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RESEARCH PAPER

Synthetic PMMA-Grafted Polysaccharides as Hydrophilic Matrix for Controlled-Release Forms

I. Castellano,[1] I. Goñi,[1] M. C. Ferrero,[2] A. Muñoz,[2] R. Jiménez-Castellanos,[2] and M. Gurruchaga[1,*]

[1]*Dpto. de C. y T. de Polímeros, Fac. de Química, Universidad del País Vasco, Apdo. 1072, 20.080 San Sebastián, Spain*
[2]*Dpto. Farmacia, Tecnología Farmacéutica, Fac. de Farmacia, Universidad de Sevilla, c/Tramontana s/n, 41012 Sevilla, Spain*

ABSTRACT

This paper describes the rheological behavior of starch and cellulose acrylic graft copolymers synthesized with the aim of obtaining controlled-release excipients. The rheological characteristics determine the final release properties of matrix tablets. The study of the storage and loss moduli (G′and G″, respectively) and the viscosity allowed us to know if the polymer behavior was that of a gel and, hence, if it could act as a barrier to drug diffusion. Since dynamic measurements showed a storage modulus higher than the loss modulus, we assessed that all the polymers were gels. Thus, knowing that all the graft copolymers had acceptable properties for compression, the release of theophylline as a model drug at different pH was studied. Polymers with higher absorption capacity, viscosity, and compactibility allowed formulations with slower release rates.

Key Words: *Acrylic graft copolymers; Kinetics; Polysaccharides; Sustained-release tablets; Theophylline.*

* Telephone: 943 01 53 61. Fax: 943 21 22 36. E-mail: popgutom@sq.ehu.es

INTRODUCTION

When hydrophilic glassy polymer networks are placed in a swelling agent such as water they swell and form gels (1). During this process, the swelling agent plasticizes the polymer network, decreases its effective glass transition temperature, and increases the mobility of the polymer chains, rendering the polymer rubbery (like a gel). Tablets are one of the most frequent dosage forms used in the pharmaceutical industry. In this case, swelling starts at the tablet periphery, forming a gel that acts as a barrier to drug diffusion.

In the last years, different types of native and modified starches have been evaluated for their use as hydrophilic matrices. The carboxymethyl derivative of starch (CMS) is a well-known product that has been extensively examined in the past. Also, pregelatinized–cross-linked starches and dextrins have shown characteristics as promising excipients to control drug release (2). Furthermore, acrylic polymers have been studied and commercialized as hydrophilic matrices for drug delivery systems. Taking advantage of our experience in the synthesis of graft copolymers with acrylic and natural polymers (3) and knowing the need for the development of new delivery systems, we have synthesized various copolymers with the aim of testing them for use in this field. The following graft copolymers were obtained: hydroxypropyl starch–methyl methacrylate (HS-MMA), carboxymethyl starch–MMA (CS-MMA), and hydroxypropyl cellulose–MMA (HC-MMA). All these copolymers give powdery products, and in these previous works, we characterized them as products with potential for direct compression excipients. Two kinds of standard tablet formulations were evaluated by means of dissolution tests (4,5); however, the possibility of grafted copolymers as the only excipient has not been tested yet.

To know the release properties of the graft copolymers synthesized, the rheological properties of aqueous dispersions of the polymers have been studied in this work. Also, we have characterized the tablets prepared with the different polymers to elucidate relationships between drug release kinetics and viscosity.

EXPERIMENTAL

Materials

The graft copolymers synthesized in a previous work (6), obtained in an aqueous medium using Ce(IV) as initiator, were used. Copolymers were obtained two different ways: dried in an oven at 50°C (called O products) and dried by lyophilization (called L products). Graft copolymers used were HS-MMA O and L, CS-MMA O and L, and HC-MMA O and L. Powders were stored under controlled temperature (30°C) at 75.5% relative humidity. All the products were passed through a 500-μm mesh to remove excessive coarse granules.

