Drug Development and Industrial Pharmacy, 32:531–538, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040600599939

Taylor & Francis

Noncross-Linked Copolymers of Dimethylaminoethyl Methacrylate and Methacrylic Acid as Oral Drug Carriers

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ABSTRACT The purpose of this study was to synthesize new water-soluble ampholytic copolymers consisting of tertiary amine and carboxylic acid pendent groups for oral drug carriers. The polymers were prepared with a 1:1 molar ratio of dimethylaminoethyl methacrylate and methacrylic acid by free radical polymerization. After polymerization, polymer rods were recovered, dissolved (or swollen) in de-ionized water, and freeze-dried before obtaining fine powders. Drug release experiments with various drugs, representing a variety of drug solubility and types of amine, were carried out with compressed tablets (total weight of 600 mg) containing a variety of basic drugs in pH's of 1.5 and 7. Surprisingly, zero-order release kinetics even from a tablet geometry has been obtained with drug loading ranging from 20–50%. Drug release in pH 7 maintains a zero-order rate up to 80–85% release after a slight initial burst, whereas in pH 1.5 one may not find the initial burst and zero-order kinetics is extended up to 90–95% release. Drug release becomes faster in pH 1.5 than pH 7 due to the faster rate of protonation of the tertiary amine in acidic conditions. The release of basic drugs in pH 1.5 is not significantly different even with varying solubility and types of amine (primary, secondary, and tertiary). However, different drug release profiles in pH 7 are observed with different types of amine and solubility.

INTRODUCTION

One of the various methods to extend drug release for a longer period of time is to incorporate polymeric materials into conventional pharmaceutical dosage forms. Numerous water-insoluble and water-soluble polymers have been used for oral controlled release dosage forms. Water-soluble polymers are preferentially chosen over water-insoluble ones when monolithic matrix systems are employed because drug release kinetics from water-soluble polymers may deviate from Fickian kinetics to furnish anomalous or zero-order kinetics. For example, cellulose derivatives (HPMC, MC, HEC, and HPC), polyethylene

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oxide (PEO), polysaccharides, and others have been extensively investigated for oral controlled release dosage forms. During drug release from the matrix systems based on these polymers, the swelling and/or erosion of the polymers take place simultaneously. The relative contribution of these processes toward drug release, along with drug diffusion in the matrix, governs the overall drug release kinetics. The synchronization of erosion and drug diffusion fronts, or of swelling and erosion fronts, is prerequisite to obtain zero-order release kinetics from these matrices (Harland et al., 1988; Narashihana & Peppas, 1997; Lee, 1992; Kim, 1996). Comprehensive mathematical models describing polymer swelling/erosion processes during drug release have been reviewed (Narasimhan, 2001). In addition, three fronts (i.e., swelling, diffusion, and erosion) that occurred during drug release were video recorded and photographs analyzed by image software. Mathematical models were applied to simulate drug release profiles as well as three fronts with a good agreement with experimental data (Kiil & Dam-Johansen, 2003). However, the synchronization of the fronts is not a common phenomenon in oral pharmaceutical dosage forms. The erosion of the polymer controls drug release kinetics from low molecular weight HPMC, whereas drug release from high molecular weight HPMC is governed by the swelling of the polymer followed by the erosion of the polymer (Kim, 1996; Pham & Lee, 1993). On the other hand, PEO of a molecular weight smaller than 2×10^6, provides synchronized swelling and erosion of the polymer whereas the swelling of the polymer and drug diffusion control drug release kinetics for PEO of a molecular weight larger than 4×10^6 (Kim, 1995, 1998). High molecular weight PEO gave the drug release exponent of 0.44–0.47 for the release of verapamil HCl (Dimitrov & Lambov, 1999).

Even though water-soluble polymers are used which have the characteristics providing zero-order release kinetics, the zero-order release kinetics can be obtained only with low drug loading conditions (<10%). As drug loading increases, the space occupied by the drugs becomes larger and interconnected so that open channels are formed resulting in a faster rate of drug diffusion through the channels. Additionally, as the water-soluble polymers are incorporated into conventional dosage forms (i.e., tablets, caplets), drug release kinetics deviate from zero-order to Fickian due to a decrease in the releasing surface area with time. These polymers were used originally for other applications (e.g., suspending, thickening, and flocculating agents, adhesives, etc.) but subsequently were adopted for oral controlled release systems.

