Ethyl Methacrylate Grafted on Two Starches as Polymeric Matrices for Drug Delivery

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ABSTRACT: The use of copolymers grafted on starch for controlled-release technology is an interesting proposal, since a modification of a natural polymer is more suitable than synthetic polymers because of its biocompatibility and biodegradability. The aim of this paper is to synthesize acrylic polymers grafted on carbohydrates to investigate the release kinetic of different solubility drugs from polymeric matrix systems and to observe the effect of grafted copolymers and drug solubility on the release mechanism. Copolymer variables such as carbohydrate content, stereoregularity of grafted chains, particle size, morphology, sensitivity to hydration, and rheological properties are discussed. Tablets were prepared by direct compression of the graft copolymer and drug. The drugs' release in vitro kinetics was studied by dissolution testing. Drug release from tablets depends on polymer matrix, polymer content, drug, and pH. An increase in drug solubility results in an increase in the rate of dissolution, as in the case of a poor hydrophilic matrix.
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Key words: graft copolymers; polysaccharides; drug delivery systems; matrix

INTRODUCTION

Diffusion and relaxation processes in polymers have been widely studied.[1,2] Today, it is well known that when a solid polymer is brought into contact with a penetrating liquid or vapor, these diffuse into the polymer and the polymer swells.[3] Diffusion involves migration of the small molecules into pre-existing or dynamically formed spaces between polymer chains. Swelling involves large-scale segmental motion, resulting in an increased distance of separation between polymer molecules. As a result of this behavior, the embedding of a drug into an inert porous polymeric matrix was proposed 40 years ago[4] as a technique to obtain controlled release. Since then, the use of drugs incorporated in a polymer matrix to achieve controlled-release dosage forms has been the focus of increasing attention in drug delivery research.

For many drugs, the optimal therapeutic response is only observed when adequate blood levels are attained and maintained with minimal fluctuations. Drug delivery systems work to develop systems to obtain drug delivery at a desirable rate and time of release. Furthermore, sustained release has been developed and commercialized, mainly for the oral administration of some drugs because they offer more consistent blood levels.[5]

The development of improved drug release systems is strictly dependent on the selection of an appropriate carrier capable of controlling delivery. Responsive polymers, in particular hydrophilic polymers, are promising new versatile carriers for the preparation of oral controlled drug delivery systems.[6,7] Nowadays, the majority of oral drug delivery systems are still matrix based. These matrices are swellable and are developed by compression of a hydrophilic polymer and a drug. Their success is linked to polymers, which respond to the presence of water or biological fluids and can change their structure to form a gel layer enabling drug-controlled delivery from the matrix throughout the gastrointestinal tract at a desirable rate and time release.[7] Upon contact with biological fluids, water penetrates the tablet, gradually dissolving the drug, which then diffuses out through the tablet. In contrast to purely diffusion-controlled drug delivery systems, swelling and polymer dissolution must also be taken into account.[6]

Polymers that absorb more than 5% (w/w) water can be considered hydrophilic.[8] Several biocompatible natural and synthetic polymers are used for controlled-release dosage form technology. Among hydrophilic natural polymers we can highlight starch. Starch is probably the most abundant and low-cost

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natural polymer commercially available. Moreover, starch can be modified easily into a variety of useful monomeric and polymeric products by chemical means. Graft copolymerization of synthetic polymers onto a polysaccharide backbone perhaps offers one of the best ways to use polysaccharides for a variety of purposes.[9] Among synthetic polymers, acrylics occupy a significant position.[10] Thus, in the past few decades, the wide range of vinyl and other monomers available suggests that grafting is a powerful method for producing substantial modification of starch properties, thereby enlarging its range of utilization.[11]

Native starch may not be suitable in some controlled drug delivery systems due to its substantial swelling and rapid enzymatic degradation in biological fluids.[12] Graft copolymerization introduces hydrophobicity and steric bulkiness, which considerably protect the starch and carbohydrate backbone and retard drug release. In previous works, we have seen that acrylic polymers grafted onto starch allow the controlled delivery of drugs.[13] There is still a wide range of acrylic monomers and starch derivatives that have to be tested. The aim of this work is to obtain new dosification forms based on acrylic graft copolymers as the hydrophilic matrix and study their characteristics for controlled release with different solubility drugs. So, ethyl methacrylate (EMA) was grafted on starch (S) and hydroxypropyl starch (HS). The use of native starch is a good alternative because it is the cheapest form of starch. The use of the hydroxypropyl starch is very extended in the food industry. In this last product, factors such as heating or pH will affect the rheological properties and hence the release behavior.

EXPERIMENTAL

Materials

The preparation of hydroxypropyl starch-ethyl methacrylate (HS-EMA) and starch-ethyl methacrylate (S-EMA) grafted copolymers was carried out using the ceric ion redox initiation method.[9,14] The copolymerization initiator was ceric ammonium nitrate (CAN) (Fluka, Germany). EMA (Merck, Germany), HS, and S (Avebe, Holland) were used. The starch derivative came from potato starch with a substitution degree of 0.04–0.06. The unmodified starch is a native potato starch in which the amylose represents about 22% of its composition.

