to the colon had been examined by using pellets coated with poly(hydroxyethyl methacrylate-co-styrene) containing azoaromatic crosslinks.⁹⁰

Synthetic Biodegradable Polymers. There are lots of applicable synthetic biodegradable polymers such as poly(ester)s, poly(ortho ester)s, poly(phosphazene)s, poly(anhydride)s, poly(alkyl cyanoacrylate)s, and multiblock copolymers. Some excellent samples developed recently for drug delivery systems will be described in the followings:

Poly(ester)s: Synthetic poly(ester)s are the most examined biodegradable polymers for biomedical applications, including suture, tissue engineering and drug delivery systems.⁹¹⁻⁹³ The biodegradable poly(ester)s such as poly(glycolide) and poly(lactide) are typically made by ring-opening polymerization of their respective cyclic diester dimers, glycolide and lactide, respectively. However, high molecular weight poly(ester)s of glycolic and lactic acids are difficult to prepare by direct condensation of the related carboxylic acids. The synthesis and characterization of high molecular-weight poly(D, L-lactic acid)s prepared by direct thermal condensation were carried out.⁹⁴ The copolymers (PLGA) of lactic and glycolic acids were also synthesized by a ring-opening polymerization of cyclic dimers, lactide and glycolide, with a catalyst such as stannous octoate or stannic chloride dihydrate. Solid-state polymerization has been useful in forming high molecular weight polymers. The synthesis and degradation of star-shaped poly(lactide)s were also investigated.⁹⁵ PLGA microsphere systems have been designed for injectable delivery of leuprorelin acetate, a potent LHRH agonist.⁹⁶ PLGA microspheres were also prepared for the drug delivery systems of TRH.⁹⁷ These systems had contained a hydrophobic barrier of PLA in PLGA core microspheres loaded with peptide drugs. PLGA microspheres for vaccine delivery have been recently used as complex antigens of viral and bacterial origins to examine both mucosal and systemic immune responses.⁹⁸

Poly(ortho ester)s: The reaction of diols with diketene acetals and the reaction of transesterification can be produced to poly(ortho ester)s. Four distinct families of such polymers have been now prepared.⁹⁹ These may be designated as poly(ortho ester) I, poly(ortho ester) II, poly(ortho ester) III, and poly(ortho ester) IV. The first example of a poly(ortho ester) was described in a series

of patents.¹⁰⁰⁻¹⁰⁴ When this poly(ortho ester) is placed in an aqueous solution, an initial hydrolysis takes place to a diol and hydroxybutyric acid. The polymers have been used for the release of indomethacin in the prevention of reossification, the release of naltrexone, and the release of 5-fluorouracil and a LHRH analogue.^{105,106} Poly(ortho ester) II can also be prepared by the reaction between a ketene acetal and an alcohol.¹⁰⁷ The polymers are easily prepared by the addition of a diol to the diketene acetal.¹⁰⁸ These polymers have been extensively applied in short-term delivery,^{109,110} long-term delivery,^{111,112} and insulin self-regulated delivery systems.¹¹³

Poly(ortho ester) III can be prepared by reacting a triol with two vicinal hydroxyl groups.¹¹⁴ The initial hydrolysis of the polymer is followed by a much slower hydrolysis of the monoesters to produce a carboxylic acid and a triol. The potential applications are the treatments of periodontal diseases.^{115,116} The poly(ortho ester) IV can be also prepared using a triol, 1,1,4-cyclohexanetri-methanol and trimethyl orthoacetate in the general synthetic procedures.¹¹⁷ The polymer is the only example of a crystalline poly(ortho ester). The monomer, 1,1,4-cyclohexanetri-methanol can be readily prepared in small quantities, but scale-up has not yet been successful.⁹⁹

Poly(phosphazene)s: Poly(phosphazene)s consist of alternating phosphorous and nitrogen atoms linked by alternating single and double bonds with two side groups attached to phosphorous atoms. The two side R groups can be an alkoxy, alkyl, amino, aryloxy, heterocyclic ring or an inorganic unit. The poly(phosphazene)s have been extensively synthesized.¹¹⁸⁻¹²⁰ The water-soluble poly(phosphazene)s have attracted much attention due to their potential applications in drug delivery systems.^{121,122} Hydrogels based on alkylether-substituted poly(organophosphazene)s can be also prepared by the displacement of chlorine in poly(dichlorophosphazene)s.^{123,124} Biodegradable poly(organophosphazene)s can be used as drug delivery systems.^{125,126} The rate of degradation can be controlled by a proper choice of the chemical composition. The poly(phosphazene)s can be degraded by undergoing nonenzymatic hydrolysis in the body, resulting with the products of ammonia,

phosphate, water, and side chain substituents.¹²⁷ If the side chain substituents are nontoxic, excretable or metabolite, the poly(phosphazene)s are useful for drug delivery systems without any toxic response. The release rates of bovine serum albumin and B galactosidase were examined for the microspheres coated with poly(L-lysine). The poly(phosphazene) microspheres were prepared by using droplet-forming method in calcium solution of ionically cross-linked matrix.¹²⁸

