Water-Soluble Quaternary Amine Polymers as Controlled Release Carriers

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ABSTRACT: New bioerodible materials, which are noncrosslinked and water-soluble copolymers of quaternary amines, and alkyl (meth)acrylate were synthesized and then bound with anionic drugs (sodium sulfathiazole and diclofenac sodium) to form water-insoluble complexes. Sodium sulfathiazole was bound to the copolymers more strongly than diclofenac sodium. As the quaternary amine content of the copolymer was increased, the degree of binding of diclofenac sodium to the polymer increased (from 79.9 to 96.2%). Compressed tablets were prepared from the drug–polymer complexes, and their release profiles were well described by the dissociation/erosion mechanism. The release rate constant increased with increasing quaternary amine content of the polymer and decreased as longer alkyl methacrylates were used in the copolymer. The release kinetics were also dependent on the structures of the quaternary amines used (trimethylaminoethyl methacrylate chloride, trimethylaminoethyl acrylate chloride, and methacrylamidopropyltrimethylammonium chloride). Drug release from these systems were found to be independent of the ionic strength (0.05–0.2*M* NaCl) of the release medium. © 1998 John Wiley & Sons, Inc. J Appl Polym Sci 69: 263–269, 1998

Key words: polyelectrolyte; controlled release; erosion; dissociation; complex; quaternary amine

INTRODUCTION

Cross-linked ion exchange resins used in the past gave square root of time release kinetics with a long tailing toward the end as drug release from these systems are diffusion controlled.[1,2] This drawback can be overcome by altering the polymer structure so that it becomes water soluble. Recent developments have demonstrated zero-order drug release when water-soluble ionic polymers were used as drug carriers for controlled drug delivery.[3,4] Complexes formed between a drug and a water-soluble polyelectrolyte dissociate in the presence of counter ions present in the dissolution medium to provide a linear release, as a result of an erosion-controlled release mechanism.

The interaction of cationic drugs with water-soluble anionic polyelectrolytes have been studied as early as 1957, and such long-acting preparations have been reported as early as 1958; but, despite this early interest, no substantial amount of literature has been reported.[5] Such systems are essentially erodible systems, because they entail the eventual dissolution of the polymer matrix. Lee and colleagues[6] studied binding of the cationic drug (propranolol HCl) with a copolymer of methacrylic acid and methyl methacrylate (MMA) (Eudragit® L). Kim[7] reported a linear release from gel matrices of a swellable/erodible system, based on poly(MMA-*co*-sodium acrylate), loaded with diphenhydramine HCl. Because these systems contained carboxylate groups, a pH-dependent release profile was observed. Nujoma and Kim[3] have shown linear and pH-independent re-

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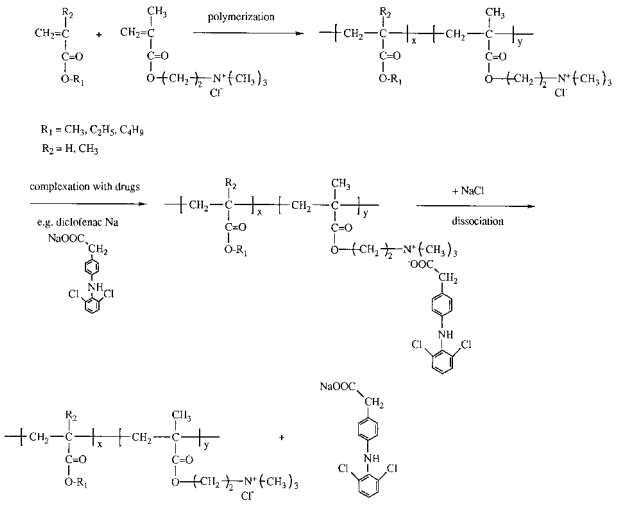

Scheme 1 Synthesis of cationic polymers, drug–polymer complexation, and dissociation.

