Effect of Loading on Swelling-Controlled Drug Release from Hydrophobic Polyelectrolyte Gel Beads

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The effect of oxprenolol HCl loading on the kinetics of polymer swelling and drug release from suspension-polymerized poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads has been studied in detail. Within the range of variables studied, the polymer swelling rate increases with buffer pH and concentration. And an ionization-controlled swelling mechanism (analogous to the relaxation-controlled mechanism) seems to become more rate-limiting at higher buffer concentrations. At oxprenolol HCL loading levels below 17.8%, the drug release and associated dimensional changes (in pH 7.4) exhibit an extended quasi-linear region despite the inherent limitation of spherical geometry. At higher loading levels, the drug release becomes faster and first-order in nature. This is apparently a result of the transition from a dissolved to a dispersed system above a percolation threshold (15–18% loading in the present study). As a result of competition from processes such as the reduction of bead dimension due to drug release and the dimensional increase due to polymer swelling and osmotic contributions from the drug, the transient bead diameter increases monotonically during drug release at loading levels up to 25.6%, whereas upon further increasing the drug loading, the bead diameter goes through a maximum during the early drug release, which eventually increases again as a result of the slow but continuous increase in polymer swelling due to further ionization. In all cases, both the drug release and the dimensional changes approach completion as the penetrating ionization fronts meet at the center, indicating a true swelling-controlled behavior.

KEY WORDS: swelling-controlled drug release; polyelectrolyte gel beads; poly(methyl methacrylate-co-methacrylic acid); loading effect; swelling kinetics.

INTRODUCTION

Cross-linked polyelectrolytes in the form of ion-exchange resins were introduced over 50 years ago (1). Their reported pharmaceutical applications range from tablet disintegration, to sustained release, to taste-masking (2). However, most of these existing ion exchange resins are highly cross-linked and macroreticular, with a sponge-like structure. As a result, ionic drugs are absorbed or eluted quite rapidly due to the fast exchange process in the porous structure of the resin. This is not surprising since the major intended utilities for these ion-exchange resins have been in the area of separations, where a rapid exchange rate is important. Although attempts have been made to utilize some of these resins in sustained-release dosage forms, the duration of the drug release and the release rate profile are generally not very satisfactory (3). More recently, there has been a renewed interest in gel-type polyelectrolytes as potential controlled-release drug carriers (4) or as gel extraction media for protein separations (5). This is achieved primarily through a better modulation of the swelling dynamics of polyelectrolyte gels by varying the charge density, extent of cross-linking, and chemical composition of the polymer.

The swelling of polyelectrolyte gels is known to be sensitive to the pH, ionic strength, and ionic composition of the swelling medium (6). Depending on the polymer composition, a cationic gel, for example, can result from the protonation of pendent tertiary amine groups, and an anionic gel from the hydrolysis of pendent carboxylic acid groups. Both anionic and cationic gels have been studied extensively in terms of their equilibrium swelling properties (7–9). The kinetics of swelling in hydrated polyelectrolyte gels have been shown to be governed by a diffusion reaction-limited process, which determines the rate of ion exchange, and a deformation process, which controls the mechanical readjustment of the gel matrix in response to the swelling stress (10). In the case of drug release from initially dry polyelectrolyte gels, the swelling kinetics are further complicated by the glass-to-rubbery phase transition (11).

Previously, we have shown that the level of drug loading can affect significantly the kinetics of swelling and drug release from nonionic glassy hydrogels (12,13). Despite its obvious importance to the design of practical drug delivery systems, this aspect has often been overlooked in the hydrogel literature. Therefore, it is not surprising that the effects of loading on the kinetics of swelling and drug release from glassy polyelectrolyte gels have been investigated only to a limited extent. For example, the release of theophylline from poly(hydroxyethyl methacrylate-co-methacrylic acid) (PHEMA/MAA) and poly(hydroxyethyl methacrylate-co-maleic anhydride) (PHEMA/MAH) was studied by Brennon-Peppas and Peppas (11). And the release of caffeine from poly(methyl methacrylate-co-dimethylaminoethyl methacrylate) (PMMA/DMAEMA) was reported by Siegal *et al.* (8). The results from both studies show a quasi-linear release pattern. On the other hand, a first-order or Fickian release kinetics has been reported by Kou *et al.* (4) on the release of phenylpropanolamine from preswollen PHEMA/MAA. All these reported studies were based on disc samples of flat sheet geometry which could easily be affected by the well-known anisotropic swelling effect in glassy polymer samples. In addition to a total release period of 2 to 3 hr, too short to be useful for most pharmaceutical applications, no mention was made of the drug loading employed by these previous studies and its effect on drug release was therefore not assessed.

