Hydrophobic Anionic Gel Beads for Swelling-Controlled Drug Delivery

Cherng-Ju Kim[1] and Ping I. Lee[1-3]

Received February 19, 1991; accepted August 18, 1991

Using oxprenolol HCl as a model drug, the effects of pH and buffer concentration on the swelling and drug release properties in cross-linked poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads have been investigated. The kinetics of swelling of such hydrophobic anionic gel beads from the dehydrated state appear to be governed primarily by a diffusion–ionization process which becomes more ionization-controlled at higher buffer concentrations. Within the range of ionic compositions studied, the swelling rate increases and the initial swelling/ionization front penetration becomes increasingly linear in time with increasing pH or buffer concentration of the swelling medium. The corresponding swelling bead diameter appears to reach an equilibrium value as soon as the penetrating ionization fronts meet at the center, suggesting a swelling equilibrium in the ionized shell due to rapid mechanical readjustment in the gel phase. At oxprenolol loading levels up to 15%, both the transient drug release and swelling bead diameter exhibit extended quasi-linear regions despite the inherent limitation of decreasing surface area at the penetrating front in the spherical geometry. In addition, both the drug release and the dimensional changes reach completion when the penetrating ionization fronts meet at the center, suggesting a true swelling-controlled drug release behavior.

KEY WORDS: swelling-controlled drug release; polyelectrolyte gel beads; poly(methyl methacrylate-co-methacrylic acid); swelling front penetration; ion exchange.

INTRODUCTION

Polyelectrolyte gels are known to exhibit swelling properties that are sensitive to the pH, ionic strength, and specific ionic composition of the swelling medium (1). Typically, the ionic contribution to the swelling in polyelectrolyte gels is a result of either the protonation of pendant tertiary amine groups, in the case of cationic gels, or the hydrolysis of pendant carboxylic acid groups, in the case of anionic gels. Often, the extent of such swelling is further affected by factors such as the charge density, extent of cross-linking, and chemical composition of the polymer gel (2). The potential to modulate the dynamics of gel swelling by varying these parameters has led to proposed applications ranging from separation by gel extraction (3) to controlled-release drug delivery (4,5).

The kinetics of swelling in hydrated polyelectrolyte gels are generally controlled by a diffusion-reaction process, which governs the rate of ion exchange, and a deformation (often called relaxation) process, which determines the rate of mechanical readjustment of the elastic gel matrix in response to the swelling stress. This aspect has been examined in preswollen gels by Grodzinsky and co-workers (6,7) using a continuum theory that considers ion transport within the gel, dissociation of fixed charge groups, and the simultaneous swelling and mechanical deformation of the gel matrix. It is anticipated that similar mechanisms are also involved in the swelling of dehydrated polyelectrolytes. In the case of drug release from initially dry polyelectrolyte gels, it has been suggested that, similar to the rate considerations in nonionic glassy polymers, the relative importance of the rate of macromolecular chain relaxation during swelling to that of drug diffusion governs the exact release mechanism (5). Although the nature of such macromolecular relaxation was not specified, it is believed to be related to some electrochemical processes occurring at the swelling front. Such processes can be affected significantly by the local ionic environment and drug concentration.

Both anionic and cationic gels have been studied extensively in terms of their equilibrium swelling properties as a function of solvent pH, ionic strength, and ionic composition (8–12). However, the kinetics of swelling and drug release from dehydrated polyelectrolyte gels have been investigated only to a limited extent (5,11). Almost all of these reported studies were based on disk samples of flat-sheet geometry with thicknesses ranging from 0.5 to 1 mm. As a result of the well-known anisotropic swelling effect in glassy polymer samples with large aspect ratios, an accelerated water swelling was observed in an initially dry polybasic gel disk (11); however, no corresponding acceleration of drug release was detected. In addition to a total release duration of 2 to 3 hr, too short to be useful for most pharmaceutical applications, no mention was made on the level of drug loading employed and its effect on drug release in these previous studies. Here, we investigate the kinetics of swelling and drug release, including solvent front penetration and the corresponding dimensional changes, in initially dry spherical gel beads of poly(methyl methacrylate-co-methacrylic acid) as a function of pH, buffer concentration, and drug loading. This inherently hydrophobic polymer is similar in composition to a widely used enteric coating polymer, Eudradgit L, except the present system contains loose cross-links to prevent a complete polymer dissolution above neutral pH. The spherical geometry employed here eliminates the anisotropic swelling behavior normally associated with sheet samples. It will be shown later that this system exhibits true swelling-controlled release characteristics and offers an extended release period up to 24 hr or more.

