Chapter 1

Hydrogels in Bioapplications

Haesun Park and Kinam Park[1]

School of Pharmacy, Purdue University, Robert E. Heine Pharmacy Building, West Lafayette, IN 47907–1336

Research on hydrogels has been geared toward biomedical applications from the beginning due to their relatively high biocompatibility. Initially only the hydrophilic nature and the large swelling properties of hydrogels was explored. Continued research on hydrogels has resulted in the development of new types of hydrogels, such as environment-sensitive hydrogels, thermoplastic hydrogels, hydrogel foams, and sol-gel phase-reversible hydrogels. Application of hydrogels ranges from biomedical devices to solute separation. Examples of hydrogel applications in pharmaceutics, biomaterials, and biotechnology are briefly described.

Hydrogel is a three-dimensional network of hydrophilic polymers in which a large amount of water is present. In general, the amount of water is at least 20% of the total weight. If water is composed of more than 95% of the total weight, then the hydrogel is called superabsorbent. The most characteristic property of hydrogel is that it swells in the presence of water and shrink in the absence of water. The extent of swelling is determined by the nature (mainly hydrophilicity) of polymer chains and the crosslinking density. If hydrogel is dried, the swollen network of the hydrogel is collapsed during drying due to the high surface tension of water. Thus, the dried hydrogel (or xerogel) becomes much smaller in size than the hydrogel swollen in water. During swelling and shrinking process, hydrogels can preserve its overall shape.

To maintain the three-dimensional structures, polymer chains of hydrogels are usually crosslinked either chemically or physically. In chemical gels polymer chains are connected by covalent bonds, and thus it is difficult to change the shape of chemical gels. On the other hand, polymer chains of physical gels are connected through non-covalent bonds, such as van der Waals interactions, ionic interactions, hydrogen bonding, or hydrophobic interactions (1). Since the bonding between polymer chains are reversible, physical gels possess sol-gel reversibility. For example, sodium alginate becomes a gel in the presence of calcium ions, but the gel becomes sol if the divalent cations are removed.

Strong interest in biomedical applications of hydrogels was caused by the landmark paper by Wichterle and Lim on poly(2-hydroxyethyl methacrylate) or p(HEMA)(2). Since then the research on hydrogel has been steadily increased. It is

[1]Corresponding author

0097–6156/96/0627–0002$15.00/0

not until the end of 1970's, however, when the research on hydrogels began to take off. Fig. 1 shows the number of articles on gels published each year from 1907 to 1994. As shown in Fig. 1, the number of publications on gel started to increase in the late 70's and continued to increase during 80's and early 90's. The number increased dramatically in 1994. The involvement of a large number of scientists resulted in more understanding on the physicochemical properties of hydrogels and development of new types of hydrogels (3,4).

New Types of Hydrogels

Environment-Sensitive Hydrogels

One of the inherent properties of hydrogels is their ability to swell in the presence of water and to shrink in the absence of water. This property is common to all hydrogels. Thus, by merely having the swelling-shrinking properties does not make any particular hydrogel of great interest. Recently, many investigators have prepared hydrogels with additional functions, such as the ability to swell or shrink in response to a signal. These hydrogels with additional functions are called "smart (or intelligent) hydrogels" (5).

The most widely known smart hydrogels are those which respond (i.e., either swell, shrink, bend, or degrade) to changes in environmental conditions. For this reason, they are usually known as environment-sensitive hydrogels. One of the unique properties of environment-sensitive hydrogels is that they change their swelling ratio (which is the volume of the swollen hydrogel divided by the volume of the dried hydrogel) rather abruptly upon small changes in environmental factors. Table 1 lists the environmental factors which are known to cause such an abrupt volume change. Fig. 2 shows dramatic volume changes as a result of only a minute change in the environmental condition. Volume change is so dramatic it is often called volume collapse (or volume phase transition) (6). The volume collapse phenomena have been applied in a variety of areas ranging from pharmaceutics to biotechnology (see below).