In this report, a new polymer consisting of dimethylaminoethyl methacrylate (DMAEM) and methacrylic acid (MAA) is synthesized specifically as an oral controlled drug carrier providing zero-order release kinetics with high drug loading (20%–50%).

EXPERIMENTAL

Materials

All reagents were used without further purification. Methacrylic acid (MAA) and DMAEM were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). T-butylperoctoate was acquired from Atochem NA (Philadelphia, PA, USA). Diltiazem HCl, verapamil HCl, propranolol HCl, labetalol HCl, oxprenolol HCl, and phenylpropranolamine HCl were purchased from Sigma Chemical Co. (St. Louis, MO, USA) $NaNO_3$, Na_2HPO_4, KH_2PO_4, and NaCl were obtained from Fisher Scientific Co. Deionized water was produced by a Nanopure water purification system (Fisher Scientific Co.).

Instrumentation

An aqueous gel permeation chromatography (GPC) was used to determine the molecular weight distributions of synthesized polymers by using a Thermal Separation pump, a TOSOHASS column (TSK-GEL G6000PW, 7.5 mm × 60 cm), sulfonated polystyrene standards (Polysciences), a differential reflective index detector (Shimazu), and 0.25 M $NaNO_3$, 0.01 M Na_2HPO_4, and 0.1 M NaCl at pH 9 as mobile phase.

Synthesis of Poly(dimethylaminoethyl methacrylate –co- methacrylic Acid) (PDMAEM/MAA)

A molar ratio of 1:1 of DMAEM and MAA were mixed with initiator (*t*-butylperoctoate) and polymerized in an oil bath equilibrated at different temperatures (45°C, 55°C, and 65°C) in glass ampoules (1.1 cm diameter) for 24 h. The glass ampoules were broken and solid polymer rods were obtained. The polymers (PDMAEM/MAA) prepared at 65°C and at lower temperatures (45°C and 55°C) were dissolved and swollen in deionized water, respectively, and were freeze-dried

to obtain fine powders. The nitrogen contents of the purified polymer were determined by elemental analysis (Qunatitative Technologies, Whitehouse, NJ) to calculate the actual copolymer composition.

Fabrication and Testing of Tablets

The polymer powders were blended well in a mortar and pestle with the model drugs (i.e., diltiazem HCl, verapamil HCl, propranolol HCl, labetalol HCl, oxprenolol HCl, and phenylpropranolamine HCl). The well blended powders were compressed to form tablets using a Carver press and a flat punch (12 mm diameter) under a 9,000 lb compression force. Each tablet produced weighed 600 mg and contained drug ranging from 20% w/w to 50% w/w. Drug release studies, in duplicate, were carried out in medium containing 0.1 M NaCl with HCl and 0.1 M NaCl with 0.01 M phosphate buffer at pH 1.5 and pH 7, respectively, at 37°C using the USP apparatus basket method unless otherwise noted. The concentrations of diltiazem HCl, verapamil HCl, propranol HCl, labetalol HCl, oxprenolol HCl, and phenylpropranolamine HCl in the dissolution medium (1 L) was monitored on a HP 8252A diode-array spectrophotometer at 278 nm, 280 nm, 292 nm, 306 nm, 274 nm, and 258 nm, respectively.

The linearity of drug release kinetics was assessed by fitting the release profiles (up to 60% and 80%) with the phenomenological equation (Ritger & Peppas, 1987):

