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ENHANCED AND RETARDED DRUG RELEASE FROM HYDROPHOBIC IONIC BEADS

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ABSTRACT

The effect of drug solubility and drug loading on the kinetics of polymer ionization and drug release from poly(methyl methacrylate-*co*-methacrylic acid) (PMMA/MAA) beads has been investigated. Acebutalol HCl, labetalol HCl, and propranolol HCl were chosen as model drugs, representing a range of liphophilicity. Polymer ionization and drug release rates increase with drug loading for a highly water-soluble drug, i.e., acebutalol HCl. Drug release and ionization rates, however, decrease with drug loading up to 11.0 and 12.2% for less water-soluble drugs, i.e., labetalol HCl and propranolol HCl, respectively, and then increase above the loading level of 18.6%. This decrease in rate is attributable to the low solubility of the drug, resulting in its slow diffusion and the need for increased electrolyte uptake to ionize the acidic components (i.e., polymer matrix and HCl). At a loading level below 18.6%, the ionization kinetics were governed by intraparticle diffusion and chemical reaction resistances, with an additional minor contribution from film diffusion resistance. At higher loading, above 24.6% of acebutalol HCl, however, the film diffusion resistance controlled the overall ionization kinetics of drug-loaded PMMA/MAA beads.

INTRODUCTION

Ionic polymer networks containing anionic or cationic charge groups exhibit a swelling phenomenon in response to changes in pH, ionic strength, and specific ionic composition of the swelling medium [1, 2]. Polyelectrolyte gels swell due to water absorption and charge repulsion between ionized groups in the polymer chain. This has led to the use of such gels for controlled drug release systems [3] and for separation of macromolecules by gel extraction [4, 5]. By varying the charge-carrying monomer composition and the degree of crosslinking, the swelling properties of a charged polymer can be tailored. Both anionic and cationic polyelectrolyte gels have been studied extensively in terms of their equilibrium swelling properties. The kinetics of swelling and drug release from dehydrated ionizable polyelectrolyte gels are only in the early stages of research. The swelling kinetics of drug-free ionizable polyelectrolyte gels may be controlled by a diffusion-reaction limited process and a deformation process [6]. The drug release kinetics of drug-loaded polyelectrolyte gels is further complicated by the transition from the glassy to rubbery state of a polymer chain.

Siegal and coworkers studied the swelling and release of caffeine from poly(methyl methacrylate-*co*-dimethylaminoethyl methacrylate) [7]. The release was shown to be controlled by the protonation of the polymer-derived amino group and sorption of water at pH 3 and 5, which follows Case II kinetics. Brennon-Peppas and Peppas [8] reported the quasi-linear release of theophylline from poly(hydroxyethyl methacrylate-*co*-methacrylic acid) and poly(hydroxyethyl methacrylate-*co*-maleic anhydride). Hariharan and Peppas [9] studied the release of insulin and oxprenolol HCl from a cationic polymer, poly(hydroxyethyl methacrylate-*co*-diethylaminoethyl methacrylate), and showed that the initial release of insulin was nonlinear followed by a quasi-linear release. These studies indicated that drug release from the ionizable polymer matrix was governed by protonation or ionization of pendant groups in the polymer chain. The studies reported were based on disk samples, which characteristically exhibit anisotropic swelling effects with glassy polymers. Recently, Kim and Lee [10, 11] showed the effects of the swelling medium on drug-free polymer swelling, as well as the effect of drug loading of oxprenolol HCl in poly(methyl methacrylate-*co*-methacrylic acid) (PMMA/MAA) beads on polymer swelling and drug release. The spherical geometry employed in the beads has the advantage of eliminating the anisotropic swelling behavior normally associated with sheet geometry. In addition, it may demonstrate a potential utility for multiparticulate oral dosage forms. As a result of an ionization-controlled swelling process of the carboxylic acid pendant group, the dimensional changes of swelling beads were shown to exhibit an unexpected quasi-linear region at varying pH and ionic strength not found with nonionic hydrogels such as PHEMA beads [12]. An interesting feature of the PMMA/MAA bead system is that both the drug release and dimensional changes appear to end when the penetrating fronts meet at the center, suggesting that there is a negligible concentration gradient behind the sharp moving front, and therefore a precise swelling-controlled behavior. This PMMA/MAA bead is similar in composition to the commercially utilized enteric polymer, Eudragit L (with the exception that, due to the presence of moderate crosslinking, it did not dissolve at basic pH). At drug loading below 15%, the drug release

occurred with quasi-linear kinetics even with the inherent limitation of spherical geometry [11].