Table 1. Factors which cause volume collapse of hydrogels

1. pH	(7,8)
2. Temperature	(9-11)
3. Electric field	(12-15)
4. Ionic strength	(16)
5. Salt type	(17,18)
6. Solvent	(19,20)
7. Stress	(21,22)
8. Light	(23,24)
9. Pressure	(25)

Thermoplastic Hydrogels

One of the physical gels is thermoplastic hydrogels (26). Thermoplastic hydrogels are based on linear copolymers of hydrophilic and hydrophobic monomers. Physical gel is formed by hydrophobic interactions between hydrophobic chains of the copolymer. They dissolve in organic solvents, while only swell without dissolving in water, and

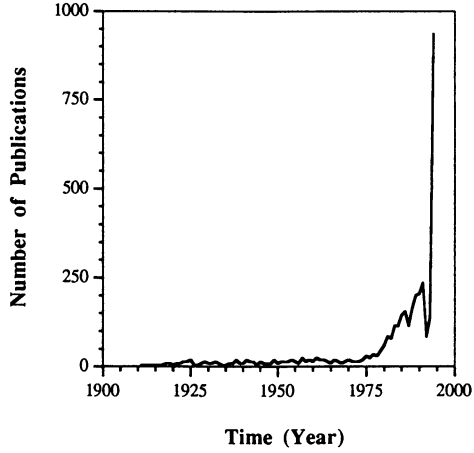

Figure 1. The number of articles on gels published between 1907 and 1994. The articles appeared on Chemical Abstract were counted. For the years earlier than 1982, keywords of "gels/hydrophilic" and "hydrogels" were searched under the subject heading of "colloid". For later years articles under the heading of "gels/hydrophilic & hydrogels" were counted.

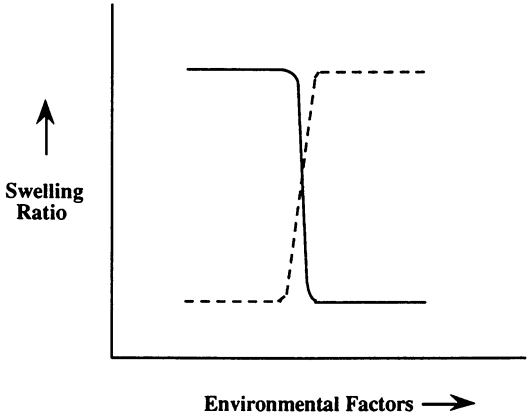

Figure 2. Volume collapse (or volume phase transition) of smart hydrogels in response to a small change in environmental factors. Hydrogels may undergo dramatic increase (dotted line) or decrease (solid line) in the swelling ratio.

this property provides an advantage of easy processibility. Copolymers of N-vinyl-2-pyrrolidone and methyl methacrylate are known to form thermoplastic hydrogels which have useful properties such as film-forming capacity and melt-processibility (27).

Hydrogel Foams

While hydrogels swell to a large extent in water, the equilibrium swelling usually takes a long time from hours to days depending on the size and shape of hydrogels. To overcome this slow swelling of hydrogels, hydrogel foam was recently developed (28,29). Hydrogel foams were made by synthesizing hydrogels in the presence of gas bubbles. The hydrogel foams prepared with macroscopic gas cells are different from hydrogel sponges (30) or macroporous hydrogels (31). The size of pores in the hydrogel foams is orders of magnitude larger than the pore size (which is typically a few micrometers) in hydrogel sponges or macroporous hydrogels. In addition, the kinetics and the extent of swelling of hydrogel foams are much faster and larger than others.

The kinetics of hydrogel swelling is limited by the diffusion of water through the glassy layer of dried hydrogels. Thus, the swelling is actually quite slow for many applications. On the other hand, hydrogel foams swell much faster since water is absorbed into hydrogel foams by capillary reaction by the pores in dried hydrogels rather than the diffusion of water through the glassy layer. Recently developed comb-type grafted hydrogels (11) showed faster deswelling but the swelling was still quite slow. The hydrogel foams made of poly(acrylic acid) can swell more than thousand times its original size. The property of fast swelling with a very large swelling ratio of hydrogel foams should be useful in many bioapplications.

Ligand-Specific Sol-Gel Phase-Reversible Hydrogels

Physical gels are capable of undergoing sol-gel phase transition due to non-covalent crosslinking of polymer chains. There are only a few hydrogels which undergo such a phase change in response to interaction with specific molecules. For example, hydrogels which become sol in the presence of glucose were developed. Hydrogels made of boronic acid-containing polymers and poly(vinyl alcohol) are known to degrade in the presence of glucose in the environment (32-34). Recently, glucose-containing copolymer and concanavalin-A molecules were used to prepare hydrogels which are more specific to glucose than boronic acid gels (35,36). The hydrogels become sol in the presence of glucose in the medium, and the sol becomes gel again if the free glucose molecules are removed by dialysis. Since there are many ligand specific interactions, such as antigen-antibody, avidin-biotin, and carbohydrate-lectin, various types of ligand-specific phase-reversible hydrogels can be made for different applications.

