NOTES

A Linear Drug Release from Erosion-Controlled Drug/Resin Complex Systems

INTRODUCTION

Bioerodible polymers were investigated for controlled-release drug-delivery systems to achieve zero-order release kinetics.[1] Poly(vinyl alcohol) (PVA), hydroxypropyl methyl cellulose (HPMC), and sodium carboxymethyl cellulose (CMC), which are swellable-soluble polymers, have been utilized for oral drug-delivery systems.[2-4] During the release of drugs from these polymers, two distinctive phenomena occur: the swelling and dissolution of the polymer. The release kinetics are dependent upon the relative contribution of these two processes. Lee[5] showed that it is necessary to attain the synchronized movement of the eroding front and the diffusion front in order to achieve zero-order release kinetics in the erodible matrices. Conte et al.[2] and Harland et al.[3] demonstrated that a constant gel thickness (synchronization of front movement) is observed with linear release kinetics. However, the attainment of front synchronization is not common in pharmaceutical dosage forms because of the usage of poorly water-soluble polymers. In this case, the swelling process predominantly controls drug release over the erosion/dissolution process. Pham and Lee[6] showed that polymer swelling was the foremost process controlling drug release from HPMC cylinders, resulting in anomalous Fickian kinetics. Besides this problem, drug loading plays an important role in regulating the release kinetics. Fickian release kinetics result at higher drug-loading levels, because the release is controlled by the diffusion of drug rather than by the swelling or erosion of the polymer.[7]

On the other hand, ion-exchange resins with negligible swelling sustain the release of drug with a tailing. One of the advantages of using ion-exchange resins, however, is that one can load as much of a drug as possible in proportion to the charge density of the resins by forming the drug/resin complex. Kim and Nujoma[8] reported anomalous Fickian kinetics of the erodible drug–PMMA/MANa beads due to the limitation of spherical geometry. We suggested that if one employs the combined principles of ion-exchange resins and swelling/erosion polymers one may achieve zero-order release kinetics from a constant surface area matrix with a high loading.

In this study, we present the linear release of water-soluble drugs from erodible, drug/resin complex, gel matrices using poly(methyl methacrylate-*co*-sodium acrylate) (PMMA/A-Na).

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EXPERIMENTAL

Synthesis of Water-insoluble PMMA/AA

Polymer gels were prepared by the free-radical polymerization of methyl methacrylate (MMA) (Fisher) and acrylic acid (AA) (Polysciences) whose inhibitors had been removed by a Di-Hibit column (Polysciences). A mixture of monomers with the initiator V-65B (Wako Chemical) was discharged into a glass ampule (11 mm i.d.) and sealed with a cap. The polymerization was carried out in an oil bath at 50°C for 20 h. The glass ampule was broken and the polymer rod was dissolved in acetone. The PMMA/AA was recovered by precipitating the polymer from the polymer solution in water before being dried in vacuum for several days.

Characterization of the Polymer

The content of AA in PMMA/AA was determined by titrating an alcoholic solution of the polymer with a 0.05 M NaOH solution until the phenolphthalein endpoint.[9] The pK_a and pH at which the polymer precipitates were determined by backtitrating a known excess amount of aqueous NaOH solution of PMMA/AA with 0.1 M HCl. The point of precipitation was the pH at which the turbid solution of insoluble PMMA/AA was formed.

Drug Loading and Drug Release Experiments

A calculated equimolar amount of the NaOH solution with respect to the AA content of the polymer was added to a measured amount of PMMA/AA in order to convert the acid polymer to PMMA/A-Na. An equimolar quantity of drug was added subsequently. Diphenhydramine HCl and propranolol HCl were chosen as model drugs. Following the addition of the chosen drug, an equal volume of the aqueous alcoholic solution was added to the aqueous solution of the drug/resin complex. Portions of the resultant solutions were poured in Teflon-coated pans and allowed to evaporate at room temperature for several days. The dry films were cut with a cork borer and dried in a vacuum for a few days. Afterward, the films were stored in a desiccator until the release study could be performed.