Procaine hydrochloride (M_w = 272.80) (Sigma–Aldrich, Germany) and anhydrous theophylline (M_w = 180.20) (Sigma–Aldrich) were used as model drugs for controlled-release tests. Procaine hydrochloride as a highly water-soluble drug (100% solubility in water at 25°C) and anhydrous theophylline as a slightly soluble drug (0.85% solubility in water at 25°C).

Some tablets were prepared with the addition of the following excipients: anhydrous dicalcium phosphate dihydrate (Emcompress, Juliá/Parrera, Spain) as a filler and stearic acid (Estearina, Acofarma, Spain) as a lubricant.

Hydrochloride acid (Panreac, Spain), potassium chloride (Sigma–Aldrich), citric acid monohydrate (Sigma–Aldrich), and sodium hydrogen phosphate heptahydrate (Sigma–Aldrich) were used for the preparation of different media for dissolution testing. All were reagent grade or the equivalent.

Methods

Synthesis of graft copolymers

As in previous works,[13] the carbohydrate (40 g), either hydroxypropyl starch or potato starch, was dispersed in 550 mL of bidistilled water. First, the medium was purged by passing purified nitrogen through it; the bath temperature was maintained at 30°C. Next, 118 mL of EMA was added to the initial dispersion, followed by 50 mL of the initiator solution (0.1 *M* ceric ammonium nitrate in 1 *N* nitric acid) 15 min later. Thus, grafting was allowed to proceed for 4 h under a constant light source. After this, the synthesized HS-EMA or S-EMA graft copolymers were filtered and washed with diluted nitric acid and bidistilled water. Finally, the solid obtained, which is a white powder, was freeze-dried by lyophilization. This solid is composed of unreacted carbohydrate, polyethyl methacrylate homopolymer (PEMA), and grafted copolymer.

Grafting yields

To characterize the graft copolymers we followed various steps. For greater accuracy, the ungrafted carbohydrate should be removed; however, we saw that the amount of the remaining carbohydrate was less than 3%, so this step was ruled out. Then we started by removing the PEMA homopolymer from the total reaction product with tetrahydrofuran (THF) by Soxhlet extraction for 72 h. Thus, the pure graft copolymer was obtained. Finally, the grafted PEMA was isolated from the carbohydrate chains by acid hydrolysis of the sample in 1 *N* HCl at reflux for 6 h.[9] The molecular weights of acrylic chains were measured by gel permeation chromatography (GPC).

Afterward, the following parameters were calculated:[13,14]

- percent grafting efficiency (% GE = percentage weight of graft copolymer with respect to total product), to ascertain the amount of homopolymer formed during the grafting reaction;
- percentage grafting (% G = percentage weight of grafted acrylic polymer with respect to grafted

carbohydrate) to asses the relationship between the acrylic and the natural component;
- percentage grafted carbohydrate (% GCH = percentage weight of carbohydrate with respect to graft copolymer) to calculate the percent of carbohydrate included in the graft copolymer;
- percentage total conversion (% CT = percentage weight of total acrylic polymer with respect to initial monomer), which is calculated to see the amount of monomer that polymerizes, either as a homopolymer or copolymer.

GPC

The weight-average and number-average molecular weights were determined by GPC (Waters 150-C). Four columns packed with Microstyragel of pore sizes 500, 10^4, 10^5, and 10^6Å were used. The elution solvent was THF and the flow rate was maintained at 1 mL/min.

The weight-average molecular weight ($\bar{M}_w$), number-average molecular weight ($\bar{M}_n$), and polydispersity ratio ($\bar{M}_w/\bar{M}_n$) were calculated from GPC chromatograms and the following ratio Mark–Houwink parameters for PSt were used: $K = 1.60 \times 10^4$ and $a = 0.706$. The following constants were calculated:

- Number of moles of grafted chains (% NG) is the weight of grafted polymer divided by the number-average molecular weight of the grafter polymer. It shows the number of moles of grafted side chain per mole of glucosidic unit;
- frequency of grafting (F) corresponds to the number of glucose units between two consecutive grafted chains.

NMR spectroscopy

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

Particle size distribution

Formulators of controlled-release matrices should take into account the particle size of the polymer incorporated into the matrix, since particle size can be one of the factors that affects hydration and, thus, the rate of gel formation and drug release.[15] Also, the rheological properties of the powders are a key factor in obtaining tablets by direct compression. Thus, bearing in mind the importance of powder particle characteristics in the pharmaceutical industry, powders were passed through a 500-μm mesh to remove excessively coarse granules. Particles smaller than 25 μm were also removed.

Owing to the complexity and heterogeneity of particles, the particle size distribution was measured with an optic microscope (model Leitz Aristomet). Microscopy is a technique that allows direct examination of the particles. More than 400 particles were analyzed, and a statistical analysis of the maximum diameter distribution was performed with specific software (Origin 5.1).

Scanning electron microscopy (SEM)

The surface and morphology of the particles and tablets were studied by SEM (SEM Hitachi-S-2700) with an accelerating voltage of 15 kV. Previously, the surface of the powders was coated with gold.

Rheological study

As we have explained before, drugs are released in the body by a leaching process through the polymeric matrix, which swells with physiological fluids. Thus, the hydrophilicity, the swelling capacity, and even the capacity of forming a gel are desirable and indeed necessary and the release process depends closely on these polymer characteristics.