The present study was undertaken in order to investigate the effects of solubility and drug loading of β-blocking agents on the kinetics of swelling and drug release from dehydrated PMMA/MAA beads.

EXPERIMENTAL

Materials

Inhibitors were removed by inhibitor column (Polysciences) for methyl methacrylate and methacrylic acid. 2,2′-Azobisisobutyronitrile (Polysciences) was recrystallized from methanol. Other chemicals were used as received without further purification.

Synthesis of PMMA/MAA Beads

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 (60/40 wt%) of inhibitor-free methyl methacrylate (MMA) and inhibitor-free methacrylic acid (MAA) using ethylene glycol dimethacrylate as the crosslinking agent (1.0 wt%). The polymerization was carried out in a concentrated $CaCl_2$ solution at 70°C for 5–6 hours under nitrogen using freshly precipitated hydroxyapatite [$3Ca_3(PO_4)_2 \cdot Ca(OH)_2$] as the suspending agent and 2,2′-azobisisobutyronitrile recrystallized from methanol as the initiator. The relative amount of monomer to water in the polymerization mixture was 1:8 by weight. After the completion of polymerization, concentrated HCl was added to the reaction mixture to remove the suspending agent from the beads. These beads were filtered and then extracted in a Soxhlet with methanol for 24 hours before being dried and fractionated. For this study the fractions of PMMA/MAA beads with a dry diameter of 0.6–0.85 and 1.0–1.18 mm were used.

Swelling and Drug Release

The swelling experiments were carried out in a stirred cuvette immersed in a water bath maintained at 37°C. The swelling front was observed with a Olympus SZ60 microscope equipped with a Polaroid camera attachment and digital optical measuring accessory. As model compounds, acebutalol HCl, propranolol HCl, and labetalol HCl were used, representing a series of drugs ranging in liphophilicity but with pK_a values of the same order. Drug loading was achieved by equilibrating the beads for 2 days in concentrated drug solutions in methanol. After filtering and drying, the drug-loaded beads were then used for swelling and drug release studies in 0.1 M phosphate buffer at pH 7.4. The in-vitro release at 37°C under perfect sink conditions was monitored continuously in a stirred cuvette on a Hewlett-Packard 8451A diode-array UV-Vis spectrophotometer equipped with a water-jacketed cuvette holder and a built-in magnetic stirrer at 250, 272, and 244 nm for acebutalol HCl, propranolol HCl, and labetalol HCl, respectively. Release profiles and swelling thickness measurements show a good reproducibility (95% confidence level) of

±3.6% and ±3.7%, respectively, based on the linear regression analysis of the log transformed data up to 60%.

RESULTS AND DISCUSSION

As model compounds for this study, three β-blocking agents were chosen, with varying hydrophilicity and similar molecular weight and pK_a values, as shown in Table 1. In general, it is well known that the drug release rate from a monolithic matrix system increases with the drug-loading level [14]. The higher drug loading is, the more probable the drug molecules are in contact one another, creating the fluid-fill pores or channels which increase the system's permeability to the drugs. In this study, attempts were made to determine whether or not the general kinetics of drug release from a monolithic matrix is applicable to such a system and that the drug release is controlled by the ionization of the polymer chain.