The release kinetics from dry drug/resin complex discs

were carried out at 23°C in phosphate buffers of various pHs in a 2–3 L beaker with vigorous magnetic stirring. Drug release was monitored on an HP 8451A diode-array spectrophotometer at 222 and 270 nm for diphenhydramine HCl and propranolol HCl, respectively. Exponent (n) of $M_t/M_\infty = kt^n$, where M_t and M_∞ are the amount of drug released at time t and infinite time, respectively, was determined from the regression up to 60% release data.

RESULTS AND DISCUSSION

Several copolymers of MMA and AA were synthesized to obtain erodible drug/resin matrices. It was observed that copolymers having an AA content of 38 mol % and above dissolved in phosphate buffers of greater than pH 5.0 and that it was difficult to recover the precipitated copolymers having AA contents of 47 mol % and more due to the swelling of PMMA/AA in water. The PMMA/AA (47 mol % AA) does not have structural rigidity compared to the PMMA/AA (38 mol % AA). In this study, only 38 and 47 mol % copolymers were chosen to investigate drug-release kinetics. The pK_a of the copolymer (PMMA/AA) was determined graphically to be 5.5, as shown in Figure 1, which is about the same as the monoisopropyl ester of poly(vinyl methyl ether-*co*-maleic anhydride) (PVME-MA).[10] It was found that the pK_a was relatively independent of the content of AA in the polymers studied herein. Figure 1 shows the dependence of the pH of precipitation on the AA content. The PMMA/A-Na (47 mol % AA) precipitated at pH 4.5, which is about the same as that of the monoisopropyl ester and monoethyl ester of PVME-MA,[11] whereas the pH of precipitation of PMMA/A-Na (38 mol % AA) is 5.1. The lower the AA content, the more hydrophobic the polymer, and as a result, the higher the pH of precipitation. The high pH of precipitation of PMMA/A-Na (38 mol % AA) affects the release of the drug from the matrices, as will be discussed.

Upon contact with drugs, the aqueous solution of PMMA/A-Na precipitated, forming the complex between the amine HCl of the drug and carboxylate of PMMA/A-Na. To obtain a homogeneous solution, an aqueous alcoholic solution (95% v/v) was added to dissolve the precipitate before obtaining the dry films. The release of diphenhydramine HCl from erodible drug–PMMA/A-Na matrices is shown in Figure 2(A) and (B). Release time is normalized with respect to the disc thickness. Release profiles show a good reproducibility [pH 8.0 and 6.0 in Fig. 2(A)] within experimental error. During the drug release, the drug–PMMA/A-Na complex is dissociated by the incoming counterions (i.e., Na^+) from the dissolution medium. The dissociated drug diffuses out of the matrix, while the drug-free PMMA/A-Na starts swelling. When the polymer concentration reaches a threshold level, the swollen gel begins to erode.[8] The release of diphenhydramine HCl from erodible drug–PMMA/A-Na complexes (47 mol % A-Na) is independent of pH's higher than 6.5. However, the release of diphenhydramine HCl, in pH 6.0 buffer, is significantly retarded because the erosion rate is slow due to the less available carboxylate content in the polymer chain with the higher content of carboxylic acid. In all cases, the drug-release kinetics are accelerated after about 60–70% release because the drug–PMMA/A-Na matrices do not maintain their rigidity and