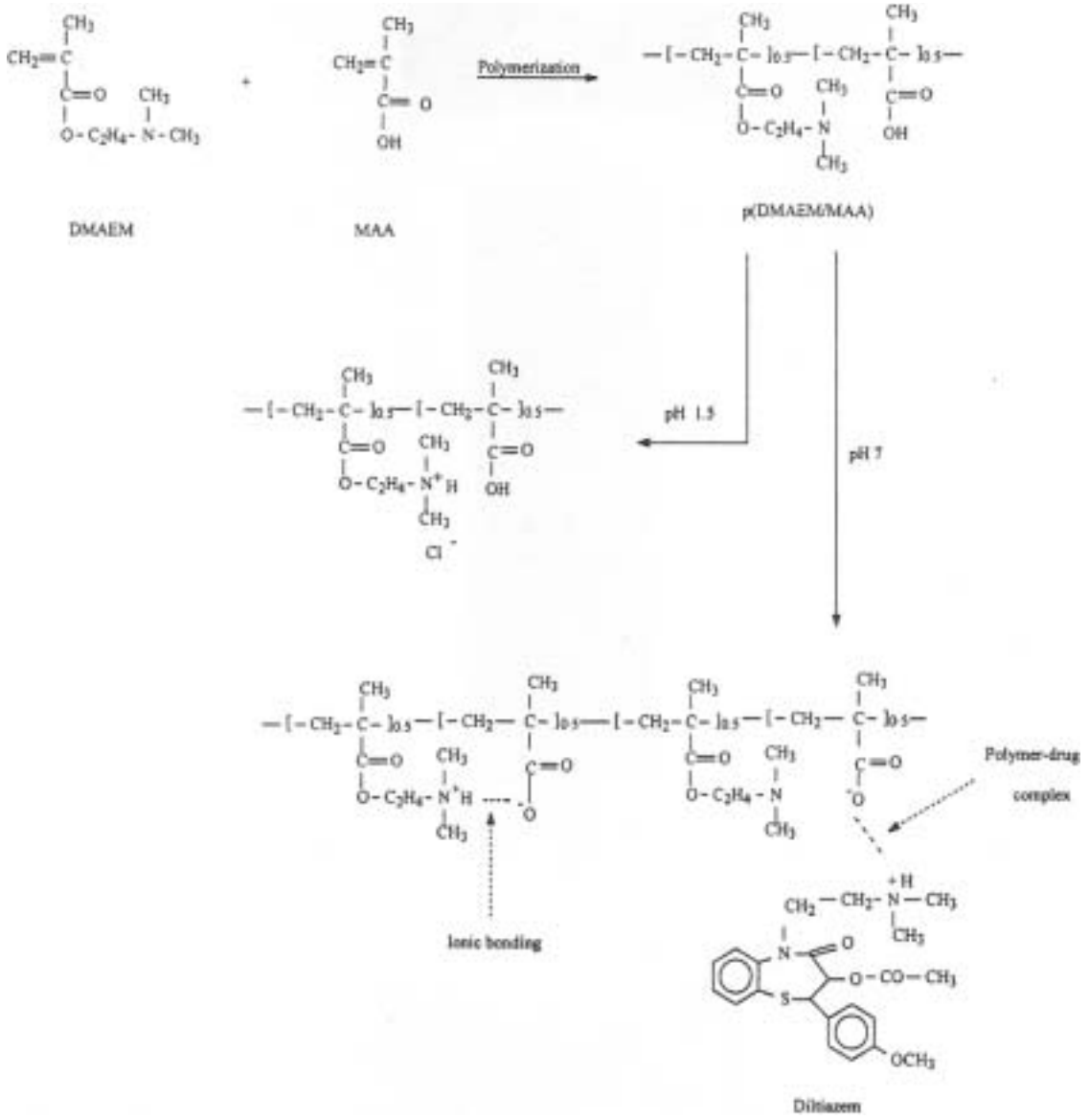
$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t and M_∞ are the amounts of drugs released at time, t, and the total amount of drug in the tablet, respectively, and k and n are a constant and a release exponent, which characterizes the release kinetics, respectively. According to the criteria for release kinetics from a swellable matrix (cylindrical shape), anomalous and zero-order kinetics are represented by $0.45 < n < 0.89$ and $0.89 < n < 1.0$, respectively. A regression analysis (Graph Pad, San Diego, CA) of Eq. 1 was performed with $R^2 \geq 0.99$. A 95% confidence level was calculated.