The effect of drug loading level on the release of acebutalol HCl, labetalol HCl, and propranolol HCl from PMMA/MAA beads in 0.1 M phosphate buffer (pH 7.4) is shown in Fig. 1(a), 1(b), and 1(c), respectively. The time scale has been normalized with respect to the dry bead size to avoid the influence of bead size on the drug release and ionization kinetics. As expected, the drug release of acebutalol HCl from PMMA/MAA beads increases with drug loading. At the loading level of 10.9%, drug release appears to be initially nonlinear (to 6 h/mm^2) followed by an extended quasi-linear release region before leveling off, as found in the release of oxprenolol HCl (solubility in water 77%) from PMMA/MAA beads [11]. At higher loading levels the release of acebutalol HCl becomes faster and first-order in nature. As shown in other hydrogels (PHEMA and PHEMA/MMA beads [12, 19]), the transition from a dissolved to a dispersed system may occur above a drug-loading level of 18–20% for release of acebutalol HCl from PMMA/MAA beads. However, the release of labetalol HCl, the least hydrophilic drug among the drugs studied herein, from PMMA/MAA beads decrease as the drug-loading level increases. This trend was not observed in the release of diclofenac Na (solubility <2%) from nonionic hydrogels such as PHEMA and PHEMA/MMA beads [19]. Even though the release rate decreases with drug loading, the release of labetalol HCl appears to be quasi-linear at a loading below 11.0%, as observed in the release of acebutalol HCl. Drug loading higher than 11.0% for labetalol HCl could not be obtained due

TABLE 1. Properties of β-Blocking Agents

Compound	MW	pK_a	Solubility, g/mL[c]
Acebutalol HCl	336.4	9.20[a]	>1/1
Labetalol HCl	328.4	9.45[a]	1/60
Propranolol HCl	259.3	9.45[b]	1/20

[a]Ref. 20.
[b]Ref. 21.
[c]Ref. 22.

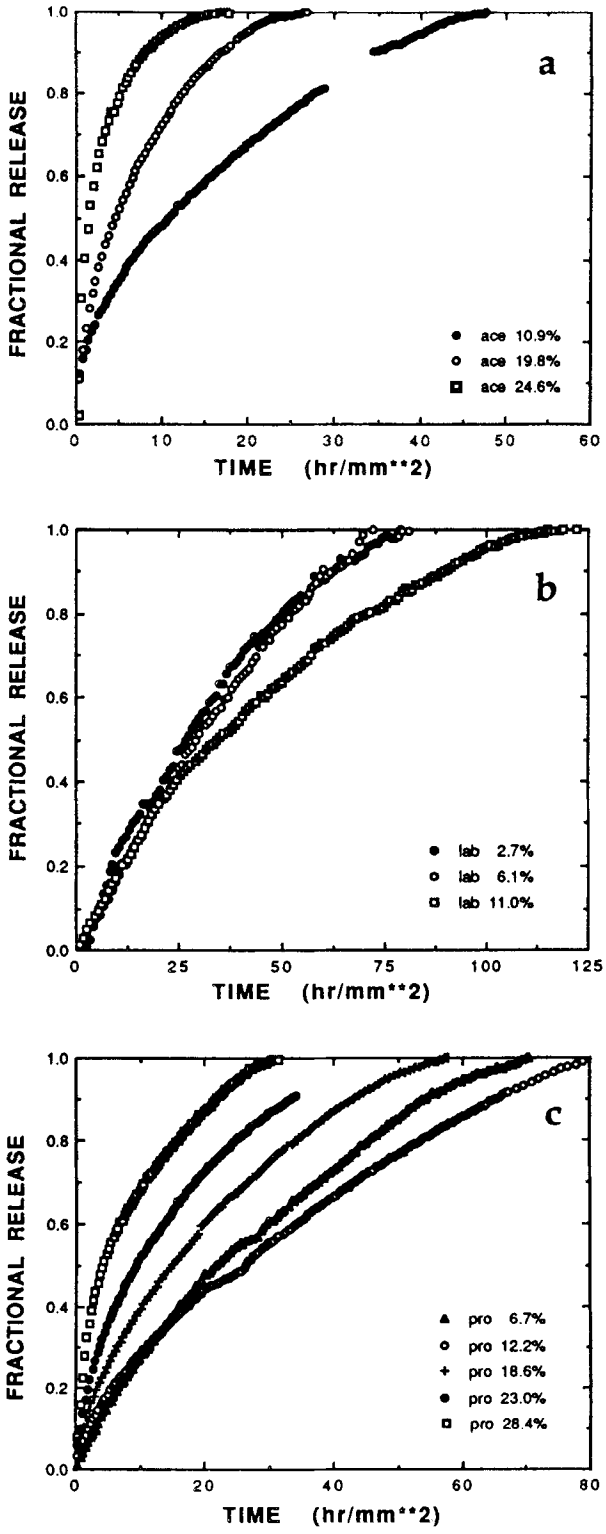


FIG. 1. Effect of drug loading on the drug release kinetics from PMMA/MAA beads: (a) acebutalol HCl, (b) labetalol HCl, (c) propranolol HCl.