EXPERIMENTAL

Synthesis of Poly(Methyl Methacrylate-co-Methacrylic Acid). Using a modification of a previously reported method (13), poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads were prepared by free radical suspension polymerization of a mixture (54/46 mol%) of freshly distilled methyl methacrylate (MMA) and inhibitor-free methacrylic acid (MAA) using ethylene glycol dimeth-

[1] Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 2S2, Canada.
[2] Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Ontario M5S 1A4, Canada.
[3] To whom correspondence should be addressed at Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ontario, M5S 2S2, Canada.

0724-8741/92/0200-0195$06.50/0

acrylate as the cross-linking agent (0.7 mol%). The polymerization was carried out in a concentrated $CaCl_2$ solution at 70°C and 150 rpm for 5–6 hr under nitrogen using freshly precipitated hydroxyapatite [$3Ca_3(PO_4)_2 \cdot Ca(OH)_2$] as the suspending agent and 2,2′-azobisisobutyronitrile (Vazo 64, DuPont) as the initiator. The relative amount of monomer to water in the polymerization mixture was 1:5 by weight. After the completion of polymerization, concentrated HCl was added to the reaction mixture to remove the suspending agent. These beads were filtered and then extracted in a Soxhlet with methanol for 24 hr before being dried and fractionated. For this study, the fraction of PMMA/MAA beads with a dry diameter of 0.1–0.118 cm was used.

Swelling and Drug Release. The swelling experiments were carried out in a cuvette immersed in a water bath maintained at 37°C. The swelling front was observed with a Wild M420 stereomicroscope equipped with camera attachments and digital optical measuring accessory. Oxprenolol HCl (solubility in water, ~77%) was used as a model drug. The drug loading was achieved by equilibrating the beads for 5 days in concentrated drug solutions prepared in a 70/30 methanol/water mixture. After filtering and drying, the drug-loaded beads were then used for swelling and drug release studies in Sørensen phosphate buffer solutions. The *in vitro* drug release at 37°C under perfect sink condition was monitored at 274 nm continuously in a stirred cuvette on a Hewlett Packard 8452A diode-array UV-Vis spectrophotometer equipped with a water-jacketed cuvette holder and a built-in magnetic stirrer. The Sørensen phosphate buffer solutions were prepared by mixing stock solutions of monobasic potassium phosphate (KH_2PO_4) and dibasic sodium phosphate (Na_2HPO_4) in different proportions, either at a constant pH but different ionic strengths by adjusting the concentration of stock solutions or at the same buffer concentration but different pH's while maintaining a constant ionic strength by the addition of a calculated amount of NaCl. In all cases, the buffer solution to sample volume ratio was maintained to be larger than 6000.

RESULTS AND DISCUSSION

The dynamic swelling behavior and transient dimensional changes of the present anionic copolymer gel were investigated by following their respective solvent moving boundary and outer diameter changes. When these glassy PMMA/MAA beads (T_g ~115°C) were immersed in distilled/deionized water (pH 5.5–6) or another more acidic environment, a very diffused but fast-moving front attributable to water penetration was visible. However, the corresponding dimensional changes were negligible due to the hydrophobic nature (~13% swelling in DI water) and the lack of ionization in the polymer under the given condition. Such a low level of water penetration in the nonionized PMMA/MAA did not result in a glassy/rubbery phase transition. On the other hand, upon contact with a neutral or weakly basic medium, a sharp swelling front lagging behind the diffused water penetrating front developed as a result of the ionization of pendant carboxylic acid groups. This led to the formation of a swollen ionized shell surrounding a glassy nonionized core. Since the polyelectrolyte gel swelling at any time is a function of the extent of both ionization and deviation from mechanical equilibrium, the progression of this moving ionization/swelling front separating the swollen shell from a glassy core should reflect the relative contributions from the following three rate processes: electrolyte diffusion through the gel, ionization at the penetrating front, and mechanical readjustment of the gel phase in response to the swelling stress. The diffusion-ionization process considered here is formally identical to the well-known mechanism of diffusion with heterogeneous reactions. Previously, Grodzinsky and co-workers (6,7) have shown that the swelling kinetics in poly(methacrylic acid) (PMAA) and articular cartilage are governed primarily by a diffusion-limited ionization process because of the rapid approach to mechanical equilibrium in the swollen phase.

