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RESEARCH PAPER

Synthesis and Characterization of Methacrylic Derivatives as Drug Carriers

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ABSTRACT

p-Methoxyphenyl methacrylate (ESMAA) was copolymerized with methacrylic acid (MAA) in dioxane solutions using azobisisobutyronitrile (AIBN) as an initiator. The compositions of the copolymers were assayed for the aromatic ester content by measuring the ultraviolet (UV) absorbance at 240 nm in dioxane. The monomer reactivity ratios r_1 *and* r_2 *for copolymerization of MAA(*M_1*) and ESMAA(*M_2*) are 1.52 and 3.01. The glass transition temperatures of MAA-ESMAA copolymers are almost equal to the weight-average values. The drug released from copolymers increases with the composition of methacrylic acid units. The releases of piroxicam from the MAA-co-ESMAA matrices containing 55 mole% MAA in pH 7.4 and 10 buffer solutions are steady for the whole release period, and release profiles matches closely to the disintegration profiles of the MAA-55 copolymer.*

INTRODUCTION

Sustained release and affinity therapy (1) can be prepared by dispersing the drug in a biocompatible polymer (2,3) and by attaching it to a polymeric matrix (4-11). The pendant delivery system can also be prepared by first synthesizing the drug-linked monomer followed by homopolymerization (12) or copolymerization (13-16). In all cases, the main purpose is to prolong pharmacological activity by a gradual release of the free drug from the macromolecular matrix (16-19) and to reduce unfavorable side effects (20-22). Synthetic poly(meth)acrylic esters and their (meth)acrylic acid copolymers became available in 1955 with specific solubility characteristics adapted to the pH conditions in the human digestive tract. The promising properties are their glass-clear structure associated with high mechanical stability, light weight, and relatively good hardness. With modifications of the basic structure, poly(meth)acrylates have been developed for cutaneous,

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oral, and parenteral applications (23). For example, Eudragit S-100, which is soluble in intestinal juice higher than pH 7, is a polymethacrylate copolymerized with 27.6 to 30.7 mole% of methacrylic acid. The polymeric matrix we designed is a copolymer similar to Eudragit S-100, except for the aromatic methacrylate units. The benefit of this aromatic side group is that we can easily measure the disintegration mechanism of polymeric matrices by using a simple ultraviolet (UV) spectrophotometer. Moreover, *p*-methoxy phenol acts as an inexpensive model drug. In principle, any drug with properties similar to the phenol moiety can be linked to methacrylic acid by the same techniques described here. The hydrolytic stability of these polymer-drug conjugate in the different contents of carboxylic acid is also studied.

In another study, since acrylate resins have been considered as hydrophobic polymers for the preparation of controlled-release formulations, the hydrophilic celluloses were commonly used to modify the release rates of drugs (24). The material, hydroxypropyl cellulose, being studied for its liquid crystal properties in our laboratory (25), will be blended with the ESMAA copolymers, and the hydrolysis of an aromatic ester linkage from this blend will be preliminarily tested.

EXPERIMENTAL

Materials and Purification

Methacryloyl chloride and methacrylic acid were purchased from Janssen Chimica and distilled before use. Triethylamine obtained from Janssen Chimica and *p*-methoxyphenol from Aldrich Chemical Company were used as received. 1,2-Dichloroethane from Fisher Scientific was dried overnight with calcium hydride and distilled. Dioxane purchased from Fisher Scientific was refluxed with sodium for 12 hr before distillation. All reagents were purchased from Aldrich Chemical Company unless otherwise stated. Piroxicam and Eudragit-S100 were purchased from ICI Chemical Company and Rohm Pharma, respectively.