to its limited solubility in methanol. As presented in Fig. 1(c), the release of propranolol HCl from PMMA/MAA beads at a loading level lower than 12.2% follows a pattern similar to that found in the release of labetalol HCl. The magnitude of decline of the drug release rate is less than that of labetalol HCl due to a slightly increased water solubility of propranolol HCl. However, as the drug-loading level increases above 18.6%, the drug release rate of propranolol HCl increases with the drug-loading level and becomes first-order in nature. For either highly water soluble or low water soluble drugs, at drug-loading levels below 12.2%, the drug release initially seems nonlinear (or non-Fickian), followed by an extended quasi-linear release before tailing-off. It was postulated that this quasi-linearity is due to high swelling by ionization of the polymer chain, resulting in the fast diffusion of drug molecules and in the increase of surface area to compensate for the moderate decrease of diffusion rate [11]. Shah et al. also observed zero-order release at pH 11 from glassy poly(hydroxyethyl methacrylate-*co*-4-carboxyl styrene) due to an increase in the diffusivity of the active ingredient via the enhanced swelling of the polymer matrix [15]. The decrease of the drug release rate with respect to drug loading at a loading level lower than 12.2% is an observation contrary to the general kinetics of drug release in the polymer matrix, in which the release rate increases with drug loading. This finding is further evident with observation of the ionization front movement.

The slow moving ionization fronts during the release of acebutalol HCl, labetalol HCl, and propranolol HCl from the PMMA/MAA beads are shown in Figs. 2(a), 2(b), and 2(c), respectively. Ionization front movement exhibits an initially nonlinear region followed by a constant-rate movement before accelerating toward the center at all drug loading levels for all the drugs investigated herein. The accelerating rate of the ionization front toward the center for the highly water-soluble drug (acebutalol HCl) is faster and the period of constant rate is shorter as the drug-loading level increases. On the other hand, for the less water-soluble drugs such as labetalol HCl and propranolol HCl (Figs. 2b and 2c), it is clearly shown that below the drug-loading level of 12.2% the ionization rate slows down as the drug loading increases, whereas above the loading level of 18.6% the ionization front moves faster as the loading increases. This retarded ionization rate contributes to the slow release rate of labetalol HCl and propranolol HCl at the loading level below 12.2%.

As pointed out above, there is a distinctive transition in the ionization and drug release kinetics of drug-loaded PMMA/MAA beads for both highly water-soluble drugs and less water-soluble drugs. For highly water-soluble drugs such as acebutalol HCl and oxprenolol HCl [11], below the drug loading level of 18–20%, the drug is homogeneously dissolved in the polymer matrix and the drug release involves diffusion through the polymer matrix. The presence of dissolved drug in the matrix generates osmotic forces to drive the influx of additional water and increases the diffusion of electrolyte, which leads to faster ionization and drug release. These osmotic forces from the dissolved drugs suppress the retardation of drug release and ionization due to the presence of the additional chemical (HCl) in the polymer matrix. At loading levels above 19.8% the drug is presented in a dispersed state within the polymer matrix and serves to form channels due to the presence of excess solid. In this case the initial drug release is rapid as a result of diffusion through these channels. However, for low water-soluble drugs (labetalol