Recently, in a preliminary report, we studied the effects of swelling medium on the polymer swelling and oxprenolol HCl release in glassy poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads (14). As a result of an ionization-controlled swelling process, both the drug release and the swelling bead dimension showed an unexpected quasi-linear region at physiological pH for drug loadings up to 15%, despite the inherent limitation of decreasing

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surface area at the penetrating front in the spherical geometry. This hydrophobic anionic gel was similar in composition to the widely used enteric polymer, Eudragit L, except our system contained loose cross-links to prevent complete polymer dissolution at physiological pH. The spherical geometry employed has the advantage of eliminating the anisotropic swelling behavior normally associated with sheet samples. The present study was undertaken in order to examine the important effect of drug loading on the kinetics of swelling and oxprenolol HCl release from glassy PMMA/MAA beads as a function of buffer concentration and pH. We demonstrate here the existence of loading-induced transition in the dynamic swelling and drug release behavior in such swellable polyelectrolyte gels.

EXPERIMENTAL

Synthesis of PMMA/MAA Beads

Based on a modification of a previously published method (15), PMMA/MAA beads were prepared by free radical suspension polymerization of a mixture of freshly distilled methyl methacrylate (MMA) and inhibitor-free methacrylic acid (MAA) (54/46 mol%), with ethylene glycol dimethacrylate as the cross-linking agent (0.7 mol%). The polymerization was carried out in a concentrated aqueous solution of $CaCl_2$ at 70°C and 150 rpm for 5–6 hr under nitrogen, using freshly precipitated hydroxyapatite $[3Ca_3(PO_4)_2\ Ca(OH)_2]$ as the suspending medium. 2,2′-Azobisisobutyronitrile (Vazo 64, DuPont) was used as the initiator. The relative amount of monomer to water in the polymerization mixture was 1 to 5 by weight. After the completion of polymerization, concentrated HCl was added to the reaction mixture to dissolve the suspending agent. The resulting beads were filtered and extracted in Soxhlet with methanol for 24 hr before being dried and fractionated. The PMMA/MAA beads so prepared were glassy (T_g ~115°C) as well as smooth and spherical, with diameters up to 1.4 mm. In this study, the fraction of beads with a dry diameter of 0.1–0.118 cm was used.

Swelling and Drug Release Experiments

The swelling experiments were carried out in a cuvette immersed in a constant-temperature water bath (Haake D8-G) 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 in concentrated drug solutions in a 70/30 methanol/water mixture for 5 days. After filtering and drying, the drug-loaded beads were then used for subsequent swelling and drug release studies in Sørensen phosphate buffer solutions. The *in vitro* drug release at 37°C under perfect sink conditions 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 a different ionic strength, by adjusting the concentration of stock solutions, or at the same buffer condition 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

Effect of Buffer pH and Concentration

The effect of buffer pH on the release of oxprenolol HCl from 15% loaded PMMA/MAA beads was investigated at a constant ionic strength (0.1 *M* Sørensen phosphate buffer with ionic strength $I = 0.26$ *M*). At pH 5.5, a minimal drug release (<15%) was attained at 24 hr, whereas at pH 7.4 and 9, the drug release was completed within 20–30 hr and the release rate was higher at pH 9. This pH dependence of drug release follows the same trend as that in the swelling of drug-free PMMA/MAA beads reported previously (14). Figure 1 is a photograph of the typical swelling front penetration during the release of oxprenolol HCl from the resent PMMA/MAA beads in a neutral or weakly basic medium, where a sharp ionization front lagging behind a diffused water penetrating front is observed. This leads to the formation of a swollen ionized shell surrounding a glassy nonionized core and the diffusional drug release through the swollen rubbery region. The higher rate of drug release at pH 9 can be directly attributed to the faster rate of ionization at higher pH's. On the other hand, in a weakly acidic medium (pH 5.5–6), the sharp ionization front is generally absent; only a fast-moving but very diffused water penetration front can be observed. This lack of ionization and the hydrophobic nature of the polymer (~13% swelling in DI water) are responsible for the negligible polymer swelling and change in bead di-