Poly(anhydride)s: Poly(anhydride)s are one of the useful bioabsorbable materials for controlled drug delivery system. The backbone of this polymer is composed of either aliphatic or aromatic groups connected by a highly labile anhydride linkage. They are hydrolyzed in aqueous solution to produce monomers such as dicarboxylic acids. The degradation products of the poly(anhydride)s are the respective diacids. The rate of degradation can be varied by changing the length of alkyl chains in poly(anhydride)s such as poly(bis(*p*-carboxyphenoxy)alkane anhydride)s. By incorporating hydrophilic sebacic acid into the copolymer such as poly(bis(*p*-carboxyphenoxy)propane anhydride), the rate of degradation can be increased.¹²⁹ The syntheses of poly(anhydride)s have been carried out by melt polycondensation of activated diacids, dehydrochlorination, and dehydrative coupling.¹³⁰⁻¹³³ The branched poly(anhydride)s are synthesized from branched poly(sebacic anhydride) and 1,3,5-benzenetricarboxylic acid or poly(acrylic acid) to decrease the crystallinity and alter physicochemical properties of aliphatic poly(anhydride)s.¹³⁴ The synthesis of poly(anhydride adipic acid) from cyclic adipic anhydride (oxepane-2, 7-dione) has been carried out.¹³⁵ Biodegradable poly(anhydride)s for antibiotic drug delivery systems were examined¹³⁶ and polymeric drug carrier systems in the brain were also reported.¹³⁷ Some other applications of poly(anhydride)s have been also discussed in detail.^{138,139}

Poly(alkyl cyanoacrylate)s: Poly(alkyl cyanoacrylate) can be synthesized by both anionic or zwitterionic and free radical mechanisms.¹⁴⁰⁻¹⁴² The alkyl cyanoacrylate monomer presents different lateral alkyl chain of length ranging from methyl to decyl. The synthetic methods of poly(alkyl 2-cyanoacrylate)s were previously described.¹⁴³ The

biodegradation of poly(alkylcyanoacrylate) was found to be degraded as a random scission of the polymer backbone.¹⁴⁴ The backbones were broken down by the initiation of hydroxyl ion interaction, resulting in formaldehyde and alkyl cyanoacetate products. The rate of degradation was decreased with an increase in the alkyl group chain lengths *in vitro* and *in vivo* studies.^{145,146} Poly(alkyl cyanoacrylate)s have been recently interested in the application of drug delivery system. Because its adhesive properties are remarkably good, the strong reactivity of the corresponding monomers are also able to polymerize easily in various aqueous media. The poly(alkyl cyanoacrylate)s have been started to be used extensively as surgical glue and particular drug carriers for biomedical applications. Their nanoparticles are now as a most promising polymeric colloidal drug delivery system. The clinical trial test in phase I for the nanoparticles loaded with doxorubicin was carried out successfully in twenty-one patients with refractory solid tumors.¹⁴⁷ The nanoparticles of poly(alkyl 2-cyanoacrylate)s were also used as drug carriers to deliver anticancer agents and peptides.¹⁴⁸⁻¹⁵⁰

Diblock and Triblock Copolymers: The controlled drug delivery has been recently investigated to overcome many problems of conventional dosage forms such as adjustable drug concentration in blood, targeting the drugs to specific sites, and patient compliances. The drug loaded polymeric devices are used as the supported materials in the drug delivery systems. The degradable products in the polymeric devices should be nontoxic in the body. After their functions are completed, the polymers in the systems should be removed from the living body. The biodegradable implantable drug delivery are recently used by fabricating from polylactide(PL), poly(ethylene glycol)(PEG), poly(lactic acid)(PLA), and poly(glycolic acid)(PGA).^{151,152} The final products of degradation such as lactic acid, glycolic acid, and poly(ethylene glycol) are biocompatible and nontoxic.^{153,154} The dendrimer-based biodegradable hydrogels were developed to use as drug carriers for long-term parenteral delivery.¹⁵⁵ The synthesis of a biodegradable, thermosensitive hydrogels consisting of blocks of poly(L-lactic acid) and poly(ethylene