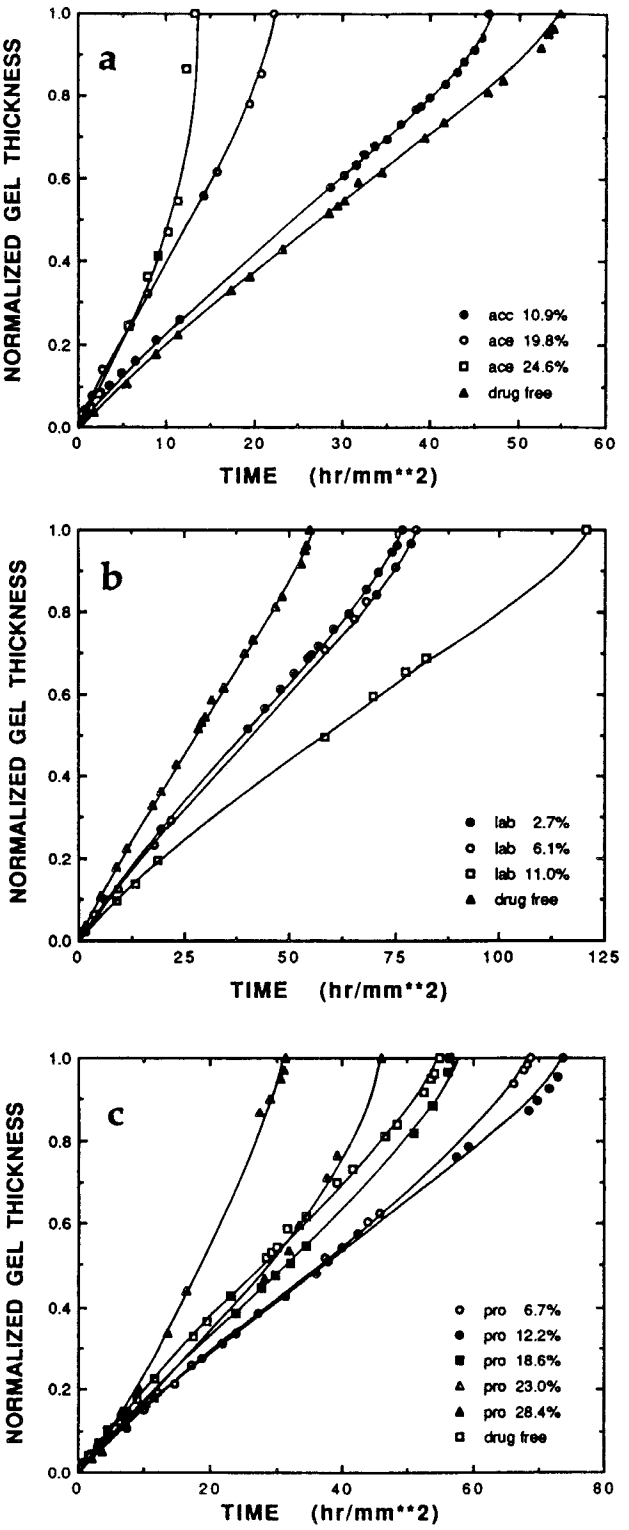


FIG. 2. Effect of drug loading on the ionization front penetration in PMMA/MAA beads: (a) acebutalol HCl, (b) labetalol HCl, (c) propranolol HCl.

HCl and propranolol HCl) there is another transition in addition to the change of dissolved to the dispersed state of drug in the polymer matrix as drug loading increases.

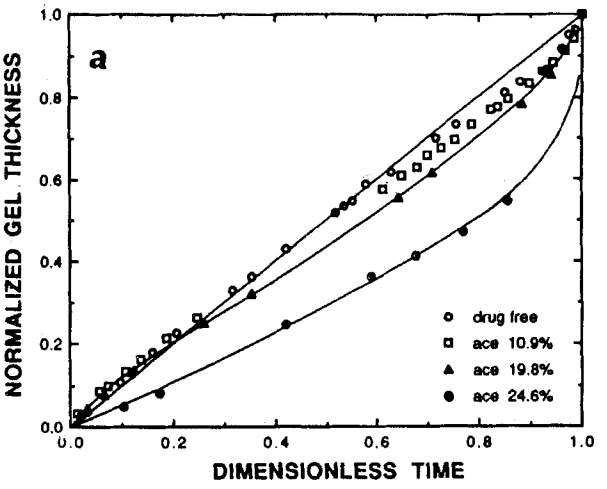
At the loading level below 12.2% the ionization of drug-loaded PMMA/MAA beads is much slower than that of drug-free beads. Since the cavities occupied by drugs are not connected to each other to form continuous channels to the outer surface, the dissolution of drug in the polymer matrix due to its solubility is much slower, resulting in slower water influx and electrolyte uptake from the buffer solution. As a result, the ionization of PMMA/MAA beads is retarded. On the other hand, at a loading level above 18.6%, the movement of the ionization front is enhanced by the drug loading due to the formation of interconnected pores. This enhances drug diffusion through the interconnected pore network as well as the influx of water and electrolyte. At higher loadings the enhancement of drug release and ionization by rapid drug diffusion (which creates the microporous structure from the loss of drug) exceeds the retardation of ionization of PMMA/MAA beads promoted by the presence of additional acidic chemical (HCl).