Synthesis of *p*-Methoxyphenyl Methacrylate and *p*-Methoxyphenyl Acrylate

Initially, *p*-methoxyphenyl methacrylate (ESMAA) was synthesized by the method described by Koton (26). A 9.5 g (0.077 mole) of *p*-methoxy phenol was melted at 80°C and 7.5 ml of methacryloyl chloride was added dropwise. The reaction was continued for 3 hr. The yellowish liquid was dissolved in 30 ml of dried ethyl ether and washed with 5% NaOH 3 times and with distilled water twice. The organic portion was dried over anhydrous magnesium sulfate and the ether was removed on a rotaevaporator. A brown solid was obtained. The ESMAA product was crystallized with anhydrous ethanol twice and the colorless crystal was collected in a 50% yield (*mp* = 55 ~ 56°C). H^1-NMR was recorded using a Varian, Germinal 200 MHz apparatus. NMR($CDCl_3$) δ 2.02(3H, s -CH_3), 3.73(3H, s, -OCH_3), 5.69(1H, m, *cis*-H), 6.30(1H, m, *trans*-H), 6.85(2H, m, ArH), 7.01(2H, m, ArH).

In later experiments, the yield of ESMAA was improved by using triethylamine as base. Six milliliters of triethylamine was added dropwise into 5 g (0.040 mol) of *p*-methoxy phenol and 3.7 ml of methacryloyl chloride in 20 ml of 1,2-dichloroethane. The reaction was carried out in an ice bath for 20 min. The mixture was washed with 10% solution of HCl and subsequently with 5% solution of NaOH several times till all unreacted *p*-methoxyphenol was removed. The crude product was a white powder (yield ~ 93%) and after crystallization became a colorless and plate-like solid (yield ~ 85%).

Synthesis of Copolymers

The various mole ratios of MAA(M_1) and ESMAA(M_2) were dissolved in dioxane (20 wt%). After deoxygenation by alternate connection of the polymerization reactor to vacuum and nitrogen gas, 2 wt% of azobisisobutyronitrile (AIBN) with respect to the total weight of monomers was added. Each mixture was stirred for 4 hr at 60°C under nitrogen. The MAA-*co*-ESMAA copolymers were precipitated with either methanol or *n*-hexane. Typically, the copolymer was obtained in a 50% yield. Low conversion samples used to determine monomer reactivity ratios were withdrawn from the reaction mixtures after reaction time of 1 hr. The composition of each copolymer was assayed in dioxane solution for aromatic ester content by measuring the UV absorbance at 240 nm. The numeral after MAA indicates the mole percent of MAA units in a copolymer.

Preparation of Blend Films

Hydroxypropyl cellulose (HPC)/MAA-63 (1/1 w/w) blend films were prepared by dissolving 2 wt% of each component polymer in dioxane and then mixed. After most of the solvent had evaporated at room temperature, the blend film was dried in a vacuum oven at 70°C for

2 days. The film was ground into fine particle and compressed as a disk as described in hydrolytical studies.

A blend film was also prepared by another method. After preparing a saturated ESMAA solution in methacrylic acid, 20 wt% of HPC was dissolved in the solution (about 1 day) and 0.5 wt% benzoin methyl ether, with respect to the monomers, was added. The solution was cast onto a glass plate and covered with a thin polypropylene film which served to minimize the evaporation of methacrylic acid and to reduce the inhibitory effect of oxygen during photopolymerization. The cast solution was exposed to a long-wavelength UV lamp, Black-Ray Model B-100 A, for 10 min during which the monomer polymerized to high conversion. The composition of ESMAA in the blend film was 5 mole% determined by UV spectrophotometry.

Determination of Molecular Weight

The molecular weight of polymers was measured by gel permeation chromatography (GPC) using a Waters Model 501 containing 4 Shodex® GPC KF-800 series columns with the exclusion limit from 1.5×10^3 to 4×10^5. Tetrahydrofuran (high performance liquid chromatography (HPLC) grade from Fisher Scientific) was used as the eluent at a flow rate of 1 ml/min. The column setting was calibrated by using 10 monodisperse polystyrene standards obtained from Polysciences.

Thermal Analysis

The glass transition temperatures of polymers were determined using a Perkin–Elmer differential scanning calorimeter (DSC-7) controlled by a personal computer at a heating rate of 10°C/min. The DSC was calibrated with a pure indium standard. The glass transition temperature was taken as the midpoint of the abrupt heat capacity jump in a quenched specimen. At least 3 specimens were measured and averaged.

Solubility Test

Ten milligrams of each powder sample was placed in a 10 ml of buffer solution with different pH values at 37°C. The undissolved residue was filtered and weighed.