oxide) was recently carried out to use as injectable drug delivery systems.¹⁵⁶ Using the ring opening polymerization of L-lactide on monomethoxy poly(ethylene oxide), the diblock copolymers consisting of poly(ethylene oxide) and poly(L-lactic acid) were synthesized. Triblock copolymers were also synthesized by coupling the diblock copolymers using hexamethylene diisocyanate as a coupling agent. On the basis of the biodegradability and thermosensitivity, the triblock copolymers were designed as an injectable drug delivery system.¹⁵⁷ Novel stimuli-sensitive biodegradable hydrogels have been also synthesized by crosslinking agent and polymer-polymer reaction methods.^{158,159} N-(2-hydroxypropyl)methacrylate (HPMA) copolymers have been recently synthesized and evaluated as an anticancer drug carrier.¹⁶⁰⁻¹⁶² The star-like biodegradable poly(N-(2-hydroxypropyl)methacrylate) has been recently also synthesized and characterized by SEC, MALDI-TOF MS, and proton NMR.¹⁶³ The amphiphilic poly(ethylene glycol)-*b*-polylactide (PEG/PLA) block copolymer micelles as potential drug carriers have been prepared through successive ring-opening polymerization of D, L-lactide and ethylene oxide using an anionic initiator, and their properties of multi-molecular micellization in aqueous media have been recently examined.¹⁶⁴ The supramolecular associates of DNA with poly(ethylene glycol)-*b*-poly(L-lysine) copolymers were also prepared in aqueous media.¹⁶⁵ The preparation of narrowly-distributed micelles from lysozyme and poly(ethylene glycol)-*b*-poly(aspartic acid) copolymers in aqueous medium has been first made. The core-shell supramolecular assembly from opposite charged block copolymers has also been investigated.¹⁶⁶ Using a low molecular weight, nontoxic and biodegradable amphiphilic diblock copolymer such as methoxy poly(ethylene glycol)-*b*-poly(D,L-lactide), the paclitaxel (Genexol) containing biodegradable polymeric surfactant system (PPS) has been recently developed and investigated for the test of its toxicity and therapeutic efficacy in animal models.¹⁶⁷ Poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) are known to form stereocomplexes upon mixing each other. Using these PLLA-PEO-PLLA and PDLA-PEO-PDLA triblock copolymers that are soluble in water and, at the

same time, are able to form water-insoluble stereo-complexes, new exciting possibilities in the controlled delivery system of sensitive drugs such as peptides and proteins have been recently examined.^{168,169}

Conclusions

All controlled drug delivery systems aim to improve the effectiveness of drug therapy using natural and synthetic polymers. This review has focused on biodegradable polymeric systems developed recently for the controlled drug delivery. Many of the future challenges such as gene delivery therapy may require biodegradable and biocompatible polymeric systems for specific applications. Combining of the biological, physico-chemical and mechanical properties including biodegradability, biocompatibility, thermosensitivity, and thermoplasticity, new bioconjugate polymeric drug delivery systems should be designed and developed for the real drug delivery in future. Biodegradable polymers for controlled drug delivery systems have remarkably impacted and promised to give successful health care products.

Acknowledgements. This research was supported by Dongguk University, University of Utah, the National Institute of Health, and Korea Science and Engineering Foundation.

