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POLYELECTROLYTE GELS AS DRUG CARRIERS I: POLY(METHYL METHACRYLATE-co-POTASSIUM ACRYLATE) BEADS

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ABSTRACT

Reported herein is an indirect process to synthesize highly swellable anionic gel beads based on poly(methyl methacrylate-co-potassium acrylate) (PMMA/A-K), which is highly swellable in weak acid. The Release of labetalol HCl (solubility in water 1g/60 ml) from PMMA/A-K beads was not affected by buffer concentrations above 1/15 M. However, as the buffer concentration was decreased from 1/15 M to 0.01 M, the release rate decreased. Release kinetics are close to zero-order with an exponent of n = 0.904 in 0.01 M buffer concentration, whereas the exponent n in 0.2 M and 1/15 M is 0.635 and 0.768, respectively. With a 0.01 M buffer concentration, n ranges from 0.876 to 0.933 as pH changes from 9.0 to 6.8, indicating that the release kinetics maintain a zero-order irrespective of the pH's examined in this study. This zero-order kinetics at 0.01 M results from large dimensional changes of about D_f/D_i = 2.35 to 2.63. The degree of swelling during drug release contribute to the increase in the diffusion coefficient of the drug in the swollen matrix, which in turn can lead to zero-order kinetics.

INTRODUCTION

Hydrophilic polymeric materials, cross-linked or noncross-linked, have been extensively investigated for drug delivery systems and other applications (1). In particular, the homopolymer of 2-hydroxyethyl methacrylate (PHEMA), and copolymers of HEMA and co-monomers, have been widely investigated for drug delivery applications (2,3). To prolong the duration of drug release from the PHEMA matrix, following moderate water absorption, hydrophobic co-monomers have been incorporated, resulting in materials that are less water swellable, but which maintain good alcohol swelling. The low water swelling hydrogels have a drawback, however, wherein drug release rapidly reaches 80% of the load, after which it tails off very slowly to exhaustion (3). This is attributable to the early stage contribution of osmotic forces produced by the dissolved drug in the matrix, which contribute to a larger degree than the swelling of polymer (4).

Charged hydrogels, on the other hand, are responsive to the swelling environment, and are able to swell to a greater degree compared to non-ionic hydrogels; this may avoid the tailing-off of drug release. Equilibrium and dynamic swelling of charged hydrogels has been studied by various workers (5-7). The application of ionic hydrogels to drug delivery systems is in the early stage of research. The release of oxprenolol HCl from poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) beads has been reported (8). Drug release from PMMA/MAA beads not only avoids the tailing-off phenomenom, but also finishes with associated dimensional changes when the ionization fronts meet at the core. As one may observe in other hydrogel systems, the drug release rate from PMMA/MAA beads increases with the drug loading. However, the complex of drug with ionized PMMA/MAA (PMMA/MANa) beads minimizes the drug loading effect on drug release because the drug loading level does not vary much during the loading process. Below pH 6.5, however, the drug release from PMMA/MANa beads is substantially retarded, because conversion of the carboxylate anion to carboxylic acid provides a less swellable matrix. It has been reported that carboxylic acid groups in polyacrylic acid are more prone to greater swelling, even below pH 6, than corresponding groups in polymethacrylic acid (9). Acrylic acid-based homopolymer or copolymer beads, which provide a desirable geometry for oral drug dosage forms, cannot be obtained by suspension polymerization due to the solubility of acrylic acid in water.

Herein we report an indirect process to synthesize highly swellable gel beads which can be used for drug delivery systems, based on a copolymer of methyl methacrylate and potassium acrylate.

EXPERIMENTAL

Synthesis of poly(methyl methacrylate-co-ethylacrylate) (PMMA/EA) beads: Crosslinked PMMA/EA beads were prepared via a free-radical suspension polymerization process reported in the literature (10). The polymerization of methyl methacrylate (46 wt%) and ethyl acrylate (54 wt%), with ethylene glycol dimethacrylate (EDMA) (1.9 wt%) as a cross-linking agent, was performed at 70°C for 3-4 hrs, using $Mg(OH)_2$ as the suspending agent and AIBN as the initiater. After removing the suspending agent with concentrated HCl, the beads were extracted with methanol for several days before being dried.