Polymer Dissolution and Drug Release

Each specimen was tested as a disk with a dimension of 5 mm in diameter and 1 mm thick, fabricated by Carver Laboratory press equipment at pressure of 50 kg/cm^2 and room temperature. The release agent was piroxicam with loading levels of 1 and 2 wt% with respect to polymer matrices. Release experiments were conducted in 50 ml of 0.1 M pH 7.4 phosphate buffer as well as 0.1 M pH 10 glycine buffer solutions at 37°C. To approximate perfect sink conditions, the frequency of changing the buffer solutions was adjusted during the course of the release study. The polymer disintegration and drug-release kinetics were followed by measuring the UV absorbance in a Shimadzu UV-160A spectrophotometer. The optical densities at 349 and 288 nm were measured to determine the respective concentrations. The amount of dissolved polymers (including the hydrolytic cleavage of aromatic ester bonds) and piroxicam was calculated by using the Lamber–Beer equation:

$$A_{349} = \varepsilon'_{\text{drug}}\, C_{\text{drug}}$$

$$A_{288} = \varepsilon''_{\text{drug}}\, C_{\text{drug}} + \varepsilon_{\text{polymer}}\, C_{\text{polymer}}$$

where at pH 10 buffer solution, the molar absorptivities were $\varepsilon'_{\text{drug}} = 18554$, $\varepsilon''_{\text{drug}} = 12057$, and $\varepsilon_{\text{polymer}} = 3228$ liters cm^{-1} mol^{-1}. However, at pH 7.4 buffer solution, the molar absorptivities were $\varepsilon'_{\text{drug}} = 15857$, $\varepsilon''_{\text{drug}} = 10103$ and $\varepsilon_{\text{polymer}} = 3958$ liters cm^{-1} mol^{-1}, respectively.

The hydrolytic cleavage of the aromatic ester bonds in copolymers was assayed by using a Hewlett-Packard 1090M HPLC system equiped with a diode array and a refractive index refractometer. Samples were filtered with 0.45-μm Millipore filters and eluted with 65% acetonitrile/water (v/v) at 1 ml/min. The eluent was monitored at 275 nm for the determination of free *p*-methoxyphenol. Each experiment was done in triplicate.

RESULTS AND DISCUSSION

Synthesis and Properties of Copolymers

Feed composition, copolymer composition, number-average molecular weight, and glass transition temperature are summarized for each MAA-ESMAA copolymer in Table 1. The polydispersity of MAA-*co*-ESMAA is about twice as commonly seen in free-radical solution polymerization. In order to estimate the randomness of the ESMAA units in their copolymers, the monomer reactivity ratios for copolymerization of MAA(M_1) and ESMAA(M_2) were calculated by using low-conversion samples. Reactivity ratios were computed from the Fineman–Ross equation (27), where *F* and *f* represented

Table 1

Copolymerization of MAA(M_1) with ESMAA(M_2)

Sample No.	Feed Ratio (M_1/M_2)	Copolymer Ratio (m_1/m_2)	M_n ($\times 10^{-4}$)	T_g (°C)
MAA-93	10.068	12.651	—[a]	194.0
MAA-82	5.642	6.240	2.5	175.1
MAA-77	3.481	3.349	2.9	156.2
MAA-63	2.255	1.707	5.7	166.8
MAA-55	1.559	1.293	5.9	147.8
PESMAA			57	111.8
PMAA				190.5

All copolymers were precipitated with *n*-hexane except MAA-55, which was precipitated with methanol.

[a] The copolymer was insoluble in THF.

the monomer ratios in feed and in copolymer (plotted in Fig. 1). The values of r_1 and r_2 were obtained by reading the slopes and the intercepts from the plots, which are 1.52 and 3.01 with 0.994 linearity for MAA-*co*-ESMAA. Although both r_1 and r_2 are larger than unity, there is a tendency to form a block copolymer. The glass transition temperatures of MAA-ESMAA copolymers are almost equal to the weight-average values calculated from the values of component polymers as indicated in Fig. 2. The T_g values indicated that the homogeneous distribution of 2 monomer units in the copolymers was still well.