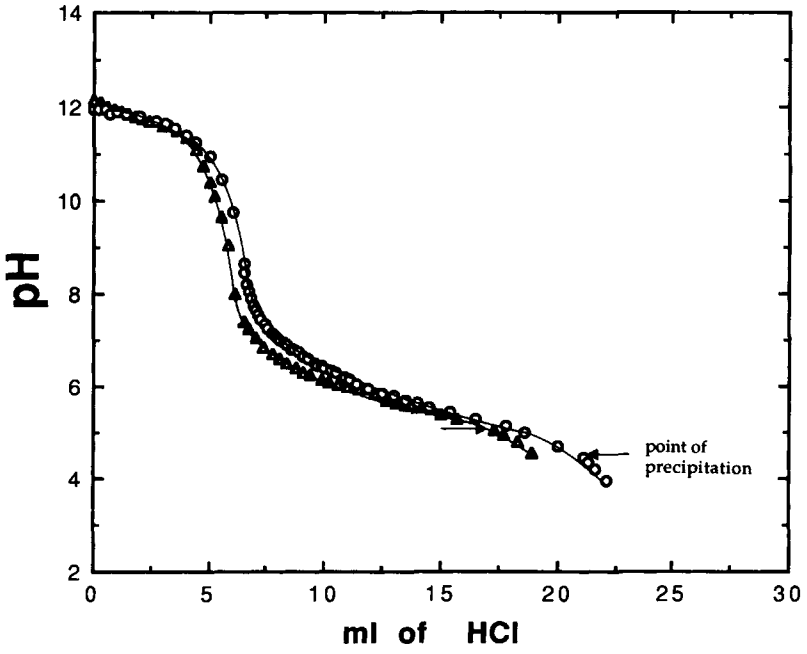

Figure 1 Titration curves of PMMA/AA: (△) 38 mol % AA; (○) 47 mol % AA.