Hydrolysis of PMMA/EA beads to poly(methyl methacrylate-co-potassium acrylate) (PMMA/A-K) beads: The cross-linked PMMA/EA beads were hydrolyzed according to the method reported by Thanoo and Jayakrishnan (11). The PMMA/EA beads were charged with 100 ml ethylene glycol containing 7.5% KOH in a 250 ml flat-bottom flask with a condenser. The solution was heated to 125°C for 7-8 hrs, and periodically a sample was taken to observe the hydrolysis under a stereomicroscope (Olympus SZ60). The hydrolyzed beads (PMMA/A-K) were then discharged into a large volume of distilled/deionized water, filtered, washed, and equilibrated in distilled/deionized water until further study.

Drug loading and release study: The swollen PMMA/A-K beads were poured into a 2.5% aqueous drug loading solution and equilibrated for 3 days at room temperature. They were then filtered and dried under vacuum. Labetalol HCl, a beta-blocking agent, was chosen as a model drug. Drug release from dry drug loaded beads was measured at 37°C in phosphate buffer at 244 nm in a stirred cuvette, via an HP8452A thermostated diode-array spectrophotometer. The rate of stirring was controlled and maintained at 300 rpm by a Peltier temperature control accessory (HP 89090A). Dry drug-loaded beads of 700-900 μm were used for the release study.

RESULTS AND DISCUSSION

The conventional process for producing homo- or co-polymers of alkali acrylate is to polymerize the alkali acrylate or acrylic acid in water with a water-soluble cross-linking agent. In this process only slab and cylinderical geometry polymer matrices may

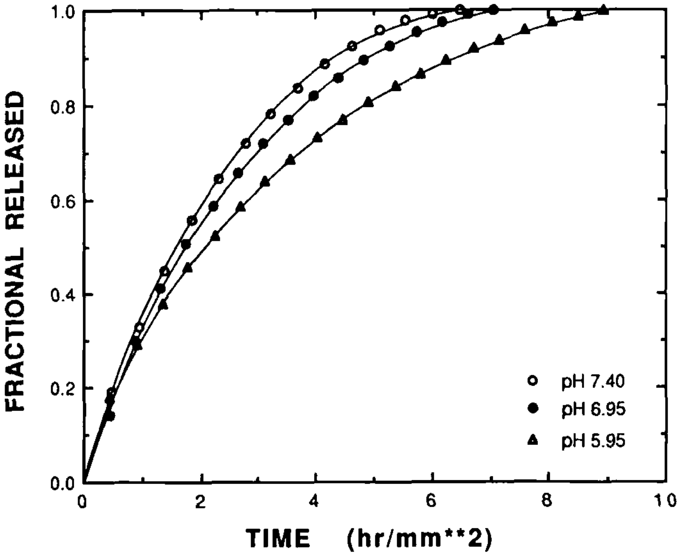

FIGURE 1
Effect of pH on the release of labetalol HCl from PMMA/A-K beads in 1/15 M phosphate buffer.

be manufactured. However, spherical geometry has an advantage over other geometries for oral drug delivery systems. The monomer (alkai acrylate or acrylic acid) is highly water soluble and does not salt out as do other water soluble monomers such as HEMA and methacrylic acid. As a result, conventional suspension polymerization cannot be used to produce the spherical beads. Even though the inverse suspension polymerization process can be employed for the synthesis of PA-K beads, the bead size produced is too small for application in oral drug delivery systems. In addition, there are difficulties in the inverse suspension process for using the water-soluble monomer (AA or A-K) and nonwater-soluble monomer (MMA). We proceeded to produce the PMMA/A-K beads indirectly from the precursor polymer (i.e. PMMA/EA) beads cross-linked with EDMA 1.9 wt%. The suspension-polymerized PMMA/EA beads were hydrolyzed in ethylene glycol KOH solution at high temperature (11). It was observed that the methacrylate chain in the poly(methyl methacrylate) was not hydrolyzed below 175°C. When the hydrolyzed beads were poured into water, they were enormously swollen according to their degree of cross-linking.