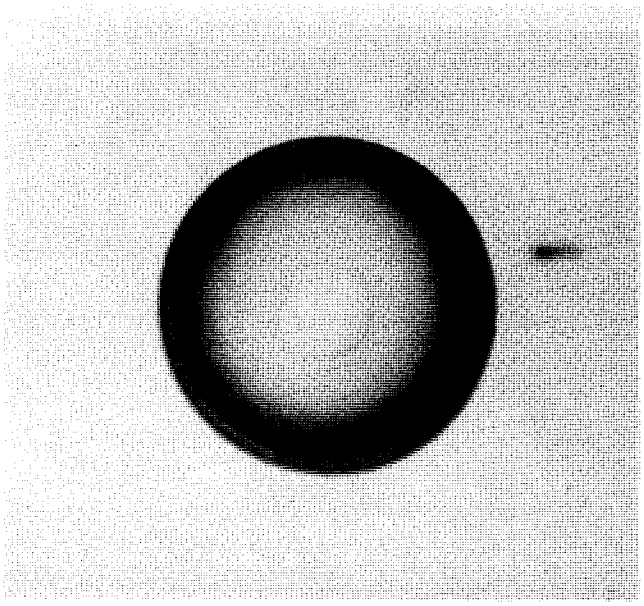

Fig. 1. Photograph showing a typical front penetration behavior during the release of oxprenolol HCL.

mension as well as the minimal drug release observed at low pH's.

Figures 2a, b, and c illustrate the effect of phosphate buffer concentration on, respectively, the oxprenolol HCl release, ionization front movement, and transient dimensional changes in drug-loaded glassy PMMA/MAA beads (15% drug loading) at pH 7.4. Previously, the ionization front movement and transient dimensional changes were investigated only in drug-free PMMA/MAA beads (14). In the present cases, an increasing rate of change is evident at higher buffer concentrations. This is a result primarily of faster electrolyte uptake due to a more effective reduction of Donnan potential at higher buffer concentrations. In Fig. 2a, the drug release appears to be initially nonlinear for a short duration. This is followed by an extended quasi-linear release region (up to 40–50% of total release) before leveling off. Such a quasi-linear region seems to become more pronounced with increasing buffer concentrations, despite the inherent limitation of decreasing surface area at the penetrating front in the spherical geometry. Similar transient behavior is also observed in the corresponding changes in sample dimension (Fig. 2c). At present, the exact causes of these quasi-linear regions in drug release and sample dimensional changes are still uncertain. Some possible mechanisms are discussed below. It is to be noted that, in Fig. 2c, the bead diameter has been normalized to the swollen diameter. In reality, the actual swollen bead diameter decreases slightly with increasing buffer concentration. This is the result of a decrease in ion osmotic pressure difference between the gel and the solution due to an increase in the solution osmotic pressure at higher buffer concentrations.