References

- (1) S. W. Kim, J. Kopecek, and J. M. Anderson, Eds., *Ninth International Symposium on Recent Advances in Drug Delivery Systems*, CCCD, University of Utah, Salt Lake City, Utah, U.S.A. 1999.
- (2) K. Urich, S. Cannizzaro, R. Langer, and K. Shakesheff, *Chem. Rev.*, **99**, 3181 (1999).
- (3) A. J. Domb, J. Kost, and D. M. Wiseman, Eds., *Handbook of Biodegradable Polymers*, Harwood Academic Publishers, Netherlands, 1997.
- (4) M. Chain and R. Langer, Eds., *Biodegradable Polymers as Drug Delivery Systems*, Marcel Dekker Inc., New York, 1990.
- (5) R. L. Juliano, *Drug Delivery Systems*, Oxford University Press, Oxford, U.K., 1980.
- (6) S. W. Kim, R. V. Peterson, and J. Feijen, in *Polymeric Drug Delivery Systems-Drug Design*, J. Ariens, Ed., Academic Press, New York, 1980. Vol. 5, pp 193-215.
- (7) B. Jeong, Y. H. Bae, D. S. Lee, and S. W. Kim, *Nature*, **388**, 860 (1997).
- (8) R. Langer, *Science*, **249**, 1527 (1990).
- (9) K. Park, W. S. W. Shalaby, and H. Park, *Biodegradable Hydrogels for Drug Delivery*, Technomic Publishing Co. Inc., Lancaster, Pennsylvania, 1993.
- (10) R. M. Ottenbrite, S. J. Huang, and K. Park, Eds., *Hydrogels and Biodegradable Polymers for Bioapplications*, ACS Symposium Series **627**, American Chemical Society, Washington, D. C., 1994.
- (11) Y. K. Sung, I. K. Kang, and D. R. Kwon, *Polymer (Korea)*, **15**, 481 (1991).
- (12) Y. K. Sung, J. Y. Kim, Y. M. Lee, Y. K. Kim, and C. S. Cho, *Polymer (Korea)*, **15**, 695 (1991).
- (13) Y. K. Sung, J. H. Ha, S. H. Kim, S. Y. Han, and C. S. Cho, *J. Control. Rel.*, **49**, 253 (1997).
- (14) H. R. Dickinson, A. Hiltner, D. F. Gibbons, and J. M. Anderson, *J. Biomed. Materials Res.*, **15**, 577 (1981).
- (15) H. R. Dickinson and A. Hiltner, *J. Biomed. Materials Res.*, **15**, 590 (1981).
- (16) H. Okada, M. Yamamoto, T. Heya, Y. Inoue, K. Kamei, Y. Ogawa, and H. Toguchi, *J. Control. Rel.*, **28**, 121 (1994).
- (17) L. M. Sanders, G. I. McRac, K. M. Vitale, and B. A. Kell, *J. Control. Rel.*, **12**, 187 (1985).
- (18) H. Brem, S. Piantadosi, P. C. Burger, M. Walker, R. Selker, N. A. Black, M. Sisti, S. Brem, and G. Mohr, *Lancet*, **345**, 1008 (1995).
- (19) H. Brem, K. A. Walter, R. J. Tamargo, A. Olivi, and R. Langer, *Drug Delivery to the Brain*, in *Polymeric Site Specific Pharmacotherapy*, A. Domb, Ed., Wiley, New York, 1994, pp 117-140.
- (20) M. H. Seo, C. S. Kim, D. W. Kim, Y. H. Shim, S. W. Kim, and J. H. Oh, *J. Control. Rel.*, in press (2000).
- (21) A. Maheshwari, R. I. Mahato, J. McGregor, S. Han, W. E. Samlowski, J. Park, and S. W. Kim, *Molecular Therapy*, **2**(2), in press (2000).
- (22) J. Kost and R. Goldbalt, *Natural and Modified Polysaccharides*, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost, and D. M. Wiseman, Eds., 1997, Chap. 14, pp 275-289.
- (23) W. S. W. Shalby and K. Park, *Chemical Modification of Proteins and Polysaccharides and Its Effect on Enzyme-Catalyzed Degradation*, in *Biomedical Polymers*, W. S. W. Shalby, Ed., Hanser International, Munchen, Germany, 1994.
- (24) G. Vandenbossche, R. Leffebvre, G. De Wilde, and J. P. Remon, *J. Pharm. Sci.*, **81**, 245 (1992).
- (25) T. Laakso and I. Sjöholm, *J. Pharm. Sci.*, **76**, 935 (1987).
- (26) T. Laakso, P. Artursson, and I. Sjöholm, *J. Pharm. Sci.*, **75**, 962 (1986).
- (27) P. Stjärnkvist, L. Degling, and I. Sjöholm, *J. Pharm.*