The effects of pH on the release of labetalol HCl from PMMA/A-K beads is presented in Figure 1. The time scale was normalized with respect to the bead size in order to minimize its effect on drug release. During the drug loading process, the secondary amine (labetalol HCl) forms a complex with anionic carboxylate groups. This is similar to ion exchange resin drug delivery systems, where a cationic exchange resin containing sulfonate groups forms a complex with amine drugs (primary, secondary or tertiary). Drug release ocurrs in the following sequences: (i) diffusion of counter ions through the imaginary boundary film layer, if any, (ii) diffusion through the intraparticle gel layer (drug depleted PMMA/A-K), (iii) dissociation reaction between the drug resin complex and counter ions, (iv) diffusion of liberated drug through the intraparticle gel layer, and finally (v) diffusion of the drug through the boundary film layer to the sink. These kind of sequential steps can also be observed in non-catalytic solid reactions and mineral leaching from ore. During drug release, the cuvette containing a drug loaded bead is stirred by a magnetic bar which is operated by a Peltier controller. In this case the stirring rate was maintained higher than 300 rpm, in which the mass transfer resistance in the boundary layer is negligible (12,13). As soon as the water containing counter ions diffuses into the beads, the dissociated drug precipitates due to its poor solubility (1g/60 ml). As shown in Figure 1, the rate of drug release increases with pH in 1/15 M phosphate buffer (I = 0.2 M). The swelling of acrylate carboxylate groups at lower pH (weak acid), (in which D_f/D_i is 1.87), is less than that at higher pH (neutral or weak base) in which D_f/D_i is 2.01 and 2.08, respectively, resulting in slower diffusion of the drug through the swollen gel layer. The release rate from PMMA/A-K beads, however, is much higher than that from PMMA/MANa beads (12) (from which the drug release is minimal at below pH 6.5 due to lower swelling of methacrylic acid chain).

The release data was treated with the phenomenological expression below (14):

$$M_t/M_{oo} = k\,t^n$$

where M_t is the amount of drug released at time t, M_{oo} is the initial amount of drug, k is a constant, and n is the exponent. As shown in Table 1, the exponent n increases as pH increases, ranging from 0.667 to 0.768, indicating the release kinetics are anamolous. The degree of swelling follows the same trend.

Figure 2 illustrates the effect of buffer concentration on the drug release from PMMA/A-K beads. At buffer concentrations above 1/15 M phosphate, drug release

TABLE 1

Effects of pH and buffer concentration on the exponent n and degree of swelling.

pH	Buffer	n	D_f/D_i*
5.95	1/15 M	0.667	1.87
6.95	1/15 M	0.742	2.01
7.40	1/15 M	0.768	2.08
7.40	0.20 M	0.635	1.84
7.40	0.01 M	0.904	2.35
6.80	0.01 M	0.933	2.63
9.00	0.01 M	0.876	2.48

*D_f: final bead diameter.

D_i: initial bead diameter.

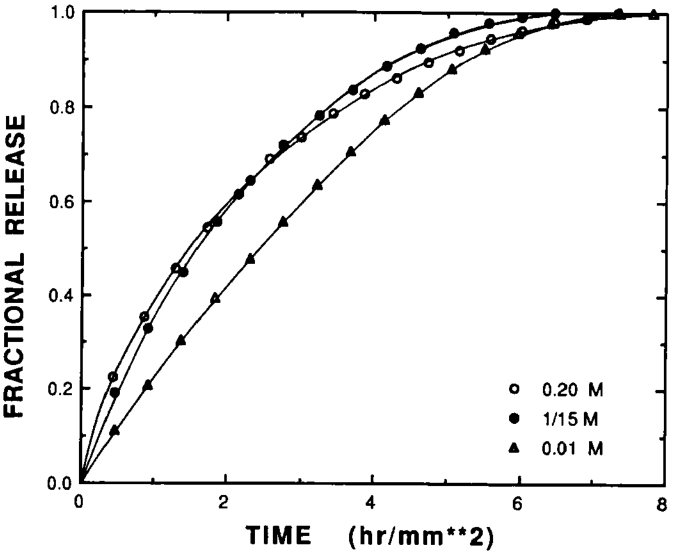

FIGURE 2
Effect of buffer concentration on the release of labetalol HCl from PMMA/A-K beads (pH 7.4).