RESULTS AND DISCUSSION

The use of ionic polymeric materials for oral drug delivery systems has been investigated by many researchers. Kim and Lee (1992), Siegal and co-workers (1990), and Brannen-Peppas and Peppas (1989) have all investigated drug release from such systems. The degree of swelling of the polymer could be manipulated by changing the charge density of the pendent ionic groups and/or the degree of cross-linking of the polymer. However, drug release kinetics from these polymers was strongly pH-dependent. Polymers containing carboxylic acid groups alone do not release drugs at low pH (<5) due to the unionization of carboxylic acid resulting in negligible swelling at low pH. Drug release from polymers containing tertiary amine groups alone occurs only at pH less than 7 because pK_a of tertiary amine groups of the polymers is approximately 7.7 (Shatkay & Michaeli, 1966). In addition, these polymers were cross-linked, so that once formed in a particular shape, the polymers cannot be transformed into any other shapes. Effect of the incorporation of enteric polymers (e.g., Eudragit® L and S) into HPMC tablets on the release of propranolol HCl was investigated and it was found that the ratio of HPMC/Eudragit L of 1:1 produced pH-independent release kinetics (Takka et al., 2001). A polymer synthesized from two monomers, containing both carboxylic acid and tertiary amine, were made in the notion that drug release from the copolymers may lead to pH-independent or much less pH-dependent release kinetics even with tablet geometry. Scheme 1 shows the chemical structure of PDMAEM/MAA. When two monomers were mixed, a lot of heat was generated in the solution due to the hydrogen bonding between the nitrogen of tertiary amine and the hydrogen of carboxylic acid. The synthesized copolymers consist of less tertiary amines than the theoretical values as shown in Table 1.

The release of diltiazem HCl (solubility in water at 37°C ≈ 62% w/v) from PDMAEM/MAA tablets containing 30% drug loading is shown in Fig. 1. As shown, the rate of drug release was strongly dependent upon the polymerization temperature. As the polymerization temperature increased, the rate of drug release increased because much smaller molecular weight polymers are formed at higher temperatures leading to faster disentanglement/dissolution of the polymer. GPC chromatograms (insert in Fig. 1) indicate that at a polymerization temperature of 45°C, a much higher fraction of high molecular weight polymers are formed compared to those obtained at 55°C. It is interesting to point out that these polymers are not soluble in common organic solvents (i.e., alcohol,



SCHEME 1 **Synthesis of Ampholytic Polymers, Pendent–Pendent Complexation, and Drug-Polymer Complexation.**

acetone, chlorinated hydrocarbon, etc.) but soluble in aqueous buffer solutions.

For a given polymer, drug release is also dependent on the pH of the dissolution medium. At low pH (1.5), tertiary amine groups of the polymer are completely protonated while the carboxylic acid moiety of the copolymers is maintained. However, at pH 7, 97% of the carboxylic acid group (pK_a 5.5) is ionized, and 83% of tertiary amine groups (pK_a 7.7) (Shatkay & Michaeli, 1966) are protonated. One may postulate that upon contact with a pH 7 medium, anionic carboxylate and cationic protonated amine groups react to produce a temporary complex link which is dissociated later by incoming ions (i.e., Na^+ and Cl^-). In addition to the temporary link between the carboxylate and protonated tertiary amine of the polymer, diltiazem HCl, which contains also a protonated tertiary amine group, could be complexed with the anionic carboxylate of the polymer, as shown in Scheme 1. Because of this phenomenon, drug release at pH 7 becomes much slower. Complete drug release time at pH 1.5 is approximately half of that at pH 7. In general, even though drug loading is high (30%), drug release at pH 7 is maintained at a zero-order rate up to 80–85% of release after an initial burst, whereas at pH 1.5 one may not find an initial burst but zero-order release kinetics is obtained up to 90–95% of release. This demonstrates that the copolymers consisting of