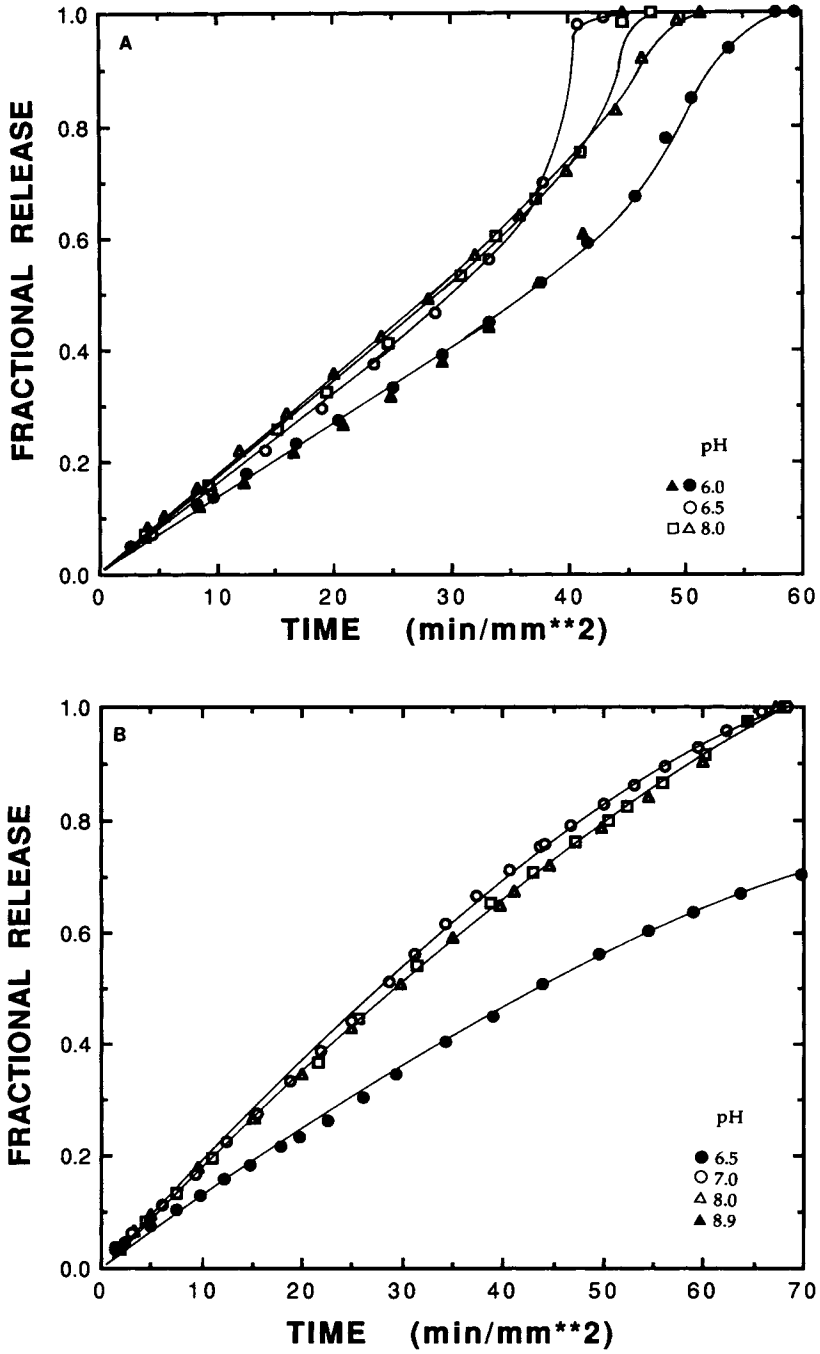

Figure 2 Effect of pH on the release of diphenhydramine HCl from erodible PMMA/A-Na complex gel film: (A) 47 mol % AA; (B) 38 mol % AA.

break down into pieces. Depending upon how the matrices break down (i.e., smaller pieces or bigger pieces), different degrees of acceleration occur.

Similarly, the release of diphenhydramine HCl from the drug–PMMA/A-Na (38 mol % A-Na) is shown in Figure 2(B). We observed similar release kinetics as mentioned in the 47 mol % polymer except that the release slows down at the higher pH (6.5). However, the release kinetics are superimposed with the release data from 47 mol % PMMA/A-Na above pH 6.5 and from 38 mol % PMMA/A-Na above pH 7.0. The release kinetics from 38 mol % PMMA/A-Na were not accelerated as observed in Figure 2(A) because the drug–PMMA/A-Na matrices maintain their rigidity. Since the matrices are broken down at about 90–95% release, one may not observe the acceleration of the drug release. One may estimate the critical

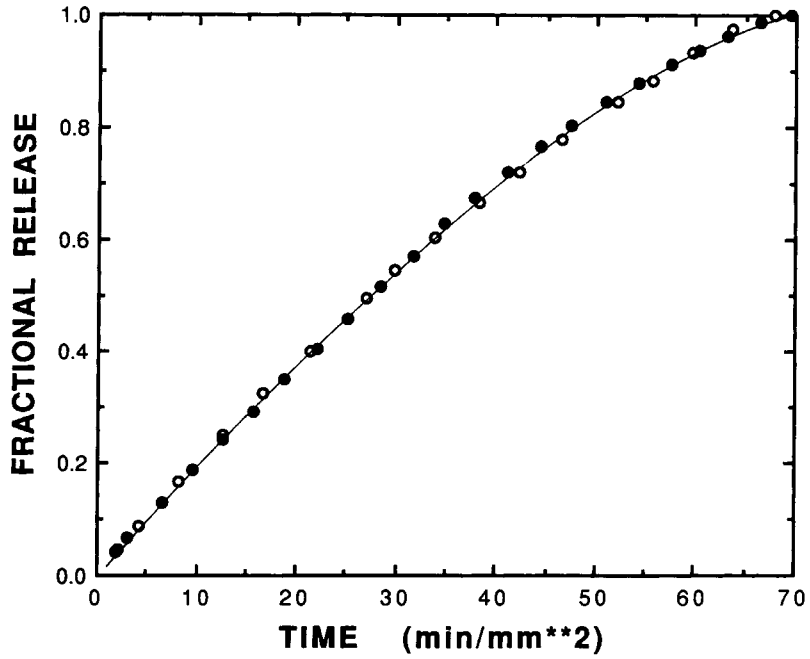

Figure 3 Effect of buffer concentration on the release of diphenhydramine HCl from erodible PMMA/A-Na (38 mol % AA) complex film: (○) 1/15*M* (●) 0.1*M*.

carboxylic acid content at which the drug release is not influenced by the pH. At pH 6.5, the carboxylate content in the polymer chain is 30 and 28 mol % of PMMA/AA for 47 and 38 mol %, respectively. At pH 7.0, there is 35 mol % of carboxylate in the PMMA/A-Na (38 mol % AA). From this analysis, when there are approximately 35 mol % of carboxylate groups in the PMMA/A-Na matrices, drug release is linear with time without the influence of pH.

