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RESEARCH PAPER

Synthesis of Hydroxypropyl Methacrylate/ Polysaccharide Graft Copolymers as Matrices for Controlled Release Tablets

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ABSTRACT

Hydrophilic matrices are an interesting option when developing drug delivery systems. With this aim, hydroxypropyl methacrylate was grafted onto hydroxypropyl starch and hydroxypropyl cellulose substrates by following the Ce(IV) redox initiation method. Different amounts of ethyleneglycol dimethacrylate, 7 and 34 mol%, as the crosslinking monomer, were also added. The drying of grafted products was carried out by lyophilization, obtaining white powders. Reaction yields (percent grafting, grafting efficiency, etc.) and some physical characteristics of the powders (particle size, moisture uptake, density, morphology, etc.) were determined. These parameters indicate how useful these products may be as potential matrices for direct compressed tablets. In this light, the powder flowability and the binding properties of each copolymer were determined. The graft copolymers can be considered of great interest as direct compression excipients. Due to their different chemical structure and composition, they showed differences in viscoelastic properties that revealed an interesting range of possibilities for use in drug delivery formulations. Tablets formulated with conventional excipients were also tested. Dissolution tests of various tablets were carried out. In 12 hr, 60–80% of the model drugs was released.

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INTRODUCTION

Nowadays, the inherent limitations of conventional pharmaceutical forms lead galenical research to look for new dosification designs. The objective is to obtain formulations that allow the drug to remain at the therapeutic limits for longer. The development of such pharmaceutical forms is associated with the use of high specific polymeric materials. Among these, the hydrophilic matrix continues to be a widely used strategy for sustained release drug delivery, polysaccharides and their derivatives being the polymers of choice as the rate-controlling carrier.

From such polymer specifications we can select:[1] substrate origin, chemical composition, physicochemical nature, biodegradability and chemical stability, mechanical properties, drug characteristics, desired pharmaceutical form, administration route, and release mechanism. In its simplest form, a hydrophilic matrix device is a compressed powder mix of drug with polymer, in which hydrophilic polymers are capable of modifying the effective diffusivity of the active principle.[2] In addition, the oral route is one of the preferred administration methods. For the above reasons in this case, we are seeking to obtain carbohydrate derivatives to give oral drug delivery systems by direct compression. Obviously, such polymers must first present two important requirements: good flowability and compactability.

In previous work,[3] we demonstrated the ability of carbohydrate–polymethyl methacrylate (PMMA) graft copolymers as excipients to prepare this kind of dosage form. Taking these results into account, for this project we have chosen the hydroxypropyl starch (HS) and the hydroxypropyl cellulose (HC) as polymeric backbones to be grafted. In order to ascertain the influence of a more hydrophilic polymer on the drug release, hydroxypropyl polymethacrylate (PHPMA)—a well-known acrylic hydrogel—was chosen as synthetic branches of the graft copolymer. In addition, a difunctional monomer, ethyleneglycol dimethacrylate (EGDMA), was added in order to obtain covalently crosslinked hydrogels with a different capacity of water retention. In this way, we were able to obtain new biocompatible polymeric materials of high molecular weight[4] with a range of hydrophilic and swelling properties, as well as chemical and mechanical ones.

Since physical, chemical, biological, and mechanical properties are the four basic strategies that govern the mechanisms of advanced drug delivery,[5] differences in the controlled release behavior of the various synthesized graft copolymers can be expected. The aim of this paper is to show the data obtained from the synthesis and from the chemical characterization of the copolymers and the powders. The rheological study of the copolymers was carried out to assess the viscoelastic properties of the grafted products in order to determine their suitability for use in drug delivery formulations.

EXPERIMENTAL

Materials

In this study, the following natural polymer derivatives were used: hydroxypropyl starch (HS) (Avebe, Holland) and hydroxypropyl cellulose (HC) (Aldrich, Milwaukee). The starch derivative came from potato starch with a substitution degree of 0.04–0.06. The cellulose derivative had a substitution degree of 2.18–2.84 and an average molecular weight of 370,000.

The monomers, hydroxypropyl methacrylate (HPMA) and ethyleneglycol dimethacrylate (EGDMA) (Merck, Germany), were purified by distillation under previously described conditions.[4] The initiator was ceric ammonium nitrate (Fluka, Switzerland) and was used at a 0.1 M solution in 1 N nitric acid.

Theophylline (anhydrous) (batch 12011094) (BP 80, Roig Farma, Barcelona, Spain) was used as the model drug, stearic acid (Acofarma, batch 2092, Terrasa, Spain) as the lubricant, and dicalcium phosphate dihydrate (Encompress®) (Julia Parrera, Barcelona, Spain, batch 1859) as the diluent.

All the other products were reagent grade or equivalent.

Synthesis of Graft Copolymers

Synthesis was carried out as described previously.[4] The carbohydrate was dispersed in

550 mL of bidistilled water in a three-necked flask. The dispersion was purged by passing purified nitrogen for 30 min and the temperature was maintained at 30°C. Then, 0.94 moles of HPMA and EGDMA were added and, 15 min later, 50 mL of Ce(IV) initiator solution. Grafting was allowed to proceed for 4 hr at 30°C by mechanical stirring under nitrogen atmosphere. Using this method, we have synthesized various graft copolymers, three from the starch derivative: HS-HPMA0 (without the crosslinking agent, EGDMA), HS-HPMA7 (with 7 mol% of EGDMA), HS-HPMA34 (with 34 mol% of EGDMA), and three more from the cellulose derivative: HC-HPMA0 (without the crosslinking agent, EGDMA), HC-HPMA7 (with 7 mol% of EGDMA), HC-HPMA34 (with 34 mol% of EGDMA).

The obtained products were filtered and the solid was recovered after washing with the nitric acid solution and water. Afterwards, the reaction products were freeze-dried in a liophylization apparatus for 48 hr, obtaining loose white powders. This technique made it possible to obtain the material in single particles in one step and with high reproducibility. The conventional drying process in the oven gives aggregates and agglomerates that should be subjected to milling.[6]

In order to learn more about the copolymerization process,[4] a portion of the reaction product was introduced into a Soxhlet apparatus to remove the non-grafted homopolymer, using tetrahydrofuran (THF) and ethanol as solvents. Afterwards, the grafted PHPMA was isolated from the carbohydrate chains by acid hydrolysis with 1 N hydrochloric acid at reflux for 6 hr.