lease of cationic drugs from sulfonate-containing polymers [poly(sulfopropyl methacrylate potassium-*co*-MMA) (SPMK/MMA)]. Erodible polyelectrolytes as drug carriers permit easy fabrication into convenient (and practical) tablets, high loading (> 40%), and controllable release profiles. A preliminary study has been conducted to deliver anionic drugs at a zero-order rate using quaternary amine containing polymers.[4]

In this article, the effects of the polymer composition (types of monomers) and the polymerization conditions on the release of anionic drugs from cationic copolymers are presented. Scheme 1 depicts polymer synthesis, complex formation, and drug dissociation.

EXPERIMENTAL

Materials

All chemicals were used as received unless otherwise noted. MMA, sodium phosphate monobasic, potassium phosphate dibasic, hydrochloric acid, and sodium chloride were purchased from Fisher Scientific (Fair Lawn, NJ). Trimethylaminoethyl methacrylate chloride (TMAEMC) and trimethylaminoethyl acrylate chloride (TMAEAC) were supplied from Rohm Tech (Boston, MA), and methacrylamidopropyltrimethylammonium chloride (MAPTMAC) and tert-butyl peroctoate (an initiator) were obtained from Polysciences (Warrington, PA) and Atochem N.A. (Buffalo, NY), respectively. Ethyl alcohol (95%) USP was purchased from Pharmaco Co. (Bayonne, NJ). Diclofenac sodium (Na) and Na sulfathiazole were purchased from Sigma Chemical Co. (St. Louis, MO). Dextrose USP was obtained from Amend Co. (Irvinton, NJ). Ethyl methacrylate (EMA), butyl methacrylate (BMA), and methyl acrylate (MA) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Water was distilled and deionized through a Nanopure® purification system. Simulated intestinal and gastric fluids without enzymes were used as the dissolution media. Simulated intestinal fluids were composed of 0.01*M* phosphate buffer (sodium phosphate monobasic and potassium phosphate dibasic) at pH 7, with different concentrations of NaCl (0.05*M*–0.2*M*) to vary the ionic strength. Simulated gastric fluids were prepared using concentrated HCl at pH 1.5, with different concentrations of NaCl (0.05*M*–0.2*M*) to vary the ionic strength.

Preparation of Quaternary Amine Copolymers and Drug–Polymer Complexes

Water-soluble quaternary amine copolymers were prepared by the free-radical solution copolymerization of one of three different quaternary amine chlorides (TMAEMC, TMAEAC, and MAPTMAC) with one of the alkyl (meth)acrylates (MMA, EMA, BMA, and MA). Typically, 5 g monomers [40 mol % quaternary amine and 60 mol % (meth) acrylate] and 3 g ethanol (95%) with the initiator (0.5 wt % of total monomer weight) were mixed in a glass ampoule (11 mm i.d.) and sealed with a cap. Polymerization was conducted in an oil bath at 75°C for 24 h unless otherwise noted. The ampoule was then broken and the polymer dried in open air for 2 days before being dried under a vacuum for several days. The polymer was dissolved in distilled/deionized water and dialyzed in Spectra/Por® dialysis membrane (MWCO = 1000; Cole-Palmer, Chicago, IL) before being lyophilized. The nitrogen contents of the purified polymer were determined by elemental analysis (Quantitative Technologies, Inc., Whitehouse, NJ) to calculate the actual copolymer composition.

An excess amount of drug solution (more than 1.5 times the mole ratio of drug to polymer) was added to an aqueous solution of quaternary amine copolymers to obtain a precipitated drug–polymer complex that was thoroughly washed free of soluble components and dried. The dried drug–polymer complexes were powdered in a mortar and pestle, and screened through stainless-steel

sieves (Newark Wire Clothe Co., Newark NJ) into different size fractions. Tablets of 200 mg weight containing drug–polymer complex and a binder (20% dextrose) were compressed using a 9.0 mm diameter die and a flat punch in a Carver press (Wabash, IN) with the 250 μm fraction. The model drugs studied were diclofenac Na and Na sulfathiazole.