In previous works, we have characterized various graft copolymers from a rheological point of view by means of a Carri-Med apparatus. In our earliest works,[13] the graft copolymers were swollen in DMSO to get a system as homogeneous as possible. In the next study,[16] they were swollen in water to get closer to real body conditions. As a result of both measurements we established that our graft copolymers were polymeric gels. However, since these polymeric powders, when dispersed in water and when swollen in the compressed tablet, do not offer a gel aspect, another system has been used to characterize them as gels and to rule out the possibility of only being swellable dispersions. For this reason, the viscoelastic measurement system used in this work was a Physica Rheolab MC100 viscoelastometer in coaxial cylinder geometry. The geometry of this apparatus is more adequate than those previously used to ascertain whether we have a polymeric dispersion or a gel.

Thus, as in the previous works,[16] 4% (w/w) water dispersions of HS-EMA and S-EMA graft copolymers were tested. This percentage was determined by reading an adequate viscosity of the dispersions in the vessel during stirring.[17] Previously, linear viscoelastic conditions were chosen from strain amplitude sweeps made at 37°C. Dynamic viscoelastic functions (storage modulus G', loss modulus G'', and complex viscosity

TABLE I
a-Formulation and b-or Standard-Formulation

a-Formulation	b-Formulation
25% drug 75% graft copolymer	24% drug 1% lubricant 50% filler 25% graft copolymer

η^*) were measured at 37°C as a function of frequency; frequency sweeps ranged between 10^{-2} and 10 Hz.

Preparation and characterization of tablets

The formulation of drugs in tablets using a swellable hydrophilic polymer as the excipient is of great interest in the field of controlled release. Due to the powdery nature of our products, in keeping with the concept of reducing production costs, a directly compressed simple formulation consisting of two principal components (polymer matrix and drug) was envisaged.

For comparative purposes, two kinds of tablet formulations were evaluated (Table I): (1) a-formulation, where the only excipient is the grafted copolymer (75% w/w), and (2) b-formulation, a standard formulation where the excipient is made up of 25% (w/w) graft copolymer as well as other products, i.e., 50% (w/w) Emcompress as filler and 1% (w/w) stearic acid as lubricant. A total of 25% (w/w) and 24% (w/w) of the drug is present in both types of tablet, respectively.

As we have mentioned before, two drugs were used in this work. The use of these two drugs with two different graft copolymers in both formulations gave eight types of matrix tablets with the following formulation codes:

hydroxypropyl starch copolymer, with anhydrous theophylline

- aHETh (a-formulation, HS-EMA copolymer, anhydrous theophylline)
- bHETh (b-formulation, HS-EMA copolymer, anhydrous theophylline)
- hydroxypropyl starch copolymer, with procaine hydrochloride
- aHEPr (a-formulation, HS-EMA copolymer, procaine hydrochloride)
- bHEPr (b-formulation, HS-EMA copolymer, procaine hydrochloride)
- potato starch copolymer, with anhydrous theophylline
- aSETh (a-formulation, S-EMA copolymer, anhydrous theophylline)
- bSETh (b-formulation, S-EMA copolymer, anhydrous theophylline)
- potato starch copolymer, with procaine hydrochloride
- aSEPr (a-formulation, S-EMA copolymer, procaine hydrochloride)
- bSEPr (b-formulation, S-EMA copolymer, procaine hydrochloride).
- The preparation of tablets was carried out with an apparatus used normally in pharmaceutical technology. The drugs, the copolymers, and the other excipients (in the standard formulation) were mixed at 50 rpm for 30 min in a double-cone mixer (Retsch, Haan, Germany).
- The physical mixtures were compressed in a single-punch tablet machine (Bonals, Model No. AMT 300, Spain) equipped with 12-mm flat-face punches to obtain tablets of 500 ± 5 mg average mass and a crushing strength of around 4 Kp. We choose this strength as one of the minimum strengths used in commercial products, as in previous works.[18]

Water content

Hydrophilic polymers are the main vehicles used for the preparation of oral controlled delivery systems. Therefore, the hydration capacity of copolymers as well as their water penetration kinetics was considered. These factors influence the concentration profile of the drug.

To study the hydration capacity of the polymeric matrices, HS-EMA and S-EMA graft copolymers were compressed in tablets at fixed crushing strength (4 Kp) and tablets were placed in three different buffered solutions, pH 1.5 (gastric fluid), pH 5, and pH 8 (intestinal fluids), at 37°C.