kinetics were not affected by the concentration of buffer in the dissolution medium. However, the rate of drug release decreases as the buffer concentration decreases from 1/15 M to 0.01 M. The exponent n increases from 0.635 to 0.904 as the buffer concentration decreases from 0.2 M to 0.01 M. At high pH (neutral and weak base) release kinetics follow an anamolous pattern in which the exponent (n) is 0.635 and 0.768 for 0.2 M and 1/15 M, respectively, as found in Figure 1 for the constant ionic strength (1/15 M buffer). However, as the buffer concentration drops to 0.01 M, the release rate slows down drastically with an exponent of 0.904, which indicates a zero-order release according to the criteria set by the phenomenological expression for a swellable polymer matrix (sphere) (14). Coincidentally the degree of swelling of spherical beads increases (D_f/D_i of 1.84 to 2.35) as the the buffer concentration decreases. This is attributable to the higher osmotic pressure exerted by higher buffer concentration, resulting in the surpression of charged coil expansion. The decreased sensitivity of release kinetics to the buffer concentration above 1/15 M suggests that the dissociation reaction is independent of the concentration of counter ions, which means a zero-order dissociation reaction. At the buffer concentration of 0.01 M, the release kinetics is zero-order. This phenomenom can be expressed by dissociation reaction kinetics, which may be the Langmuir and Hinshelwood equation. Villa et al (15) reported that in non-catalytic gas-solid reaction processes the conversion of a spherical solid with a gaseous reactant, having an order of reaction of 3/4 and high film mass transfer rate, is pseudo-zero order rate. It has been reported that the Langmuir-Hinshelwood equation can be used for ion exchange processes (16). In the Langmuir-Hinshelwood equation, at low concentration of counter ions, the order of reaction for the dissociation of complex drug in the polymer chain can be a fractional power to the concentration of counter ions, and at high concentration the order of reaction can be zero-order. In addition, the higher degree of swelling may contribute to an increase of the drug's diffusion coefficient in the swollen gel. According to Lee's time-dependent diffusion coefficient (17), the smaller initial, and larger final diffusion coefficients can influence the release kinetics to be close to zero-order. As a result, dissociation reaction kinetics (fractional order) with high swelling ($D_f/D_i = 2.35$) in 0.01 M lead to zero-order release with an exponent of 0.904.

The release of drug in the lower buffer concentration at different pH's is of interest. Figure 3 illustrates the effect of pH on the release of labetalol HCl from PMMA/A-K beads in 0.01 M buffer concentration. As observed in Figure 1, the rate of drug release is faster as the pH increases from 5.9 to 9.0. However, it maintains zero-order release behavior, which was not found in the 1/15 M buffer solution. The degree of

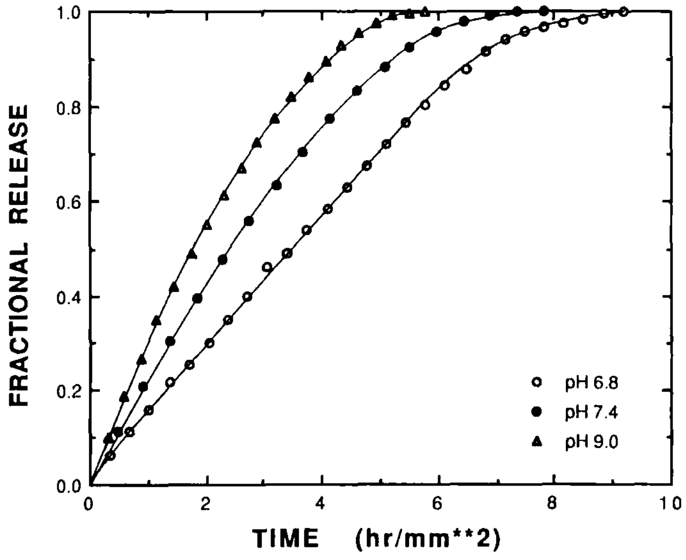

FIGURE 3
Effect of pH on the release of labetalol HCl from PMMA/A-K beads in 0.01 M phosphate buffer.