Characterization of Graft Copolymers

Reaction Yields

The following parameters were calculated: percent grafting efficiency (%GE=percent weight of graft copolymer with respect to total copolymer), percent grafting (%G=percent weight of grafted acrylic polymer with respect to grafted carbohydrate), crude grafting (%CG=percent weight of total acrylic polymer with respect to total carbohydrate).[4]

Rheology

The viscosity of polymers was measured in a Carri-Med CSL 100 rheometer with a cone and plate measuring system at 37°C in bidistilled water 4% (w/w). Rest time before running determinations was 5 min.

Formulations

The graft copolymers were obtained as powders and used to prepare three types of formulations: (a) using polymer alone, (b) using the polymer and the model drug, and (c) mixing the latter two with conventional excipients for direct compression.

Type b was prepared using 25% theophylline, as the model drug, and 75% polysaccharide or graft copolymer. Type c, in turn, was prepared using 24% theophylline plus 1% stearic acid, 50% dicalcium phosphate dihydrate (Encompress®) and 25% polysaccharide or graft copolymer. In this last case, theophylline was mixed first with one of the polymers being studied and Encompress® for 15 min in a plastic vessel using an asymmetric double-cone mixer (Retsch, Haan, Germany) at 50 rev min^{-1}. After the addition of the lubricant, the mixing procedure was continued for 5 min.

Characterization of Powders

The key factors governing the flowability of the powders are considered to be particle–particle interaction and friction. The inherent properties affecting powder flow are particle shape, particle size distribution, density, moisture content, and surface texture.[7] On the other hand, the compactability is predominantly determined by material properties such as surface energy and deformation. Although flowability factors can be technologically controlled in a relatively easy way, compactability factors are impossible or extremely difficult to modify.[8] In the case that concerns us here, we investigated the suitability of our synthesized graft copolymers for making compressed tablets such as obtained after the lyophilization process. The following parameters were studied.

Particle Size Distribution

The products were passed through different sieves (500–400–320–250–200–125–100–50 μm) in a vibrational sieve machine (CISA) for 1 hr. Afterwards, the average radius of particles was calculated according to the equation: $1/R = \sum (X_i R_i)$.

True Density

The true density of each graft copolymer was determined using a helium pycnometer (Model SPY-3 Quantachrome).

Moisture Uptake Capacity

The moisture uptake capacity (MU) of dried products was calculated by an IR Moisture Analyzer (Sartorious) at 50°C for 20 min. Previously, samples were conditioned in closed chambers with a relative humidity of 75.5% at room temperature for a week.

Surface Morphology

The morphology of particles was studied by means of scanning electron microscopy (SEM HITACHI-S-2700) with an acceleration voltage of 15 KV. The surface of the powder particles was previously gilded.

Flow Properties of Powders

The flow rate (FR) of mixtures was measured by our data acquisition flowmeter system[9] using a glass funnel as a vessel. A balance with an interface connected to a personal computer (IBM PC compatible) constitutes the whole system. A software program for data acquisition, graphics, and calculations was also used.

Compression Characteristics

The compression characteristics of powders were investigated on an instrumented 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 fixed crushing strength. In order to compare results with tablets prepared in our previously published works,[3,10] a crushing strength of 40 N was selected as a starting point for this part of the research. As we will explain further on, other tablets were made at 120 N of crushing strength.

To evaluate the compression properties of the mixtures, the following average parameters were studied:[3]

- ejection force (EF);
- lubrication coefficient (R), defined as $R = F_u/F_l$, where F_u is the maximum force exercised by the upper punch and F_l by the lower;
- plasticity (%Pl): $\%Pl = W_{NA}/W_{NA} + W_{EXP}$, where W_{NA} is the apparent net work and W_{EXP} is the expansion work;
- compactibility (CP): $CP = CS/W_{NA}$, where CS is the crushing strength.

Standard Tests of Tablets

Standard Physical Tests

Weight uniformity, friability (%F) and disintegration time (DT) were determined by the previously described methods.[3]

Dissolution Studies

Tablets of each formulation were subjected to "in vitro" dissolution using a USP XXII apparatus (Turugrau automated dissolution test) in water at different pH values maintained at 37°C and with a paddle rotating at 50 rev min^{-1}. The dissolved drug was monitored continuously and determined automatically with a UV spectrophotometer (Hewlett Packard) at 270 nm. The different dissolution media were of pH 1.5, 5, and 8, and all of them were adjusted to the same ionic strength, 0.5 M, by adding KCl.

Drug release kinetics were analyzed by applying the Peppas equation:[11]

$$M_t/M_\infty = K_1 t^n + K_2 t^{2n}$$

M_t/M_∞ being 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. n is the fickian release exponent. The $M_t/M_\infty < 60\%$ data were fitted to this equation.

RESULTS AND DISCUSSION

The reaction yield parameters of grafted carbohydrates are listed in Table 1. We can see that, in the case of both carbohydrates, as the percent of added EGDMA increases, the %CG increases too. This is to be expected if we take into account that, when we add EGDMA, we are introducing a bifunctional monomer with higher molecular weight than the HPMA.[12] The high %GE of products with 7 and 34% of EGDMA should be highlighted. This is due to the crosslinked network formed by this difunctional monomer, which probably gives out less ungrafted homopolymer which, in turn, swells without dissolving. It is necessary to mention

Table 1

Yields of Grafting Reaction: %CG, %GE, and %G, and Product Characteristics: Percent Humidity (%H) Absorbed by Graft Copolymers After a Week at a Relative Humidity of 75.5% and Average Radius (R) of Graft Copolymers

	HS Graft Copolymers			HC Graft Copolymers		
	HS-HPMA0	HS-HPMA7	HS-HPMA34	HC-HPMA0	HC-HPMA7	HC-HPMA34
%H	8.32±0.14	8.06±0.02	7.23±0.47	8.16±0.16	7.81±0.04	5.98±0.17
R (μm)	41.6	31.4	30.2	70.5	40.5	62.2
ρ (g/cm^3)	1.299±0.002	1.264±0.005	1.276±0.003	1.226±0.042	1.249±0.006	1.267±0.010
%CG	192	292	347	299	314	327
%GE	62.5	95.9	93.1	48.4	92.8	96.2
%G	121.4	—	—	259.2	—	—

the difficulty of determining the %G of products obtained using 7 and 34% EGDMA. This is again because of the high crosslinked network which prevents the action of medium during the hydrolysis process.