Drug Release Kinetics

The release kinetics from tablets of the drug–polymer complex were conducted in simulated gastric and intestinal fluids at 37°C by the USP basket method at 100 rpm. Drug release was monitored on a HP 8452A diode-array spectrophotometer at 250 nm and 296 nm for diclofenac Na and Na sulfathiazole, respectively.

The linearity of drug release was assessed by fitting the release data (up to 60% and 80%) to the phenomenological equation[8]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

where M_t and M_∞ are the amounts of released drug at time t and the total amount of drug in the tablet, respectively, and k and n are a constant and a release exponent, respectively. Drug release kinetics were also evaluated by a dissociation-erosion mechanism[3]:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_e t}{C_o r_o}\right)^2 \left(1 - \frac{2k_e t}{C_o l}\right) \qquad (2)$$

where k_e, C_o, r_o, and l are the dissociation-erosion rate constant, the initial drug concentration in a tablet, the tablet radius, and the tablet thickness, respectively.

RESULTS AND DISCUSSION

Homopolymers of quaternary amine were first synthesized to design erodible drug carriers. The drug–polymer complex formed on first contact between the homopolymers and drugs dissolved in an excess of water under stirring. However, the copolymers of quaternary amine and alkyl (meth)acrylate formed water-insoluble complexes, which proved to be ideal drug carriers for ionic drugs. Copolymers prepared with 30 mol % quaternary amine and below in feed composition were not water-soluble and hence not of interest. The copolymers described herein were synthesized with 40 mol % quaternary amine and higher in feed compositions, and were water-soluble unless otherwise described. Some copolymers investigated herein [i.e., poly(trimethylaminoethyl methacrylate chloride-*co*-MMA) (PTMAEMAC/MMA)] have a molecular structure identical to Eudragit® RS and RL, which are pharmaceutically acceptable for use in extended release dosage form design.

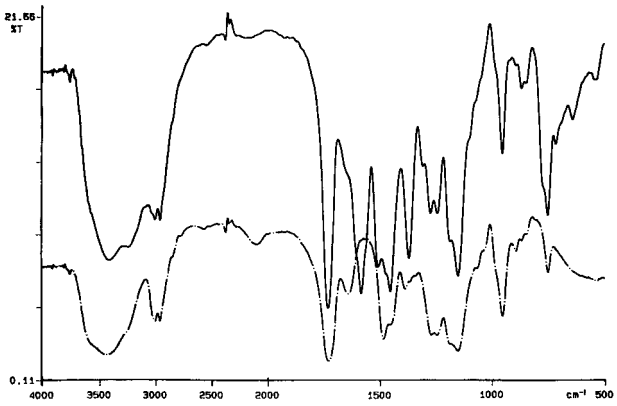

Figure 1 FTIR spectra of drug-free PTMAEMC/MMA (— · — ·) and diclofenac–PTMAEM/MMA complex (——).

An aqueous or aqueous alcoholic solution containing an excess amount of Na sulfathiazole or diclofenac Na, respectively, was poured into an aqueous solution of quaternary amine copolymers while stirring. Insoluble drug–polymer complexes were precipitated upon contact between the anionic drugs and the cationic copolymers as a white, agglomerated mass. In FTIR studies of diclofenac–polymer complexes, a new band appeared around 1580 cm^{-1}, which is attributed to the COO^- group of diclofenac ion (which is bound to the quaternary ammonium group of the polymer), as shown in Figure 1. The drug content in the drug–polymer complexes was analyzed spectrophotometrically by dissociating the complexes in a volumetric flask containing 0.2M NaCl phosphate buffer at pH 7.0. Table I presents the drug loading in different drug copolymer complexes. The copolymer compositions determined by elemental analysis of nitrogen were close to the monomer feed compositions, as shown in Table I, except for TMAEMC/MMA, in which copolymer composition was slightly less than the monomer feed composition. Diclofenac and sulfathiazole were bound to 79.9–96.2% and 94.7–105.1% of the quaternary amine groups of the copolymers,