- Sci.*, **80**, 436 (1991).
- (28) P. Stjarnkvist, T. Laakso, and I. Sjöholm, *J. Pharm. Sci.*, **78**, 52 (1989).
- (29) C. J. Johansson, *Clin. Pharmacokinet.*, **31**, 231 (1996).
- (30) P. Artursson, P. Edman, and I. Sjöholm, *J. Pharmacol. Exp. Ther.*, **231**, 705 (1984).
- (31) J. Kost and S. Shefer, *Biomaterials*, **11**, 695 (1990).
- (32) B. Crepon, J. Jozefonvicz, V. Chytry, B. Rihova, and J. Kopecek, *Biomaterials*, **12**, 550 (1991).
- (33) V. Subr, R. Duncan, and J. Kopecek, *J. Biomater. Sci. Polym. Ed.*, **1**(4), 261 (1990).
- (34) E. Harbae, C. Larsen, M. Johansen, and H. P. Olesen, *Pharm. Res.*, **6**, 919 (1989).
- (35) P. Edman, B. Ekman, and I. Sjöholm, *J. Pharm. Sci.*, **69**, 838 (1980).
- (36) S. H. Pangburn, P. V. Trescony, and J. Heller, *Biomaterials*, **3**(2), 105 (1982).
- (37) K. Itoyama, S. Tokura, and T. Hayashi, *Biotechnol. Prog.*, **10**, 225 (1994).
- (38) Y. K. Sung, S. J. Kim, Y. M. Lee, I. K. Kang, and Y. H. Park, *J. Kor. Ind. Eng. Chem.*, **4**, 785 (1994).
- (39) S. Hirano, H. Tsuchida, and N. Nagao, *Biomaterials*, **10**, 574 (1989).
- (40) C. Bindschäedler, R. Gurney, and E. Doelker, *J. Pharm. Pharmacol.*, **39**, 335 (1987).
- (41) R. L. Stitwell, M. G. Marks, L. Saferstein, and D. M. Wiseman, *Oxidized Cellulose*, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost, and D. M. Wiseman, Eds., Harwood Academic Publishers, U. K., 1997, Chap. 15, pp 291-306.
- (42) K. S. Scher and J. A. Coil, *Surg.*, **91**, 301 (1982).
- (43) P. Dineen, *J. Surg. Res.*, **23**, 114 (1977).
- (44) P. Dineen, *Surg. Gynecol. Obstet.*, **142**, 481 (1976).
- (45) R. L. Reid, K. Lie, J. E. Spence, T. Tulandi, and A. Yuzpe, *Prog. Clin. Biol. Res.*, **381**, 261 (1993).
- (46) D. M. Wiseman, L. Kamp, C. B. Linsky, R. F. Jochen, R. H. Pang, and P. M. Scholz, *J. Surg. Res.*, **53**, 362 (1992).
- (47) C. Bindschäedler, R. Gurny, and E. Doelker, *J. Pharm. Pharmacol.*, **39**, 335 (1987).
- (48) E. R. Tovey, S. A. Ford, and B. A. Baldo, *J. Biochem. Biophys. Methods*, **14**, 1 (1987).
- (49) J. L. Ford, M. H. Rubinstein, F. McCaul, J. E. Hogan, and P. Edgar, *Int. J. Pharm.*, **40**, 223 (1987).
- (50) E. Katchalsky and M. Sela, *Protein Chem.*, **13**, 243 (1958).
- (51) J. M. Anderson, S. M. Fang, J. Feijen, D. Gregonis, and S. W. Kim, *Polymer Preprints*, **20**, 20 (1979).
- (52) A. Negishi, D. B. Bennett, S. Y. Jeong, W. van Heeswijk, J. Feijen, and S. W. Kim, *Pharm. Res.*, **4**, 305 (1987).
- (53) D. B. Bennett, X. Li, N. W. Adams, C. J. T. Hoes, J. Feijen, and S. W. Kim, *J. Control. Rel.*, **22**, 181 (1992).