We can observe that the HC-HPMA graft copolymer has higher %G and lower %GE than the HS-HPMA graft copolymer. In previous works, we observed that a higher %G together with a lower %GE is associated with larger amounts of grafted chains.[13] Therefore, in this case, data would predict higher numbers of grafted PHPMA chains in HC than in HS. This same tendency is observed if we compare these values with those obtained on grafting MMA.[3] When using HPMA, the %G is higher than with MMA. A factor to take into account to explain these differences in percent grafting is the higher molecular weight of the HPMA monomer, but we should not ignore the higher reactivity of the HPMA.[14]

As a characteristic which will later influence the flowability, the density (ρ) of all the synthesized graft copolymers was determined (Table 1). Differences are not very noticeable.

The water absorption capacity of the graft copolymers was measured gravimetrically (%W=increase in weight after equilibrium absorption/weight of dry copolymer). All copolymers absorb more than 40% water without dissolving, so we can refer to them as hydrogels. However, it is well known that drug release from hydrophilic matrices is due to a combination of diffusion through the gel layer formed as the tablet periphery hydrates and of attrition of this gel layer. Despite the fact that release behavior based on the rheological properties of polymeric excipients is not already clearly defined,[15] rheological characterization will inform us about gel properties of our graft copolymers. Thus, together with the polymer viscosity measurement, we need to know the storage and loss moduli to determine if the graft copolymers show gel behavior and subsequently could act as a barrier to control the diffusion of the drug.

As we have commented in previous papers,[16] in order to carry out dynamic measurements, the viscoelastic zone where the shear stress shows linear behavior must be previously determined. Once determined, we observed that the storage modulus and the loss viscosity were independent of the shear stress. Therefore, we took a fixed value for this parameter to carry out the other rheological measurements. Figures 1 and 2 show flow curves of HS and HC, together with those of the corresponding grafted copolymers. Graft copolymerization of these substrates causes a big structural change and an enormous growth of the molecular weight, leading to products with a much higher viscosity. We can see an increase of the viscosity as the EGDMA content of the copolymers increases. An explanation for this may be the following: as the fraction of crosslinking monomer increases, the number of covalent bonds between chains increases too and subsequently, the ability of polymer chains to go in the flow direction decreases. This difficulty of the polymer to move is shown by a higher viscosity. The Ostwald equation applied to these data is collected in Table 2, where an n value of less than 1 corresponds to a pseudoplastic behavior in all cases. The more viscous the material, the higher the relationship between consistence index m and flowability index n, and so the gel layer formed will be firmer. Thus, in the light of the data collected in Table 2, we can deduce that

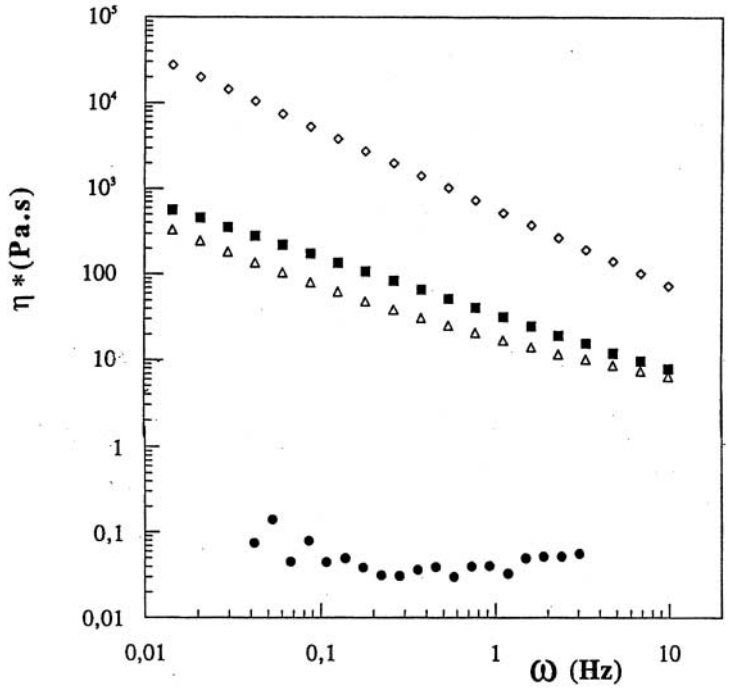

Figure 1. Flow curves of (●) HS and HS-HPMA graft copolymers: (△) HS-HPMA0, (■) HS-HPMA7, and (◇) HS-HPMA34, in water.

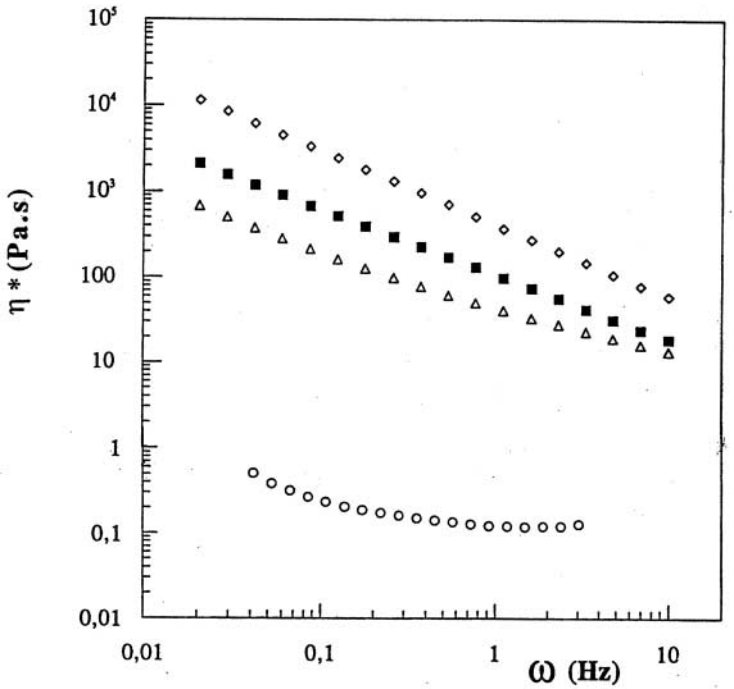

Figure 2. Flow curves of (○) HC and HC-HPMA graft copolymers: (△) HC-HPMA0, (■) HC-HPMA7, and (◇) HC-HPMA34, in water.

