Synthesis and Rheological Characterization of Graft Copolymers of Butyl and Hydroxyethyl Methacrylates on Starches

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ABSTRACT: To study the possibility of using some acrylic-grafted polysaccharides as matrix tablets, graft copolymers of butyl methacrylate and hydroxyethyl methacrylate on starch and on hydroxypropyl starch were synthesized. In this work, the effects of the different chemical compositions of the various synthesized graft copolymers on the hydrophilicity and rheological characteristics were examined. Water absorption values that ranged from 5 to 45% were obtained. Rheological testing determined with dispersions (5% w/w) in water showed that the graft copolymers formed weak gels of high viscosity. Moreover, the synthesized powders showed good flow and good compaction. These measurements pointed toward the possibility of their application for drug release. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 108: 4029–4037, 2008

Key words: drug delivery systems; graft copolymers; polysaccharides; rheology

INTRODUCTION

Starch (S) has proved to be a very interesting raw material for many technological applications. It is a natural renewable polysaccharide with two particularly noteworthy properties: biodegradability and high hydrophilicity. Moreover, it can be chemically and physically transformed in a number of interesting ways that open up a wide field of application. One of these transformations would be grafting with synthetic polymers, which offers the potential to produce a large variety of useful materials for applications in areas such as agriculture,[1] packaging,[2] water treatment,[3] textiles,[4] and drug release.[5] The choice of the monomer, the grafting method, and the carbohydrate backbone are key factors that directly affect the finished product.

In our research, we sought to obtain powdery materials that could be compacted for use in tablets. Once compacted into matrix tablets, these materials should absorb water and thus be apt to release a model drug. Hydrophilic polymers are the main vehicles used for the preparation of such tablets,[6] so the use of carbohydrates for the graft backbone can be considered a good selection. Moreover, poly(butyl methacrylate) (PBMA) is a polymer that shows a low glass-transition temperature, allowing deformation and compaction of the grafted particles, which facilitate the formation of a matrix. However, the hydrophobic character of these acrylic branches must be taken into account. At the far end of the hydrophilic spectrum, there is another acrylic polymer, that is, poly(hydroxyethyl methacrylate) (PHEMA), which shows a low glass-transition temperature after swelling in an aqueous medium.[7]

To study the possibilities of acrylic-grafted polysaccharides as matrix tablets and taking into account the results obtained in previous works,[5,8] we decided to synthesize graft copolymers of butyl methacrylate (BMA) and hydroxyethyl methacrylate (HEMA) on S and on hydroxypropyl starch (HS). Because the rheological behavior of dispersions is a main factor in the development of drug-release applications, a study of the rheological parameters was also performed. Thus, the aim of this work was to synthesize various graft copolymers with a range of hydrophilicities and to examine the effects of the different chemical compositions on the rheological characteristics to test for their eventual application to drug release. The drug-release tests will give rise to another article.

EXPERIMENTAL

Materials

In this study, two different types of S were used: potato S and HS (Avebe, Veendam, the Netherlands).

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The monomers, BMA and HEMA (Merck), were purified by distillation under previously described conditions.[9] The initiator was ceric ammonium nitrate (Fluka, Milano, Italy), and it was used as a 0.1*M* solution in 1*N* nitric acid.

All the other products were reagent-grade or equivalent.

Synthesis of the graft copolymers

The synthesis of BMA–S and BMA–HS was carried out as previously described.[9] The carbohydrate (40 g, 0.072 g/mL) was dispersed in 550 mL of double-distilled water in a three-necked flask. The dispersion was purged by the infiltration of purified nitrogen for 30 min, and the temperature was maintained at 30°C. BMA monomer (0.8389 mol, 134 mL) and, 15 min later, a Ce(IV) initiator solution (0.005 mol, 50 mL) were added. Grafting was allowed to proceed for 4 h at 30°C with continuous mechanical stirring under a nitrogen atmosphere.

For the synthesis of HEMA–S and HEMA–HS, a more dilute reaction medium was necessary because of the rapid gelification of the process that impeded constant stirring. Thus, 4 g (0.0069 g/mL) of carbohydrate was dispersed in 580 mL of double-distilled water, and after water deoxygenation, 12.2 mL (0.096 mol) of HEMA and 20 mL (0.002 mol) of the initiator solution were added as in the previous case.

The obtained products were filtered *in vacuo* and washed with a diluted nitric acid solution and water. Afterwards, the reaction products were recovered and freeze-dried in a lyophilization apparatus for 48 h at 70 mTorr and −50°C, and loose, white powders were obtained.

To calculate the copolymerization process yields, a portion of each reaction product was subjected to the following: first, ungrafted carbohydrate was removed by extraction with a 0.5*N* NaOH solution with stirring for 2 h. The solid was filtered, washed with water, and dried before it was introduced into a Soxhlet apparatus to remove the nongrafted homopolymer with tetrahydrofuran and ethanol as solvents. Finally, the pure grafted acrylic chains were isolated from the carbohydrate by acid hydrolysis with 1*N* hydrochloric acid for 6 h.