Table I Polymer Composition, Drug Loading, Release Exponent (n), and Dissociation/Erosion Rate Constant (k_e)

Designation	Feed (Quat.[a]) Composition (mol %)	Polymer (Quat.)[b] Composition (mol %)	Loading[c]		Binding		n		k_e (mg cm^{-2} h^{-1})	
			Diclofenac (%)	Sulfathiazole (%)	Diclofenac (%)	Sulfathiazole (%)	Diclofenac (%)	Sulfathiazole (%)	Diclofenac (%)	Sulfathiazole (%)
PTMAEMC/MMA (40/60)	40	43.0	39.3	43.6	79.9	95.8	1.10	0.92	5.59	22.70
PTMAEMC/MMA (50/50)	50	52.3	46.5	48.6	88.1	99.0	0.90	0.89	6.30	36.78
PTMAEMC/MMA (60/40)	60	62.9	48.5	49.6	86.5	94.7	0.93	0.87	9.78	43.52
PTMAEMC/EMA (40/60)	40	37.0	42.3	43.0	94.8	105.1	0.81	0.82	1.39	8.80
PTMAEMC/MA (40/60)	40	44.5	47.1	48.6	91.8	102.1	0.78	0.95	3.23	64.06
PTMAEMC/BMA (60/40)	60	58.8	NT[d]	37.6	NT	73.4	NT	0.83	NT	9.39
PMAPTAC/MMA (50/50)	50	49.3	45.7	45.4	90.3	100.0	0.84	0.81	5.06	30.87
PTMAEAC/MMA (50/50)	60	48.1	50.6	49.5	96.2	101.2	0.89	0.89	5.14	73.08

[a] Quarternary amine.
[b] By elemental analysis of nitrogen.
[c] By UV spectrophotometry.
[d] NT, Not tested.

respectively, as shown in Table I, except for sulfathiazole-PTMAEM/MMA (60/40), which was 73.4% bound. It appeared that Na sulfathiazole was bound to the polymer chain more strongly than diclofenac Na. Binding of sulfathiazole exceeding 100% is combined experimental errors, while determining the polymer composition (by elemental analysis) and drug loading (by UV analysis). However, the errors were about 5% or less. As the quaternary amine group in the polymer chain increased, the degree of binding of diclofenac to the polymer increased from 79.9% to 94.5% for 40% TMAEMC/MMA and 60% TMAEMC/MMA, respectively. Diclofenac Na was found to PTMAEMC/MA more strongly than it was bound to PTMAEMC/MMA (91.8% and 79.9%, respectively).

The total release time of a highly soluble drug from the drug–polymer complex is highly dependent on the hydrophilicity of the polymeric carrier. The hydrophilicity of the carrier may be altered by varying the hydrophobic monomer (i.e., MMA, EMA, BMA, and MA). The longer alkyl group is responsible for reducing the hydrophilicity of the copolymer, causing it to erode more slowly, thereby extending the release time of any bound anionic drug. This effect may be observed in Figure 2, where the release times of sulfathiazole and diclofenac ions from the drug–polymer complexes were increased from 2.5 to 12 h and from 12 to 43 h, respectively, when EMA was substituted for MMA as a comonomer. As water (carrying counter ions: $H_2PO_4^-$, HPO_4^{-4}, Cl^-) diffused into the tablets, the drug–polymer bonds dissociated as shown in Scheme 1, releasing the bound drug into the surrounding water, and the drug-free PTMAEM dissolved. The release exponent became smaller with the longer alkyl group: for diclofenac $n = 1.10$ for MMA and $n = 0.81$ for EMA for the copolymer based on TMAEMC, and for sulfathiazole $n = 0.92$ and 0.82 for MMA and EMA, respectively. However, a different phenomenon was observed when MA was substituted for MMA. Release of the diclofenac ion from drug–PTMAEM/MA tablets slowed down, compared with that from drug–PTMAEM/MMA tablets, whereas the reverse was observed for sulfathiazole. This may be due to the higher degree of diclofenac binding in the drug–PTMAEM/MA than that in the drug–PTMAEM/MMA (91.2% and 79.9%, respectively). However, the same degree of binding was observed for sulfathiazole with PTMAEMC/MMA and PTMAEMC/MA (95.8% and 102.1%, respectively). From this, it may be