We have also used anhydrous theophylline (Teofilina BP 80, Roig Farma, Barcelona, Spain) (batch 1201094) as a model drug for controlled-release tests.

All other chemicals were reagent grade.

Viscosity

The viscosity measurements of polymers were performed in a Carri-Med CSL100 viscometer at 37°C in H_2O (4% w/w) and fitted with a 4 cm and 1°58″00 angle stainless steel cone-plate geometry. Rest time in the measuring system before running determinations was 5 min. Samples were tested using a frequency sweep at 10 and 0.1 Hz. Mean storage modulus G' and loss modulus G'' were calculated. All polymers tested were dispersed at 4% (w/w) concentration in water. This percentage was determined by reaching an adequate viscosity of the dispersions in the vessel during stirring (7).

Flow Properties of Powders

Theophylline (25%) was mixed with 75% of the polymer under study for 15 min. The mixture was made in a plastic vessel with an asymmetric double-cone mixer (Retsch, Haan, Germany) at 50 rpm. The flow rate (FR) of mixtures was measured by our data acquisition flow

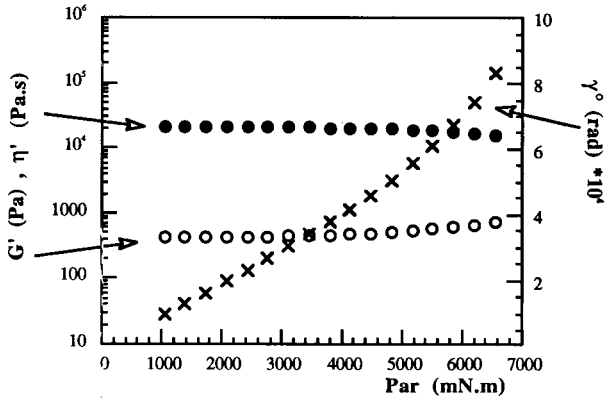

Figure 1. Determination of the viscoelastic zone of HS-MMAL polymer: ●, storage modulus G'; ○, loss viscosity η'; and ×, displacement equivalent γ^0.