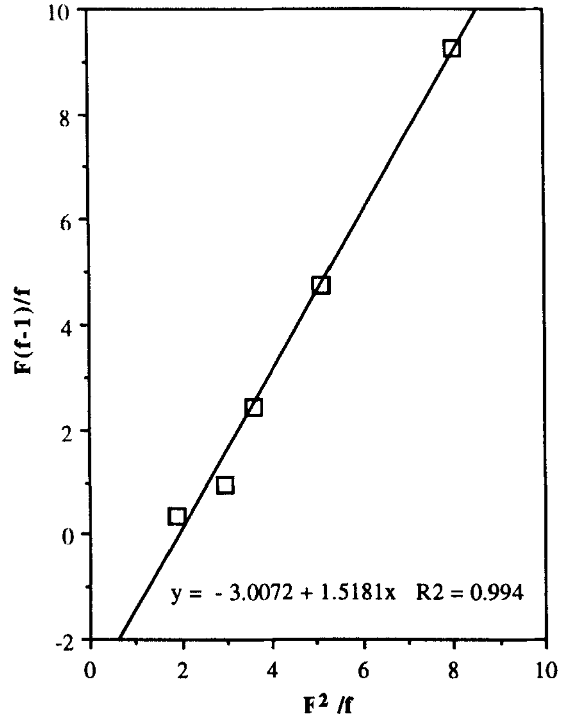

Figure 1. The plot for determination of monomer reactivity ratios for copolymerization of MAA($_1$) and ESMAA($_2$). *F* and *f* are, respectively, the ratios of 2 monomers in feed and in copolymer.

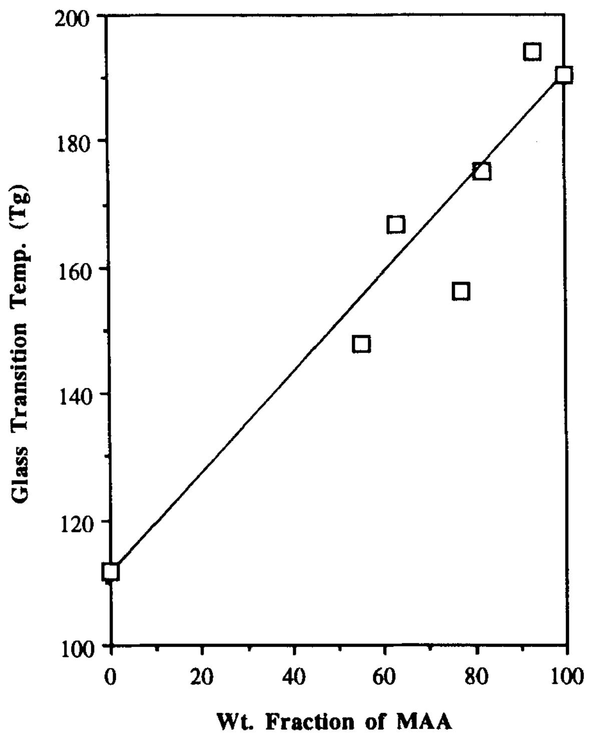

Figure 2. Glass transition temperature vs. weight fraction of MAA in MAA-*co*-ESMAA copolymers.

The Solubility of the Monomer and Copolymers

The solubility of ESMAA powder in the buffer solutions increases in the order of pH 7.4 ≤ pH 4 < pH 10. After polymerization, the PESMAA was insoluble in all buffer solutions. The solubility of an MAA-*co*-ESMAA copolymer containing 63 mole% of MAA increases in the same order as ESMAA monomer. After blending with a 50 wt% of hydroxypropyl cellulose (HPC) by a solution casting method, the solubility changes in the order of pH 4 < pH 7.4 < pH 10. The hydrolysis of ester bonds is catalyzed by acids and bases and the ionization of carboxylic acid increases with the basic condition. Both factors led to the fastest solubility at pH 10. Blending with water-soluble HPC with copolymers increased the solubility of polymeric matrices; for example, it took 8.3 hr for MAA-63 to be dissolved in the pH 10 buffer solution and only 2 hr for a 50/50 blend of HPC/MAA-63. The powder solubility of copolymers also increases with the composition of methacrylic acid units. MAA-63, MAA-77, and MAA-93 copolymers dissolved in the periods of 8.5, 4.5, and 4 hr, respectively, in the pH 10 buffer solutions.