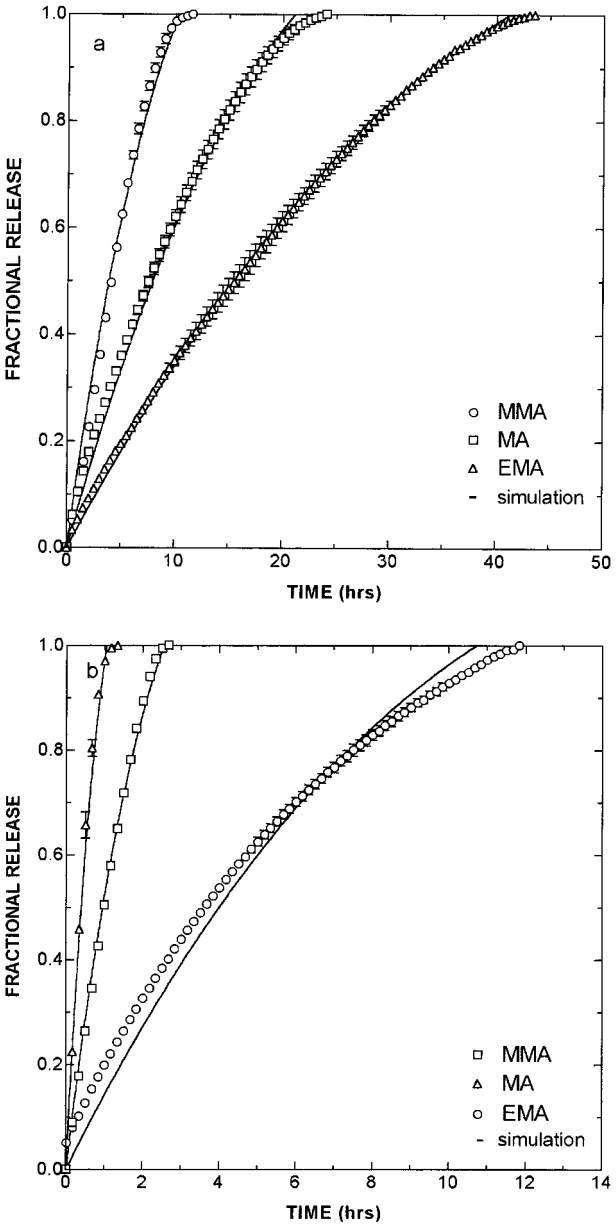

Figure 2 Effect of hydrophobic groups on the release of drugs from tablets of drug–polymer complexes consisting of 40 mol % TMAEMC at pH 7 (0.2*M* NaCl): (a) diclofenac and (b) sulfathiazole.

postulated that diclofenac–PTMAEM/MA is more hydrophobic than diclofenac–PTMAEM/MMA, leading to the slower dissociation/erosion.