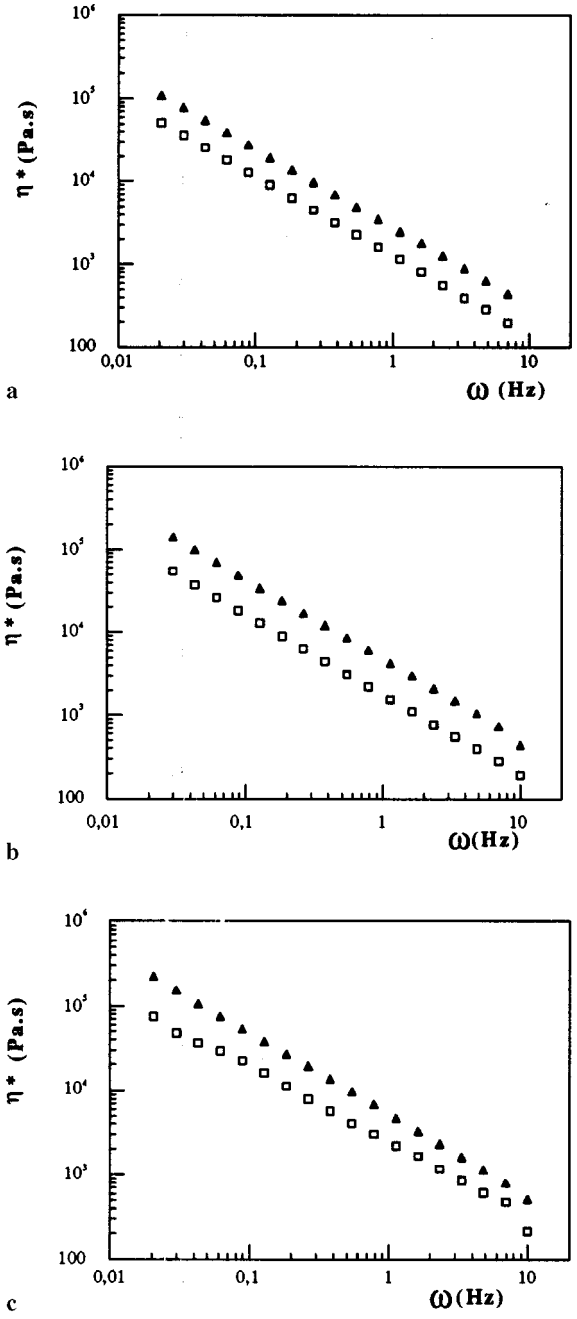

Figure 2. Flow curves of (a) HS-MMAO (□) and HS-MMAL (▲); (b) CS-MMAO (□) and CS-MMAL (▲); and (c) HC-MMAO (□) and HC-MMAL (△) graft copolymers in water at 4% (w/w) at 37°C versus frequency ω.

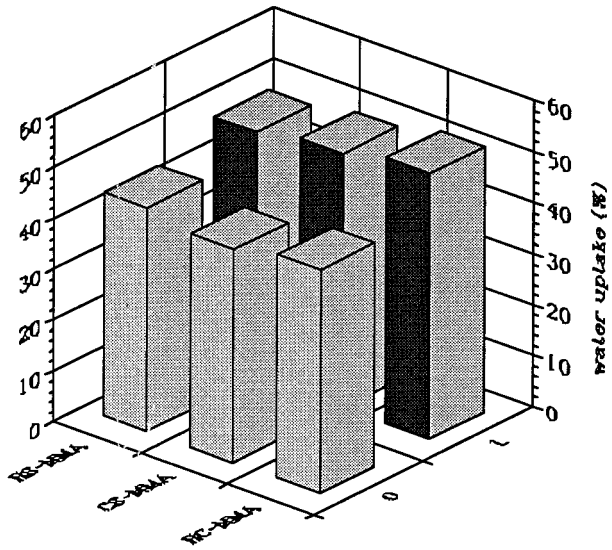

Figure 3. Swelling ratio of different graft copolymers in water at 37°C.

meter system (8). The vessel used was a glass funnel. A balance with an interface connected to a computer (IBM PC compatible) constitutes the whole system. A software program for data acquisition, graphics, and calculations was used.

Compression Characteristics

The compression characteristics of powders (polymer plus theophylline) were investigated on an instrumental single-punch tablet machine (Bonals AMT 300, Barcelona, Spain). A quantity of powder (500 mg) was manually filled into the die (12 mm), and flat compacts were prepared at a fixed crushing strength (4 Kp). To evaluate the compression properties of the mixtures, the averages

Table 1

Ostwald Equation Parameters from the Flow Curves of MMA Copolymers in Water

	m	*n*	*m*/*n*
HS-MMAO	1271.16	0.046	27,634
HS-MMAL	2653.38	0.029	91,496
CS-MMAO	1779.01	0.035	50,829
CS-MMAL	4698.92	0.031	151,578
HC-MMAO	2390.00	0.123	19,431
HC-MMAL	5199.96	0.034	152,940