Table 2

Ostwald Equation Parameters from Flow Curves of HPMA Copolymers in Water at 37°C:[23] $\eta = m(\delta)^{n-1}$, Where η Is the Viscosity, δ Is the Shear Rate, m the Consistency Index, and n the Fluency Index

	HS-Derivatives			
	Unmodified HS	HS-HPMA0	HS-HPMA7	HS-HPMA34
m	0.028	19.78	35.08	593.19
n	0.693	0.389	0.344	0.093
	HC-Derivatives			
	Unmodified HC	HC-HPMA0	HC-HPMA7	HC-HPMA34
m	0.084	48.51	108.32	327
n	0.423	0.371	0.236	0.147

grafting modification of carbohydrates leads to the obtaining of polymers that are able to give more consistent gels.

To get a better understanding of the influence of chemical changes on the carbohydrates, viscoelasticity, oscillatory measurements were carried out. The results are presented in Figs. 3 and 4. The change in the behavior as a result of grafting is noteworthy. Non-grafted carbohydrates show a smaller storage modulus G' than loss modulus G'' at practically all frequency ranges. If $G'' > G'$ we can consider that we have a homogeneous and uniform liquid state, which means that HS and HC solutions show a "sol" behavior.[17] However, it should be noted that the HS shows an intersection point at high frequencies that can be regarded as a relaxation time of the entanglement network in the solution.[18]

Graft copolymers show an inversion of this behavior in both cases. Here, both HS and HC graft copolymers show $G' > G''$, and this difference is clearer as the EGDMA content increases, which means that obviously the elastic component becomes more important as the copolymer is more crosslinked but retaining the gel character in all frequency ranges.[18] This solid-like behavior where elastic and viscous moduli are slightly frequency-dependent is typical of "weak gels,"[19] and is more noticeable as the material is more crosslinked.

The above-mentioned results show these polymers as interesting materials for drug release formulations. However, as we mentioned before, if these materials are to be used in tablet formulations, it is desirable to also have good flowability and binding properties. If we take into account that hydrogels can absorb and retain large amounts of water in their amorphous portions when exposed to water vapor at various relative humidities, we must remember that this absorbed water can influence the flowability of the powder during the manufacturing process and storage.[20] It is assumed that the rate and amount of moisture sorption are dependent on the surface area of the powder. Therefore, the correlation of the moisture uptake values with the particle size and the particle size distribution of powders, as well as with the surface topography of the grafted polymers, is a very interesting aspect. In general, we can say that the moisture uptake of one product decreases as the particle size increases. Powders of lower particle size have a higher surface area, where larger amounts of water can be retained.

In order to relate size and chemical composition, all the products were fractionated. Furthermore, the moisture uptake of copolymer components was measured, showing that HS and HC, exposed at a relative humidity of 75.5% at room temperature, have a %H of 13.3% and 6.6% respectively, and PHPMA approximately 6.3%. Also, the particle size distribution of carbohydrates graft copolymers was calculated, and their corresponding average radii are collected in Table 1. The addition of HPMA to the HS leads to a drop of its moisture uptake, as we can expect in the light of the lower capacity of the HPMA. Taking into account that the average radius of the HS particles is 14.16 μm, the results are quite

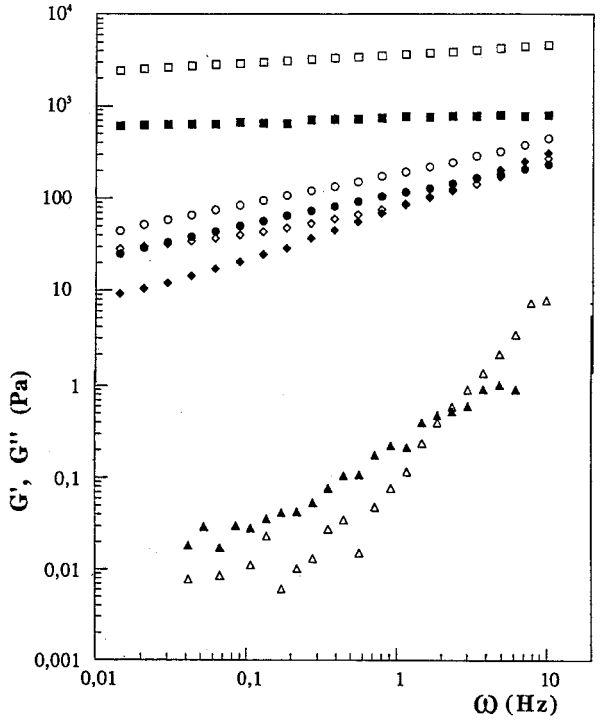

Figure 3. HS (△) storage modulus (G') and (▲) loss modulus (G''), and storage modulus of HS-HPMA graft copolymers: (◇) HS-HPMA0, (○) HS-HPMA7, and (□) HS-HPMA34, and loss modulus of HS-HPMA graft copolymers: (◆) HS-HPMA0, (●) HS-HPMA7, and (■) HS-HPMA34.