For a given copolymer composition, one may obtain a specific drug loading in a drug–polymer tablet. The task of preparing dosage forms with different drug loadings may partially be accomplished by altering the tablet geometry (of different diameter, while maintaining the same thickness), with the total release time being determined by the thickness of the tablet.[3] However, based on a single copolymer composition, the limitation of a practical diameter size dictates the maximum loading permissible. Drug–polymer complexes were prepared from different mol compositions of TMAEMC, thereby increasing the number of quaternary amine functional groups (i.e., the number of attachment sites for the anionic drugs). As expected, higher drug amounts could be loaded by increasing the mol % of TMAEMC, as shown in Table I. As the drug loading increased, its release was faster due to the greater hydrophilicity of the drug polymer complex. A higher ratio of TMAEMC to BMA is needed to increase the drug loading and the dissociation/erosion rate of drug–polymer complex matrices, as shown in Figure 3. Thus, one may generate almost superimposable drug release profiles from different dosage forms, merely by altering the diameter/thickness ratio of a tablet and copolymer composition.

The effect of the type of quaternary amine on the release of anionic drugs from drug–polymer complex tablets is shown in Figure 4. PTMAEMC/MMA (40/60) was found to be more hydrophilic, compared with the copolymers composed of MAPTAC and TMAEAC which, at 40 mol % quaternary amine content, were not water-soluble, giving swellable gels instead. The effect of solubility (of

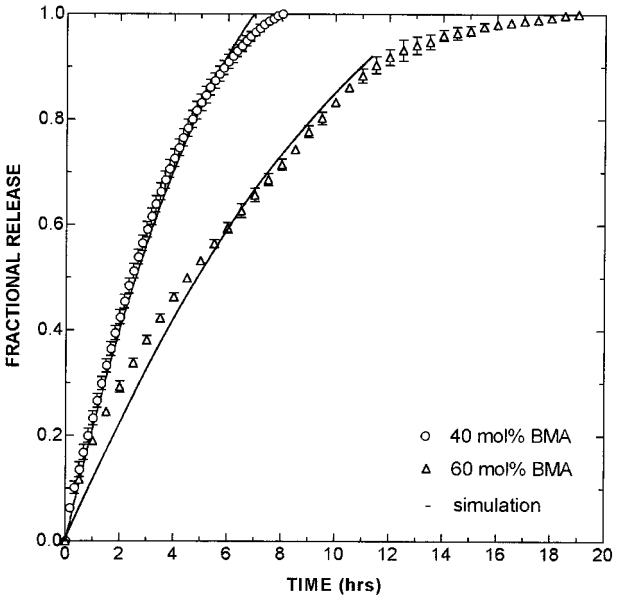

Figure 3 Effect of copolymer composition on the release of sulfathiazole from tablets of drug–polymer complexes consisting of PTMAEM/BMA at pH 7 (0.2*M* NaCl).

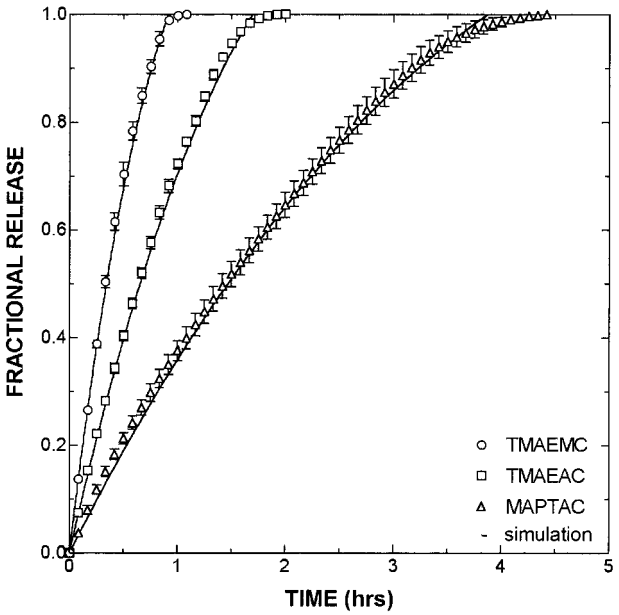

Figure 4 Effect of type of quaternary amine groups on the release of sulfathiazole from tablets of drug–polymer complexes consisting of 50 mol % MMA at pH 7 (0.2*M* NaCl).