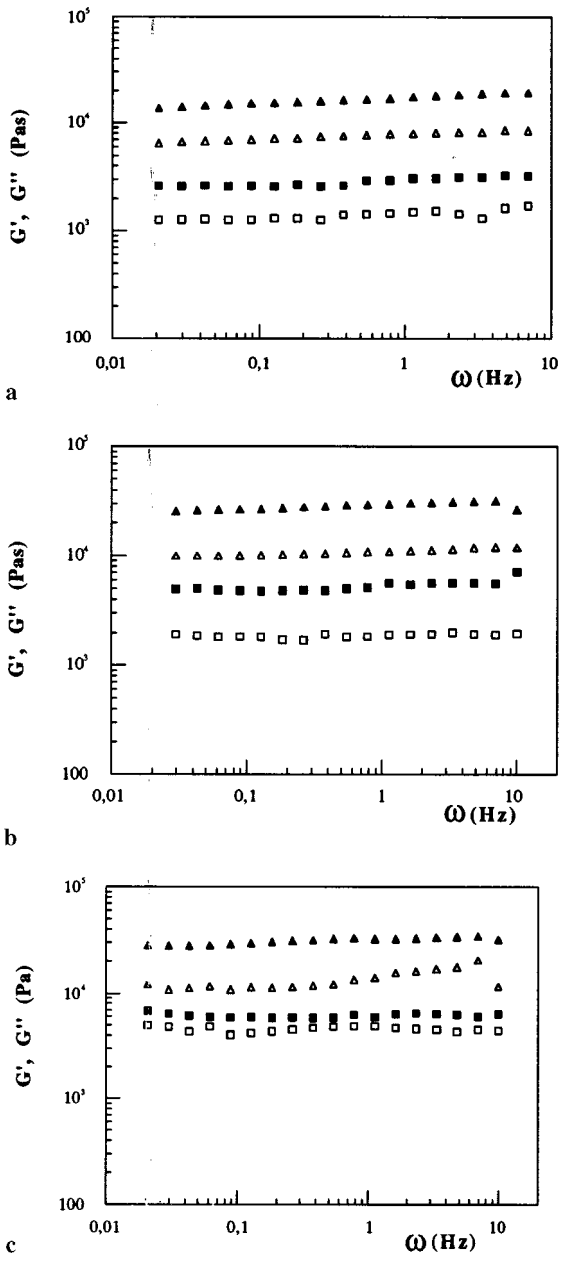

Figure 4. The storage modulus G'' (△ is O and ▲ is L) and the loss modulus G'' (□ is O and ■ is L), of (a) HS-MMA; (b) CS-MMA; and (c) HC-MMA in water versus frequency ω.

of maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient *R*, plasticity (%Pl), and compactibility *C* were studied.

Standard Physical Tests of Tablets

To study the variations in the tablet properties, the mixture were tableted in a single-punch tablet machine (Bonals model AMT 300) equipped with a forced feeding system running at 30 cycles/min. Weight uniformity, thickness measurement, friability, and disintegration time (DT) were determined by the previously described methods (4).

Dissolution Tests

Dissolution profiles were obtained for six tablets of each formulation with a USP apparatus (Turugrau automated dissolution test) and using the basket method at 50 rpm. The dissolution media were different buffer solutions, prepared with HCl for acid medium (1.5) and phosphate heptahydrate, citric acid, and potassium chloride for the media at pH 5 and pH 8; all had the same ionic strength (0.5 M). The amount of theophylline in solution was monitored continuously by spectrophotometry (diode array spectrophotometer, Hewlett Packard, Walbbronn, Germany) at 270 nm.

RESULTS AND DISCUSSION

The viscosity characteristics of the polymers are of great importance to obtain the desired release profile. To obtain an adequate rheological characterization, besides the viscosity, it is necessary to know the storage and loss moduli (G' and G''). These parameters will permit us to know if the polymer behavior is that of a gel and, therefore, if it can act as a barrier to drug diffusion. To carry

Table 2

Flow Rate (FR) of MMA Copolymers with 25% Theophylline

	FR (g/sec)
HS-MMAO	Does not flow
HS-MMAL	3.92 ± 0.15
CS-MMAO	5.20 ± 0.58
CS-MMAL	6.55 ± 0.22
HC-MMAO	5.36 ± 0.62
HC-MMAL	4.32 ± 0.30

Table 3

Average of Maximum Upper Force (MUF), Ejection Force (EF), Lubrication Coefficient R, *and Compactibility (Comp) of Tablets with 75% MMA Graft Copolymers and 25% Theophylline Compressed at 40* N *Crushing Strength*