The effect of buffer concentration on the release of diphenhydramine HCl is shown in Figure 3. The concentration of phosphate buffer does not change the release

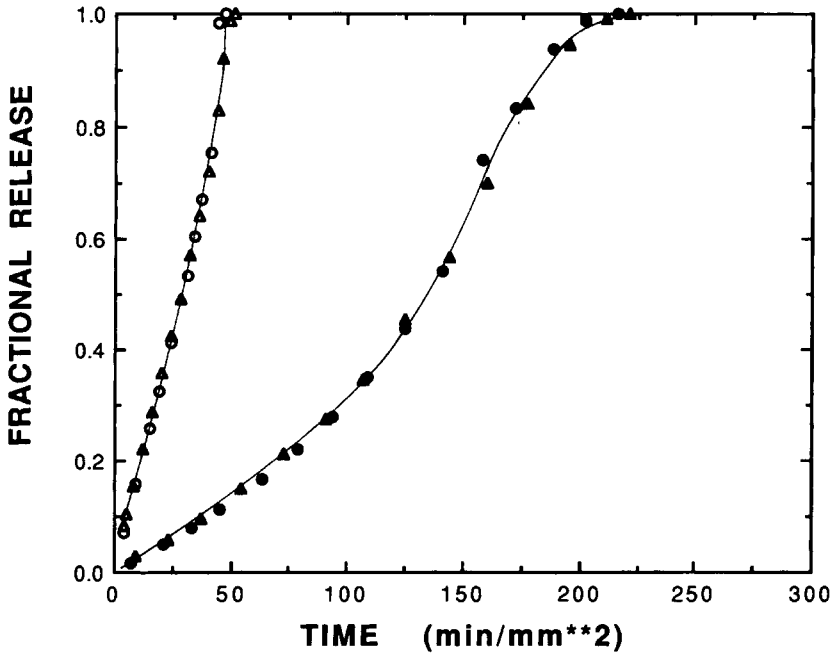

Figure 4 Effect of drug solubility on drug release from erodible PMMA/A-Na complex gel films at pH 8: (○, △) diphenhydramine HCl; (●, ▲) propranolol HCl.

Table I The Exponent of Releases Kinetics

Polymer	Drug	pH	Buffer Concentration	n
47 mol %	A	6.0	0.1M NaCl	0.89
	A	6.5	0.1M NaCl	1.00
	A	8.0	0.1M NaCl	0.95
	B	8.0	0.1M NaCl	0.93
38 mol %	A	6.5	0.1M NaCl	0.82
	A	7.0	0.1M NaCl	0.92
	A	8.0	0.1M NaCl	0.93
	A	8.9	0.1M NaCl	0.96
	A	7.4	0.07M[a]	0.94
	A	7.4	1.0M[a]	0.92

A: diphenhydramine HCl; B: propranolol HCl.
[a] No NaCl.

kinetics of the drug–PMMA/A-Na matrices. These observations (pH and buffer concentration-independent) suggest that erodible, drug–resin complex systems exhibit more promising characteristics compared to the release of a drug from the polymer matrix consisting of unionized carboxylic acid groups.[10–12] The release of a drug from those unionized poly(carboxylic acids) is strongly dependent upon the hydrolysis of carboxylic acid via either surface erosion or swelling/erosion-controlled systems.[10–12] In contrast, the dissociation of the drug/resin complex is not greatly dependent on the pH and buffer concentration.[13,14]