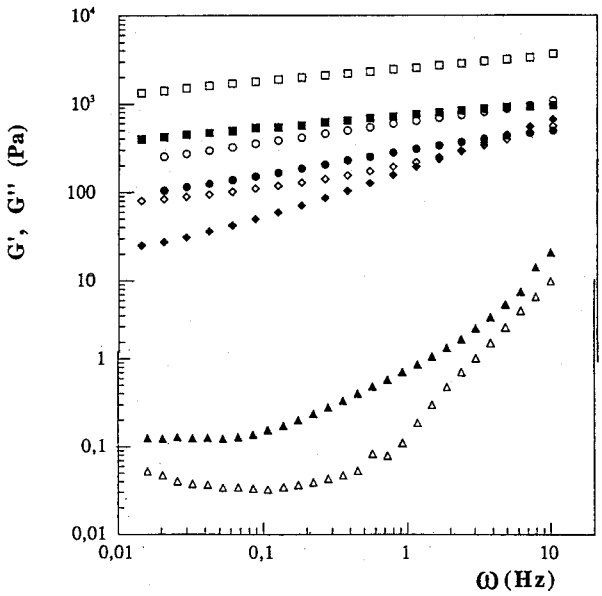

Figure 4. HC (△) storage modulus (G') and (▲) loss modulus (G''), and storage modulus of HC-HPMA graft copolymers: (◇) HC-HPMA0, (○) HC-HPMA7, and (□) HC-HPMA34, and loss modulus of HC-HPMA graft copolymers: (◆) HC-HPMA0, (●) HC-HPMA7, and (■) HC-HPMA34.

logical; that is, grafted copolymers are bigger than ungrafted carbohydrates, the more crosslinked copolymers being slightly smaller but more hydrophobic. Therefore, as the crosslinking agent content increases, the higher crude grafting compensates for size differences. By contrast, in the HC case, we observed a more unexpected effect. The average size of the HC particles is 81.75 μm, bigger than that of its grafted copolymers, probably due to the solution of carbohydrate chains before the grafting. In this case, the sizes of HC derivatives do not follow a linear behavior, but we can also say that differences in sizes compensate for hydrophobia. Nevertheless, in both cases, data show a slight decrease of the moisture uptake of grafted copolymers as the content of EGDMA—a more hydrophobic monomer—increases.

With these it is not possible to draw valuable conclusions about differences between both carbohydrate copolymers, which led us to use the SEM technique to learn about the influence of morphology. As we know, shape, surface, and particle aggregation influence compaction characteristics. So, the SEM images give us valuable information to relate to moisture uptake and hence to flowing but, also, valuable information to relate later to binding properties. Figures 5 and 6 show very different shapes and images of grafted particles. They look like single particles in all cases except for the HC-HPMA34 particles, which look cut. In the light of these photographs, the similar moisture uptake capacity of the more hydrophilic and lower sized HC copolymers than that of the HS copolymers could only be related to the clearly lower porosity of the latter.

Having characterized our products from a chemical and physical point of view, we went on to characterize them from the point of view of pharmaceutical technology, focussing on obtaining tablets from these powdery materials. First, the flow rate through an orifice (FR) was selected as an index to determine the flowability of powders. Before analyzing Table 3, we should point out the great differences observed between the structures of the six synthesized products. Thus, rather than making a comparison of the various graft copolymer powders, we found it more interesting

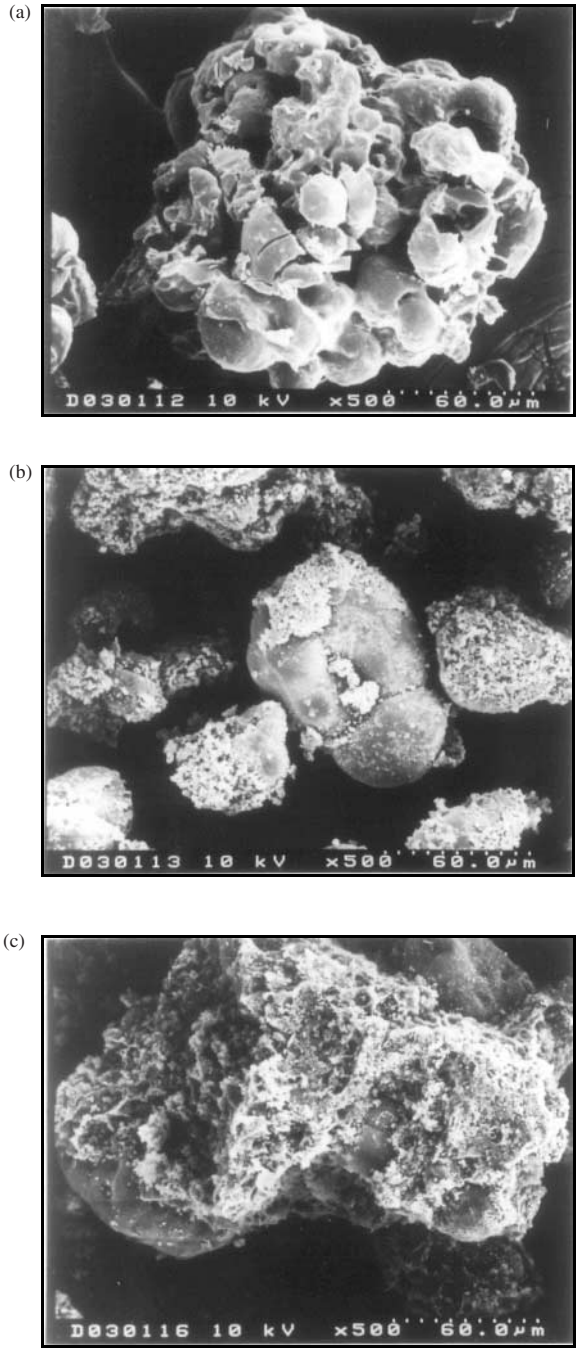

Figure 5. SEM fractographs of (a) HS-HPMA0 graft copolymer, (b) HS-HPMA7 graft copolymer, and (c) HS-HPMA34.