The water uptake capacity was determined gravimetrically. The water content (% EWC) of the hydrophilic matrices was measured as the mass changes due to the swelling: $\%\ EWC = 100\ (W_S - W_D)/W_S$, where W_S and W_D are the weights of the swollen matrix and the dried matrix, respectively.[19–21]

In vitro dissolution tests

The rate of absorption of an orally administered solid drug is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Therefore, the release kinetics of the drug was subjected to an "in vitro" dissolution test at 37°C. The dissolution testing was performed with a USP apparatus (Turugrau automated dissolution test) 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 in each case. Six tablets of each formulation were examined. As in the water absorption tests, the dissolution media

TABLE II
Yields of the Graft Copolymerization of EMA on HS and S Carbohydrates

Copolymer	Weight (g)	% GE	% G	% CT	% CG
HS-EMA	134.0 ± 3.5	86.7 ± 2.6	248.9 ± 7.5	93.8 ± 6.1	335.7 ± 8.7
S-EMA	133.9 ± 6.2	79.3 ± 4.8	237.7 ± 4.7	95.2 ± 11.0	334.7 ± 15.5

were three different buffered solutions: pH 1.5 (gastric fluid), pH 5, and pH 8 (intestinal fluids).

The concentration of the drug delivered was determined by UV-VIS spectrophotometry at their maximum absorbance: 271 nm for the anhydrous theophylline and 291 nm for the procaine hydrochloride. Each data point is the average of six individual measurements. In all cases, the relative statistical deviation was less than 3%.

Generally, in swelling-controlled matrix systems, there are two major factors that control the rate of drug release from the matrix. One factor is the rate of the medium diffusion into the matrix, which is normally followed by a relaxation process involving gelation or swelling. The other factor is the rate of erosion of the matrix. These two processes take place simultaneously, giving rise to a swelling front and an eroding front. The distance between these two fronts is the diffusion layer thickness, which depends on the relative rates at which the swelling and eroding fronts move in relation to each other.

The quantity of drug released from matrix tablets is often analyzed as a function of the square root of time according to the Higuchi equation[4]; this occurs when the drug release is governed by pure diffusion. However, the use of this relationship in swellable systems is not completely justified, because such systems can also be erodible and the contribution of the relaxation of polymeric chains to drug transport must be taken into account. Therefore, analysis of drug release from swellable matrices must be performed with a flexible model that can identify the different contributions to the overall kinetics.[7]

Therefore, the release kinetics of the drug from the polymeric matrices was analyzed by the application of the equation proposed by Peppas and colleagues,[22,23] in which the contribution of the relaxation or erosion mechanism and of the diffusive mechanism can be quantified,

$$\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n},$$

where M_t/M_∞ is the fraction of drug release up to time t (the drug loading was considered M_∞), k_1 and k_2 are the kinetic constants characteristic of each system, and n is the diffusional exponent that depends on the release mechanism and the shape of the matrix tested. The first term is related to the Fickian diffusion and the second to the relaxation mechanisms. $M_t/M_\infty <$ 60% data were fitted to this equation. Since the value of the n exponent depends on the shape and size of the polymeric matrix, the relationship of the Fickian diffusional exponent with the aspect ratio (2a/L) of the tablet[23] was used to obtain the most appropriate n values for our tablets. For a-formulation matrices the diameter/thickness was approximately 3, and for b-formulation matrices it was around 4, so that they corresponded to $n = 0.435 \pm 0.001$ and $n = 0.454 \pm 0.003$, as the diffusional exponents, respectively.

RESULTS AND DISCUSSION

Synthesis and characterization

The reaction yields obtained when grafting EMA on hydroxypropyl starch and on potato starch are shown in Table II. In both cases, the yields were very high, showing that in these reactions the fraction of the formed homopolymer is not greater than 20% although the total conversion is higher than 90%. Thus, we obtained very high percentage of grafting. We can only appreciate that % GE and % G values of S-EMA are slightly lower than for HS-EMA. The percentage of grafted carbohydrate is around 35% in both cases; thus, the hydrophobic component is the main component of the final product. However, the distribution of grafted chains is different in each carbohydrate. As we can see in Table III, molecular weights of PEMA

TABLE III
Molecular Weight Averages and Number of Grafted PEMA Chains on HS and S Carbohydrates

Grafted copolymer	$M_w \times 10^{-3}$	$M_n \times 10^{-3}$	M_w/M_n	NG $\times 10^3$ (mmol)	F (UAG)
HS-EMA	1147	517	2.22	0.160	1250
S-EMA	2715	977	2.75	0.076	2540