Chemical characterization

Reaction yields

The following parameters were calculated: percent grafting efficiency (%GE), percent grafting (%G), crude grafting (%CG), and total conversion (%CT)[10]:

$$\%GE = 100 \times (\text{Total weight of the graft copolymer}/\text{Total weight of the polymer})$$

$$\%G = 100 \times (\text{Total weight of the grafted acrylic polymer}/\text{Total weight of the grafted carbohydrate})$$

$$\%CG = 100 \times (\text{Total weight of the total acrylic polymer}/\text{Total weight of the carbohydrate})$$

$$\%CT = 100 \times (\text{Total weight of the total acrylic polymer}/\text{Total weight of the added monomer})$$

NMR spectroscopy

^{13}C-NMR spectra measurements were recorded on a Bruker (Kalkar, Germany) 300-MHz FT-NMR spectrophotometer at 20–25°C. The graft copolymers' spectra were obtained after swelling of the sample until a homogeneous gel was obtained. A mixture of deuterated dimethyl sulfoxide and deuterated pyridine solvents was used to give a concentration of 100 mg/mL with tetramethylsilane as an internal reference.

Characterization of the powders

Particle size distribution

First, the powders were passed through a 500-μm mesh to remove excessively coarse granules. Particles smaller than 25 μm were also removed. Afterwards, the particle size distribution was measured with an optic microscope (Leitz Aristomet, Leica Instruments, Wetzlar, Germany). A small portion of the powder was placed and dispersed between microscope slides. More than 400 particles were analyzed, and a statistical analysis of the maximum diameter distribution was performed with specific software (Origin 5.1, Barcelona, Spain), which operated by the conversion of the irregularly shaped particles into spherical analog particles.

Water absorption

To study the hydration capacity of the new copolymers, 500 mg of graft copolymer powders was compressed into tablets at a fixed crushing strength (4 kp) and placed in double-distilled water at 37°C.

The water uptake capacity was determined gravimetrically. The equilibrium water content of the hydrophilic matrices was measured as the mass change due to absorption: equilibrium water content (%) = $100(W_S - W_D)/W_S$, where W_S and W_D are the weights of the swollen matrix and dried matrix, respectively.[11]

Viscometry

The viscosity of aqueous dispersions (4% w/w) of the respective graft copolymers in double-distilled water

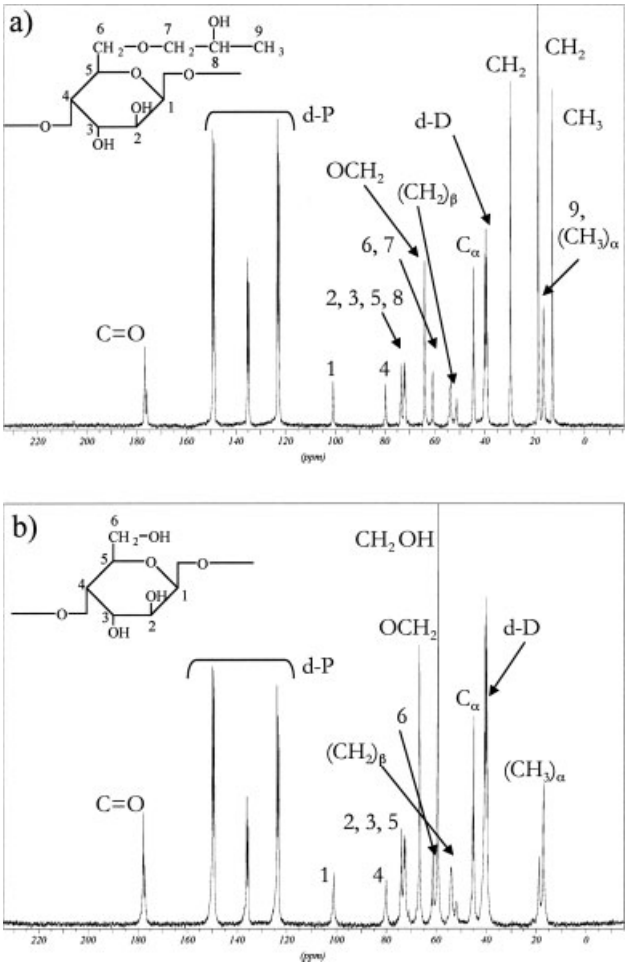

Figure 1 ^{13}C-NMR spectra of the graft copolymers in deuterated pyridine (*d*-P) and deuterated dimethyl sulfoxide (*d*-D): (a) HS–BMA and (b) S–HEMA. Peaks marked with only a number correspond to a glucopyranose unit. Acrylic monomer peaks are marked with the corresponding carbon group.

was measured in a Physica Rheolab (Stuttgar, Germany) MC100 viscoelastometer with a cylindrical coaxial geometry at 37°C. The rest time before running checks was 5 min.

Surface morphology

The morphology of the particles and matrices was studied with a Hitachi (Berkshire, UK) S-2700 scanning electron microscope with an acceleration voltage of 15 kV. The surface of powder particles was previously gilded.

Flow properties of the powders

The flow rate of mixtures was measured with a data acquisition flowmeter system[12] using a glass funnel as the vessel. A balance with an interface connected to a personnel computer (IBM-compatible) constituted the whole system. For data acquisition, graphics, and calculations, a software program was used.

Preliminary *in vitro* dissolution tests

A dissolution test was performed with copolymer tablets at 37°C and pH 6.8 in a vessel provided with a paddle that operated at 60 rpm. In the paddle assembly, the tablets were introduced in a basket to prevent their floating. The volume of the dissolution medium was 900 mL.