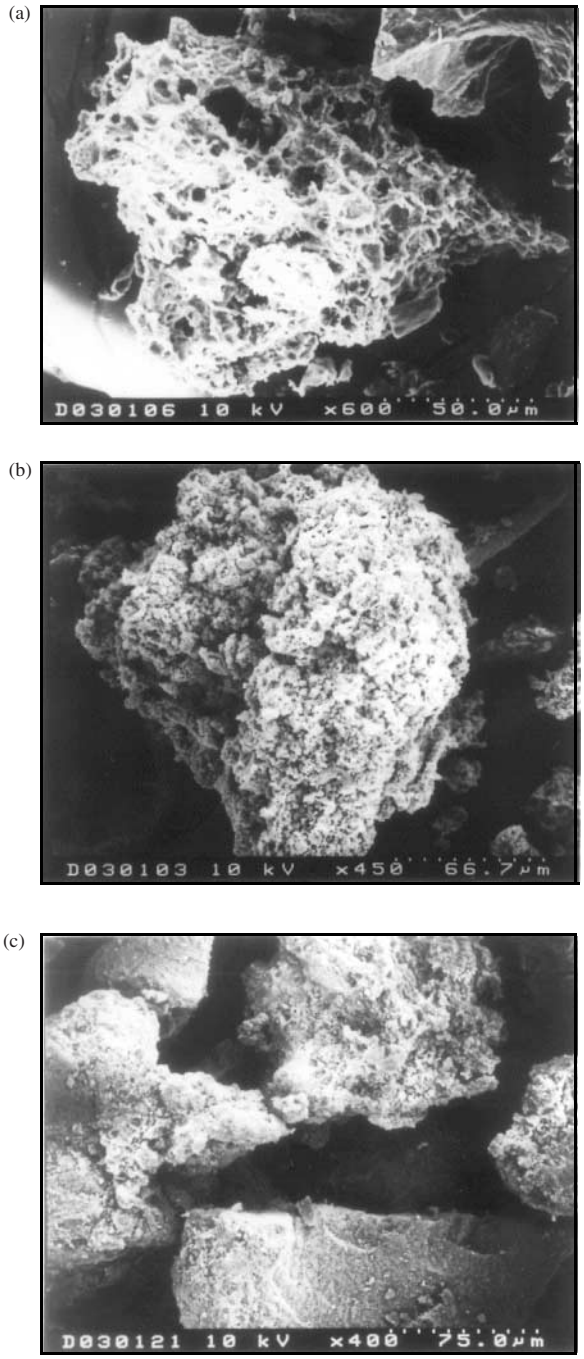

Figure 6. SEM fractographs of (a) HC-HPMA0 graft copolymer, (b) HC-HPMA7 graft copolymer, and (c) HC-HPMA34.

Table 3

Flow Properties of Polysaccharides and Their Graft Copolymers Involved in the Three Types of Formulation: (a) Grafted Copolymers Alone, (b) 75% Polymer + 25% Theophylline, and (c) 25% Polymer + 24% Theophylline + 50% Emcompress® + 1% Stearic Acid

	FR (g/sec)		
	a	b	c
HS	No flow	No flow	10.01±0.46
HS-HPMA0	24.51±2.99	No flow	7.66±0.22
HS-HPMA7	35.97±5.40	11.73±2.71	10.79±0.73
HS-HPMA34	No flow	No flow	31.99±2.95
HC	20.57±1.10	No flow	15.22±2.36
HC-HPMA0	25.25±2.10	5.22±0.18	10.34±1.31
HC-HPMA7	22.72±1.81	2.41±0.26	39.46±9.17
HC-HPMA34	21.02±6.27	No flow	35.17±18.82

to compare the flowability of the three formulations used in this work and previously described in the Experimental section. So, the more noteworthy conclusions that can be extracted from this table are:

- All graft copolymers, except HS-HPMA34, exhibit good FR because they are higher than 10 g/sec. Lack of fluidity observed in the HS-HPMA34 could probably be attributed to its higher percentage of small particles.[21] Therefore, we can say that five of the six products show good flow properties, which make them suitable for preparation of the formulations by direct compression.
- The addition of theophylline—b formulations—produces a clear drop in the flowability.
- The addition of excipients—c formulations—makes it possible to obtain good flow with all the polymers, including those that did not flow alone.

Afterwards, we made tablets in an instrumental excentric tablet press at 40 N. In the first stage, all the tablets were prepared with the copolymers alone—a formulations—without mixing with active ingredients or excipients. Copolymers showed an EF value (Table 4) lower than 750 N, as Bolhuis established for direct compression,[22] however HS-HPMA34 gave problems and did not allow tablets to be made. In this case, the lack of ability to compact is attributed to high crosslinking density, which means low polarity of particle surface and less particle–particle interaction.

Plasticity of HS grafted copolymers is greater than that of cellulosics, decreasing in both cases as the EGDMA content increases. When we applied a stress to a polymer, the macromolecular chains were displaced and the material deformed. If the bonds between chains are weak, they break and do not recover the initial state. But, if the material is crosslinked, the interchain bonds act as springs and the permanent deformation decreases. We can appreciate this behavior as the EGDMA content increases; since the higher the amount of crosslinking the lower the plasticity.

Both polysaccharide derivatives show a decreasing compactibility after copolymerization with EGDMA, indicating again that the crosslinks prevent the intermolecular bonding by particle–particle interaction, and this leads to a mechanical weakening of the tablet.

This same study applied to b formulations is also reflected in Table 4. Data of compressional properties of polymer–theophylline mixtures show that various formulations have values for EF higher than those of the polymers alone but all of them, except that of the HC-HPMA7, fulfilled the requirements for direct compression formulations.[23] Plasticity does not offer remarkable changes in relation to polymers alone. With respect to CP, we can say that theophylline slightly enhances this parameter.[24] This slight improvement could be attributed to the small particle size of the drug, which allows a better filling of the holes between polymer particles and prevents the stress concentration in the tablet pores.