	MUF (*N*)	EF (*N*)	*R*	Comp
HS-MMAO	12,200 ± 249	373 ± 19	0.74 ± 0.01	3.69 ± 0.11
HS-MMAL	8590 ± 287	561 ± 38	0.71 ± 0.01	4.68 ± 0.14
CS-MMAO	11,300 ± 66	575 ± 67	0.76 ± 0.01	5.62 ± 0.13
CS-MMAL	4410 ± 232	402 ± 45	0.62 ± 0.01	8.15 ± 0.75
HC-MMAO	10,600 ± 99	1040 ± 60	0.67 ± 0.01	6.38 ± 0.08
HC-MMAL	5900 ± 196	1120 ± 136	0.56 ± 0.01	6.55 ± 0.10

out these measurements, the shear stress must be in the linear viscoelastic zone. To determine this zone, we have applied an increasing shear stress at a frequency of 1 Hz and at 37°C. Figure 1 shows the results obtained for HS-MMAL (4% w/w) in water. It can be observed that the storage modulus G' and the loss viscosity η' are independent of the shear stress, and the equivalent displacement γ increases linearly with the shear stress. Similar behavior by the other products led us to follow this study.

Figure 2 shows the flow curves of all the polymers. There are no big differences between the various polymers, but a higher viscosity of the L products than the corresponding O products can be observed. Two factors can explain the rheological behavior of the polymers: water absorption capacity and disperse phase particle size. Taking into account the water absorption percentage (Fig. 3), defined as

$$\text{Equilibrium water absorption} = [(\text{Absorbed water weight})/(\text{Dry polymer weight})] \times 100$$

we can observe that the polymers with the largest absorption values are also the most viscous. As for the particle size, the higher the absorption capacity is, the greater is the retention of solvent molecules in a polymeric particle and, therefore, the larger is the volume. This larger volume contributes to increase the size of the flow unit and so the resistance displacement; subsequently, the system viscosity increases.

In this study, we fit our flow curves to the Ostwald equation, which is often used to describe macromolecular solution behaviors, obtaining a linear correlation of 0.99:

$$\eta = m(\delta)^{n-1}$$

where the *m* and *n* parameters represent the consistency and fluency index, respectively, and δ is the shear rate. The *m* and *n* values obtained for each polymer are listed in Table 1. All the polymers present a pseudoplastic behavior ($n < 1$). To compare the different polymers, the ratios between consistency and the fluency index are calculated. The values of L products are higher than of the O products. The higher the ratio between both indexes, the greater the gel consistency (higher *m*), and this is a reflection of the higher viscosity observed in the flow curves. Rossi et al. (9) relate the higher viscosity of a product to the higher number of entanglements between

Table 4

Uniformity of Weight (W), Coefficient of Weight Variation (CV), Thickness (Th), Friability (F), and Disintegration Time (D) of Tablets Formulated with 75% MMA Copolymer

	W (mg)	CV (%)	Th (mm)	F (%)	DT (min)
HS-MMAO	485 ± 6	1.24	4.475 ± 0.018	2.58	>30
HS-MMAL	501 ± 17	3.39	4.713 ± 0.027	1.36	>30
CS-MMAO	501 ± 5	0.99	4.263 ± 0.014	2.74	>30
CS-MMAL	516 ± 12	2.32	5.223 ± 0.025	2.61	>30
HC-MMAO	488 ± 5	1.02	4.188 ± 0.008	2.80	25 ± 7
HC-MMAL	502 ± 14	2.79	4.793 ± 0.026	1.63	>30

the chains. These entanglements hinder the motion of the chain; therefore, dissolution viscosity increases. In our case, taking into account the slight mechanical degradation of O products, the decreased viscosity of these products may be explained as a consequence of chains breaking during the milling process.

If we plot the storage and loss moduli versus frequency, we can know if our polymers are gel or sol (7). Figure 4 shows that all the polymers are gels because their storage moduli are higher than their loss moduli. On the other hand, L copolymers have higher storage and loss moduli than their corresponding O products; this agrees with the higher viscosity and consistency of L products. These results allow us to find that all products fulfill the first necessary condition for good control of drug release: The viscosity of the products is high enough to decrease the release rate of the drug (10).