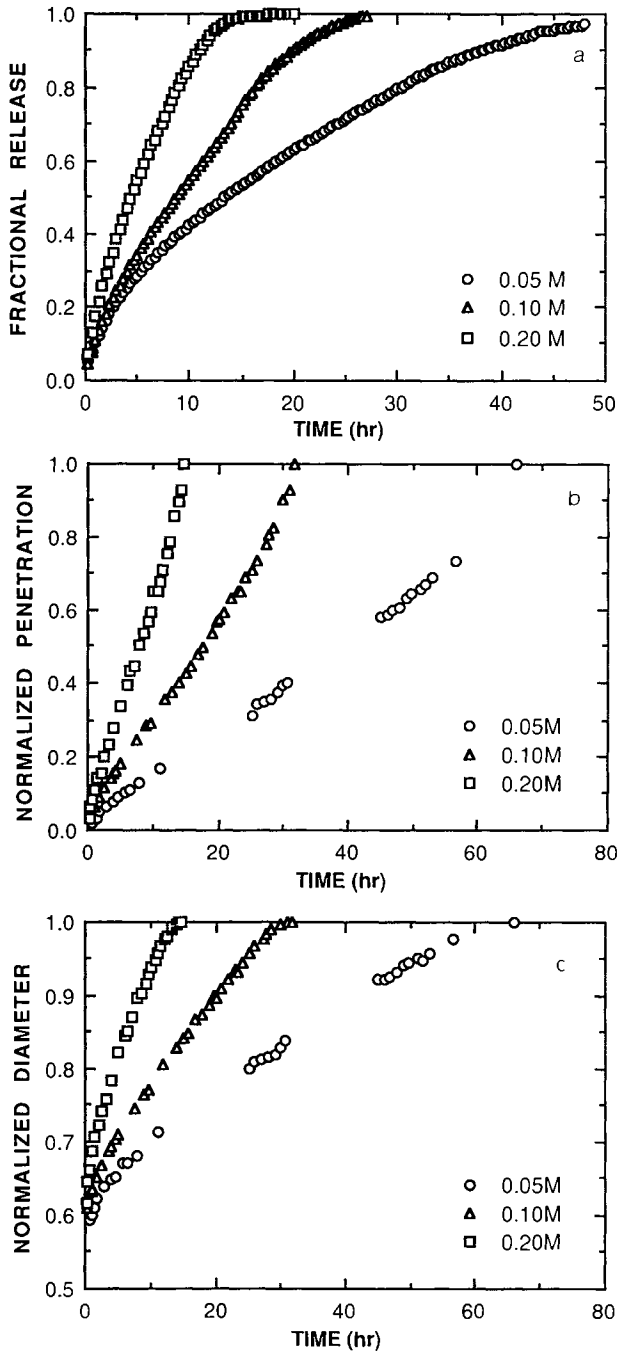

Fig. 2. Effect of buffer concentration on (a) oxprenolol HCl release, (b) penetrating ionization front, and (c) transient dimensional changes in PMMA/MAA beads.

As shown in Fig. 2b, a slight nonlinearity appears in the initial ionization front penetration at the lowest buffer concentration studied (0.05 *M*), indicative of contributions from a diffusion-limited ionization process. This nonlinearity diminishes at higher buffer concentrations as a result of increased diffusion rates. Since the progression of the ionization/swelling front is a result of contributions from factors such as electrolyte diffusion, ionization, and deviation from mechanical equilibrium (10), this observation represents a shift toward an ionization-limited swelling process. Also observed in Fig. 2b is that the initial front penetration is followed by an apparent constant-rate front movement before accelerating toward the center. This acceleration of front movement near the center has been shown to be a natural outcome of the spherical geometry (13,16). It should be noted that the drug release and dimensional changes in the present PMMA/MAA beads (Figs. 2a and c) seem to approach completion as the penetrating ionization fronts (Fig. 2b) meet at the center, suggesting a near-swelling equilibrium in the ionized shell of the present system. Similar swelling behavior involving both the linear front movement and the simultaneous completion of swelling front penetration and sample weight gain is well-known in the Case II swelling of glassy PMMA by methanol (17). Thus, the observed drug release in the present PMMA/MAA system is a result of the ionization-controlled swelling process, which exhibits analogous swelling kinetics as in a relaxation-controlled system.

Effect of Drug Loading

The effect of loading level on the release of oxprenolol HCl from PMMA/MAA beads in unbuffered DI water (pH 6) is shown in Fig. 3. The oxprenolol HCl release in DI water at a drug loading of 15% appears to be minimal at 24 hr. However, the initial rate of release is seen to increase with the drug loading as expected. It is interesting to note that, at loading levels above 17.8%, the drug release appears to be initially rapid, followed by a distinct transition to a protracted tailing with significantly reduced release rate. The transition to such "tailing" seems to occur earlier in time

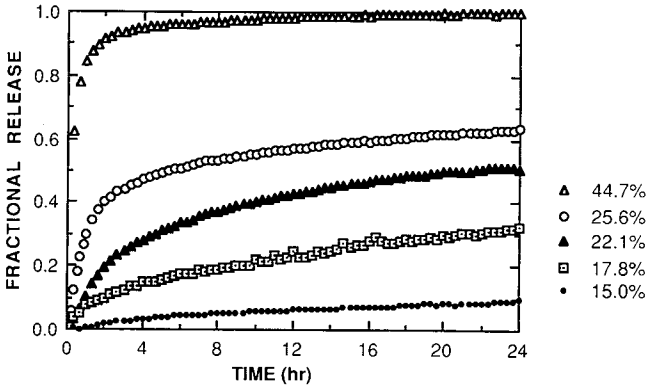

Fig. 3. Effect of drug loading on the release of oxprenolol from PMMA/MAA beads in DI water (pH 6).

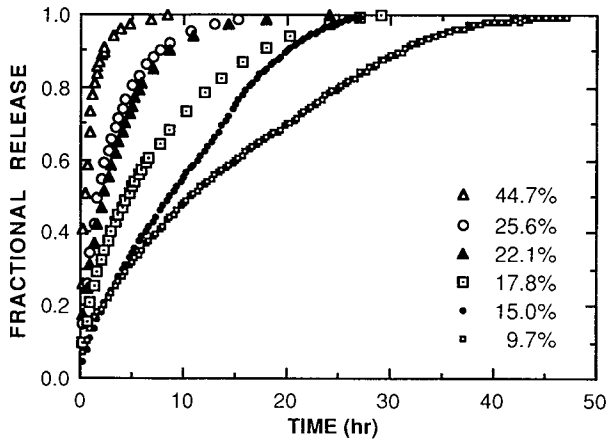

Fig. 4. Effect of drug loading on the release kinetics of oxprenolol from PMMA/MAA beads in pH 7.4 buffer of 0.1 *M* concentration and 0.26 *M* ionic strength.