Procaine hydrochloride (Pr; Sigma–Aldrich, Munich, Germany) was used as a highly soluble model drug. The concentration of the drug delivered was determined by ultraviolet–visible spectrophotometry at the maximum absorbance (291 nm). Each data point was the average of six individual measurements. In all cases, the relative statistical deviation was less than 3%.

RESULTS AND DISCUSSION

As in previous studies,[13] we used ^{13}C-NMR spectroscopy to observe the formation of graft copolymers. Thus, the spectra were recorded after the removal of the ungrafted carbohydrates and acrylic homopolymers with the appropriate solvents. We selected the spectra of HS–BMA and S–HEMA (Fig. 1) as examples of the results obtained. In these, we can distinguish the signals attributed to the carbons of the glucopyranose unit of both carbohydrates and polymethacrylates. Chemical shifts are quoted in parts per million with respect to tetramethylsilane at 0 ppm, and the assignments are indicated on each peak. Thus, in view of the spectra, ^{13}C-NMR spectroscopy confirms the fact that graft copolymerization took place.

The reaction yield parameters of the grafted carbohydrates are listed in Table I. The obtained results are not unlike others obtained under similar condi-

TABLE I
Yields for the Graft Copolymerization of BMA and HEMA onto S and HS

	%GE	%G	%CT	%CG
HS–BMA	74.5 ± 3.1	195.2 ± 7.0	86.3 ± 5.3	386.5 ± 6.5
S–BMA	49.7 ± 0.4	224.1 ± 5.0	75.9 ± 14.4	300.0 ± 15.0
HS–HEMA	98.1 ± 0.4	312.1 ± 4.0	91.2 ± 2.6	365.0 ± 5.0
S–HEMA	99.9 ± 0.1	228.2 ± 5.1	66.1 ± 2.4	290.0 ± 4.2

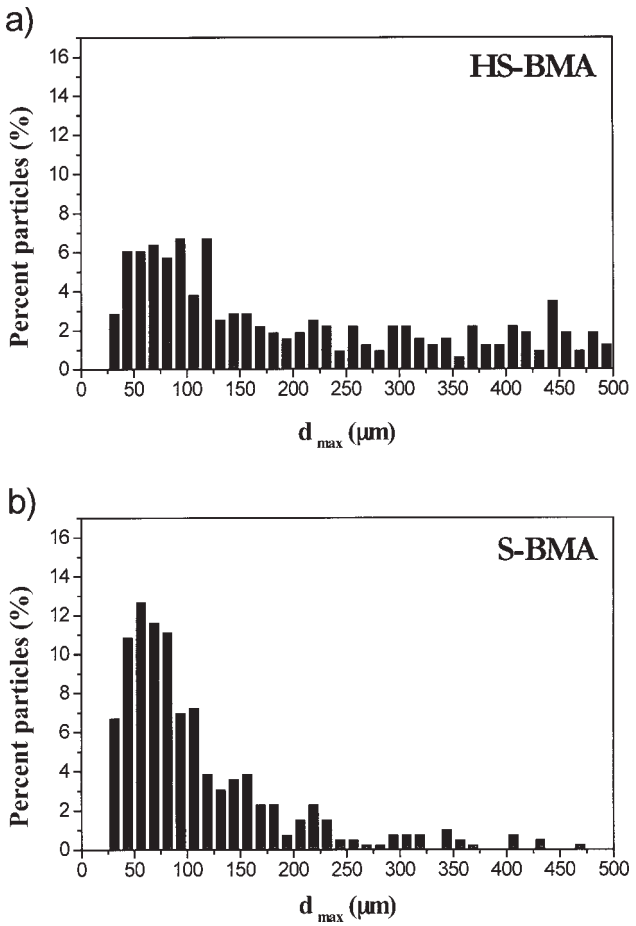

Figure 2 Particle size distribution of BMA graft copolymers: (a) HS–BMA and (b) S–BMA.

tions.[14,15] However, we would first like to highlight the very high values of %GE shown by the HEMA copolymers, which can be attributed to the crosslinking of this monomer during polymerization. Although the HEMA monomer is purified, small amounts of a difunctional monomer are usually formed, and this leads to a small amount of crosslinking as the monomer polymerization progresses.[16] This makes it difficult to remove the homopolymer by dissolution, giving rise to high values of %GE. On the contrary, BMA copolymers showed low %GE values, which in this case were attributed to the low solubility of this monomer in the reaction medium and to its large size. Both factors render difficult the entrance of the monomer into the carbohydrate structure and favor homopolymerization. Second, in the case of %CT, the low values obtained in the S–HEMA case can be attributed to the fact that it is difficult for the monomer to reach the radical side of the complex structure of the carbohydrate because of its large size. However, this does not occur when the monomer is grafted onto HS. We must remember that S predominantly consists of long chains of glucopyranose units linked together. Because of their linearity and mobility and the presence of hydroxyl groups, these chains have a tendency to orient themselves in a parallel fashion, which gives rise to a helicoidal structure. This close approach permits hydrogen bonding between hydroxyls on adjacent polymers forming a close structure.[17] The partial replacement of hydroxyl groups of S by the bulkier hydroxypropyl groups leads to a reduction in its hydrogen bonding ability and a less organized structure. This fact and the high solubility of HEMA in distilled water facilitate the attack of the monomer.[18] We can relate this explanation to the behavior of BMA. In this case, %CT increases with the formation of a high amount of the homopolymer.