The pharmaceutical industry needs to characterize flow properties of the powders to estimate their suitability for direct compression excipients. In previous works, we measured the most representative polymer characteristics to be used to this end (11) and the influence of these characteristics when polymers are part of a standard formulation with a lubricant and a filler (4). Now, we studied how a model drug addition (theophylline 25%) modified powder flowability and compression parameters of each polymer under study.

Table 2 gives the results of the flow rate test of these mixtures. The comparison of these results with those obtained in a previous study of the same polymer powders without theophylline (11) shows that, when theophylline is added to graft copolymers, the flow rate worsens. This can be due to the small size of theophylline particles (37.70 ± 2.38 μm).

To evaluate the compression properties of the mixtures, the averages of the following selected parameters were calculated for tablets obtained at 40 N crushing strength: MUF, EF, *R*, and CP. These parameters are listed in Table 3. According to the results obtained, we can say that the force needed to make the tablets is higher for the O products than for the corresponding L products, as we found by testing the standard formulation (4). The addition of theophylline decreases MUF, and the values are also lower than those obtained for the standard formulation. The results demonstrated that all formulations fulfilled the requirements for direct compression proposed by Boulhuis and Lerk (12), who established that EF values must be lower than 750 N, but not in relation to *R* (lower than 0.9). This last parameter improved clearly by the addition of the lubricant (4). The compactibility increased by the use of the model drug and reached an almost medium value, close to 5, in the standard formulation of each polymer. Also, the compactibility of L products was better than that of O formulations.

Tablets from all mixtures passed the test for weight uniformity (Table 4). The friability values are in all cases higher than 1%. Relating to disintegration time, only HS-MMAO showed a negative influence of the model drug; that means that theophylline does not worsen the integrity of the tablet as did the addition of a high percentage of Encompress® (4).

The dissolution tests for each formulation at different pH are shown in Figs. 5, 6, and 7. All the formulations with O polymers show faster release of the drug at the three pH used, which agrees with the rheological behavior of the polymers since L products give gels more consistent than O products. These results are in good agree-

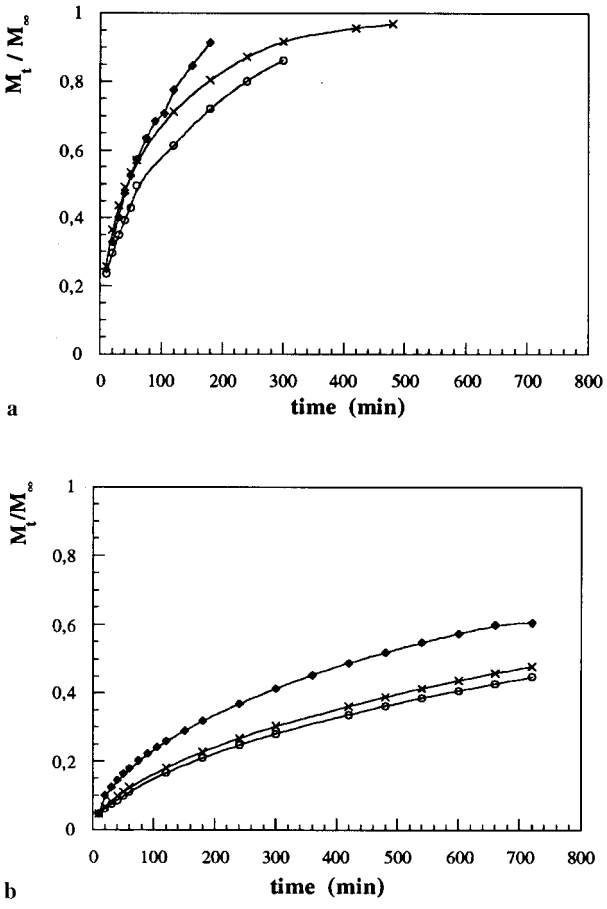

Figure 5. Theophylline fraction released (M_t/M_∞) from formulations with 25% theophylline and 75% of (A) HS-MMAO and (B) HS-MMAL at 37°C and pH 1.5 (◆), pH 5 (○), and pH 8 (×).