and at a higher fractional release when the drug loading is increased. In contrast, below 17.8% loading, such transition is absent and the drug release rate appears to be slow but comparable to that in the tailing portion of the release at higher drug loadings. This is most likely caused by a transition from the dissolved to the dispersed system at oxprenolol HCl loading levels above 17.8%. Thus, in a dissolved system, the drug is homogeneously dissolved in the polymer and the drug release involves diffusion through the polymer matrix, whereas in a dispersed system, in addition to the dissolved drug, the polymer network is further expanded and forms transient interconnecting channels due to the presence of the excess solid drug. The initial drug release from such a dispersed system is therefore rapid as a result of diffusion through micropores. In fact, the higher the drug loading, the larger is the contribution from such pore diffusion mechanism due to the concomitant increase in pore fractional volume. This usually leads to a higher rate of drug release. In such cases, the larger fractional volume of the dispersed drug also translates to a larger fraction of the total drug release. Once the excess dispersed drug is released, the slower diffusional release of the dissolved drug will dominate the rate process. These interpretations are consistent with the known percolation concepts on drug release from porous polymer matrices (18). Previously, we demonstrated a transition of release mechanism from anomalous to Fickian diffusion kinetics for the release of thiamine HCl from glassy poly(2-hydroxyethyl methacrylate) (PHEMA) beads at a loading level above 18.8% (12). In the present case, the lack of PMMA/MAA swelling in DI water (pH 6) has prevented the occurrence of such chain mobility-related transition (Fig. 3). However, as shown below, such a transition does occur in PMMA/MAA beads undergoing extensive swelling in neutral pH buffers.

Figure 4 illustrates the effect of drug loading on the kinetics of release of oxprenolol HCl at pH 7.4 (0.1 *M* Sørensen phosphate buffer; $I = 0.26\ M$). With loadings up to 15%, the drug release appears to be initially nonlinear, followed by an extended quasi-linear release region before tailing off. The observed quasi-linear release region at low drug loadings is basically a manifestation of the ionization-controlled swelling process involved in the present PMMA/MAA system. Also observed is that the release rate generally increases with the drug loading. However, as the drug loading level increases above about 17.8%, the quasi-linear release region disappears and the drug release appears to follow a first-order process. As discussed earlier, this appears to be the result of a change of release mechanisms due to the transition from a dissolved to a dispersed system above a threshold loading level of 15–18%. This rationale agrees with the predicted percolation threshold of 20% or so for drug release from porous polymer matrices (18).

During the release of oxprenolol HCl from the present PMMA/MAA beads, a slow-moving but sharp ionization front lagging behind a diffused water penetrating front is typically observed (Fig. 1). The movement of both of these fronts corresponding to the release results in Fig. 4 is further enhanced by the increasing drug loading as shown in Figs. 5 and 6. Since the overall polymer swelling in the present PMMA/MAA beads is governed by the formation of a swollen ionized shell and the disappearance of the glassy unionized core, the contribution to swelling from water penetration alone is therefore minimal. In fact the time required to complete water penetration amounts to only 2–5% of the total time required for the ionization front penetration (see Figs. 5 and 6). As shown in Fig. 5, at a loading level of 25.6%

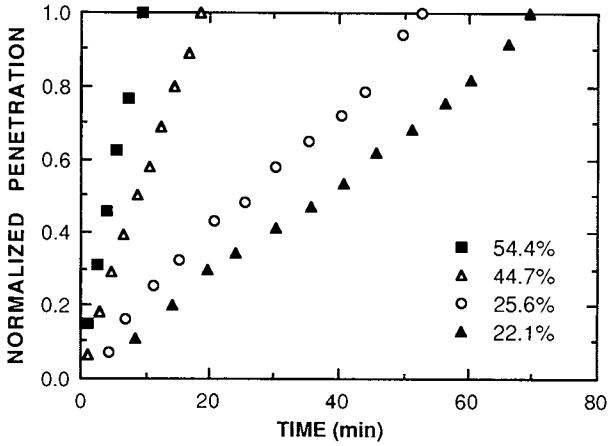

Fig. 5. Effect of oxprenolol HCl loading on water swelling front penetration in PMMA/MAA beads in pH 7.4 buffer of 0.1 *M* concentration and 0.26 *M* ionic strength.