Hydrogels in Bioapplications

Pharmaceutical applications

Much of the research on hydrogels have been focused on the application in controlled drug delivery (37,38). While zero-order drug release is important for most drugs, there are many drugs that need to be delivered in a pulsatile fashion (39). The most widely used example is the delivery of insulin. Temporal control of insulin delivery can be achieved by utilization of smart hydrogels which release more insulin in response to increase in glucose level. Most glucose-responsive hydrogel systems are made of pH-sensitive polymers such as poly(diethylaminoethyl methacrylate) (PDEAEMA) (40-42) and glucose oxidase, which transforms glucose into gluconic

acid. In addition to the pH-responsive hydrogels, the glucose-sensitive dissolvable hydrogels have been used to control the insulin release (34,43). Microspherical hydrogels such as alginate microparticles have been used to encapsulate insulin-producing cells for the delivery of insulin (44).

Pulsatile delivery of drugs can also be achieved by temperature-responsive hydrogels. Thermo-sensitive hydrogels are usually made of polyacrylamide derivatives with hydrophobic groups which promote hydrophobic interactions necessary for shrinking at elevated temperatures. The volume collapse temperature can be adjusted by varying the hydrophobic groups. By altering the temperature around the thermosensitive hydrogels, the release of drug from the gel can be turned on and off at will (10,45).

Biomedical Applications

The applications of hydrogels in biomedical fields are diverse ranging from diagnostic device (46) to artificial muscle (47). Application of hydrogels as contact lenses and intraocular lenses has a rather long history compared with other applications. Soft contact lenses made of hydrogels possess desirable properties such as high oxygen permeability, although they have problems of protein deposits and lens spoilation (48). Soft intraocular lenses have advantages over rigid types. Their ability to be folded allows surgeon to use a much smaller surgical incision (49). The hydrogel contact and intraocular lenses can be sterilized by autoclaving, which is more convenient than the sterilization by ethylene oxide needed for rigid lenses made of poly(methyl methacrylate).

Hydrogels are commonly used as wound dressing materials, since they are flexible, durable, non-antigenic, and permeable to water vapor and metabolites, while securely covering the wound to prevent bacterial infection (50). Methylcellulose hydrogel has been used to deliver allergens in skin testing. When test allergens are delivered in the hydrogel vehicle, less skin irritation was observed (51). Hydrogels are also often coated on the urinary catheter surface to improve its biocompatibility (52). The hydrogel layer not only provide smooth, slippery surface, but also it can prevent bacterial colonization on the surface (53).

Hydrogel layers formed on the inner surface of injured arteries are known to reduce thrombosis and intimal thickening in animal models (54). Intimal thickening was prevented by inhibiting contact between blood and subendothelial tissue with a hydrogel layer. The swelling pressure of p(HEMA) hydrogel was used to stabilize the bone implants (55). With improved design of the implant, such hydrogels are expected to be effectively used as a stabilizing interface.

The potential applications of hydrogels in sterilization and cervical dilatation have been explored (56). When a hydrogel which forms an in situ plug was placed into fallopian tubes of rabbits by transcervical catheterization, conception was prevented. With more structurally rigid and biocompatible hydrogels the tubular sterilization system can be developed (57). Hydrogel rods were developed to deliver hormones such as prostaglandin analogs as well as to mechanically dilate the cervix. Dilatation of the cervical canal is necessary for the first trimester-induced abortion by suction curettage (56).

One of the advanced applications of hydrogels is in the development of artificial muscles. Smart hydrogels which can transform electrochemical stimuli into mechanical work (i.e., contraction) can function like the human muscle tissue (58). Polymeric gels capable of reversible contraction and expansion under physicochemical stimuli are essential in the development of advanced robotics with electrically driven muscle-like actuators (12) Smart materials that emulate the contractions and secretions of human organs in response to changes in environmental conditions such as temperature, pH, or electric field may soon find a use in medical implants, prosthetic muscles or organs, and robotic grippers (59).

Applications in Biotechnology

Hydrogels have been used as reactive matrix membranes in sensors. Hydrogels possess many advantageous properties, such as rapid and selective diffusion of the analyte, necessary for effective sensing. Hydrogels can also be made tough and flexible with desirable refractive indices (60).