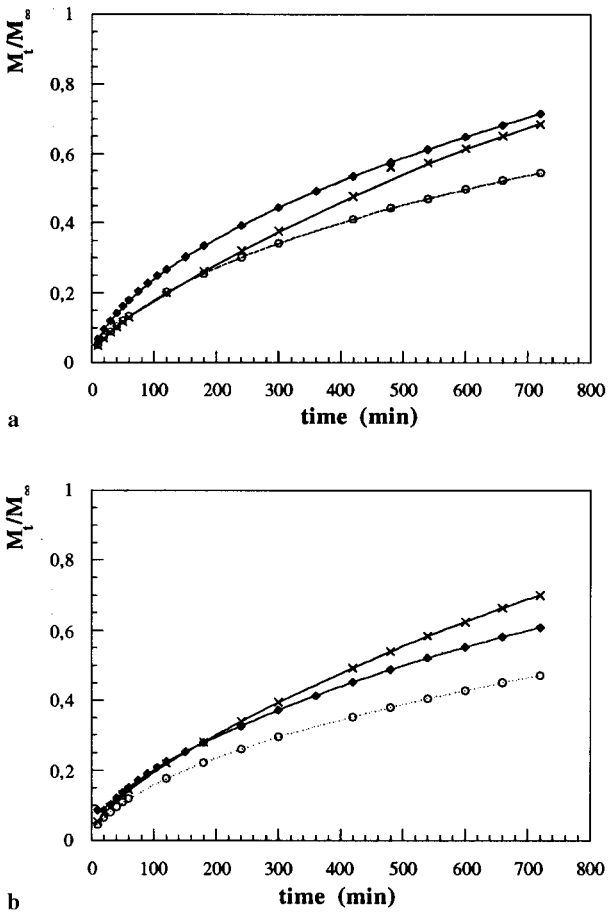

Figure 6. Theophylline fraction released (M_t/M_∞) from formulations with 25% theophylline and 75% of (A) CS-MMAO and (B) CS-MMAL at 37°C and pH 1.5 (◆), pH 5 (○), and pH 8 (×).

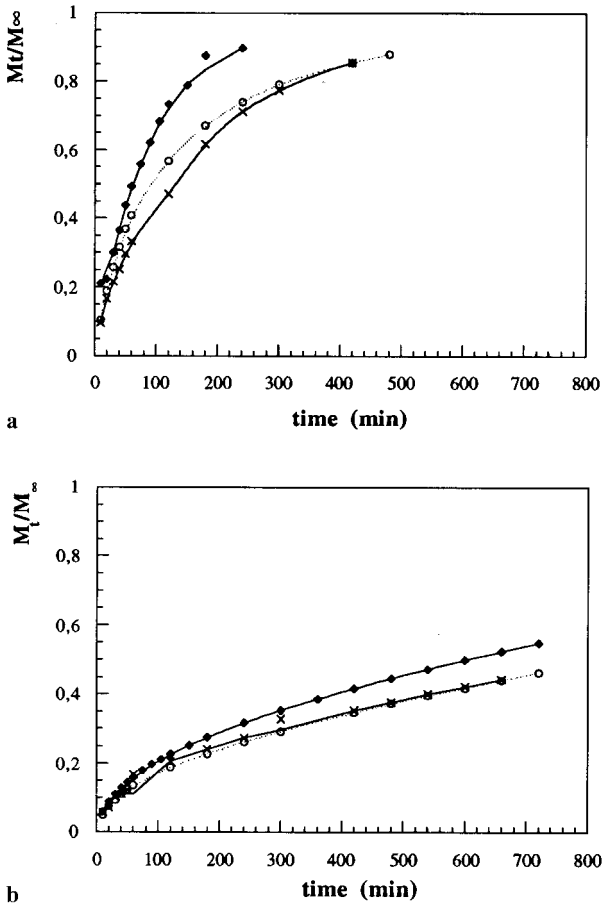

Figure 7. Theophylline fraction released (M_t/M_∞) from formulations with 25% theophylline and 75% of (A) HC-MMAO and (B) HC-MMAL at 37°C and pH 1.5 (◆), pH 5 (○), and pH 8 (×).

ment with those of Ford et al. (13) and Delargy et al. (14), which showed that the higher the polymer viscosity was, the larger the release time of the drug was.