TABLE 1 **Polymer Composition, Drug Loading, and Release Exponent (*n*)**

Designation	Feed composition (mol %)	Polymer composition (mol %)	Drug	Loading (%)	pH	Buffer concentration (M)	RPM	*n* 60%	*n* 80%	n^a 80%
PDMAEM/MAA65	50	43.1[e]	diltiazem	30	1.5	0.1	100	0.85 ± 0.079[b]	NA[c]	NA
(polym. temp. 65°C)			diltiazem	30	7.0	0.1	100	1.02 ± 0.059	1.10 ± 0.068	NA
PDMAEM/MAA55	50	42.4	Diltiazem	30	1.5	0.1	100	1.10 ± 0.031	1.13 ± 0.039	NA
(polym. temp. 55°C)			Diltiazem	30	7.0	0.1	100	0.91 ± 0.009	0.91 ± 0.013	1.00 ± 0.013
PDMAEM/MAA45	50	46.6	diltiazem	30	1.5	0.05	100	1.13 ± 0.041	1.10 ± 0.031	NA
(polym. temp. 45°C)			diltiazem	30	7.0	0.05	100	0.89 ± 0.036	0.92 ± 0.025	1.05 ± 0.029
			diltiazem	30	1.5	0.1	100	1.04 ± 0.070	1.00 ± 0.042	NA
			diltiazem	30	7.0	0.1	100	0.92 ± 0.015	0.88 ± 0.020	1.07 ± 0.010
			diltiazem	30	1.5	0.2	100	0.96 ± 0.022	0.94 ± 0.017	NA
			diltiazem	30	7.0	0.2	100	0.88 ± 0.030	0.85 ± 0.026	0.98 ± 0.037
			diltiazem	30	1.5	0.1	100	1.05 ± 0.024	1.03 ± 0.018	NA
			diltiazem	30	7.0	0.1	100	0.85 ± 0.029	0.87 ± 0.021	1.00 ± 0.024
			diltiazem	30	1.5	0.1	100	1.08 ± 0.068	1.02 ± 0.042	NA
			diltiazem	30	7.0	0.1	100	1.03 ± 0.039	0.95 ± 0.032	1.09 ± 0.053
			diltiazem	30	1.5	0.1	50	1.09 ± 0.032	1.10 ± 0.019	NA
			diltiazem	30	7.0	0.1	50	0.79 ± 0.014	0.77 ± 0.009	0.89 ± 0.021
			verapamil	30	1.5	0.1	100	1.13 ± 0.079	1.09 ± 0.070	NA
			verapamil	30	7.0	0.1	100	0.84 ± 0.022	NC[d]	NC
			propranolol	30	1.5	0.1	100	0.94 ± 0.030	0.85 ± 0.040	NA
			propranolol	30	7.0	0.1	100	0.80 ± 0.018	0.80 ± 0.014	0.94 ± 0.022
			labetalol	30	1.5	0.1	100	1.18 ± 0.017	1.12 ± 0.029	NA
			labetalol	30	7.0	0.1	100	0.88 ± 0.018	0.91 ± 0.014	1.03 ± 0.016
			oxprenolol	30	1.5	0.1	100	0.95 ± 0.045	0.94 ± 0.035	NA
			oxprenolol	30	7.0	0.1	100	0.70 ± 0.046	0.71 ± 0.032	NC
			phenylpropranolamine	30	1.5	0.1	100	0.63 ± 0.033	0.66 ± 0.021	NA
			phenylpropranolamine	30	7.0	0.1	100	0.51 ± 0.013	0.51 ± 0.008	NA

[a]First data removed.
[b]95% confidence level.
[c]Not applicable.
[d]Not calculated.
[e]DMAEM.

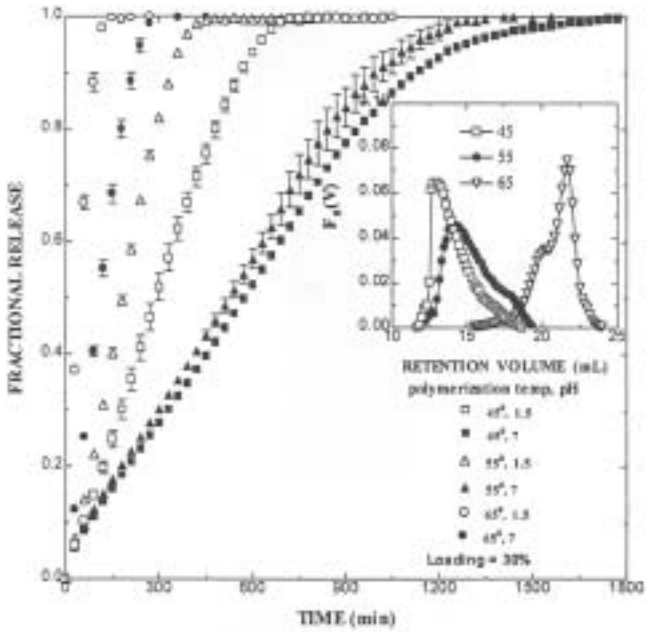


FIGURE 1 **Effect of Polymerization Temperature and pH on the Release of Diltiazem HCl from PDMAEM/MAA Tablets.**

both tertiary amine and carboxylic acid groups furnish much less dependence of drug release based upon the pH of the test condition than those consisting only of either tertiary amine or carboxylic groups.