The %G values are very similar, with the exception again of that of the HS–HEMA copolymer, which is clearly the highest. The affinity of HEMA to HS is probably higher than that of hydrophobic BMA and even higher than the affinity between HEMA and S. In previous works, we studied the influence of the carbohydrate structure in grafting results, and we observed that the chain arrangement clearly influences the grafting yield.[19] In the same way, we observed the strong influence of the chemical nature of the monomer.[3,10]

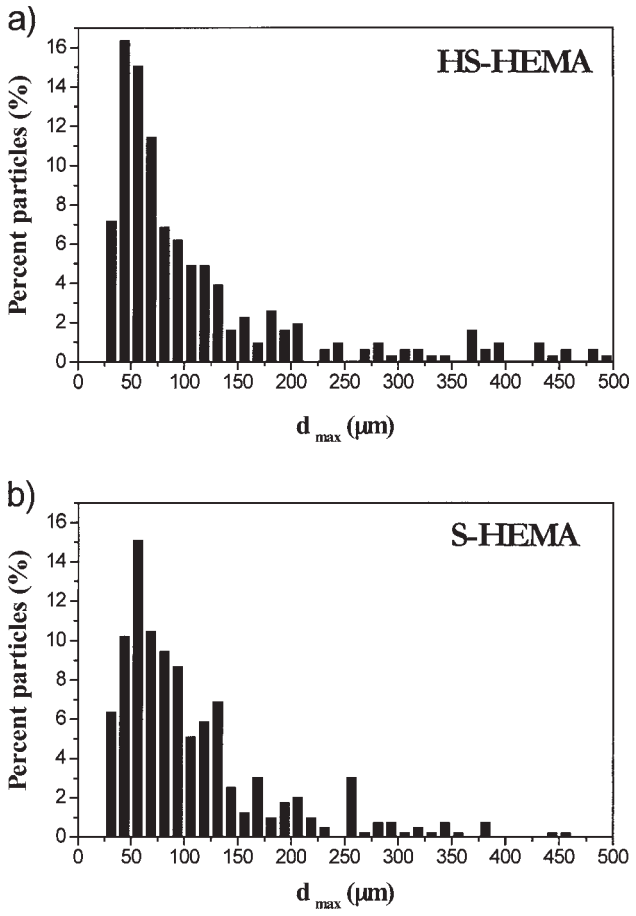

Figure 3 Particle size distribution of HEMA graft copolymers: (a) HS–HEMA and (b) S–HEMA.