both the drug as well as the polymer) on drug release from the drug–polymer complex was found to be more pronounced in the case of the slightly soluble diclofenac ion. However, due to the much higher solubility of the sulfathiazole ion, its complexes did not show a marked difference in drug release rates from different polymers consisting of more than 50 mol % quaternary amine. Thus, the effect of polymer hydrophilicity on the rate of drug release was masked by the effect of drug solubility in the case of a complex between a highly soluble drug and a highly hydrophilic polymer. The reduced hydrophilicity of the polymer (50 mol % composition or less) permits observation of the effect of the polymer hydrophilicity on the drug release, as shown in Figure 4.

The effect of polymerization conditions on the release of diclofenac ions from drug–PTMAEM/MMA (40/60) is shown in Figure 5. As the polymerization temperature was decreased, the rate of polymerization was slowed down, resulting in a higher molecular weight. Consequently, the rate of dissolution of the polymer became slower due to the higher viscous environment at the dissolution front. This effect is observed in Figure 5.

The effect of the ionic strength of the buffer medium on the release of the diclofenac and sulfathiazole ions from the drug–PMAPTAC/MMA (50/50) complex tablets at pH 7 is shown in Figure 6. The buffers contained 0.01*M* phosphate and sodium chloride ranging from 0.05*M* to 0.2*M*. The release kinetics of tablets tested in 0.05*M*, 0.1*M*, and 0.2*M* NaCl were very close each other. Similar results have been reported for drug release from drug–PSPMK/MMA tablets[3] and PTMAEMC/MMA.[4] At the much lower pH value of 1.5, the release of diclofenac ions from drug–PMAPTAC/MMA (50/50) was severely retarded due to the negligible solubility of diclofenac in the acid form.[4] The insoluble diclofenac acid remained within the tablets, inhibiting the dissolution of the PTMAEM/MMA. As the pH was increased, the release of sulfathiazole ion decreased. Nujoma and Kim[3] reported that the release of propranolol from drug–PSPMK/MMA tablets was independent of pH for the buffer containing 0.2*M* NaCl. The release of drug from hydrogels based on tertiary amine and carboxylic acid was reported to be highly pH-dependent, so that drug release was stopped at weak base and weak acid conditions, respectively.[9–11] On the contrary, quaternary amine-containing water-soluble polymers based on quaternary amine studied herein released anionic drugs at a wide range of pH (1.5–7), as long as the solubility of the drug did not inhibit the dissolution of the polymer.

The release kinetics were evaluated by a dissociation/erosion mechanism [eq. (2)]. No swelling of drug–polymer complex tablets was observed. The overall dimensional change of tablets of the

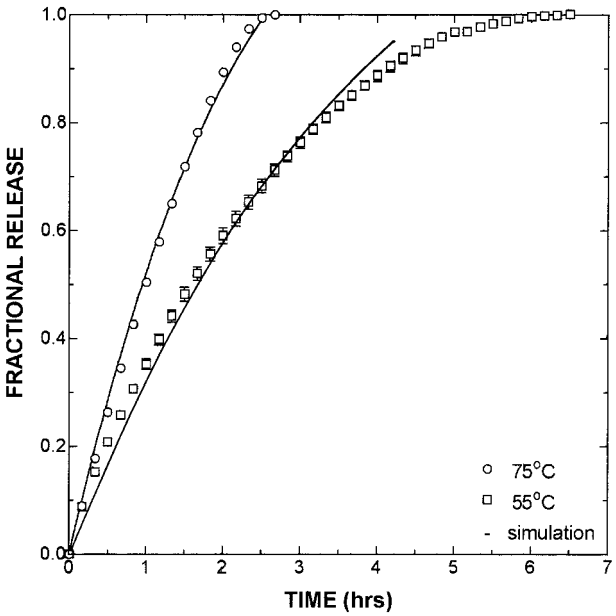

Figure 5 Effect of polymerization temperature on the release of sulfathiazole from tablets of drug–polymer complexes consisting of PTMAEM/MMA (40/60).