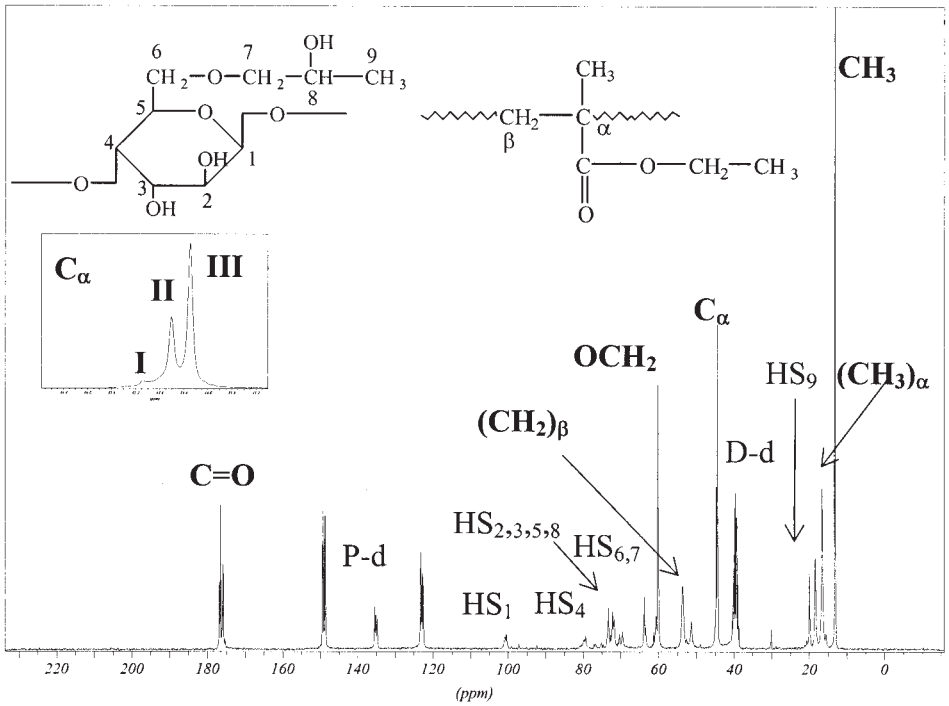

Figure 1 ^{13}C-NMR spectra of HS-EMA graft copolymer in *d*-pyridine (d-P) and *d*-DMSO (d-D).

chains grafted on starch are slightly higher than that of those grafted on HS. On the contrary, the number of grafted chains is less and these chains are situated at larger anhydroglucose units' intervals. Another aspect to be considered is that the use of water as the reaction medium and the solubility of all the reactants in water guarantee the absence of toxic substances in the final product.

Furthermore, the graft copolymers were characterized by NMR-C^{13} spectroscopy. In 1992 our team pub-

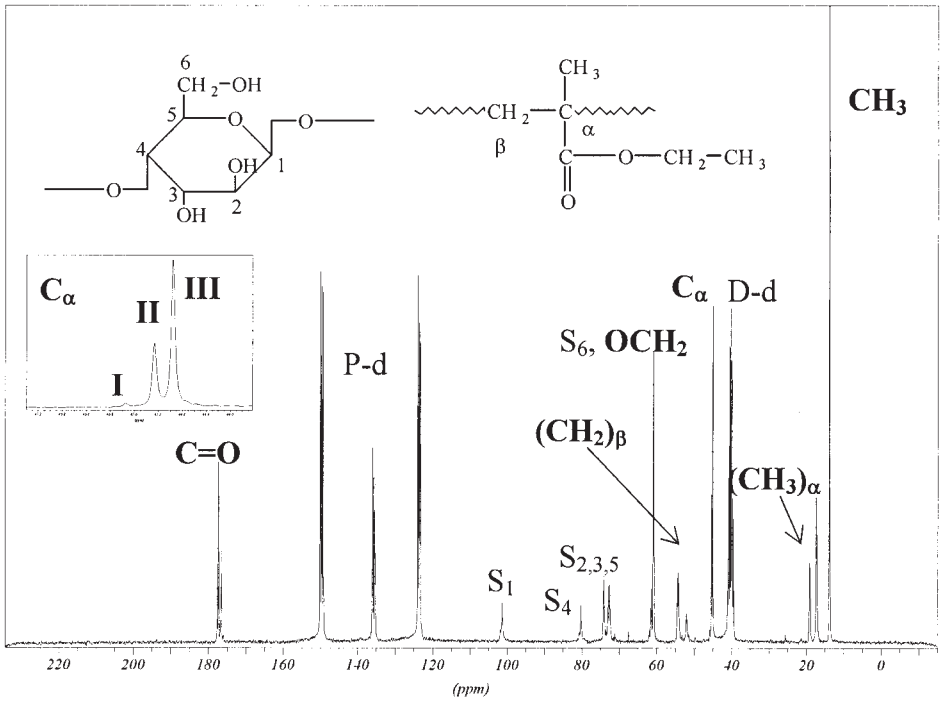

Figure 2 ^{13}C-NMR spectra of S-EMA graft copolymer in *d*-pyridine (d-P) and *d*-DMSO (d-D).