Hydrogels made of p(HEMA) in an electrolyte solution were used as a salt bridge which separate the metallic electrodes from the biological system to prevent contamination by electrolysis products (61). The p(HEMA) salt bridges are inexpensive, easy to make, easy to sterilize, very durable, and nontoxic to cell systems. They provides a viable and effective alternative to the widely used agar salt bridge.

The ability of smart hydrogels in solutions to reversibly swell and shrink with small changes in the environmental conditions can be used to prepare purification devices (62). Smart hydrogels, especially thermo- and pH-sensitive hydrogels, have been used to concentrate dilute aqueous solutions of macromolecular solutes including proteins and enzymes, with no adverse effect on the activity of the enzyme (63). Water is absorbed into the hydrogel while macromolecules are excluded from the hydrogel network primarily by size and net charge (64). The absorbed water can be released from the hydrogel by altering temperature or pH of the environment, and thus the hydrogels can be reused repeatedly. Separation of bioactive proteins produced by recombinant DNA technology in a cost effective manner remains as one of the major huddles for the wide use of the technology. Separation of products by direct adsorption to adsorbents is attractive, but the adsorbents become fouled by colloidal contaminants and large macromolecules. This problem can be overcome by immobilizing adsorbents into hydrogels such as agarose and calcium alginate gel (52). Since the immobilized adsorbents do not contact with contaminants, separation becomes easier and more effective.

The smart hydrogels can also be used to control the reactions of substrates with immobilized enzymes by controlling the substrate diffusivity via swelling changes (65). Park and Hoffman immobilized Arthrobacter simplex in a thermally reversible hydrogel and examined the effect of temperature cycling on steroid conversion (66). The steroid conversion was higher in more hydrophobic gels due to the high partitioning of water-insoluble steroids into the hydrophobic regions and the reduced product inhibition within the hydrophobic gel matrices (66).

Future of Hydrogels

In the age of nanofabrication (67), the size of hydrogels in various applications is also expected to shrink. Gel electrophoresis is widely used for the separation of proteins and DNA. Recent report showed that miniaturized electrophoresis gel instrument in the size of 25 mm long and 50 μm wide was constructed (68). The gels that can be used in the instrument is orders of magnitude smaller than the gels used in conventional instruments. Miniaturization of hydrogels is also important in all the areas mentioned above. For example, the ability to reproducibly prepare hydrogels in microscale is essential in the preparation of glucose microsensors (69).

Hydrogels are generally biocompatible, but they are not perfect biomaterials, i.e., they still cause undesirable body reactions. Further improvement in biocompatibility will be critical in the wider applications of hydrogels in biomedical and pharmaceutical areas. Hydrogels have rather poor mechanical strength and durability for some applications. Enhancing these properties will make hydrogels more acceptable for many applications to come.