Figure 1a illustrates the effect of phosphate buffer concentration on the dynamic swelling behavior of glassy PMMA/MAA beads at pH 7.4, where it is seen that the penetrating ionization front is moving at a faster rate with increasing buffer concentrations. This is a result primarily of faster ionization at an increased electrolyte uptake due to a more effective reduction of Donnan potential (or suppression of Donnan effect) at higher buffer concentrations. At the lowest buffer concentration of Fig. 1a, a slight nonlinearity appears in the early portion of the front penetration indicative of contributions from a diffusion-limited ionization process. As the buffer concentration increases, this early stage of nonlinear penetration diminishes, indicating a reduction of such diffusion-limited contributions due to increased diffusion rates at higher buffer concentrations. Mechanistically, this represents a shift toward an ionization-limited or ionization-controlled swelling process. This initial region of front penetration appears to be followed by an

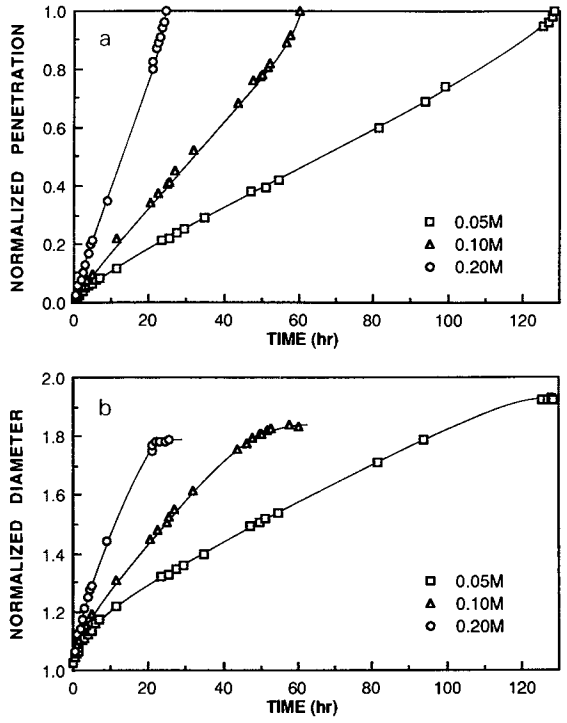

Fig. 1. Effect of buffer concentration on (a) ionization front penetration and (b) dimensional changes in PMMA/MAA beads at pH 7.4 and 37°C.

apparent constant-rate front movement before accelerating toward the centre. We have shown previously (15,16) that this acceleration of front movement near the center is a natural outcome of the spherical geometry and not a super Case II transport behavior. The effect of buffer pH on the swelling kinetics in PMMA/MMA beads at a constant ionic strength (0.2 *M* Sørensen phosphate buffer adjusted to ionic strength $I = 0.6$ *M* with NaCl) is presented in Fig. 2a for pH 6.9, 7.4, and 9.0. The highest buffer concentration (0.2 *M*) was employed to shorten the observation time on the dynamic swelling of these beads at different pH's. In this case, a penetration behavior similar to that in Fig. 1a is evident. Here, in addition to a better reduction of Donnan potential, which facilitates the electrolyte diffusion into the gel, the faster rate of ionization front movement at higher pH's is directly attributable to the increasing availability of mobile hydroxide ions, which can lead to a faster ionization of pendant carboxylic acid groups.

Figures 1b and 2b illustrate the corresponding transient dimensional changes during the swelling front penetration in PMMA/MAA beads. After a brief initial increase in the bead diameter (normalized to the original diameter), an extended quasi-linear boundary movement prevails, which is followed by a rapid plateau toward swelling equilibrium. The equilibrium swollen diameter at the plateau is seen to decrease slightly with increasing buffer concentration (Fig. 1b) and decreasing pH (Fig. 2b), within the range of variables studied here. This is the result primarily of a decrease in ion osmotic pressure difference between the gel and the solution either due to an increase in solution osmotic pressure at higher buffer concentrations or due to a decrease in gel osmotic pressure caused by a reduction in mobile counterion content in the gel network at lower pH's. The observed transient dimensional changes in the present anionic PMMA/MAA gel beads are significantly different from those observed in nonionic hydrogel beads such as poly(2-hydroxyethyl methacrylate) (PHEMA) (15,16). It is important to note that, in the present anionic gel beads, the swelling bead diameter reaches an equilibrium value as soon as the ionization fronts meet at the centre suggesting a negligible solvent concentration gradient behind the sharp front. In other words, a swelling equilibrium is maintained in the ionized shell due to rapid mechanical readjustment in the gel phase. In contrast, the swelling bead diameter in nonionic PHEMA beads would continue to progress much longer after the swelling fronts have met at the center as a result of a significant solvent concentration gradient behind the sharp front due to a slow approach to swelling equilibrium (16).