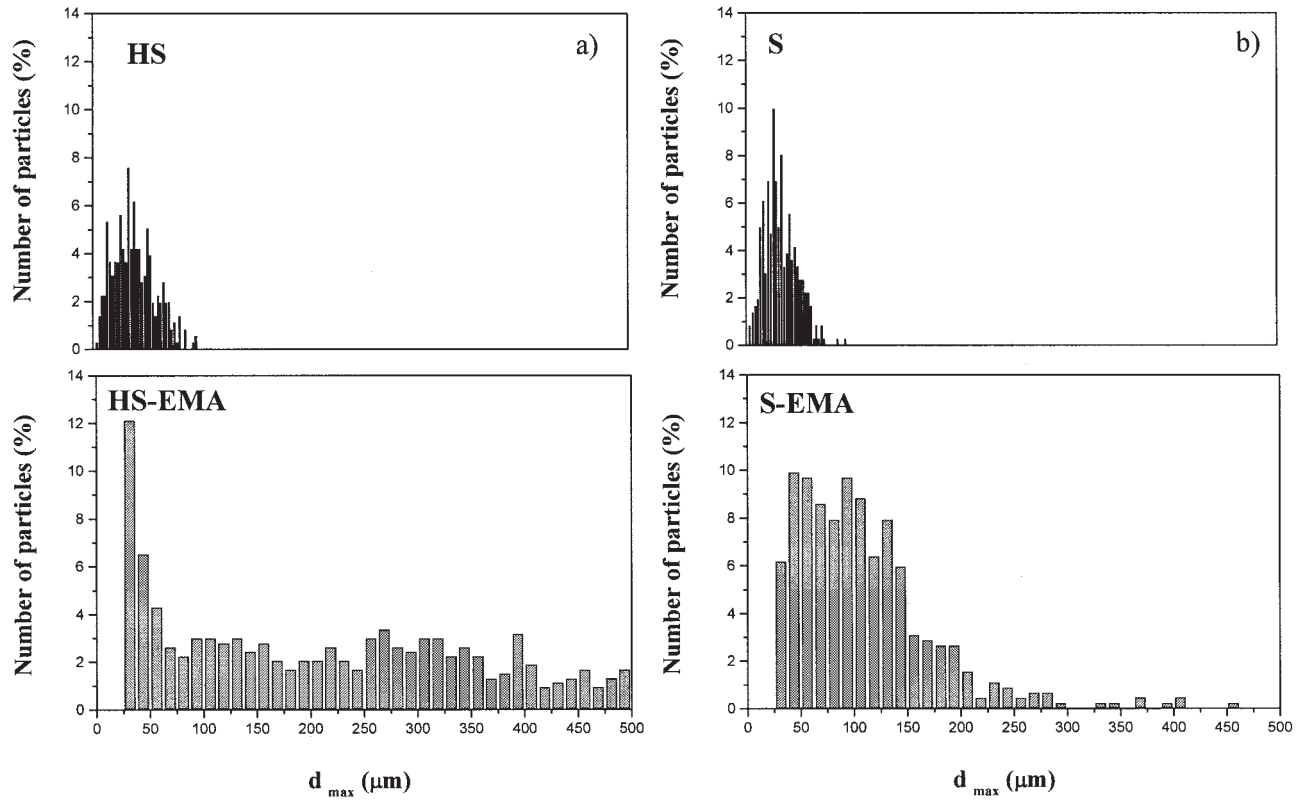

Figure 3 Particle size distribution of HS (a) and S (b) carbohydrates and HS-EMA (c) and S-EMA (d) graft copolymers.

lished a ^{13}C-NMR spectroscopy study of this kind of graft copolymers.[24] This technique provided the opportunity to observe well-resolved spectra of swollen samples. Nowadays, the improvement ine NMR spectroscopy equipment makes possible a study of higher sensitivity of the stereoregularity of the acrylic grafted chains. In Figures 1 and 2 we can distinguish the peaks attributed to the carbons of the anhydroglucose unit and those of the poly(ethyl methacrylate) of both carbohydrates. Chemical shifts are quoted in parts per million relative to TMS at 0 ppm and the assignments are indicated on each peak.

We can also see the magnification of peaks corresponding to the C-α signal, which can be analyzed from a configurational point of view.[25] Applying Bernouillian statistics to the spectrum signals, we can take the value of having a meso placement (P_m = [mm]$^{1/2}$) and use it to analyze the stereochemistry of the PEMA chains. The C-α signal splits into a triplet due to the presence of isotactic, heterotactic, and syndiotactic triads, from which we can deduce that $P_m = 0.17_6$ for PEMA chains grafted on HS and $P_m = 0.17_8$ for chains grafted on S. As expected, the P_m values are practically equal in both cases and correspond to heterotactic polymers.

As we demonstrated in a previous paper,[24] ^{13}C-NMR spectroscopy can also be used to determine the graft copolymer composition. Oone of the characteristics of this technique is the proportionality between the signal intensity and the concentration of each carbon type. Thus, if the spectra are registered under determined conditions, the % G can be calculated from the relative areas of the C_4 of the anhydroglucose unit and one suitable peak of the PEMA, i.e., the $(CH_2)\beta$. The % G values obtained using this method were 253.6 $\pm$ 5.2 for S-EMA and 265.6 $\pm$ 8.1 for HS-EMA, very close to those calculated from the hydrolysis values.

Since the aim of this work is to find a powdery polymer to be used for the elaboration of tablets, various specific tests were run.[26] Polymer granulometry is an important factor to be considered since the compaction, fluidity, and release properties depend on this characteristic. As a generalization, it could be said that small particles compact better. However, with respect to its influence on drug release, the polymeric matrix matters much more than the particle size distribution when considered alone. Figure 3 shows the particle size distribution of the carbohydrate and graft copolymers obtained after the sieving process. By comparison of copolymer size distribution with the distribution of the ungrafted HS and S, we can say that the growth of the acrylic chains from the carbohydrate particle is very different in each case, although in both cases we can appreciate a clear increase in the particle size, notably in the HS copolymers. We can see that the range of particle sizes for the HS-EMA copolymer