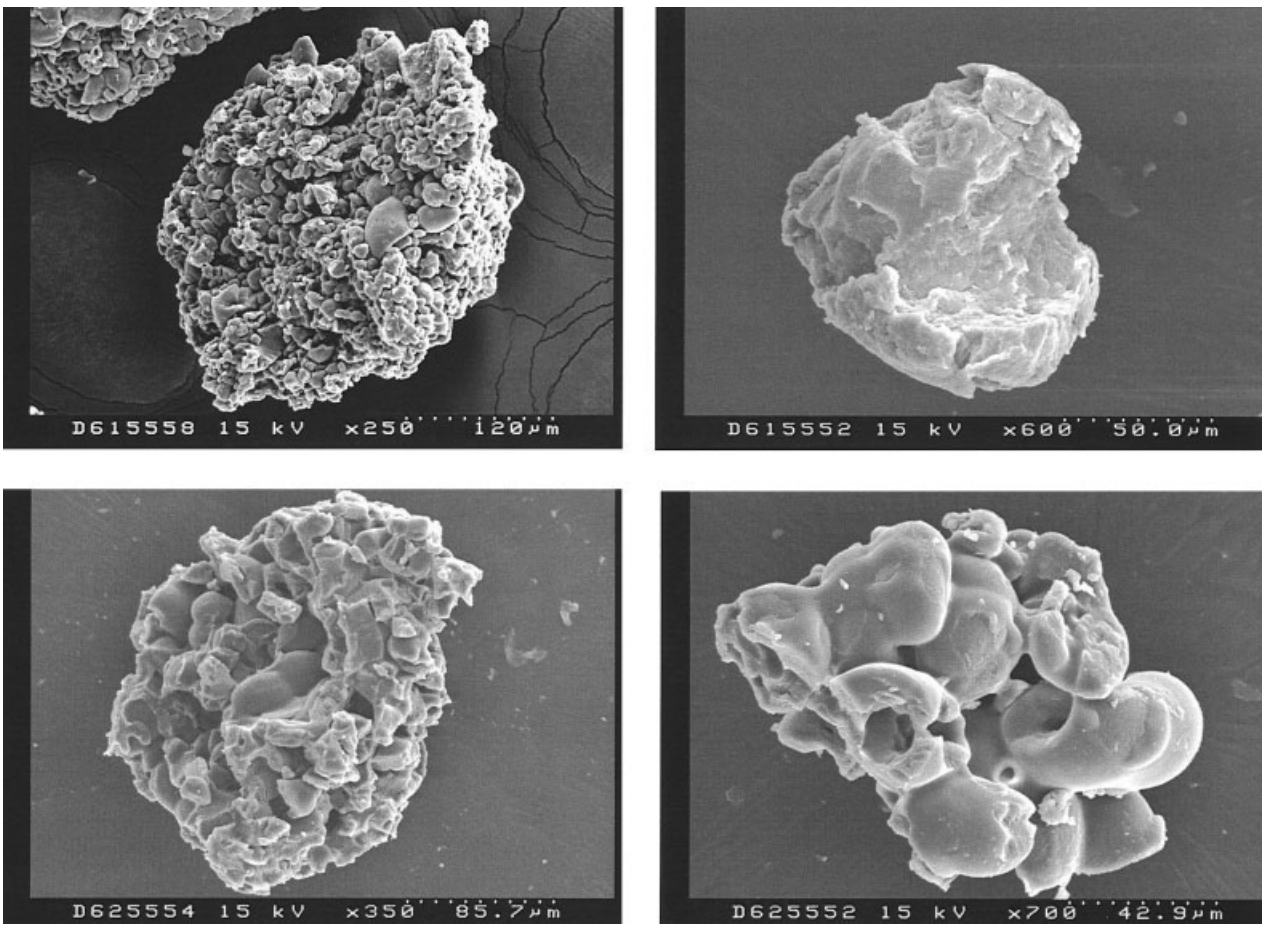

Figure 4 SEM micrographs of BMA graft copolymers HS–BMA (top) and S–BMA (bottom): whole particle (left) and cut particle (right).

The study of the particle size distribution of each copolymer (Figs. 2 and 3) showed higher percentages of big particles of HS–BMA than in the other cases. The rest of the distributions presented a Gaussian shape. The particle sizes of both HEMA copolymer powders were very similar, probably because of the crosslinking produced during the copolymerization process. These differences can also be appreciated in the photographs obtained with scanning electron microscopy (SEM; Figs. 4 and 5). In these pictures, we can also see the high particle massing of the BMA graft copolymers. Furthermore, the view of the cut particles shows that the grafting onto natural S produces hollows, but the grafting onto modified S gives rise to compact particles. Once again, the small modification of S when transformed into HS, which is due to the hydroxypropyl group introduced into the glucopyranose unit and the disruption of the native granular structure during the modification reaction, probably explains the enhanced accessibility of the monomers to the polysaccharide chains inside the granule.

Anticipating the application of these products in the pharmaceutical area to obtain compressed tablets in which the polymer acts as a matrix that controls the release of drugs, we characterized the graft copolymers first by means of two determinations: the absorption capacity of water and the rheological behavior of the dispersions in water. It must be taken into account that liquid penetration into the matrix is the rate-limiting step for sustaining the release of the drug in such systems. It is well known that hydrophobic materials are potentially erodible and control the release of the drug through pore diffusion and erosion. However, polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, do not disintegrate but immediately after hydration develop a highly viscous gelatinous surface barrier that controls the liquid penetration into the matrix and the drug release from it.[20]

The water absorption capacity of the graft copolymers was measured gravimetrically. Figure 6 shows the kinetic plots of absorption of grafted and ungrafted carbohydrates. In every case, the steady state was reached before 1 h of the test. First of all, we must mention that the highest capacity of HS to absorb water, higher than that of S, is due to the breaking of hydrogen bonding because of the chemi-