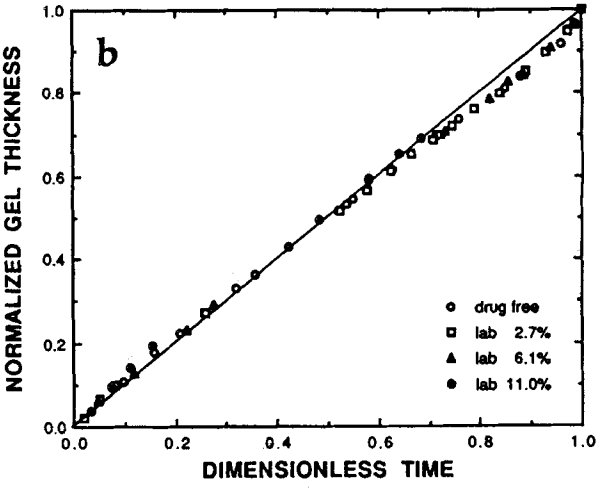
An interesting feature one can derive from this study is that without even having to consider percolation theory parameters, one can deduce a threshold level from the ionization front movement data. If one plots the dimensionless penetration thickness vs dimensionless time as shown in Figs. 3(a), 3(b), and 3(c), one can identify the changes in ionization mechanism as a function of the drug-loading level as compared with Figs. 4 and 5 and the following mechanistic explanation. Figure 4 depicts the concentration gradient of the inward-moving counterion. The kinetics are dependent upon the film diffusion resistance at the outer imaginary boundary, upon counterion diffusion resistance in the rubbery gel layer, and the ionization reaction resistance at the interface.

Kim [16] applied the kinetics based on a pseudo-steady-state shrinking core model (PSSCM), as depicted in Fig. 4, on the ionization of drug-free PMMA/MAA beads as given by

$$\phi = \delta \{1 + (Y_2/6)[2 - \delta - 2(1 - \delta)^2] + (Y_1 Y_2/3)[2 - \delta + (1 - \delta)^2]\}/[1 + Y_2/6 + Y_1 Y_2/3] \quad (1)$$

where ϕ denotes the dimensionless time, δ the normalized gel thickness, Y_1 the $D/k_f R_0$, Y_2 the $k_s R_0/D$, D the diffusion coefficient of the counterion species, k_f the film diffusion coefficient, k_s the specific reaction rate constant, and R_0 the bead radius. This is an approach analogous to that derived by Levenspiel [17] and Shen and Smith [18] for the noncatalytic gas–solid reaction within nonporous particles. A plot shown in Fig. 5 can be used for pinpointing the controlling ionization mechanism. The moving front data at the loading level below 18.6% retain the same shape (S) as the ionization of drug-free beads. This shape suggests that the ionization kinetics is governed by the intraparticle diffusion through the swollen gel layer and chemical reaction at the front, with the limited contribution of film diffusion at the boundary layer [16] (see Fig. 5). As the drug-loading level increases to 18.6–19.8%, the ionization front data points start lying below the diagonal line at the earlier time whereas above the loading level of 24.6% for acebutalol HCl and 28.4% for propranolol HCl, all data are situated below the diagonal line. Therefore, one may approximate the threshold drug-loading level to be 18.6–19.8%, at which the state





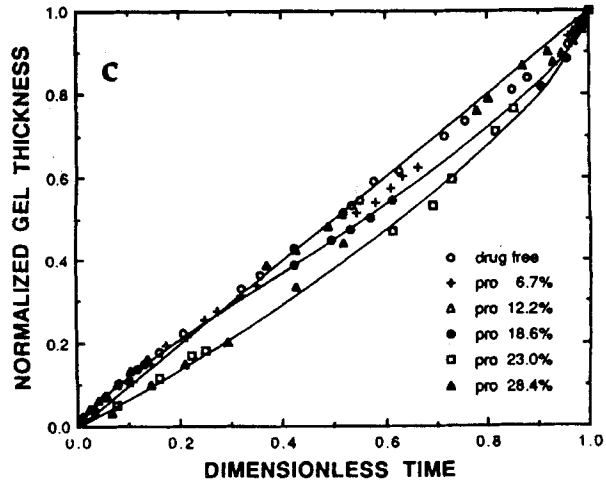


FIG. 3. Normalized gel thickness vs dimensionless ionization time: (a) acebutalol HCl, (b) labetalol HCl, (c) propranolol HCl.