The release of oxprenolol HCl from PMMA/MAA gel beads in 0.1 *M* Sørensen phosphate buffer (pH 7.4, $I = 0.26$ *M*) is illustrated in Fig. 3a for a drug loading of 15% and in Fig. 3b for a drug loading of 9.7%, along with the corresponding ionization front penetration and transient dimensional changes. The drug release appears to be initially nonlinear (or non-Fickian) only for a short period of time. This is followed by an extended quasi-linear release region before leveling off, where the release rate is seen to increase with the drug loading. A total release duration of about 25–30 hr has been achieved with the 15% drug loading, compared to the range of 40–45 hr for the 9.7% drug loading; shorter durations of drug release are expected at higher drug loadings. A similar transient pattern is also observed in the cor-

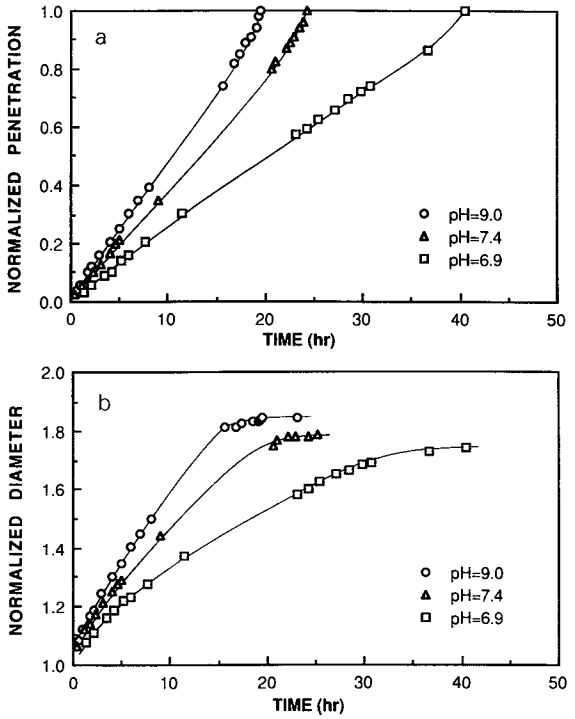

Fig. 2. Effect of pH on (a) ionization front penetration and (b) dimensional changes in PMMA/MAA beads at a buffer concentration of 0.2 *M* and a constant ionic strength of 0.6 *M* and 37°C.