The UV absorption of the aliquot of MAA-63 disk after being immersed in a pH 7.4 buffer solution for 2 days showed a UV spectrum identical to that of the *p*-methoxy phenol (Fig. 3). The hydrolysis of aromatic esters in the copolymers was confirmed by using the HPLC assay, where the free *p*-methoxy phenol was eluted at 1.79 min as shown in Fig. 4(a). Fig. 4(b) illustrates the HPLC diagram of a 20 wt% of HPC blended with MAA-95 after being immersed in a pH 7.4 buffer solution for 24 hr. The elution peak at 1.77 min confirmed by photodiode array, was attributed to the *p*-methoxy phenol. Both UV spectrophotometry and HPLC studies provided the same results: the aromatic ester bonds are hydrolyzable, albeit slowly. The concentration of free *p*-methoxy phenol was calculated by integration of the peak area under the baseline from 1.65 to 1.85 min. The results showed that about 20 wt% of free *p*-methoxy phenol was hydrolyzed after 2.83 hr and maintained the same values thereafter, as shown in Fig. 5. Ester hydrolysis is usually catalyzed by acids and bases. However, the hydrolysis of ester bonds indeed occurred in the pH 7.4 buffer soultions; this might be due to the phenolic esters, which can be cleaved much faster than aliphatic compounds (28).

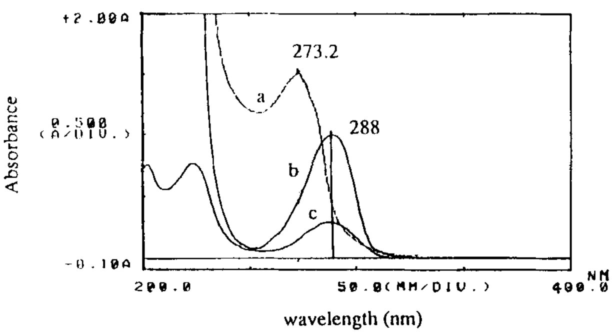

Figure 3. Ultraviolet absorbance of *p*-methoxyphenyl methacrylate (a), *p*-methoxy phenol (b), and the hydrolyzed solution of MAA-63 copolymer in the pH 7.4 buffer solution for 2 days (c).

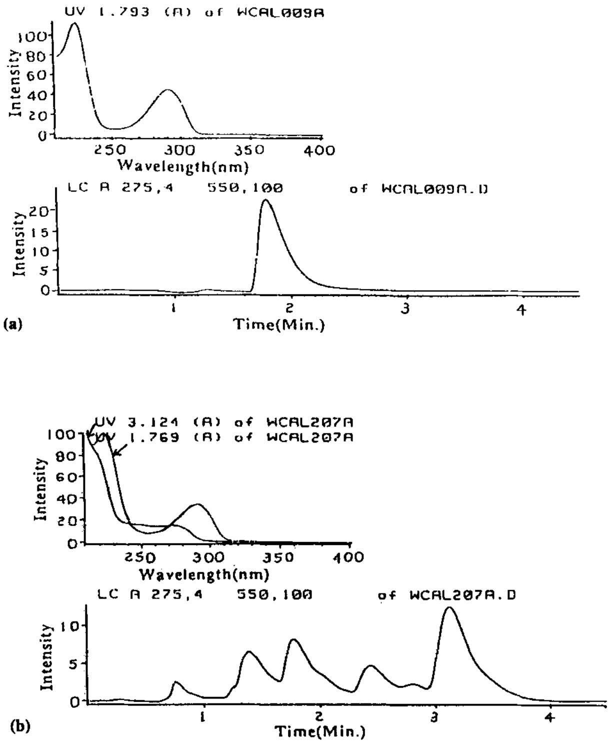

Figure 4. (a) The HPLC profiles of *p*-methoxy phenol in the pH 7.4 buffer solution (b) the HPLC profiles of 20 wt% hydroxypropyl cellulose blended with MAA-95 in the pH 7.4 buffer solution for 24 hr. The eluent is 65% acetonitrile/water (v/v) at 1 ml/min.