The effect of buffer strength (or ionic strength) on the release of diltiazem HCl from PDMAEM/MAA45 matrix tablets is shown in Fig. 2. The ionic strength of the dissolution medium at a given pH does not significantly influence drug release kinetics from the polymer prepared at 45°C. Similar findings have been reported with anionic drugs and cationic polymers, and with cationic drugs and anionic polymers (Nujoma & Kim, 1996; Konar & Kim, 1997). However, one may observe that as ionic strength increases drug release becomes slightly faster. At conditions of pH 7 and 0.2 M NaCl, drug release kinetics appears to deviate slightly from zero-order kinetics.

The effect of drug loading on the release of diltiazem HCl from PDMAEM/MAA45 matrix tablets is shown in Fig. 3. At pH 7, a faster drug release rate is obtained as drug loading increases. As drug loading decreases, a more linear profile is extended through a higher percentage of drug release. At pH 1.5, the drug release kinetics are superimposable with drug loading at 20% w/w and 30% w/w, but a faster release rate is observed with 50% w/w drug loading. As drug loading increases, the relative contribution of drug diffusion in a matrix toward the overall drug release kinetics becomes larger, resulting in a slight deviation from zero-order kinetics. The loading dependence of drug release kinetics is similar to those observed with other types of polymers. Water-soluble polymers such as PEO and HPMC provide zero-order release when moving fronts are synchronized, but deviate to anomalous kinetics as loading increases above 20% w/w for highly water-soluble drugs (e.g., diltiazem HCl) (Kim, 1995, 1998).

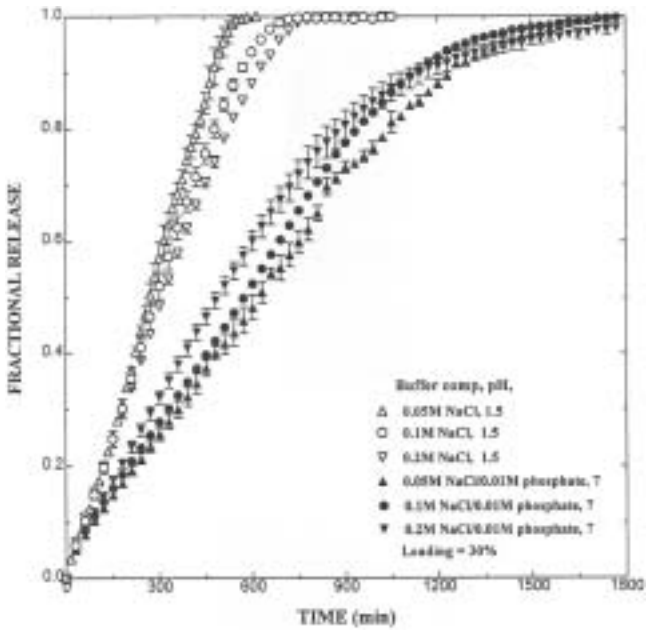


FIGURE 2 **Effect of Ionic Strength (Buffer Concentration) on the Release of Diltiazem HCl from PDMAEM/MAA45 Tablets.**

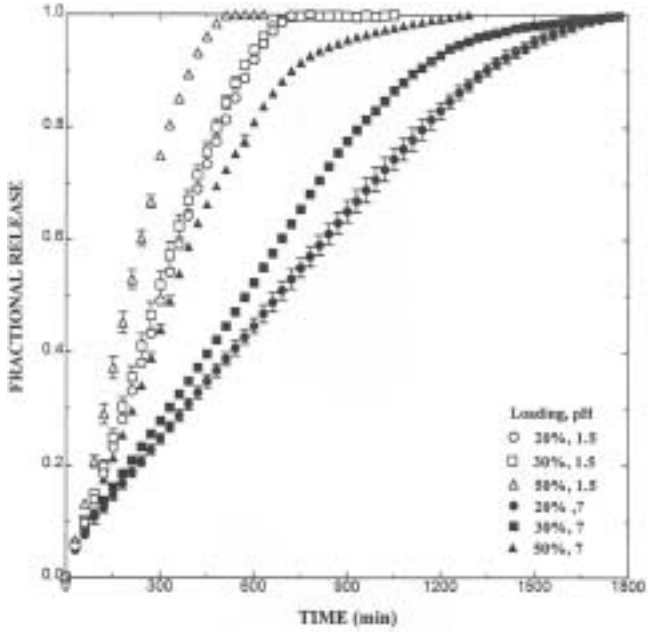


FIGURE 3 **Effect of Drug Loading on the Release of Diltiazem HCl from PDMAEM/MAA45 Tablets.**