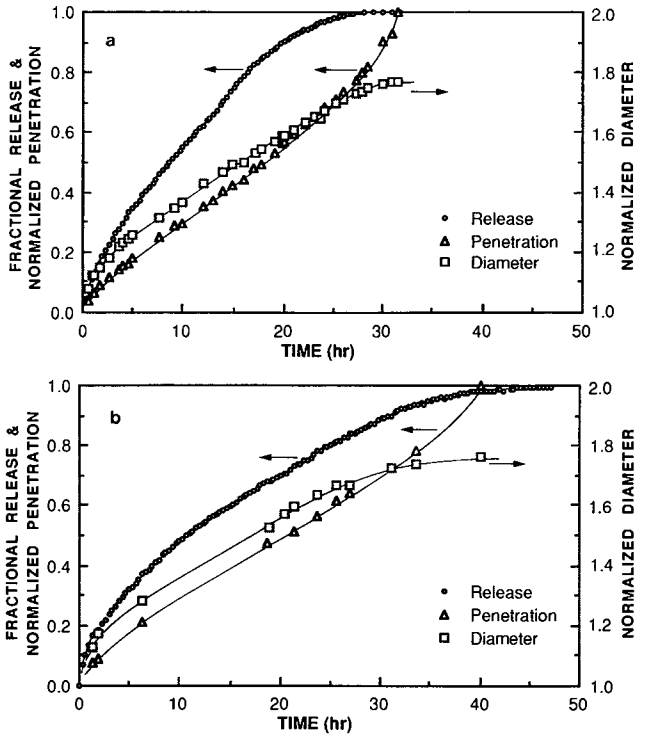

Fig. 3. Ionization front penetration and transient dimensional changes during oxprenolol HCl release from PMMA/MAA beads at pH 7.4 and 37°C with a buffer concentration of 0.1 *M* and a constant ionic strength of 0.26 M: (a) 15% loading; (b) 9.7% loading.

responding sample dimensional changes. At present, there are no satisfactory interpretations regarding the exact origin of these quasi-linear regions in drug release and sample dimensional changes, particularly relating to the spherical geometry studied here. Nevertheless, similar to Figs. 1a and 2a, the linear (or constant-rate) penetrating front movement and the subsequent front acceleration toward the core observed in drug-loaded beads (Figs. 3a and b) can be attributed directly to the known geometry effect in spheres (14,15). It is obvious that, under identical experimental conditions, the penetrating front movement and the corresponding dimensional changes in drug-loaded PMMA/MAA beads (Figs. 3a and b) follow the same kinetic behavior as observed in drug-free PMMA/MAA beads (Figs. 1a and b). The only exception is that the time frame for the completion of these changes is much shorter for the drug-loaded beads. At the present loading levels, the drug is believed to be in a dissolved state as evident from the clear appearance of drug-loaded PMMA/MAA beads. Since the presence of dissolved drug in the polymer phase provides an additional osmotic driving force which increases with the drug loading (15), the observed increases in the rate of swelling and drug release upon increasing the drug loading are a direct result of the corresponding increases in the rate of solvent and electrolyte uptake and the rate of subsequent gel ionization.

Unlike other nonionic hydrogel beads such as PHEMA, in which the diameter of a drug-loaded bead goes through a maximum before reaching equilibrium (17), the current drug-loaded PMMA/MAA gel beads exhibit a monotonic diameter increase during the time course of the drug release. This suggests that the osmotic swelling contribution from the dissolved drug in the gel network may be too small compared to the swelling contribution from the gel ionization in the present system. In fact, this rationale is supported by the fact that an increase in bead diameter of 80–90% was observed in the present PMMA/MAA upon swelling as compared to a less than 20% increase typically observed in PHEMA beads. It is worth noting that the processes of drug release and dimensional changes in the present PMMA/MAA gel beads appear to reach completion as the penetrating ionization fronts meet at the center (Figs. 3a and b), again conforming to the earlier conclusion of a swelling equilibrium in the ionized shell in the present system. Similar swelling behavior involving both the linear front movement and the simultaneous completion of swelling front penetration and sample weight gain (or dimensional changes) has been observed in sheet samples (18) as well as spherical bead samples (14) of glassy poly(methyl methacrylate) (PMMA) during methanol penetration. This is a result of the known Case II swelling behavior, or swelling-controlled penetration, of methanol in glassy PMMA. Therefore, in the present PMMA/MAA anionic gel system, it is reasonable to suggest that the observed drug release is primarily governed by a diffusion-ionization gel swelling process, which exhibits analogous swelling and drug release kinetics as in a typical swelling-controlled system.

CONCLUSIONS

We have characterized the effects of pH, buffer concentration, and drug loading on the swelling and drug release properties in dehydrated gel beads of a hydrophobic anionic polyelectrolyte, PMMA/MAA. The spherical geometry employed here eliminates the anisotropic swelling behavior normally associated with glassy polymers in sheet geometry. Although the PMMA/MAA swelling rate appears to be more diffusion-limited at low pH's and buffer concentrations, it increases with the pH and buffer concentration of the swelling medium as well as the drug loading. As a result, an ionization-controlled swelling mechanism seems to become more rate-limiting at higher buffer concentrations. An observation of particular interest is that both the drug release and the associated dimensional changes exhibit an extended quasi-linear region despite the inherent limitation of decreasing surface area at the penetrating front in the spherical geometry. In addition, both processes appear to end when the penetrating ionization fronts meet at the center, suggesting a true swelling-controlled drug release behavior.