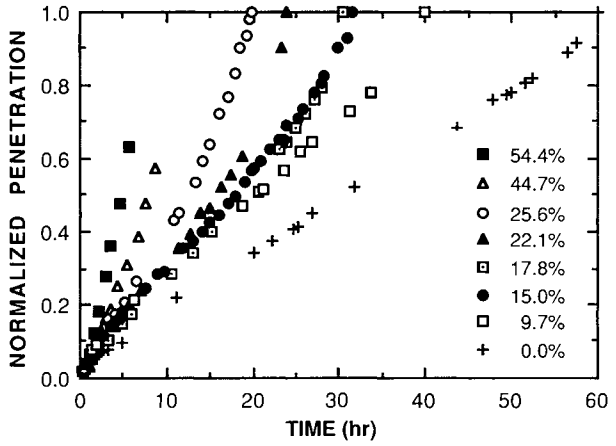

Fig. 6. Effect of oxprenolol HCl loading on ionization front penetration in PMMA/MAA beads in pH 7.4 buffer of 0.1 *M* concentration and 0.26 *M* ionic strength.

or above, the water penetration is completed before any appreciable movement of the ionization front is observed. In general, the ionization as well as the water penetration front movement at all drug loading levels exhibits an initially nonlinear region followed by a constant-rate movement before accelerating toward the center. In all cases, the front movement is faster and the onset of acceleration earlier at higher drug loadings. Again, as shown by us recently, such front acceleration is a natural outcome of the spherical geometry (13,16).

The transient dimensional changes as a function of drug loading during the release of oxprenolol HCl from the present PMMA/MAA beads are illustrated in Fig. 7. It is clear that, for loading levels up to 25.6%, the corresponding dimensional changes appear to be initially nonlinear, followed by an extended quasi-linear region before approaching an equilibrium value. This monotonic increase in diameter during drug release from PMMA/MAA beads appears to be different from that observed in nonionic hydrogel beads such as PHEMA (12) and PHEMA/MMA (13), in which the diameter of drug-loaded beads goes through a *maximum* before reaching equilibrium. This has been attributed to an insufficient reduction in bead dimension resulting from the drug release, as compared to the unusually large swelling contribution from gel ionization and drug osmotic pressure in the present system (80–90% increase in diameter upon swelling versus <20% typically observed in PHEMA beads). This rationale is supported by the results in Fig. 7, where, upon further increasing the drug loading above 40% or so, the transient bead diameter begins to show a *maximum* during the initial drug release. In this case, the reduction of dimension due to drug release is comparable to, or larger in magnitude than, that from gel ionization and osmotic swelling during the initial drug release. Since the drug release is faster at higher loading levels, the bead dimension soon diminishes as the drug is released, resulting in the reduction of bead sizes. At this point, the slow but continuous ionization process is still taking place, thus giving rise to an apparent swelling *minimum* followed by a steady rise in the bead diameter as observed in Fig. 7. As shown in the schematic drawing in Fig. 8, the observed transient dimensional changes depend on the combination of dimensional contributions from both the drug release and the polymer swelling (including the osmotic contribution from the drug). In the case of nonionic hydrogel beads such as PHEMA and PHEMA/MMA, both of these contributions are comparable in magnitude. The release of drug tends to decrease, whereas the swelling by water tends to increase the dimension of the hydrogel bead. The combination of these competing processes of similar rate and magnitude results in an observed