- (54) P. Lemieux, S. V. Vinogradov, C. L. Gebhart, N. Guerin, G. Paradis, H. K. Nguyen, B. Ochietti, Y. G. Suzdaltseva, E. V. Bartakova, T. K. Bronich, Y. St-Pierre, V. Y. Alakhov, and A. V. Kabanov, *J. Drug Target.*, **8**, 91 (2000).
- (55) A. Charlier, B. Leclerc, and G. Couarraze, *Int. J. Pharm.*, **200**, 115 (2000).
- (56) A. Bentolila, I. Vlodaysky, R. Ishai-Michaeli, O. Kovalchuk, C. Haloun, and A. J. Domb, *J. Med. Chem.*, **43**, 2591 (2000).
- (57) H. Y. Kwon and R. Langer, *Macromolecules*, **22**, 3250 (1989).
- (58) J. Kohn, *Drugs Pharm. Sci.*, **45**, 195 (1990).
- (59) S. Pulapula, C. Li, and J. Kohn, *Biomaterials*, **11**, 666 (1990).
- (60) B. S. Kim, J. S. Hrkach, and R. Langer, *Biomaterials*, **21**, 259 (2000).
- (61) M. Yoshida, M. Asano, M. Kumakura, R. Katakai, T. Mashima, H. Yuasa, K. Imai, and H. Yamanaka, *J. Biomed. Mater. Res.*, **24**, 1173 (1990).
- (62) J. Helder, Ph. D. Thesis, Twente University of Technology (1988).
- (63) J. M. Anderson, D. F. Gibbons, R. L. Martin, A. Hiltner, and R. Woods, *J. Biomed. Mater. Res. Symposium*, **5**, 197 (1974).
- (64) J. Helder, J. Dijkstra, and J. Feijen, *J. Biomed. Mater. Res.*, **24**, 1005 (1990).
- (65) M. Asano, M. Yoshida, I. Kaetsu, R. Katakai, T. Mashimo, H. Yuasa, K. Imai, and K. Yamanaka, *Polym. J.*, **20**, 281 (1988).
- (66) J. C. Myers, H. Yang, A. DiIppolito, A. Presente, M. K. Miller, and A. S. Dion, *J. Biol. Chem.*, **269**, 18549 (1994).
- (67) M. van der Rest and P. Bruckner, *Current Opinion in Structural Biology*, **3**, 430 (1993).
- (68) D. J. Prockop, *N. Engl. J. Med.*, **326**, 540 (1992).
- (69) V. S. Trubetskoy, V. G. Budker, L. J. Hanson, P. M. Slattum, J. A. Wolff, and J. E. Hagstrom, *Nucleic Acids Res.*, **26**, 4178 (1998).
- (70) B. G. Muller, H. Leuenberger, and T. Kissel, *Pharm. Res.*, **13**, 32 (1996).
- (71) J. C. Doughty, J. H. Anderson, N. Willmott, and C. S. McArdle, *Postgrad. Med. J.*, **71**, 47 (1995).
- (72) Y. H. Cheng, G. T. Liao, S. X. Hou, L. Li, and M. Zhang, *Yao Hsueh Hsueh Pao*, **28**, 68 (1993).
- (73) R. Verrijck, I. J. Smolders, J. G. McVie, and A. C. Begg, *Cancer Chemother. Pharmacol.*, **29**, 117 (1991).
- (74) S. S. Davis, I. M. Hunneyball, L. Illum, J. H. Ratecliffe, A. Smith, and C. G. Wilson, *Drugs Exp. Clin. Res.*, **11**, 633 (1985).
- (75) A. A. Bosela, M. M. el-Sayed, and M. I. Mahmoud, *Boll. Chim. Farm.*, **137**, 77 (1998).
- (76) E. Iseri, M. T. Ercan, H. S. Kas, and A. A. Hincal,