swelling presented in Table 1 indicates that the pH of the buffer does not significantly influence the magnitude of swelling (D_f/D_i = 2.35 to 2.63). Presumably dissociation kinetics at higher pH are faster than those at lower pH, resulting in further linearality of release rate at lower pH.

CONCLUSION

Highly water swellable hydrogel-beads, based on poly(methyl methacrylate-co-potassium acrylate), were prepared by an indirect synthetic process. Drug release of labetalol HCl from PMMA/A-K - drug complex beads in 1/15 M buffer concentration at different pHs follows anamolous behaviour. Even below pH 6.0, drug is released without the significant retardation as not found in methacrylic acid beads. At a low buffer concentration (i.e. 0.01 M), zero-order release kinetics were observed. This is attributed to the combined effects of complex-dissociation reaction kinetics (Langmuir-Hinshelwood equation) and an increase in swelling. However, at the same low buffer concentration (0.01 M), the lower the pH the more zero-order release kinetics were observed. In the near future, we will investigate an quantitative interpretation of release of less water-soluble drug from highly swellable hydrogels with the dissolution/diffusion controlled or time-dependent diffusion coefficient mechanisms.

REFERENCES

1. N.A. Peppas, Hydrogels in Medicine and Pharmacy, Vol. I-III, CRC Press, Boca Raton, Fl., 1987.
2. H.E. Junginger, C.-M. Lehr, D.A.v. Hal and J.A. Bouwstra, Proceed. Intern. Symp. Control. Bioact. Mater., 17, 443-444 (1990).
3. K.F. Mueller, "Release and Delayed Release of Water-Soluble Drugs from Polymer Beads with Low Water Swelling," P.I. Lee and W.R. Good, Eds., ACS Symposium Series No. 348, ACS, Washington, DC, 1987, p. 139-152.
4. P.I. Lee and C.J. Kim, J. Controlled Release, 16, 229-236 (1991).
5. L. Brannon-Peppas and N.A. Peppas, J. Control. Rel., 8, 267-274 (1989).
6. S.H. Gehrke and E.L. Cussler, Macromolecules, 21, 3254-3259 (1988).
8. C.J. Kim and P.I. Lee, Pharm. Res., 9, 1268-1274 (1992).
7. S.S. Shah, M.G. Kulkarni and R.A. Mashelkar, J. Controlled Release, 15, 121-132 (1991).
9. C.J. Kim, "Highly Swellable Poly(Potassium Acrylate) Beads as Drug Carriers", presented American Chemical Society Meeting, Chicago, August, 1993.
10. K.F. Mueller, S.J. Heiker and W.L. Plankl, US Patent 4,224,427 (1980).
11. B.C. Thanoo and A. Jayakrishnan, J. Appl. Polym. Sci., 39, 1153-1161 (1990).
12. C.J. Kim, unpublished data.
13. B.A. Firestone and R.A. Siegal, J. Appl. Polym. Sci., 43, 901-914 (1991).
14. P.L. Ritger and N.A. Peppas, J. Controlled Release, 5, 37-42 (1987).
15. L.T. Villa, O.D. Quiroga and G.V. Morales, Trans. Inst. Chem. Eng., 70, Part A, 276-281 (1992).
16. W. Holl and H. Sontheimer, Chem. Eng. Sci., 32, 755-762 (1977).
17. P.I. Lee, "Interpretation of Drug-Release Kinetics from Hydrogel Matrices in terms of Time-Dependent Diffusion Coefficients," P.I. Lee and W.R. Good, Eds., ACS Symposium Series No. 348, ACS, Washington, DC, 1987, p.71-83.