Release of Piroxicam from Polymer Matrices

Piroxicam is an acidic, nonsteroidal anti-inflammatory drug (NSAID). The drug is highly potent; has a long half-life in comparison to current NSAID agents such as indomethacin, phenylbutazone, or naproxen; and does not have unwanted cardiovascular or central ner-

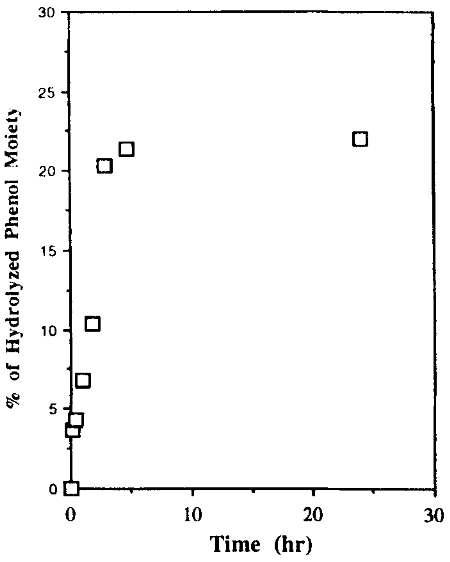

Figure 5. The percentage of the hydrolyzed phenol moiety in a blend containing 20 wt% hydroxypropyl cellulose with MAA-95 in the pH 7.4 buffer solution at 37°C.

vous effects. Oral administration of piroxicam has been the principal route for the treatment of rheumatoid arthritis (29). Although effective, oral therapy has an irritation side-effect concerning gastrointestinal mucosa (30). New dosage forms of piroxicam have been attracting interest since 1985 (31). We, therefore, attempt to study the release profiles of piroxicam based on our synthesized polymeric matrices. The model of drug released from Eudragit in the gastric liquid was explained by Vergnaud's group as two matter transfers (3,32,33). The former is concerned with the liquid entering the polymer and reacting with the polymer; the latter is concerned with the drug which is dissolved in the liquid located in the polymer. The rate of the reaction between the liquid and polymer carrier was not considered, because it was difficult to determine. The merit of our polymer matrices is that the polymer disintegration associated with the drug dissociation can be simultaneously determined by using a simple UV spectrophotometer. Since the insoluble homopolymer PESMAA in the pH 7.4 as well as pH 10, the drug released from PESMAA was less than 10 wt% of the initial loading in the period of 120 hr. The hydrophilicity was enhanced after introduction of hydrophilic methacrylic acid as a counter unit. The concentration of drug release was measured from the UV absorbance of piroxicam at 349 nm, while the amount of polymer dissociation (including the hydrolyzed aromatic moiety) was calculated from the absorbance at 288 nm. The cumulative amount at time *t* versus that at infinite time of MAA-55 is shown in Fig. 6. The results illustrate that the drug dissolution either with 1% or 2% loadings went hand-in-hand with the dissolution rate of the MAA-55 matrix. The data suggest that the release mechanism at these drug loading levels is dominated by matrix dissolution. This would be a desirable feature as other drugs can then be delivered from these matrices with predictable rates. However, more studies need to be done to confirm the matrix-dissolution-controlled release mechanism at higher drug loading levels. In the literature (34), Najib and Jalal obtained the same results: the dissolution and disintegration rate constants for acetaminophen tablets were correlated, that is, the slope of rate constant of drug dissolution versus the rate constant of matrix disintegration was approximately one, and passed through the origin, if the studies were performed in the same apparatus. The similar drug-release profile of Eudragit-S100 at pH 7.4 was obtained and is shown in Fig. 7. Although Eudragit-S100 contains the lower composition of water-soluble methacrylic acid (27.6–30.7 mol%), it showed the faster release rate than MAA-55 (the initial slope of Eudragit-S100 is 2.5 and that of MAA-55 is 1.7). This may be due to the aliphatic ester in Eudragit-S100. Furthermore, the release rate could be controlled by the composition of methacrylic