- Boll. Chim. Farm.*, **130**, 66 (1991).
- (77) C. H. Yan, X. W. Li, X. L. Chen, D. Q. Wang, D. C. Zhong, T. Z. Tan, and H. Kitano, *Biomaterials*, **12**, 640 (1991).
- (78) J. K. Rao, D. V. Ramesh, and K. P. Rao, *J. Biomater. Sci. Polym. Ed.*, **6**, 391 (1994).
- (79) T. Yasukawa, H. Kimura, Y. Tanaba, H. Miyamoto, Y. Honda, Y. Ikada, and Y. Ogura, *Invest. Ophthalmol. Vis. Sci.*, **40**, 2690 (1999).
- (80) Z. Zhang, B. Lu, G. Shu, H. Xie, Q. Yi, Y. He, and J. Wang, *Hua His Ko Ta Hsueh Hsueh Pao.*, **26**, 167 (1995).
- (81) J. H. Wang, B. Lu, P. L. Xu, D. Y. Bao, and Z. R. Zhang, *Yao Hsueh Hsueh Pao.*, **30**, 549 (1995).
- (82) D. K. Chowdhury and A. K. Mitra, *Int. J. Pharm.*, **193**, 113 (1999).
- (83) R. Herrmann, G. Schmidmaier, B. Markl, A. Resch, I. Hahnel, A. Stemberger, and E. Alt, *Thromb. Haemost.*, **82**, 51 (1999).
- (84) J. M. Schakenraad, J. A. Oosterbaan, P. Nieuwenhuis, I. Molenaar, J. Olijslager, W. Potman, M. J. Eenink, and J. Feijen, *Biomaterials*, **9**, 116 (1988).
- (85) B. Hasty, D. K. Heuer, and D. S. Minckler, *Amer. J. Ophthalmology*, **109**, 721 (1990).
- (86) D. G. Hwang, W. H. Stern, P. H. Hwang, and L. A. MacGowan-Smith, *Archives Ophthalmology*, **107**, 1375 (1989).
- (87) Y. E. Chen, B. Gebhardt, J. J. McReidy, and H. E. Kaufman, *Am. J. Ophthalmology*, **109**, 132 (1990).
- (88) J. Kopecek, *Biomaterials*, **5**, 19 (1984).
- (89) H. Brondsted and J. Kopecek, *Pharm. Res.*, **9**, 1540 (1992).
- (90) M. Saffran, G. S. Kumar, C. Savariar, J. C. Burnham, F. Williams, and D. C. Neckers, *Science*, **233**, 1081 (1986).
- (91) D. K. Gilding and A. M. Reed, *Polymer*, **20**, 1459 (1979).
- (92) D. J. Mooney, G. Organ, J. P. Vacanti, and R. Langer, *Cell Transpl.*, **2**, 203 (1994).
- (93) D. H. Lewis, in *Biodegradable Polymers as Drug Delivery Systems*, M. Chasin and R. Langer, Eds., Marcel Dekker, New York, 1990, pp 1-15.
- (94) G. I. Shin, J. H. Kim, S. H. Kim, and Y. H. Kim, *Kor. Polym. J.*, **5**, 19 (1997).
- (95) J. S. Lee, D. J. Choo, S. H. Kim, and Y. H. Kim, *Polymér (Kor.)*, **22**, 880 (1998).
- (96) H. Okada, M. Yamamoto, T. Heya, Y. Inoue, K. Kamei, Y. Ogawa, and H. Touchi, *J. Control. Rel.*, **28**, 121 (1994).
- (97) T. Heya, H. Okada, Y. Ogawa, and H. Touchi, *Int. J. Pharm.*, **72**, 199 (1991).
- (98) J. Mestecky, Z. Moldoveanu, N. Novak, W. Q. Huang, R. M. Gilly, J. K. Stags, D. Schafer, and R. W. Coupans, *J. Control. Rel.*, **28**, 131 (1994).
- (99) J. Heller, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost, and D. M. Wiseman, Eds., Harwood Academic Publishers, U. K., 1997, pp 99-118.
- (100) N. S. Choi and J. Heller, *U.S. Patent* 4,079,038 (1978).
- (101) N. S. Choi and J. Heller, *U.S. Patent* 4,093,709 (1978).
- (102) N. S. Choi and J. Heller, *U.S. Patent* 4,131,648 (1978).
- (103) N. S. Choi and J. Heller, *U.S. Patent* 4,138,344 (1979).
- (104) N. S. Choi and J. Heller, *U.S. Patent* 4,180,646 (1979).
- (105) R. C. Capozza, S. L. Sendelbeck, and W. J. Balkenhol, in *Polymeric Delivery Systems*, R. J. Kostelnik, Ed., Gordon and Breach, New York, 1978, pp 59-76.
- (106) J. Heller, S. Y. Ng, D. W. Penhale, B. K. Fritzing, L. M. Sanders, R. A. Burns, M. G. Gaynon, and S. S. Bhosale, *J. Control. Res.*, **6**, 217 (1987).
- (107) J. Heller, D. W. Penhale, and R. F. Helwing, *J. Polym. Sci., Polym. Lett., Ed.*, **18**, 619 (1980).
- (108) S. Y. Ng, D. W. Penhale, and J. Heller, *Macromolecular Synthesis*, **11**, 23 (1992).
- (109) L. W. Seymour, R. Duncan, J. Duffy, S. Y. Ng, and J. Heller, *J. Control. Rel.*, **31**, 201 (1994).
- (110) Y. F. Maa and J. Heller, *J. Control. Rel.*, **14**, 21 (1990).
- (111) J. Heller, *Advances in Polymer Sci.*, **107**, 43 (1993).
- (112) J. Heller, B. K. Fritzing, S. Y. Ng, and D. W. Penhale, *J. Control. Rel.*, **1**, 233 (1985).
- (113) J. Heller, A. C. Chang, G. Rodd, and G. M. Grodsky, *J. Control. Rel.*, **13**, 295 (1990).
- (114) J. Heller, S. Y. Ng, B. K. Fritzing, and K. V. Roskos, *Biomaterials*, **11**, 235 (1990).
- (115) K. V. Roskos, B. K. Fritzing, S. S. Rao, G. C. Armitage, and J. Heller, *Biomaterials*, **16**, 313 (1995).
- (116) P. Wuthrich, S. Y. Ng, B. K. Fritzing, K. V. Roskos, and J. Heller, *J. Control. Rel.*, **21**, 191 (1992).
- (117) J. Heller, S. Y. Ng, and B. K. Fritzing, *Macromolecules*, **25**, 3362 (1992).
- (118) H. R. Allcock, *Chem. Rev.*, **72**, 315 (1972).
- (119) H. R. Allcock, *Makromol. Chem. Macromol. Symp.*, **6**, 101 (1986).
- (120) H. R. Allcock, *Biomaterials*, **13**, 857 (1992).
- (121) H. R. Allcock, in *Biodegradable Polymers as Drug Delivery Systems*, R. Langer, and M. Chasin, Eds., M. Dekker, New York, 1990, pp 163-193.
- (122) C. T. Laurencin, H. J. Koh, T. X. Neenan, H. R. Allcock, and R. Langer, *J. Biomed. Mater. Res.*, **21**, 1231 (1987).
- (123) H. R. Allcock, S. J. OConnor, D. L. Olmeijer, M. E. Napierala, and C. G. Cameron, *Macromolecules*, **29**, 7544 (1996).