References

(1) Guenet, J.-M. *Thermoreversible Gelation of Polymers and Biopolymers*, Academic Press, New York, **1992**.
(2) Wichterle, O.; Lim, D. *Nature* **1960**, 185, 117-118.
(3) Aharoni, S. M.*Synthesis, Characterization, and Theory of Polymeric Network and Gels*, Plenum Press: New York, NY., 1992.
(4) DeRossi, D.; Kajiwara, K.; Osada, Y.; Yamauchi, A.*Polymer Gels. Fundamentals and Biomedical Applications*, Plenum Press: New York, NY., 1991.
(5) Takagi, T.; Takahashi, K.; Aizawa, M.; Miyata, S.*Proceedings of the First International Conference on Intelligent Materials*, Technomic Publishing Co., Inc.: Lanaster, PA, 1993.
(6) Tanaka, T. *Sci. Amer.* **1981**, 244, 124-138.
(7) Siegel, R. A. in *Pulsed and Self-Regulated Drug Delivery*, CRC Press, Boca Raton, FL., **1990**, Chapter 8.
(8) Brannon-Peppas, L.; Peppas, N. A. *Chem. Eng. Sci.* **1991**, 46, 715-722.
(9) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *Journal Of Membrane Science* **1991**, 64, 283-294.
(10) Dong, L. C.; Hoffman, A. S. *Journal Of Controlled Release* **1990**, 13, 21-32.
(11) Yoshida, R.; Uchida, K.; Kaneko, Y.; Sakal, K.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Nature* **1995**, 374, 240-242.
(12) De Rossi, D.; Suzuki, M.; Osada, Y.; Morasso, P. *J. Intell. Mater. Syst. Struct.* **1992**, 3, 75-95.
(13) Kaetsu, I.; Uchida, K.; Morita, Y.; Okubo, M. *Radiat. Phys. Chem.* **1992**, 40, 157-160.
(14) Tanaka, T.; Nishio, I.; Sun, S.-T.; Ueno-Nishio, S. *Science* **1982**, 218, 467-469.
(15) Kwon, I. C.; Bae, Y. H.; Kim, S. W. *Nature (Lond).* **1991**, 354, 291-293.
(16) Hooper, H. H.; Baker, J. P.; Blanch, H. W.; Prausnitz, J. M. *Macromolecules* **1990**, 23, 1096-1104.
(17) Ohmine, I.; Tanaka, T. *J. Chem. Phys.* **1982**, 77, 5725-5729.
(18) Inomata, H.; Goto, S.; Otake, K.; Saito, S. *Macromolecules* **1992**, 8, 687-690.
(19) Hu, Y.; Horie, K.; Ushiki, H.; Yamashita, T.; Tsunomori, F. *Macromolecules* **1993**, 26, 1761-1766.
(20) Amiya, T.; Tanaka, T. *Macromolecules* **1987**, 20, 1162-1164.
(21) Okuzaki, H.; Osada, Y. in *Proceedings of the First International Conference on Intelligent Materials*, Technomic Publishing Co., Inc., Lanaster, PA, **1993**, 273-278.
(22) Sawahata, K.; Hara, M.; Yasunaga, H.; Osada, Y. *J. Controlled Rel.* **1990**, 14, 253-262.
(23) Suzuki, A. in *Proceedings of the First International Conference on Intelligent Materials*, Technomic Publishing Co., Inc., Lanaster, PA, **1993**, 297-300.
(24) Mamada, A.; Tanaka, T.; Kungwatchakun, D.; Irie, M. *Macromolecules* **1990**, 23, 1517-1519.
(25) Lee, K. K.; Cussler, E. L.; Marchetti, M.; McHugh, M. A. *Chem. Eng. Sci.* **1990**, 45, 766-767.
(26) Capozza, R. C.; Meyers, W. E.; Neidlinger, H. H.; Stoy, V. A. *Polymer Preprints* **1990**, 31, 57.
(27) Liu, Y.; Huglin, M. B.; Davis, T. P. *Eur. Polym. J.* **1994**, 30, 457-463.
(28) Park, H.; Park, K. *The 20th Annual Meeting of the Society for Biomaterials* **1994**, Abstract #158.
(29) Park, H.; Park, K. *Proc. Intern. Symp. Control. Rel. Bioact. Mater.* **1994**, 21, 21-22.