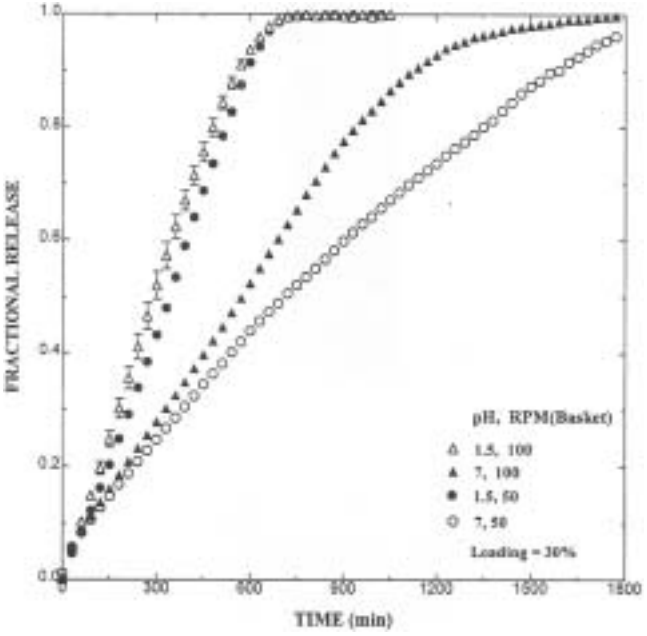


FIGURE 4 **Effect of Stirring Rate on the Release of Diltiazem HCl from PDMAEM/MAA45 Tablets.**

Figure 4 shows the effect of hydrodynamic conditions (stirring) on the release of diltiazem HCl from PDMAEM/MAA45 matrix tablets. Generally, slower stirring results in slower drug release due to slower dissolution of the polymer. However, drug release kinetics is not affected much by stirring at pH 1.5. One may postulate that drug release at pH 1.5 is not governed by the erosion of the polymer, but by the rate of protonation. At pH 7, the slower stirring rate decreases the drug release rate from the tablets. Zero-order kinetics no longer maintains at pH 7 at 50 rpm. In this case, drug diffusion in the tablets contributes to the overall release kinetics more than the erosion of the polymers, similar to that observed in other water-soluble polymers (e.g., PEO, PVA).

The effect of drug solubility and types of amine on the release of drugs is shown in Fig. 5a and 5b. There are not many differences in drug release observed at pH 1.5 with diltiazem HCl (tertiary amine, solubility in water ≈ 62% w/v), verapamil HCl (tertiary amine, solubility in water ≈ 8.2% w/v), labetalol HCl (secondary amine and solubility in water ≈ 1.3% w/v), and propranolol HCl (secondary amine and solubility in water ≈ 7.4% w/v). Highly water-soluble and secondary amine primary drugs (i.e., phenylpropranolamine HCl, solubility in water ≈ 93% w/v and oxprenolol HCl, solubility in water ≈ 107% w/v, respectively) are