In the last stage of this part of the work, we studied the compressional properties of the standard formulation proposed in this paper (Table 4). Here, all formulations fulfilled the Bolhuis and Lerk requirement[22] for direct compression excipients in relation to EF. However, the plasticity and

Table 4

Compression Parameters: Ejection Force (EF), Plasticity (Pl), Compactibility (CP) of Tablets Compressed at 40 N Crushing Strength, of (a) Graft Copolymers Alone, (b) 75% HPMA Polymer and 25% Theophylline, and (c) Standard Formulations with 25% HPMA Polymer[a]

	EF (N)			Pl (%)			CP		
	a	b	C	a	b	c	a	b	c
HS	26±3	116±12	298±59	87.22±1.34	88.59±0.04	91.2±0.99	7.07±0.36	11.39±0.69	10.05±0.30
HS-HPMA0	332±18	528±87	196±18	92.09±0.70	93.32±1.11	82.12±0.62	4.62±0.27	4.89±0.36	6.68±0.36
HS-HPMA7	749±27	527±20	456±15	90.22±0.53	88.68±1.39	82.75±0.82	4.42±0.12	6.54±0.08	5.66±0.23
HC-HPMA0	397±37	545±192	440±38	89.49±0.79	83.76±3.73	81.10±2.26	4.56±0.24	6.44±0.32	5.66±0.04
HC-HPMA7	219±111	1030±206	154±38	84.61±1.43	93.01±0.50	82.85±2.39	4.25±0.16	4.73±0.22	5.61±0.24
HC-HPMA34	414±144	390±71	412±125	82.51±1.44	79.32±2.42	88.30±1.65	3.70±0.12	4.80±0.09	4.95±0.18

[a]HS-HPMA34 and HC give problems in the compaction process.

Table 5

Tablet Properties: Coefficient of Weight Variation (CV), Friability (F), and Disintegration Time (DT) of (a) Graft Copolymers, (b) 75% Polymer + 25% Theophylline Formulations, and (c) 25% Polymer Standard Formulations[a]

	CV (%)			F (%)			DT (min)		
	a	b	c	a	b	c	a	b	c
HS	3.36	2.37	29.5	5.99	7.29	3.63	Instant	Instant	Instant
HS-HPMAL0	1.25	1.81	0.33	2.32	1.73	1.98	>30	>30	>30
HS-HPMAL7	1.21	1.56	2.33	3.23	2.39	2.92	2±1	Instant	Instant
HC-HPMAL0	2.86	1.24	1.96	5.63	3.13	3.08	2±1	Instant	Instant
HC-HPMAL7	1.20	0.98	1.14	2.60	3.83	2.30	Instant	Instant	Instant
HC-HPMAL34	0.92	—	3.03	4.57	—	3.34	Instant	—	Instant

[a]HS-HPMA34 and HC give problems in the compaction process of the polymer + drug formulations.

compactibility do not improve because of the high percentage and peculiar characteristics of Emcompress®. Comparing all the above data collected in Table 4 with compressional data of tablets made with MMA,[10] we can highlight the lower compactibility of powder from HPMA graft copolymers.

The next part of this work was the study of the most common tablet properties (Table 5). Every tablet passed the weight variation test. The CV values of the theophylline–polymer mixtures are lower as the crosslinking monomer content increases, although this behavior is not in accordance with the flow rate values.

Addition of theophylline decreases the friability with respect to polymers alone, except HS and HC-HPMA7 formulations, which only decrease with the addition of excipients. Friability values higher than 1%[23] were observed for all the polymers and in addition, the DT was practically instantaneous except for HS-HPMA0. Moreover, the addition of the model drug and excipients does not improve the DT, due to the insufficient consistency of the tablets with very high friability.

Although the HS-HPMA0 b and c formulation tablets seemed the only consistent ones, once tested under the dissolution test conditions, it was also possible to test HS-HPMA0 b formulation tablets from HC-HPMA0. Thus, only the graft copolymers without crosslinking monomer gave a measurable release.

Figures 7 and 8 show the profiles of release of the model drug from HS-HPMA0 and HC-HPMA0. A quick look at the plots suggests that tablets formulated with 75% graft copolymer could be used as controlled release forms, since in approximately 12 hr 60–80% of the model drug was dissolved. Both HS and HC copolymers showed a faster release rate

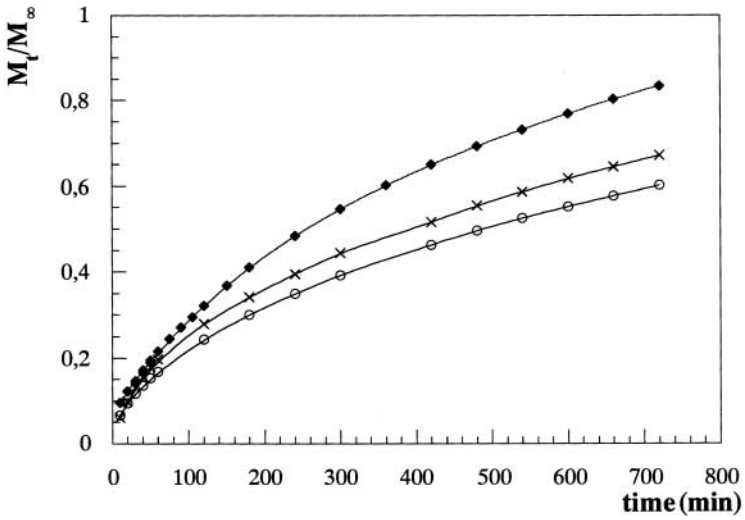

Figure 7. Theophylline fraction released from formulations with 25% theophylline and 75% HS-HPMA0 graft copolymer at 37°C: (◆) pH 1.5, (○) pH 5, and (×) pH 8.