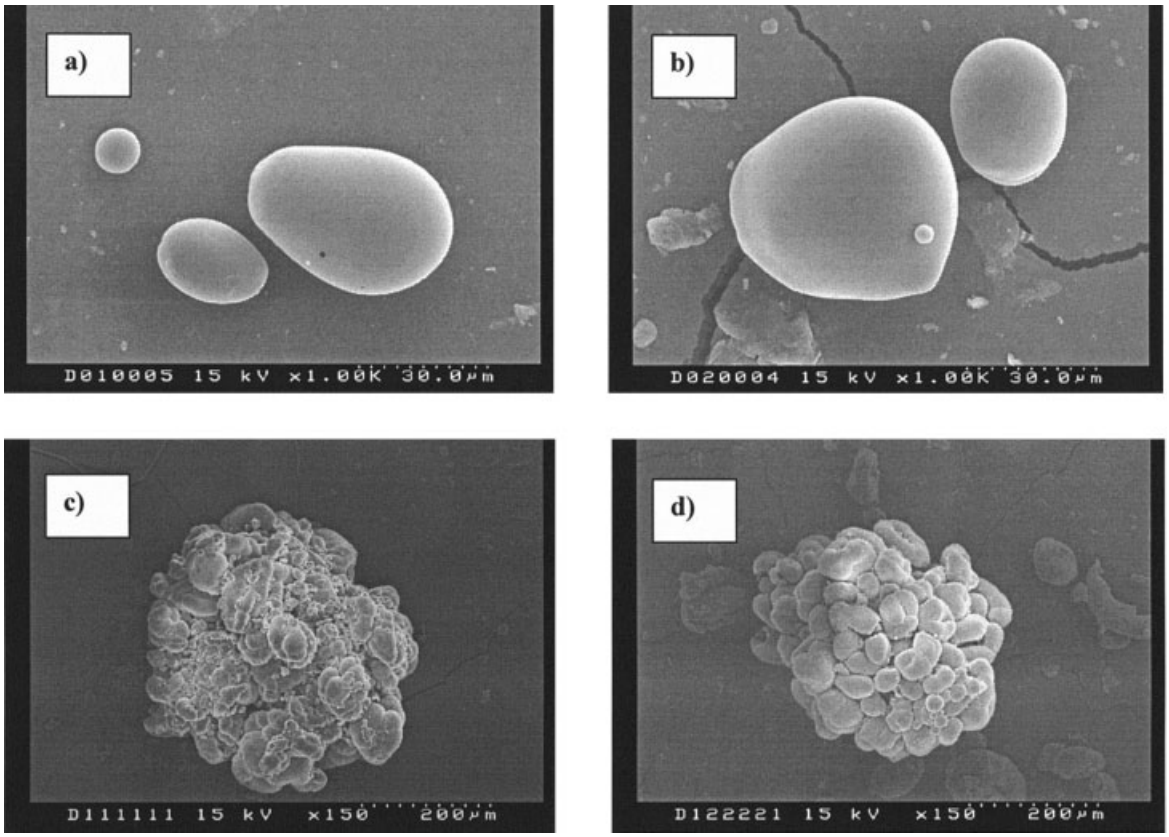

Figure 4 SEM micrographs of particles: HS (a) and S (b) carbohydrates and HS-EMA (c) and S-EMA (d) graft copolymers.

is wider than for the S-EMA copolymer. In the latter case, the particle size distribution has a shape that comes close to a Gaussian standard distribution, while that of the HS-EMA copolymer is quite uniform.

SEM allows much high magnification of the grafted copolymer particles in which we can see the shape and the surface aspect. Figure 4 shows the surface photograph of the products obtained from the graft copolymerization onto starch. The grafting introduces big changes on the surface and in the size of the carbohydrate particles. The particles, after copolymerization, show irregular morphology, as a lobule aggregate with higher heterogeneity in the case of the HS-EMA. The wrinkled or porous topography should enhance the hydrophilia and water absorption capacity, attributable to their chemical structure.[13]

The viscosity characteristics of the polymers are of great importance when obtaining a desired release profile. To obtain adequate rheological characterization, apart from the viscosity, it is necessary to know the storage and loss moduli (G' and G''). These parameters will tell us whether the polymer performs like a gel and, therefore, whether it can act as a barrier to drug diffusion.[16] To carry out these measurements, previously linear viscoelastic conditions were selected from strain amplitude sweeps made at 37°C. Figure 5 shows the amplitude sweep of 4% (w/w) water dispersions of HS-EMA and S-EMA graft copolymers. Any of the deformation amplitude values taken between the dashed lines can be used to work under linear viscoelastic conditions. We can also say that copolymers present high viscosity and consistency. Next, to ascertain G' and G'' at different strain frequencies, we performed a frequency sweep in the dispersions. Figure 6 reveals that in both systems the storage modulus overcomes the loss modulus, $G' > G''$, and none of them shows any significant dependency on

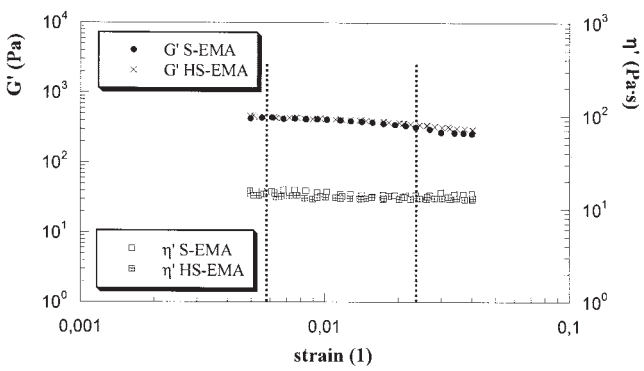

Figure 5 Torque sweep for 4% (w/w) copolymers HS-EMA and S-EMA water dispersions at 37°C and 1 Hz. Storage modulus (G') and dynamic viscosity (η').