With the present hydrophobic anionic gel beads, an extended duration of quasi-zero-order drug release has been demonstrated. The present polymer is similar in composition to the enteric polymer Eudragit L, except our bead system contains loose cross-links to prevent complete polymer dissolution at physiological pH and to augment the ionization-controlled swelling and release mechanism. Therefore, this system may be potentially useful for various drug delivery applications, particularly oral delivery. Another point worth commenting on is the lack of an observed maximum in the transient swelling diameter of drug-loaded PMMA/MAA beads, as would normally be expected in nonionic hydrogels. This has been interpreted as a result of insufficient osmotic swelling contribution from the drug loading as compared to the unusually large swelling contribution from the gel ionization in the present system. Additional investigations as to the effect of further increasing the drug loading on both the kinetics of gel swelling and drug release are currently in progress.

ACKNOWLEDGMENT

This work was supported by a grant from the Medical Research Council of Canada (DG-377).

REFERENCES

1. W. Kuhn, B. Hargitay, A. Katchalsky, and H. Eisenberg. Reversible dilation and contraction by changing the state of ionization of high-polymer acid networks. *Nature* 165:514–516 (1950).
2. F. Helfferich. *Ion Exchange*, McGraw–Hill, New York, 1962.
3. S. H. Gehrke, G. P. Andrews, and E. L. Cussler. Chemical aspects of gel extraction. *Chem. Eng. Sci.* 41:2153–2160 (1986).
4. J. H. Kou, G. L. Amidon, and P. I. Lee. pH-dependent swelling and solute diffusion characteristics of poly(hydroxyethyl methacrylate-co-methacrylic acid) hydrogels. *Pharm. Res.* 5:592–597 (1988).
5. L. Brannon-Peppas and N. A. Peppas, Solute and penetrant diffusion in swellable polymers. IX. The mechanisms of drug release from pH-sensitive swelling-controlled systems. *J. Control. Release* 8:267–274 (1989).
6. P. E. Grimshaw, J. H. Nussbaum, A. J. Grodzinsky, and M. L. Yarmush. Kinetics of electrically and chemically induced swelling in polyelectrolyte gels. *J. Chem. Phys.* 93:4462–4472 (1990).
7. S. R. Eisenberg and A. J. Grodzinsky. The kinetics of chemi-

cally induced non-equilibrium swelling of articular cartilage and corneal stroma. *J. Biomech. Eng.* **109**:79–89 (1987).
8. E. Vasheghani-Farahani, J. H. Vera, D. G. Cooper, and M. E. Weber. Swelling of ionic gels in electrolyte solutions. *Ind. Eng. Chem. Res.* **29**:554–560 (1990).
9. S. H. Gehrke and E. L. Cussler. Mass transfer in pH-sensitive hydrogels. *Chem. Eng. Sci.* **44**:559–566 (1989).
10. B. A. Firestone and R. A. Siegal. Dynamic pH-dependent swelling properties of a hydrophobic polyelectrolyte gel. *Polym. Commun.* **29**:204–208 (1988).
11. R. A. Siegal, B. A. Firestone, I. Johannes, and J. Cornejo. Weak ionic hydrogels: Effects of pH, ionic strength, and buffer composition on swelling equilibria, kinetics, and solute release. *Polym. Preprint* **31**:231–232 (1990).
12. L. Brannon-Peppas and N. A. Peppas. Equilibrium swelling behaviour of pH-sensitive hydrogels. *Chem. Eng. Sci.* **46**:715–722 (1991).
13. M. H. B. Skovby and J. Kops. Preparation by suspension polymerization of porous beads for enzyme immobilization. *J. Appl. Polym. Sci.* **39**:167–177 (1990).
14. P. I. Lee and C.-J. Kim. Effect of geometry on solvent front penetration in glassy polymers. *J. Membr. Sci.* (in press).
15. P. I. Lee and C.-J. Kim. Probing the mechanisms of drug release from hydrogels. *J. Control. Release* **16**:229–236 (1991).
16. P. I. Lee. Kinetics of drug release from hydrogel matrices. *J. Control. Release* **2**:277–288 (1988).
17. P. I. Lee. Dimensional changes during drug release from a glassy hydrogel matrix. *Polym. Commun.* **24**:45–47 (1983).
18. N. L. Thomas and A. H. Windle. Transport of methanol in poly(methyl methacrylate). *Polymer* **19**:255–265 (1978).