(30) Chirila, T. V.; Constable, I. J.; Crawford, G. J.; Vijayasekaran, S.; Thompson, D. E.; Chen, Y. C.; Fletcher, W. A.; Griffin, B. J. *Biomaterials* **1993**, 14, 26-38.
(31) Oxley, H. R.; Corkhill, P. H.; Fitton, J. H.; Tighe, B. J. *Biomaterials* **1993**, 14, 1065-1072.
(32) Miyazaki, H.; Kikuchi, A.; Kitano, S.; Kataoka, K.; Koyama, Y.; Okano, T.; Sakurai, Y. in *Proceedings of the First International Conference on Intelligent Materials*, Technomic Publishing Co., Inc., Lanaster, PA, **1993**, 481-484.
(33) Kitano, S.; Hisamitsu, I.; Koyama, Y.; Kataoka, K.; Okano, T.; Yokoyama, M.; Sakurai, Y. in *Proceedings of the First International Conference on Intelligent Materials*, Technomic Publishing Co., Inc., Lanaster, PA, **1993**, 383-388.
(34) Shino, D.; Kataoka, K.; Koyama, Y.; Yokoyama, M.; Okano, T.; Sakurai, Y. in *Proceedings of the First International Conference on Intelligent Materials*, Technomic Publishing Co., Inc., Lanaster, PA, **1993**, 301-304.
(35) Lee, S. J.; Park, K. *Polymer Preprints* **1994**, 35, 391-392.
(36) Lee, S. J.; Park, K. *J. Mol. Rec.* submitted for publication.
(37) Peppas, N. A. *Hydrogels in Medicine and Pharmacy. Volumes I-III.*, CRC Press, Boca Raton, FL, **1987**.
(38) Park, K.; Shalaby, S. W. S.; Park, H. *Biodegradable Hydrogels for Drug Delivery*, Technomic Publishing Co., Lancaster, **1993**.
(39) Kost, J.*Pulsed and Self-Regulated Drug Delivery*, CRC Press: Boca Raton, FL., **1990**.
(40) Klumb, L. A.; Horbett, T. A. *Journal Of Controlled Release* **1993**, 27, 95-114.
(41) Albin, G.; Horbett, T. A.; Ratner, B. D. in *Pulsed and Self-Regulated Drug Delivery*, CRC Press, Boca Raton, FL., **1990**, 159-185.
(42) Ishihara, K.; Kobayashi, M.; Shionohara, I. *Makromol. Chem. Rapid Commun.* **1983**, 4, 327-331.
(43) Kitano, S.; Koyama, Y.; Kataoka, K.; Okano, T.; Sakurai, Y. *J. Controlled Rel.* **1992**, 19, 162-170.
(44) Lacy, P. E. *Sci. Amer.* **1995**, 273, 50-58.
(45) Bae, Y. H.; Okano, T.; Kim, S. W. *Pharm. Res.* **1991**, 8, 624-628.
(46) Hoffman, A. S. *J. Controlled Rel.* **1987**, 6, 297-305.
(47) Suzuki, M. *Kobunshi Ronbunshu* **1989**, 46, 603-611.
(48) Myers, R. I.; Larsen, D. W.; Taso, M.; Castellano, C.; Becherer, L. D.; Fontana, F.; Ghormley, N. R.; Meier, G. *Optometry And Vision Science* **1991**, 68, 776-782.
(49) Carlson, K. H.; Cameron, J. D.; Lindstrom, R. L. *Journal Of Cataract And Refractive Surgery* **1993**, 19, 9-15.
(50) Corkhill, P. H.; Hamilton, C. J.; Tighe, B. J. *Biomaterials* **1989**, 10, 3-10.
(51) Darsow, U.; Vieluf, D.; Ring, J. *Journal Of Allergy And Clinical Immunology* **1995**, 95, 677-684.
(52) Nigam, S. C.; Sakoda, A.; Wang, H. Y. *Biotechnology Progress* **1988**, 4, 166-172.
(53) Graiver, D.; Durall, R. L.; Okada, T. *Biomaterials* **1993**, 14, 465-469.
(54) Hill-West, J. L.; Chowdhury, S. M.; Slepian, M. J.; Hubbell, J. A. *Proceedings Of The National Academy Of Sciences Of The United States Of America* **1994**, 91, 5967-5971.
(55) Netti, P. A.; Shelton, J. C.; Revell, P. A.; Pirie, C.; Smith, S.; Ambrosio, L.; Nicolais, L.; Bonfield *Biomaterials* **1993**, 14, 1098-1104.
(56) Molin, A.; Brundin, J. *Gynecologic And Obstetric Investigation* **1992**, 34, 12-14.
(57) Maubon, A. J.; Thurmond, A. S.; Laurent, A.; Honiger, J. E.; Scanlan, R. M.; Rouanet, J. P. *Radiology* **1994**, 193, 721-723.

(58) Studt, T. *R&D Magazine* **1992**, April, 55-60.
(59) Constance, J. *Mech. Eng.* **1991**, 113, 51-53.
(60) Davies, M. L.; Murphy, S. M.; Hamilton, C. J.; Tighe, B. J. *Biomaterials* **1992**, 13, 991-999.
(61) Kindler, D. D.; Bergethon, P. R. *Journal of Applied Physiology* **1990**, 69, 373-375.
(62) Marchetti, M.; Cussler, E. L. *Sep. Purif. Methods* **1989**, 18, 177-192.
(63) Gehrke, S. H.; Andrews, G. P.; Cussler, E. L. *Chem. Eng. Sci.* **1986**, 41, 2153-2169.
(64) Vasheghani-Farahani, E.; Cooper, D. G.; Vera, J. H.; Weber, M. E. *Chem. Eng. Sci.* **1992**, 47, 31-40.
(65) Park, T. G.; Hoffman, A. S. *Biotechnology Progress* **1994**, 10, 82-86.
(66) Park, T. G.; Hoffman, A. S. *Journal Of Biomedical Materials Research* **1990**, 24, 21-38.
(67) Drexler, K. E. *Nanosystems. Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, NY, **1992**.
(68) Studt, T. *R&D Magazine* **1995**, June Issue, 22-26.
(69) Pishko, M. V.; Michael, A. C.; Heller, A. *Analytical Chemistry* **1991**, 63, 2268-2272.

RECEIVED July 11, 1995