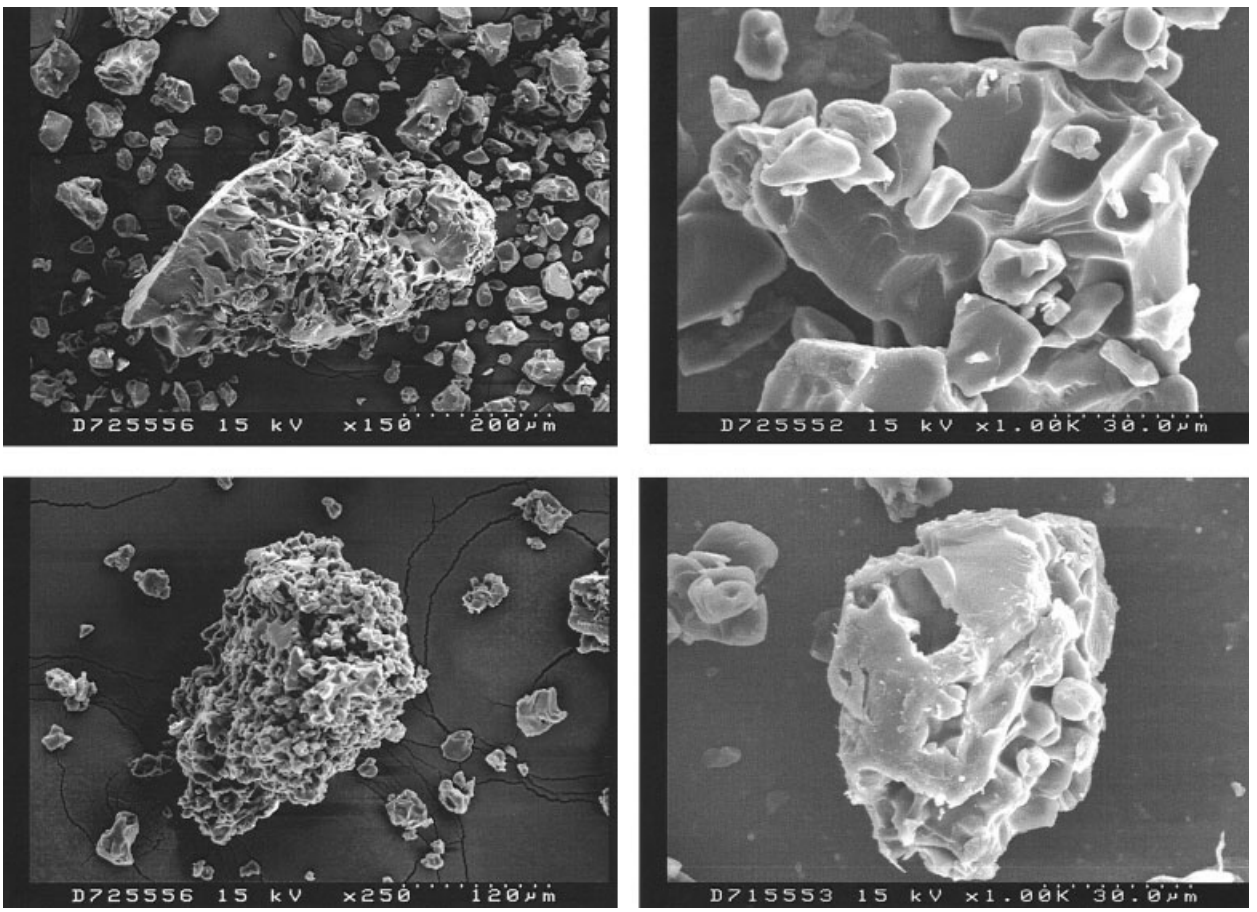

Figure 5 SEM micrographs of HEMA graft copolymers HS–HEMA (top) and S–HEMA (bottom): whole particle (left) and cut particle (right).

cal modification.[17] In the case of BMA, the grafting on both carbohydrates produces different absorption capacities, which are lower than those of the ungrafted S. However, the HEMA grafting gives products with very high hydrophilicity, which offsets the differences between both polysaccharides and offers more hydrophilic materials than S. Although these measurements clearly show the influence of grafting a hydrophobic polymer such as PBMA or a hydrophilic one such as PHEMA, we cannot classify BMA copolymers as hydrophobic because they show values of water absorption between 5 and 25%.

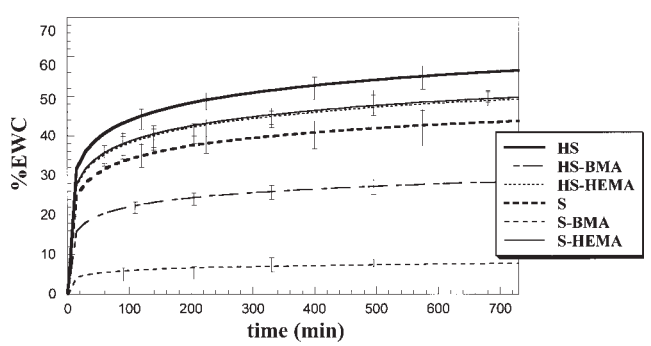

Figure 6 Equilibrium water uptake (EWC) of graft copolymers and carbohydrates in double-distilled water versus time at 37°C.

As we have demonstrated in previous articles,[5] rheological characterization informs us about the gel properties of our graft copolymers. Thus, together with the polymer viscosity measurements, we need to know the storage (G') and loss moduli (G'') to determine whether the graft copolymers form gels that could act as barriers to control the diffusion of the drug. To carry out dynamic measurements, a viscoelastic zone in which the shear stress shows a linear behavior had to be detected previously. Once we determined this, in our case, we verified that G' and the loss viscosity were independent of the shear stress. Therefore, we took a fixed value of this parameter to carry out the other rheological measurements. The flow curves of the grafted copolymers (Fig. 7) show the evolution of the complex viscosity (η^*) versus the frequency. All the products showed a high η^* value. Graft copolymerization involves a huge structural change and an enormous increase in the molecular weight, and this leads to products of very high viscosity as a result of the size of the flow