Taking into account the absorption values (4), it can be observed that the polymers with higher absorption capacity (L products) give formulations with slower release rates, which agrees with the results obtained by Kawashima et al. (15). Thus, we can say that the higher absorption capacity, viscosity, and compactibility could account for the lower release rate of these formulations.

With regard to the pH, it seems that acid pH leads to shorter release times, which is in accordance with the observed lower absorption values (4). This lower absorption capacity at acid pH is justified by secondary bonds (polymer-polymer, Van der Waals forces, etc.), which make it difficult or hinder a chain's enlargement to make a gel; consequently, there is no hindrance to drug diffusion. In contrast, at basic pH, the high absorption capacity involves a gel layer formation that acts as barrier.

The release kinetics of the drug from matrix tablets were analyzed by application of the equation of Peppas et al. (16):

$$Mt/M\infty = K_1 t^n + K_2 t^{2n}$$

where Mt/M_∞ is the fraction of drug release up to time t. The first term is related to the Fickian diffusion and the second to the relaxational mechanisms. The release Fickian exponent is n. $Mt/M_\infty < 60\%$ data were fitted to this equation.

The release kinetic is fitted to the equation of Peppas et al., obtaining the diffusion K_1 and relaxation K_2 mecha-

Table 5

Peppas Equation-Fitting Parameters at Three Different pH

	pH	K_1	K_2	r	K_2/K_1
	1.5	0.0263	0.0002	0.9986	0.0076
HS-MMAL	5	0.0156	0.0003	0.9993	0.0192
	8	0.0172	0.0003	0.9995	0.0174
	1.5	0.0237	0.0006	0.9996	0.0253
CS-MMAO	5	0.0186	0.0004	0.9992	0.0215
	8	0.0138	0.0009	0.9989	0.0652
	1.5	0.0207	0.0005	0.9993	0.0242
CS-MMAL	5	0.0166	0.0003	0.0006	0.0181
	8	0.0165	0.0008	0.9999	0.0485
	1.5	0.0465	0.0041	0.9862	0.0881
HC-MMAO	5	0.0419	0.025	0.9878	0.0596
	8	0.0459	0.0006	0.9934	0.0131
	1.5	0.0232	0.0002	0.9998	0.0089
HC-MMAL	5	0.0190	0.0002	0.9998	0.0105
	8	0.0219	0.0001	0.9968	0.0046

nism constants, which can be observed in Table 5. Generally, diffusional mechanism contribution is higher than relaxational contribution at all pH. In this sense, it can be said that, while the relaxational contribution does not change with pH, diffusional contributions drop when pH goes from acid to basic. This behavior is similar to that of nongrafted polysaccharides, which show a higher water absorption capacity at high pH, which gives rise to heavier gels. This leads to an increase of the macromolecular relaxation importance over the pure diffusion mechanism. For this reason, it seems that carbohydrate influence would be very important in this process.

In conclusion, we can say that the PMMA-graft copolymers can be used as controlled-release excipients in direct compression formulations since they show release times longer than 12 hr. Also, as we predicted in a previous paper, the release profile showed by the L products is generally slower than that showed by the O products. We must point out the relevant role of these copolymers in the release form. If we make a comparison between results obtained in this work and those obtained with a standard formulation, we can say that these PMMA-graft copolymers fill the role of various excipients since only in a few cases did the addition of filler and lubricant improve compression or flow properties, and in all cases, it gave faster release rates. Other formulations, other particle treatments, or other technological methods can be tried to fit to pharmaceutical industry requirements.

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