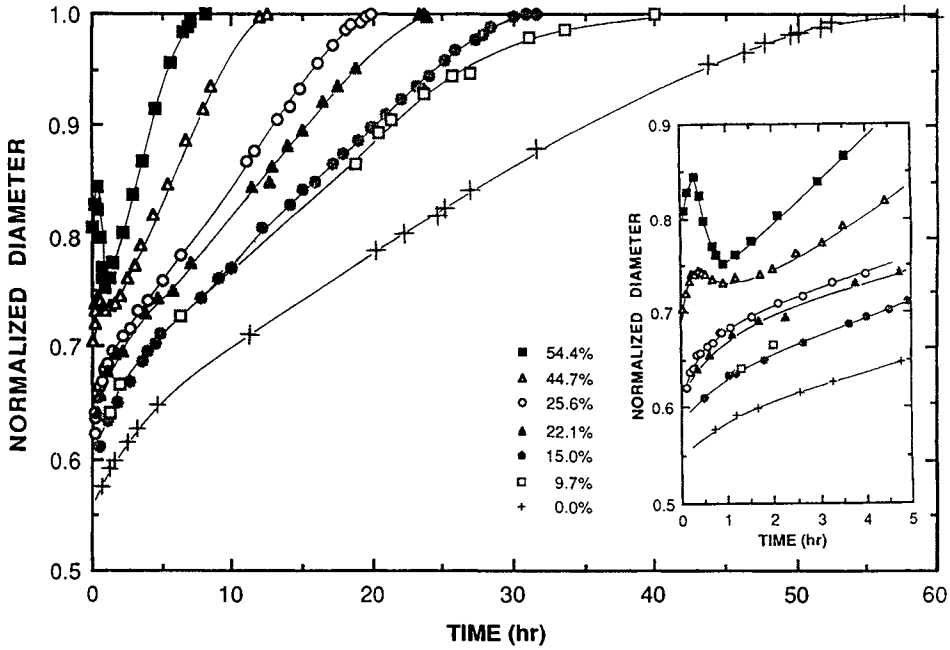

Fig. 7. Effect of drug loading on transient dimensional changes during the release of oxprenolol HCl from PMMA/MAA beads in pH 7.4 buffer of 0.1 *M* concentration and 0.26 *M* ionic strength.

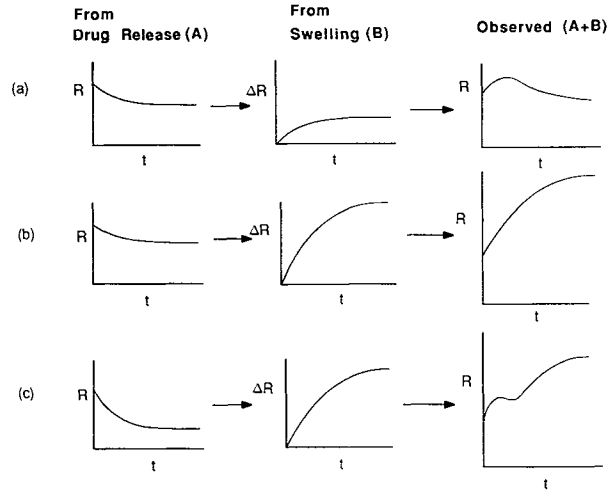

Fig. 8. Schematic drawing of proposed mechanisms for the observed differences in dimensional changes during drug release from glassy hydrogel beads: (a) nonionic PHEMA and PHEMA/MMA; (b) ionic PMMA/MAA at low drug loadings; (c) ionic PMMA/MAA at high drug loadings.

maximum before reaching equilibrium (Fig. 8a). On the other hand, at low drug loadings, the large dimensional increase due to polymer swelling overwhelms the small dimensional reduction due to drug release in the present PMMA/MAA polyelectrolyte gel beads, thus resulting in a monotonic increase in the observed dimensional changes (Fig. 8b). In contrast, above a certain loading level, the dimensional reduction due to drug release becomes comparable in magnitude to that of the dimensional increase due to swelling. Therefore, a maximum in the dimensional changes would result (Fig. 8c). In this case, the apparent swelling minimum followed by a steady rise in the bead diameter (Fig. 7) can be attributed to the slow polymer swelling as compared with the more rapid reduction of dimension due to drug release.

Mechanisms of Drug Release

The extended quasi-linear release region (up to 40–50% of total release) observed in Figs. 2a and 4 for the release of oxprenolol HCl from the present glassy PMMA/MAA beads, at loading levels up to 15%, does not seem to conform with the current understanding on the effect of sample geometry on drug release. It is well-known that finite geometries such as spheres are inherently incapable of maintaining a constant rate of drug release because of the increasing diffusional distance and the shrinking surface area at the swelling/diffusion front (19). Although at low drug loadings, the present glassy PMMA/MAA may exhibit non-Fickian swelling and release behavior in sheet samples, the spherical geometry would have rendered the fractional drug release nonlinear. This holds true even for real swelling-controlled systems unless an additional mechanism, such as a nonuniform drug distribution, is employed to compensate for the declining rate of release (20). A closer examination of the present system reveals that, upon completion of ionization at a neutral or higher pH, the unusually large degree of swelling results in a volume swelling of about 80% and an increase in bead size of about 80–90%. A plausible, albeit tentative explanation is that, during the present ionization-controlled swelling process, the unusually large time-dependent increases in surface area and diffusion coefficient may have helped to compensate the moderate decline in diffusion rate, thereby resulting in apparent quasi-linear release regions at lower drug loadings. However, at loading levels above the percolation threshold, such compensation schemes may be overwhelmed by contributions from the Fickian pore-diffusion mechanism, in addition to the geometry effect. More work is in progress to elucidate further the underlying mechanism for such anomalous quasi-linear release.