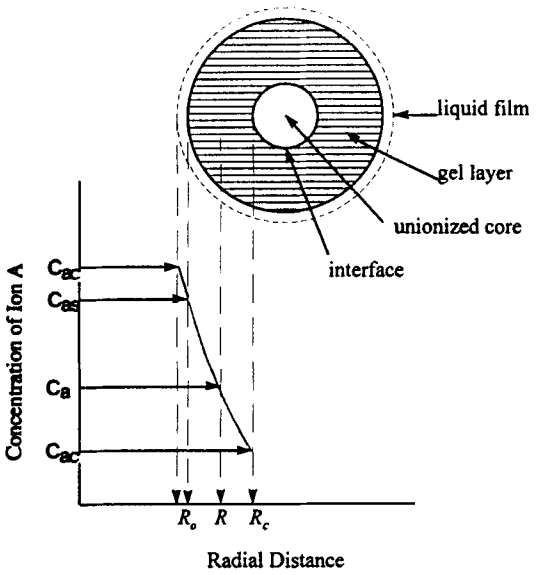


FIG. 4. A schematic profile of counterion concentration in the PMMA/MAA bead.

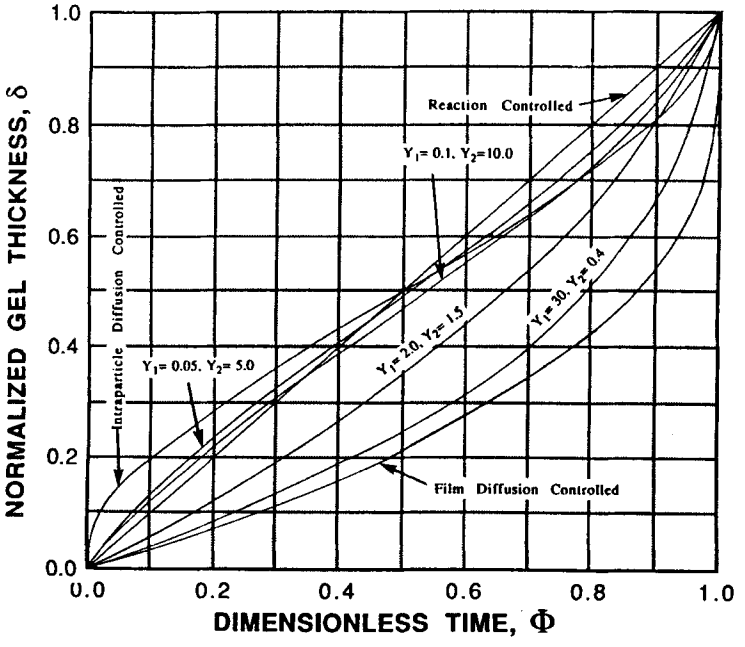


FIG. 5. Position of the moving ionization front as given in Eq. (1).

of drug in the matrix changes from dissolved to dispersed regardless of the water solubility. This loading level seems to agree with the range of 17.85–18.8% found in other hydrogels [11, 12]. At the threshold loading level the ionization kinetics are limited by the film diffusion and chemical ionization reaction resistances with a small intraparticle diffusion resistance. Above the loading of 24.6% (acebutalol HCl) the ionization kinetics of drug-loaded PMMA/MAA beads may be overwhelmingly limited by the film diffusion resistance. This dependence of ionization kinetics on film diffusion resistance is effected by the solubility of a drug. The less a drug is soluble, the later the dependence of film diffusion resistance on the ionization begins. It requires a much higher loading level for the ionization kinetics to be governed only by film diffusion resistance for a low water-soluble drug (see propranolol HCl 28.4% in Fig. 3c). One may infer qualitatively from the kinetic point of view of Eq. (1) that as drug loading increases, the rates of intraparticle diffusion and chemical reaction increase while maintaining the same rate of film diffusion at the boundary. The quantitative detailed analysis of drug release and ionization kinetics of drug-loaded PMMA/MAA beads will be reported in the near future.