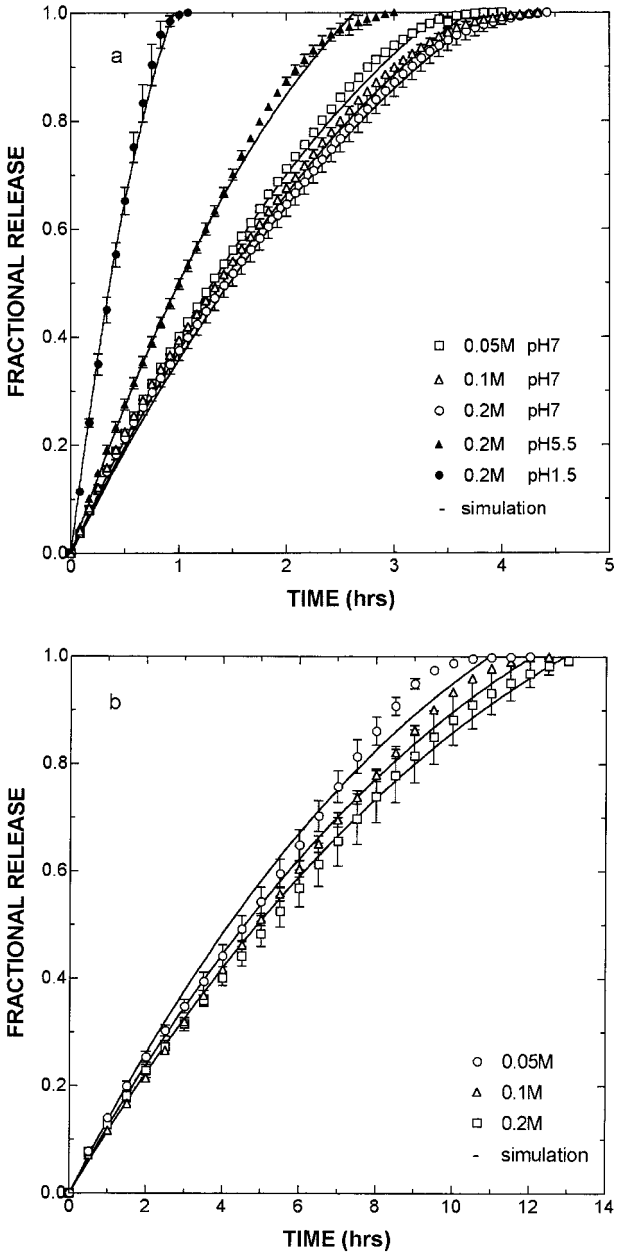

Figure 6 Effect of pH and ionic strength on the release of drugs from tablets of drug–polymer complexes consisting of PMAPTAC/MMA (50/50): (a) sulfathiazole and (b) diclofenac.

drug–polymer complexes decreased monotonously. The dissociation/erosion rate constants were estimated for tablets containing 20% dextrose using a nonlinear regression analysis (PRIZM®; Pad, San Diego, CA). In general, eq. (2) well represented the experimental data studied herein, as shown in Figures 2–6. The rate constant becomes larger as the mol % of quaternary amine content in the drug–polymer complexes increased, as shown in Table I. Similarly, the rate constant becomes smaller, because the longer alkyl methacrylate was used in the copolymer.

CONCLUSIONS

New polymeric materials based on quaternary amines have been synthesized, from which drug release may be well characterized by the dissociation/erosion mechanism. Factors affecting drug release from the drug–polymer tablet may be identified: composition of the copolymer (hydrophobic monomers), polymerization temperature, type of quaternary amine, and nature of the bound drug. Drug release from this system does not depend on external factors like pH and ionic strength, but rather on the properties of the drug and the copolymer.

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