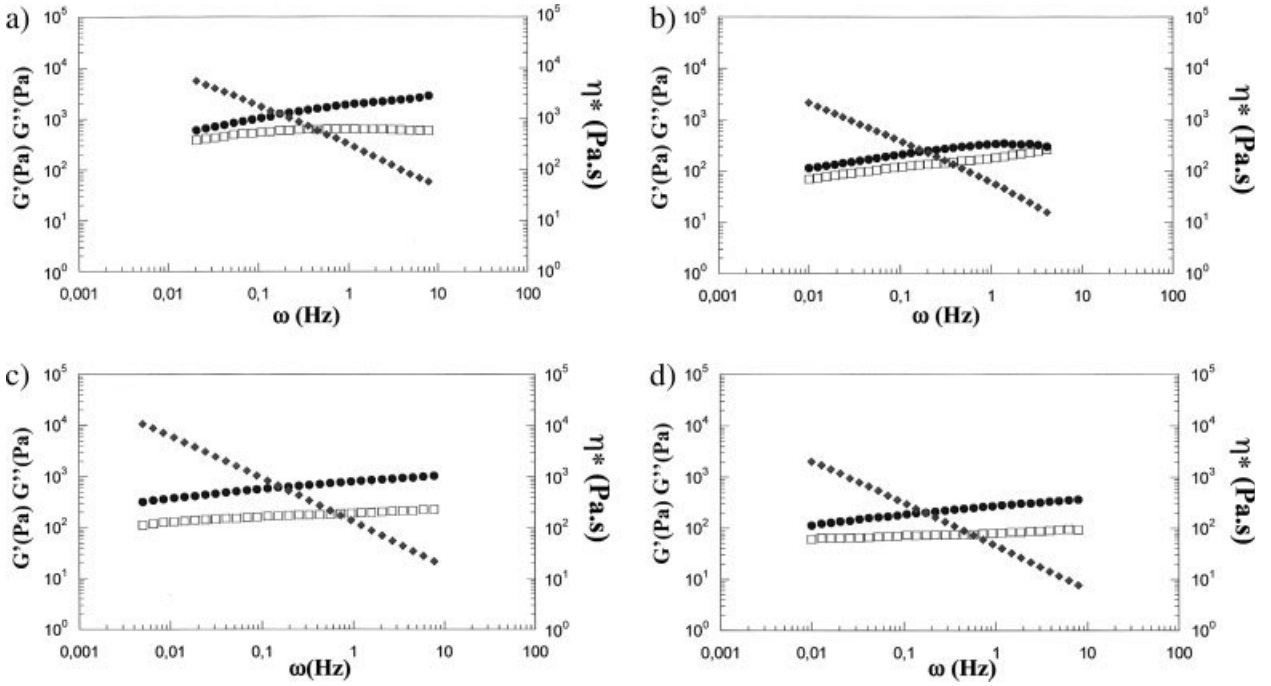

Figure 7 Frequency (ω) sweeps for graft copolymers HS–BMA (a), S–BMA (b), HS–HEMA (c), and S–HEMA (d) at 37°C under linear viscoelastic conditions: (◆) η*, (●) G', and (□) G''.

unit. However, we found no direct relationship between the water adsorption capacity and viscosity. We must take into account that this kind of graft copolymer has a hybrid structure formed by the hydrophilic carbohydrate and a cover of acrylic branches. These branches are highly hydrophobic in the case of PBMA, and the opposite is true in the case of PHEMA. Moreover, branches are bonded to the HS structure more deeply than to the S molecule. Therefore, the viscosity will be related either to the particle size and branch compaction or to the swelling. All these factors mean that the HS graft copolymers show the highest viscosities, and PBMA grafts increase the viscosity more than PHEMA chains.

Figure 7 also shows the dependence of G' and G'' on the angular frequency of aqueous dispersions of the graft copolymers. In cases a and b, it seems that just before the detected frequency region, G' becomes higher than G''. This indicates that there is a transition region to the gel state. Thus, in the four cases, the frequency-dependent curve of G' becomes almost parallel to or even coincides with that of G'' over a wide frequency range. In view of the values of G' and G'', although all the copolymers showed gel behavior ($G' > G''$), we have to say that all the copolymers also showed a slight frequency dependence in the entire range of frequencies studied. This solid-like behavior in which elastic and viscous moduli are slightly frequency-dependent is typical of weak gels.[21] In this case, they can be classified as viscoelastic gels of low crosslinking density attributed mainly to hydrogen bonding and, in the case of PHEMA graft copolymers, to a few covalent bonds.

Thus, our physical–chemical characterizations indicate that the hydrophilia and viscosity should be adequate to obtain a polymeric matrix capable of performing sustained drug release. Once these tests have been carried out, technological characterization becomes necessary.

An important pharmaceutical technological requirement in industry before a powder is accepted for manufacture is good flow. Moreover, the powder must be compacted to form the matrix; hence, powder particles must group together. These qualities can be modified by the use of additives called excipients. However, if the powder itself fulfils these requirements, as occurs with all these products, subsequent additions can be avoided. A suitable flow rate is considered to be over 10 g/s.[11] In this case, the four copolymers synthesized showed a flow rate that was higher than that required.

The compaction was evaluated by means of SEM (Fig. 8). We made the micrographs from the broken tablets. We observed that the shape of the whole particles could not be distinguished and that all the pores came from the union between the irregular masses of the particle surface. Here, the more compact structure seems to be that of HS–HEMA. The others, despite the presence of small gaps, also presented good compaction.