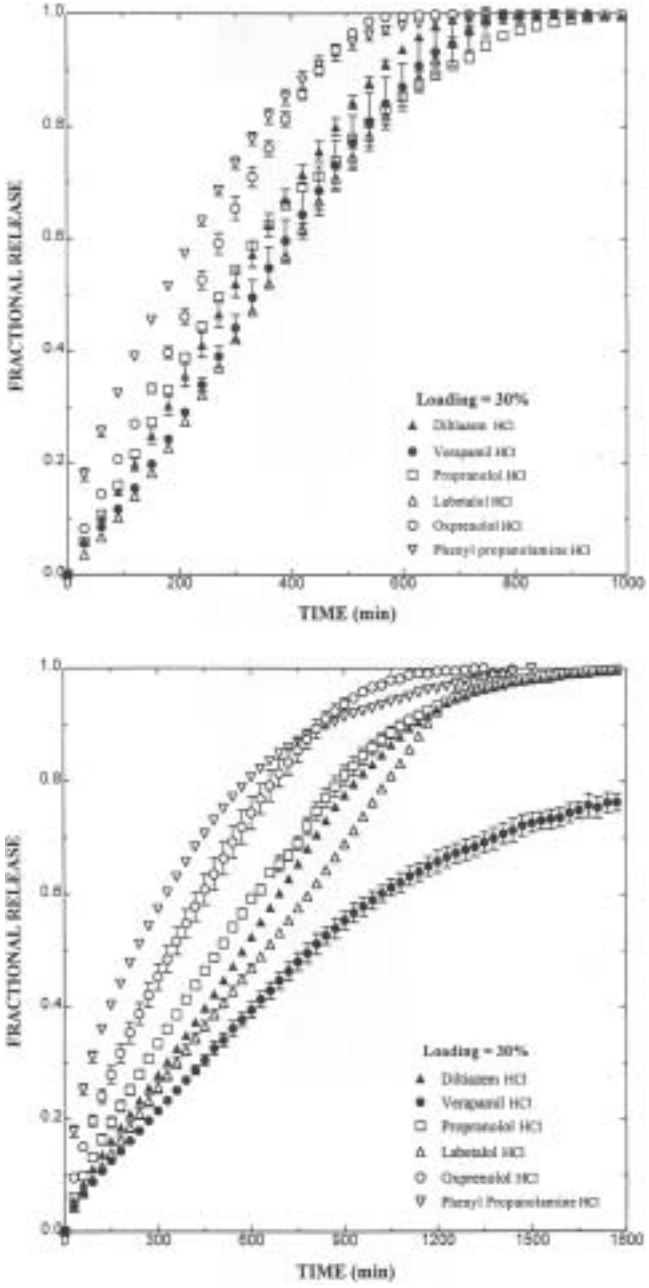


FIGURE 5 **Effect of Drug Type and Drug Solubility on the Release of Drugs from PDMAEM/MAA45 Tablets: (a) pH 1.5 and (b) pH 7.**

released from PDMAEM/MAA45 tablets at a faster rate. The release profile of phenylpropranolamine HCl deviates significantly from linearity. For a given type of amine group, drug release rates become slower as the solubility of drug decreases. It seems that temporary complexation between the carboxylate of the copolymer and verapamil HCl is much stronger than complexation between diltiazem HCl and the carboxylate. For a given solubility, tertiary amine drugs result

in slower drug release than other amine drugs, as shown in Fig. 5b, presumably due to much stronger complexation. These findings are in good agreement with previously reported experiments which were based on water-soluble sulfonated polymers (Nujoma & Kim, 1996; Konar & Kim, 1997).

Table 1 shows the linearity of drug release profiles from the copolymers prepared at 45°C, 55°C, and 65°C. For the release exponent n at up to 60% of drug release, ranges from 0.63 to 1.18 were observed at pH 1.5. Slight time lag was observed for the testing condition at pH 1.5, resulting in a release exponent greater than 1.0. Linearity ($0.85 < n < 1.13$) at pH 1.5 extends even up to 80% of drug release except for phenypropranolamine HCl. The exponent n (up to 60% of drug release) at pH 7 varies from 0.51 to 1.03. However, when initial burst effect is removed from pH 7 release data, the exponent n was close to 1.0 ($0.89 < n < 1.10$) at up to 80% of drug release with a stirring rate of 100 rpm except phenylpropranololamine HCl and oxprenolol HCl. It is because the complexation of phenylpropranololamine HCl and oxprenolol HCl with the carboxylate of the polymer is not strong. Nujoma (1998) reported similar results in the release of cationic drugs from poly(methylmethacrylate –co– Na methacrylate) beads. Recent studies of the release of diltiazem HCl from drug-lamda carrageenan complex tablets and the release of cationic drugs from drug–polyanion complex tablets showed the linear kinetics (Bonferoni et al., 2004; Konar & Kim, 1999). It may be concluded that linear drug release kinetics from the water-soluble copolymers studied herein can be obtained with a variety of cationic drugs with high loading (20%–50%) except for highly water-soluble drugs consisting of primary or secondary amine groups (i.e., phenylpropranolamine HCl and oxprenolol HCl).

Applications of the copolymers to other types of drugs (e.g., anionic, neutral, and unionized acid) and modifications of the copolymer composition (e.g., mole ratio and type of monomers) to achieve almost superimposable release profiles at both pH 1.5 and 7 should soon be reported in the literature elsewhere.

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