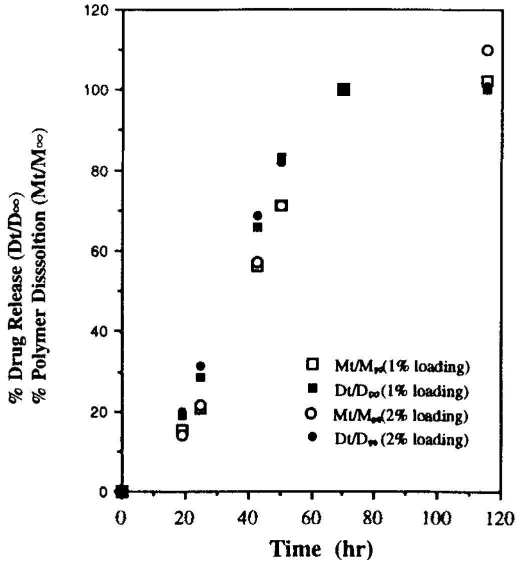

Figure 6. Piroxicam released and polymer dissolution from an MAA-55 copolymer in the pH 7.4 buffer solution at 37°C.

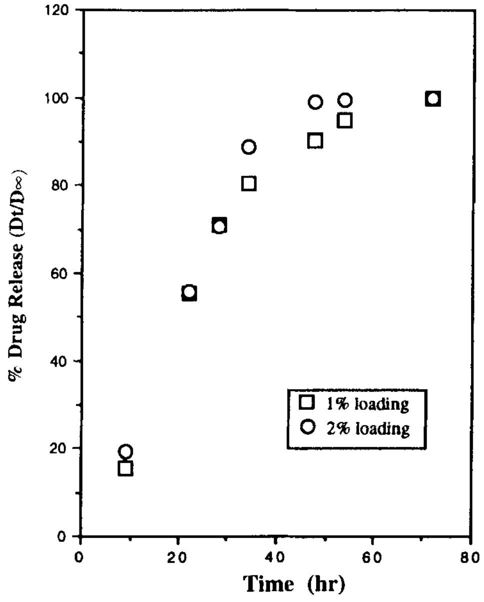

Figure 7. Piroxicam released from Eudragit-S100 in the pH 7.4 buffer solution at 37°C.

acid units in the copolymers. Figure 8 shows that the faster the drug-release rates, the higher the methacrylic acid units in the copolymers. By varying the composition of MAA units in the copolymer, the desirable release rate of the drug is obtainable.

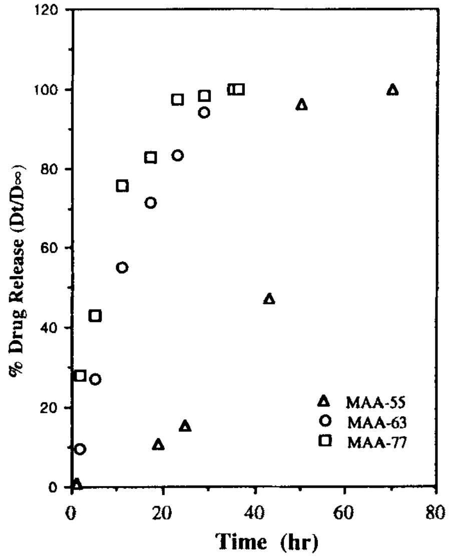

Figure 8. Piroxicam released from copolymers with 2 wt% loading in the pH 10 buffer solution at 37°C.

CONCLUSIONS

The use of polymers as prodrugs of bioactive agents can decrease the required dose and the toxicity of the drug. It may also improve the solubility and bioavailability of the drug. The present study demonstrates that the polymethacrylates could be used as polymeric matrices as well as macromolecular prodrugs. The synthesis of piroxicam-linked methacrylate through the phenol moiety has been successful. Further study of free drug released from macromolecular prodrugs is underway. By changing the composition of phenolic monomer units, the hydrophilicity of the drug–polymer conjugate can be adjusted and obtained in different release rates.

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