CONCLUSION

A suspension polymerization process has been developed to produce hydrophobic anionic gel beads (up to 1.4-mm diameter) based on cross-linked PMMA/MAA, suitable for controlled release applications. The present polymer is similar in composition to the enteric polymer Eudragit L, except our beads contain loose cross-links to prevent complete polymer dissolution at physiological pH. We have investigated in detail the effect of drug loading on the kinetics of polymer swelling and drug release, as a function of the buffer concentration and pH. Although the PMMA/MAA swelling rate increases with pH and buffer concentration, the ionization-controlled swelling mechanism (analogous to that in a relaxation-controlled system) seems to become more rate-limiting at higher buffer concentrations.

At oxprenolol HCl loading levels below 17.8%, the drug release and associated dimensional changes (in pH 7.4) exhibit an extended quasi-linear region despite the inherent geometry limitations of the present spherical system. At higher loading levels, the drug release becomes faster and first-order in nature. These and related release results obtained under nonswelling conditions (e.g., in DI water) suggest a transition from a dissolved to a dispersed system at oxprenolol HCl loading levels above 17.8%.

The transient PMMA/MAA bead diameter increases monotonically during drug release at oxprenolol HCl loading levels up to 25.6%. The lack of an observed maximum as normally occurring in PHEMA is due to an insufficient contribution of dimensional reduction due to drug release as compared to that of a significant dimensional increase from the gel swelling. This rationale is supported by the fact that, upon increasing the drug loading above 40%, a maximum in the transient bead diameter starts to appear during the initial drug release. In such cases, the bead diameter eventually increases again after going through a brief transient minimum as a result of the slow but continuous increase in swelling due to further ionization of the polymer. In all cases, both the drug release and the dimensional changes approach completion as the penetrating fronts meet at the center, indicating a true swelling-controlled behavior.

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REFERENCES

1. I. Helfferich. *Ion Exchange,* McGraw–Hill, New York, 1962.

2. S. Borodkin and M. H. Yunker. Interaction of amine drugs with polycarboxylic acid ion-exchange resin. *J. Pharm. Sci.* **59**:481–486 (1970).
3. Y. Raghunathan, L. Amsel, O. Hinsvark, and W. Bryant. Sustained-release drug delivery system. I. Coated ion-exchange resin system for phenylpropanolamine and other drugs. *J. Pharm. Sci.* **70**:379–384 (1981).
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. S. H. Gehrke, G. P. Andrews, and E. L. Cussler. *Chem. Eng. Sci.* **41**:2153–2160 (1986).
6. 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).
7. S. H. Gehrke and E. L. Cussler. Mass transfer in pH-sensitive hydrogels. *Chem. Eng. Sci.* 44:559–566 (1989).
8. 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. *Polymer Preprint* **31**:231–232 (1990).
9. L. Brannon-Peppas and N. A. Peppas. Equilibrium swelling behavior of pH-sensitive hydrogels. *Chem. Eng. Sci.* **46**:715–722 (1991).
10. 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).
11. 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. Rel.* 8:267–274 (1989).
12. P. I. Lee. Dimensional changes during drug release from a glassy hydrogel matrix. *Polym. Commun.* **24**:45–47 (1983).
13. P. I. Lee and C.-J. Kim. Probing the mechanisms of drug release from hydrogels. *J. Control. Rel.* **16**:229–236 (1991).
14. C.-J. Kim and P. I. Lee. Hydrophobic anionic gel beads for swelling-controlled drug delivery. *Pharm. Res.* **9**:195–199 (1992).
15. 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).
16. P. I. Lee and C.-J. Kim. Effect of geometry on solvent front penetration in glassy polymers. *J. Membr. Sci.* **65**:77–92 (1992).
17. N. L. Thomas and A. H. Windle. Transport of methanol in poly(methyl methacrylate). *Polymer* **19**:255–265 (1978).
18. R. A. Siegal, J. Kost, and R. Langer. Mechanistic studies of macromolecular drug release from macroporous polymers. I. Experiments and preliminary theory concerning completeness of drug release. *J. Control. Rel.* 8:223–236 (1989).
19. P. I. Lee. Diffusional release of a solute from a polymeric matrix—approximate analytical solutions. *J. Membr. Sci.* 7:255–275 (1980).
20. P. I. Lee. Effect of non-uniform initial drug concentration distribution on the kinetics of drug release from glassy hydrogel matrices. *Polymer* **25**:973–978 (1984).