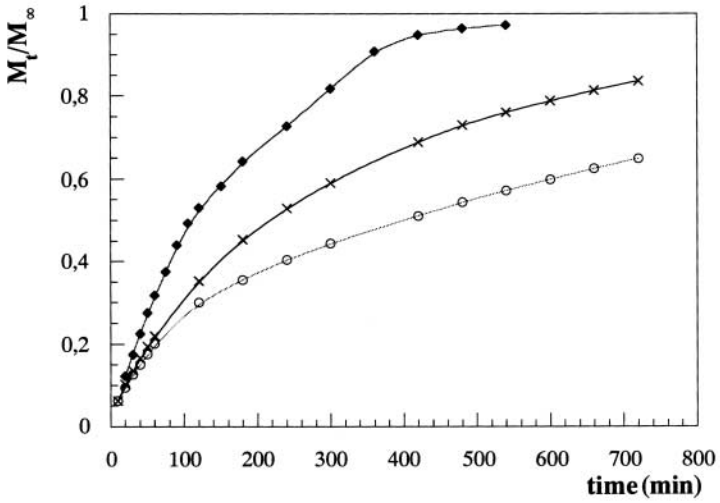

Figure 8. Theophylline fraction released from formulations with 25% theophylline and 75% HC-HPMA0 graft copolymer at 37°C: (◆) pH 1.5, (○) pH 5, and (×) pH 8, and HC-HPMA7 at (●) pH 5 and (▼) pH 8.

at pH 1.5. This sensitivity to pH is possibly due to lower water absorption, and hence lower swelling, at this pH.[25] This tendency is clearer for the HC-HPMA0 copolymers that release practically all the theophylline in less than 10 hr. At the three pH values, the release is faster from the grafted hydroxypropyl cellulose tablets, since at pH 8 the release at 700 min was approximately 80% and 65% at pH 5, and for the grafted hydroxypropyl starch tablets it was 65% at pH 8 and 60% at pH 5. When using the PMMA copolymers we observed a similar behavior too,[10] with slower release, since at the same time only approximately 50% of the drug was dissolved. Figure 9 shows that HS-HPMA0 standard tablets produce considerable worsening of the release.

As the HC-HPMA0 tablets showed a very short disintegration time, we considered the possibility of

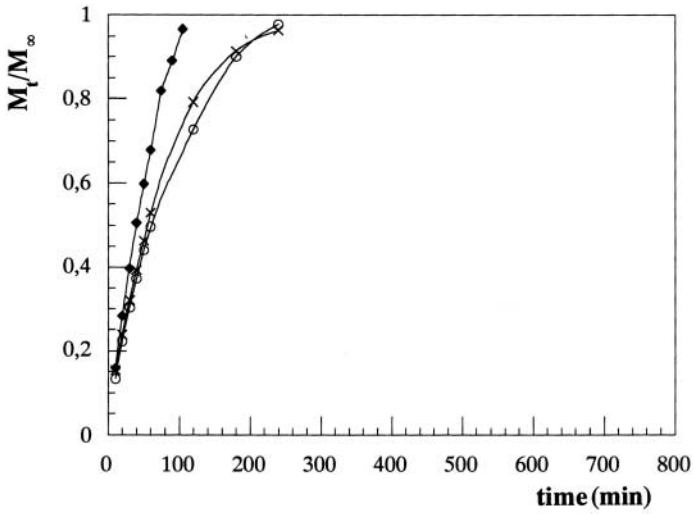

Figure 9. Theophylline fraction released from c formulations with 24% theophylline, 25% HS-HPMA0 graft copolymer, and 51% other excipients at 37°C: (◆) pH 1.5, (○) pH 5, and (×) pH 8.

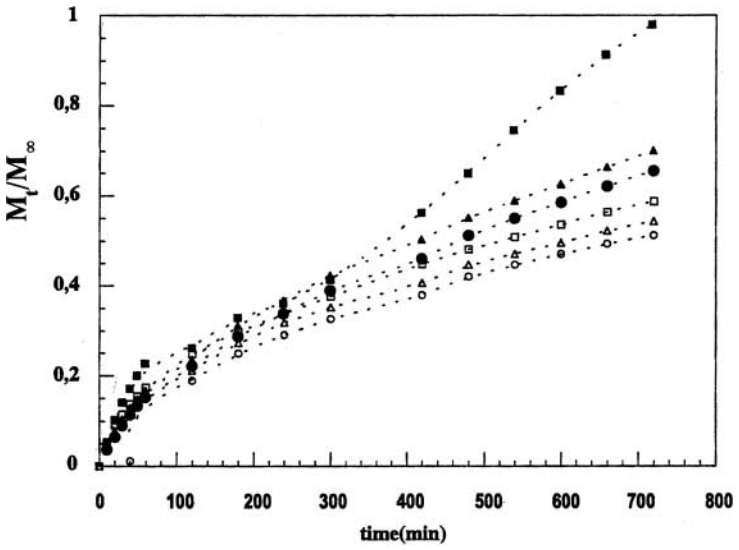

Figure 10. Theophylline fraction released from tablets of a crushing strengh 120 N at 37°C with 25% HS-HPMA0 graft copolymers: (□) pH 1.5, (○) pH 5, and (△) pH 8, and HC-HPMA0 graft copolymers: (■) pH 1.5, (●) pH 5, and (▲) pH 8.

obtaining a better release by formulating tablets of a higher crushing strength. To follow this study, we made two types of tablets: with 75% HS and HC graft copolymers at very high crushing strength (120 N). We then reached a stage where both the HS-HPMA0 and the HC-HPMA0 could give tablets with DT > 30 min. Figure 10 shows the plot of the release at the three pH values studied in this work. All of them, except for HC-HPMA0, follow a similar path. The different behavior of this polymer can be attributed to disintegration after 400 min in the most acid dissolution. In fact, the kinetic patterns of the release are not very different at this crushing strength, but a slower release and a slight decrease of the dissolved drug concentration are observed.

CONCLUSION

In conclusion, we think the percentage of crosslinking agent added might be too high to allow particle bonding for making tablets,[26] even when the direct compression excipient is incorporated in the formulation. Although no crosslinked polymer was suitable as a direct compression excipient, rheological studies suggest that the use of this kind of graft copolymer in a formulation could improve the controlled release properties. Further studies supporting this need to be performed before the use of these polymers in the industry.

Furthermore, non-crosslinked graft copolymers of HPMA on both HS and HC offer interesting characteristics as controlled release matrices. We observed that when excipients were added, performance (compressional and tablet parameters and dissolution tests) of the tablets was negatively affected. Therefore, we feel we can affirm that our graft copolymers can stand alone as an effective matrix for tablets designed for drug delivery systems.

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