The effect of drug solubility on the release of a drug from the drug–PMMA/A-Na complex matrices is shown in Figure 4. The release of propranolol HCl (5% solubility in water) from PMMA/A-Na (47 mol % AA) at pH 8.0 slows down significantly compared with that of diphenhydramine HCl (50% solubility in water). Even though the release extends to 4 (h/mm^2) for the propranolol HCl, the release kinetics maintain zero-order up to 30% release due to the thinner films (thickness $\approx$ 0.4 mm) compared to the ones loaded with diphenhydramine HCl (thickness $\approx$ 0.7 mm). Figure 4 shows that the breaking point of a film is dependent upon the thickness of the dry film, suggesting that the eroding film is not strong enough to maintain its rigidity above the threshold thickness. The drug-loading level of diphenhydramine HCl was 52.5 and 58.7 wt % for 38 and 47 mol % PMMA/A-Na, respectively, whereas that of propranolol HCl was 47.3 wt %. This characteristic is substantially different from the swelling/erosion-controlled systems consisting of only swellable-soluble polymer, where, at such high loadings, the drug release is controlled by the diffusion of the drug (Fickian) rather than the swelling or erosion of the polymer.[7]

The release of diphenhydramine HCl and propranolol HCl from the drug–PMMA/A-Na matrices is close to zero-order (n = 0.90–1.0), as illustrated in Table I. A perfect straight line with respect to time was not achieved because the edge of the matrix contributed to the drug release. It was expected that the synchronization of front movement (swelling and erosion) might be established during the drug release, resulting in a constant release.[8] However, the release exponent is smaller as the pH of the dissolution medium decreases to 6.0 and 6.5 for 38 and 47 mol % PMMA/A-Na, respectively. This suggests that the diffusional release through the swollen gel thickness plays a more important role in the kinetics than does the erosion of the polymer.[5] During drug release, a larger overall dimension was observed due to the extended swelling of gel layer in pH 6.0 and 6.5 for 38 and 47 mol % polymers, respectively.

REFERENCES

1. J. Hellers, in *Medical Applications of Controlled Release,* R. S. Langer and D. L. Wise, Eds., CRC Press, Boca Raton, FL, 1984, Vol. I.
2. U. Conte, P. Columbo, A. Gazzaniga, M. E. Sangalli, and A. La Manna, *Biomaterials,* **9,** 489–493 (1988).
3. R. S. Harland, A. Gazzaniga, M. E. Sangalli, P. Columbo, and N. A. Peppas, *Pharm. Res.,* **5,** 488–494 (1988).
4. P. Columbo, A. Gazzaniga, C. Caramella, U. Conte, and A. La Manna, *Acta Pharm. Technol.,* **33,** 15–20 (1987).
5. P. I. Lee, *J. Membr. Sci.,* **7,** 256–275 (1980).
6. A. T. Pham and P. I. Lee, *Proceed. Int. Symp. Control. Rel. Bioact. Mater.,* **20,** 220–221 (1993).
7. P. I. Lee, *Polym. Commun.,* **24,** 45–47 (1983).
8. C. J. Kim and Y. N. Nujoma, to appear.
9. U. Finne, K. Rönnkö, and A. Urtti, *J. Pharm. Sci.,* **80,** 670–673 (1991).
10. U. Finne, K. Kyyrönen, and A. Uttri, *J. Control. Rel.,* **10,** 189–194 (1989).
11. J. Heller, R. W. Baker, R. M. Gale, and J. O. Rodin, *J. Appl. Polym. Sci.,* **22,** 1991–2009 (1978).
12. C. J. Kim and P. I. Lee, *Proceed. Int. Symp. Control. Rel. Bioact. Mater.,* **19,** 208–209 (1992).
13. C. J. Kim, *Drug Dev. Ind. Pharm.,* to appear.
14. C. J. Kim, *J. Macromol. Sci. Pure Appl. Chem.,* to appear.
15. P. I. Lee, in *Treatise on Controlled Drug Delivery,* A. Kydonieus, Ed., Marcel Dekker, New York, 1992.

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