- (124) H. R. Allcock and A. Ambrosio, *Polymer Preprints*, **41**, 732 (2000).
- (125) H. R. Allcock, S. R. Pucher, and A. G. Scopelianos, *Biomaterials*, **15**, 563 (1994).
- (126) H. R. Allcock and G. K. Dudley, *Macromolecules*, **29**, 1313 (1996).
- (127) H. R. Allcock, T. J. Fuller, and K. Matsumura, *Inorg. Chem.*, **21**, 515 (1982).
- (128) S. Cohen, M. C. Bano, K. B. Visscher, M. Chow, H. R. Allcock, and R. Langer, *J. Am. Chem. Soc.*, **112**, 7832 (1990).
- (129) K. W. Leong, B. C. Brott, and R. Langer, *J. Biomed. Mater. Res.*, **19**, 941 (1985).
- (130) A. J. Domb and R. Langer, *J. Polym. Sci. Polym. Chem.*, **25**, 373 (1987).
- (131) K. W. Leong, V. Simonte, and R. Langer, *Macromolecules*, **20**, 705 (1987).
- (132) A. J. Domb, E. Ron, and R. Langer, *Macromolecules*, **21**, 1925 (1988).
- (133) A. J. Domb, C. E. Gallardo, and R. Langer, *Macromolecules*, **22**, 3200 (1989).
- (134) A. J. Domb, *Biomaterials*, **11**, 680 (1990).
- (135) A. Albertsson and S. Lundmark, *J. Macromol. Sci. Chem.*, **A22**, 23 (1990).
- (136) C. Laurencin, T. Gerhart, P. Witschger, R. Satcher, A. J. Domb, P. Hanff, L. Edsberg, W. Hayes, and R. Langer, *J. Orthop. Res.*, **11**, 256 (1993).
- (137) A. J. Domb and I. Ringel, in *Providing Pharmaceutical Access to the Brain, Methods in Neuroscience*, T. R. Flanagan, D. F. Emerich, and S. R. Winn, Eds., CRC Press, 1999, Vol. 21, pp 169-183.
- (138) C. T. Laurencin, S. E. Ibim, and R. Langer, in *Bio-medical Applications of Synthetic Biodegradable Polymers*, J. O. Hollinger, Ed., CRC Press, Boca Raton, 1995, pp 59-102.
- (139) A. J. Domb and R. Nudelman, *Biomaterials*, **16**, 319 (1995).
- (140) D. C. Pepper, *Makromol. Chem. Macromol. Symp.*, **60**, 267 (1992).
- (141) D. C. Pepper, *J. Polym. Sci.*, **62**, 65 (1978).
- (142) A. Alvoitidinov, *Dokl. Akad. Nauk. Uzb. U.S.S.R.*, **7**, 41 (1982).
- (143) F. Leonard, R. A. Kurkarni, G. Brandes, J. Nelson, and J. J. Cameron, *J. Appl. Polym. Sci.*, **10**, 259 (1966).
- (144) J. Kopecek and K. Ulbrich, *Prog. Polym. Sci.*, **9**, 1 (1983).
- (145) W. R. Vezin and A. T. Florence, *J. Biomed. Mater. Res.*, **14**, 93 (1980).
- (146) A. F. Hegyeli, *J. Biomed. Mater. Res.*, **7**, 205 (1973).
- (147) J. Kattan, J. P. Droz, P. Couvreur, J. P. Marino, A. Boutan-Laroze, P. Rougier, P. Brault, H. Vranckx, J. M. Grognet, X. Morge, and L. Sancho-Garnier, *Invest. New Drugs*, **10**, 191 (1992).
- (148) R. H. Muller, C. Lherm, J. Herbort, and P. Couvreur, *Biomaterials*, **11**, 590 (1990).
- (149) C. Verdun, F. Brasseur, H. Vranckx, P. Couvreur, and M. Roland, *Cancer Chemother. Pharmacol.*, **26**, 13 (1990).
- (150) P. Maincent, J. P. Devissaguet, R. LeVerge, P. A. Sado, and P. Couvreur, *Appl. Biochem. Biotechnol.*, **10**, 263 (1984).
- (151) K. J. Zhu, X. Lin, and S. Yang, *J. Appl. Polym. Sci.*, **39**, 1 (1990).
- (152) B. Ronneberger, W. J. Kao, J. A. Anderson, and T. Kissel, *J. Biomed. Mater. Res.*, **30**, 31 (1996).
- (153) B. Jeong, Y. H. Bae, D. S. Lee, and S. W. Kim, *Nature*, **388**, 860 (1997).
- (154) B. Jeong, Y. K. Choi, Y. H. Bae, G. Zentner, and S. W. Kim, *J. Control. Rel.*, **62**, 109 (1999).
- (155) M. X. Tang, C. T. Redemann, and F. C. Szoka, *Bioconjug. Chem.*, **7**, 703 (1996).
- (156) B. Jeong, Y. H. Bae, and S. W. Kim, *J. Control. Rel.*, **63**, 155 (2000).
- (157) B. Jeong, Y. H. Bae, and S. W. Kim, *World Biomat. Cong. Trans.*, **Vol. III**, 1941 (2000).
- (158) P. Y. Yeh, P. Kopeckova, and P. Kopecek, *Macromol. Chem. Phys.*, **196**, 2183 (1995).
- (159) H. Ghandehari, P. Kopeckova, P. Y. Yeh, and P. Kopecek, *Macromol. Chem. Phys.*, **197**, 965 (1996).
- (160) D. Putnam and P. Kopecek, *Bioconjug. Chem.*, **6**, 483 (1995).
- (161) S. Kamei and P. Kopecek, *Pharm. Res.*, **12**, 663 (1995).
- (162) T. Minko, P. Kopeckova, and P. Kopecek, *J. Control. Res.*, **59**, 133 (1999).
- (163) D. Wang, P. Kopeckova, T. Minko, V. Nanayakkara, and P. Kopecek, *Polymer Preprints*, **41**, 994 (2000).
- (164) K. Yasugi, Y. Nakasaki, M. Kao, and K. Kataoka, *J. Control. Rel.*, **62**, 89 (1999).
- (165) S. Katayose and K. Kataoka, *J. Pharm. Sci.*, **87**, 160 (1998).
- (166) A. Harada and K. Kataoka, *Science*, **283**, 65 (1999).
- (167) H. Suh, B. Jeong, R. Rathi, and S. W. Kim, *J. Biomed. Mater. Res.*, **42**, 331 (1998).
- (168) D. W. Grijpma and J. Feijen, *J. Control. Rel.*, in press (2000).
- (169) Y. Lim, S. Han, H. Kong, Y. Lee, J. Park, B. Jeong, and S. W. Kim, *Pharm. Res.*, **17**, 811 (2000).