CONCLUSIONS

We have investigated the effect of drug loading and drug solubility of β-blocking agents, i.e., acebutalol HCl, propranolol HCl, and labetalol HCl, on the kinetics of polymer ionization and drug release from lightly crosslinked PMMA/MAA beads suitable for multiparticulate controlled release dosage forms. For a highly water-soluble drug (acebutalol HCl), the drug release and ionization rates increase with the drug loading. However, for less water-soluble drugs (propranolol HCl and labetalol HCl), the drug release rates lower as the loading increases to a certain level, i.e., 11.0% for labetalol HCl and 12.2% for propranolol HCl, and then above 18.6% loading the rates are enhanced by the loading level. This is attributable to the slow ionization rate of the polymer due to the presence of an additional acidic chemical (HCl) which requires more counterions, and the low water solubility of a drug which slows down the diffusion of the drug. At a higher loading (above 18.6–19.8%), the drug release and ionization rates increase with drug loading. It was found that there is a distinctive transition of drug release and ionization kinetics due to the solubility of a drug.

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REFERENCES

[1] L. Y. Chou, H. W. Blanch, J. M. Prausnitz, and R. A. Siegel, *J. Appl. Polym. Sci., 45*, 1411–1423 (1992).

[2] B. A. Firestone and R. A. Siegal, *Ibid., 43*, 901–914 (1991).

[3] J. H. Kou, G. L. Amidon, and P. I. Lee, *Pharm. Res., 5*, 592–597 (1988).
[4] S. H. Gehrke, G. P. Andrews, and E. L. Cusller, *Chem. Eng. Sci., 41*, 2153–2160 (1986).
[5] H. G. Cussler, M. V. Rele, and V. V. Disphande, *Anal. Biochem., 133*, 260–263 (1983).
[6] P. E. Grimshaw, J. H. Nussbaum, A. J. Grodzinsky, and M. L. Yarmush, *J. Chem. Phys., 93*, 4462–4472 (1990).
[7] R. A. Siegal, B. A. Firestone, I. Johannes, and J. Cornejo, *Polym. Prep., 31*, 231–232 (1990).
[8] L. Brannon-Peppas and N. A. Peppas, *J. Control. Rel., 8*, 267–274 (1989).
[9] D. Hariharan and N. A. Peppas, *Int. Symp. Control. Rel. Bioact. Mater., 19*, 367–368 (1992).
[10] C. J. Kim and P. I. Lee, *Pharm. Res., 9*, 195–199 (1992).
[11] C. J. Kim and P. I. Lee, *Ibid., 9*, 1268–1274 (1992).
[12] P. I. Lee, *Polym. Commun., 24*, 45–47 (1983).
[13] M. H. B. Skovby and J. Kops, *J. Appl. Polym. Sci., 39*, 167–177 (1990).
[14] R. W. Baker, *Controlled Release of Biologically Active Agents*, Wiley, New York, 1987, pp. 50–71.
[15] S. S. Shah, M. G. Kulkari, and R. A. Mashelkar, *J. Control. Rel., 15*, 121–132 (1991).
[16] C. J. Kim, *Drug Dev. Ind. Pharm.*, In Press.
[17] O. Levenspiel, *Chemical Reaction Engineering*, 2nd ed., Wiley, New York, 1972, pp. 357–377.
[18] J. Shen and J. M. Smith, *Ind. Eng. Chem., Fundam., 4*, 293–301 (1965).
[19] C. J. Kim and P. I. Lee, *Int. Symp. Control. Rel. Bioact. Mater., 17*, 118–119 (1990).
[20] G. G. Raymond and J. L. Born, *Drug Intell. Clin. Pharm., 20*, 683–686 (1986).
[21] D. W. Newton and R. B. Kluza, *Drug Intell. Clin. Pharm., 12*, 546–554 (1978).
[22] Martindale, *The Extra Pharmacopoeia*, 29th ed. (J. E. F. Reynolds, Ed.), Pharmaceutical Press, London, 1989.

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