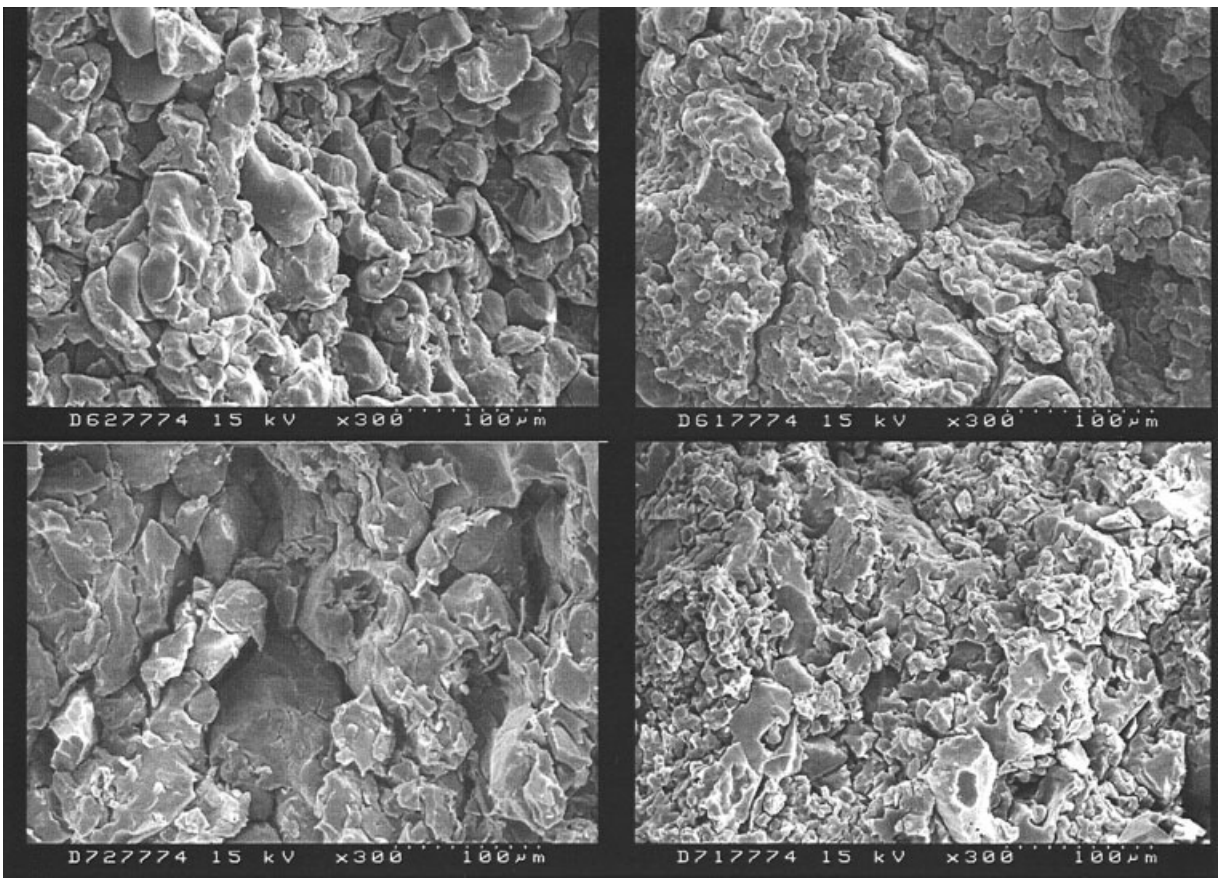

Figure 8 SEM micrographs of broken tablets of compacted graft copolymer particles: HS–BMA (left top), S–BMA (right top), HS–HEMA (left bottom), and S–HEMA (right bottom).

To prove the ability of such graft copolymers to be used in drug delivery systems, a dissolution test[8] of Pr from tablets formulated by compression (8-kp crushing strength) of 75% (w/w) copolymer and 25% (w/w) drug was carried out. Figure 9 shows the release of Pr from the HS graft copolymers obtained in this work and from others obtained in previous works.[5,8] In all the cases, a sustained release of Pr is shown. The release is represented as M_t/M_∞ vs. time, where M is the fraction of drug release up to time t (the drud loading was considered as M_∞). The changes derived from the structural differences of the copolymers are the most important finding, and a more in-depth study will be carried out.

CONCLUSIONS

The choice of BMA and HEMA for grafting onto S gave rise to low- and high-hydrophilicity polymers. The products were obtained as powders that could be compacted to form matrix tablets. The dispersions in water of graft copolymer particles showed high viscosity and gel behavior. These results allow us to say that all the products fulfill the necessary conditions for good control of drug release. The balance of hydrophilia and hydrophobia of each graft copolymer would condition the choice of the drug. A preliminary test shows the ability of these products to perform as sustained-release matrices. Further research using model drugs of different water solubilities is necessary.

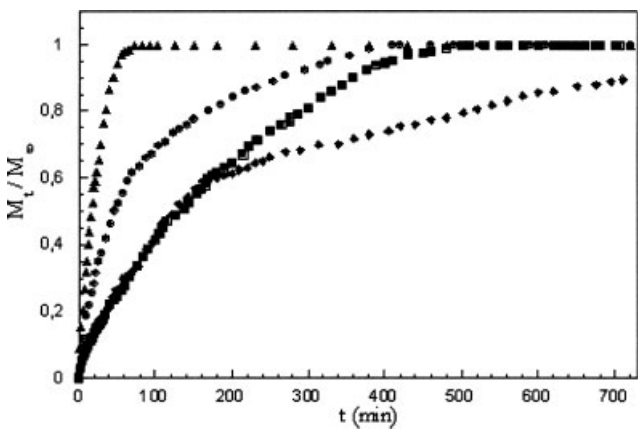

Figure 9 Pr fraction (M_t/M_∞) released from tablets formulated with 75% (w/w) copolymer: (▲) HS–MMA, (●) HS–EMA, (■) HS–BMA, and (◆) HS–HEMA.

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