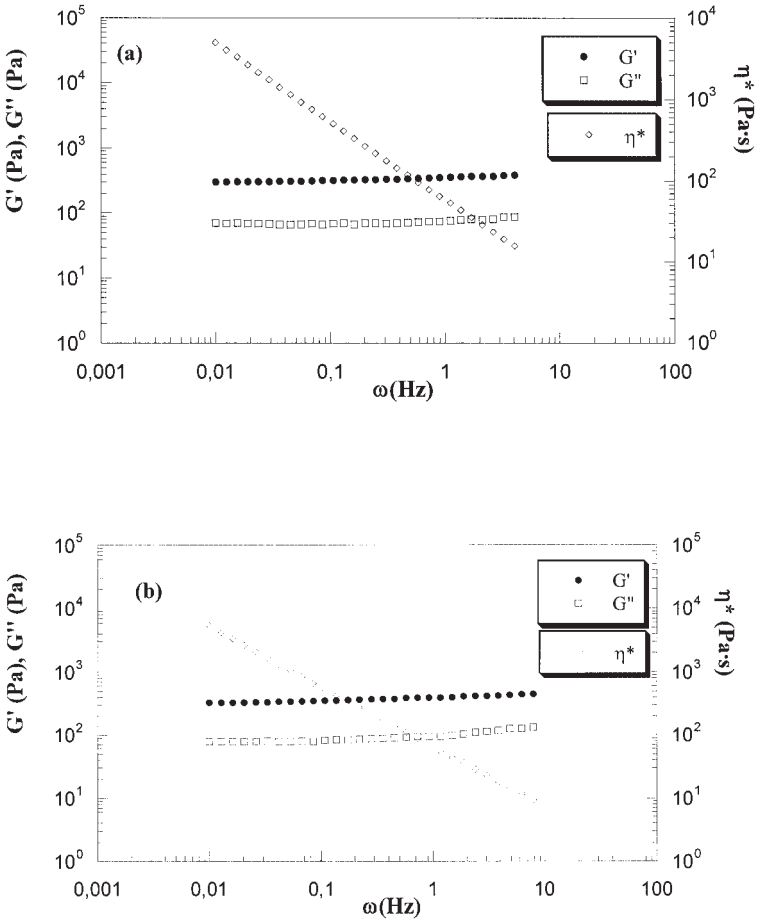

Figure 6 Frequency sweeps for HS-EMA (a) and S-EMA (b) copolymers at 37°C under linear viscoelastic conditions. Storage modulus (G') and loss modulus (G'').

frequency, so the definition of gel is fulfilled.[27] Moreover, we can say that there are no differences in the rheological behavior of the HS-EMA and S-EMA copolymers in water.

These results allow us to assert that these copolymers fulfill the first necessary condition for good control of drug release, i.e., the viscosity of the copolymers must be high enough to decrease the release rate of the drug.[15] Consequently, a diffusion mechanism through the gel layer can be expected.

Because of the influence of substitution, starch and its derivatives differ in hydrophilia. This varying affinity for water is reflected by the equilibrium water uptake, and this difference may be relevant in many pharmaceutical situations. In this sense, the amount of absorbed water and its rate of absorption may affect the drug release profile. Figure 7 shows the water absorption kinetics of the two carbohydrates used in this work and that of the graft copolymers. All the products absorb water very quickly, reaching the steady state in 6 h. In Figure 7 we can easily observe that the water uptake capacity of the HS is higher than that of the S. However, the substitution degree of the hydroxypropyl starch is very low, so that the number of hydrophobic groups is not actually very different from that of a nonsubstituted starch. We know that the amount of water taken up by a polymer also depends on the accessibility of the hydrophilic groups. On the one hand, we have to assume that the molecular structure has suffered a small modification due to the hy-

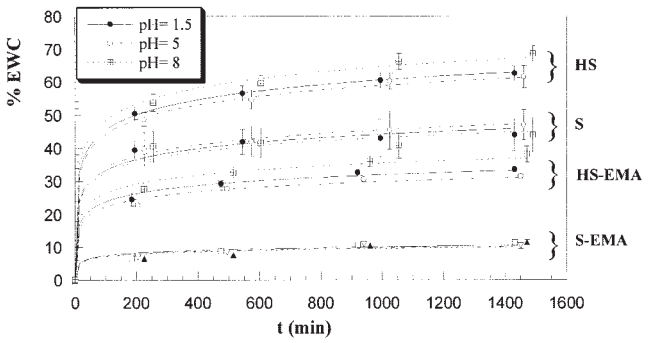

Figure 7 Percentage water uptake of HS and S carbohydrates and HS-EMA and S-EMA grafted copolymers at three pHs (pH 1.5, 5, and 8) at 37°C versus time.

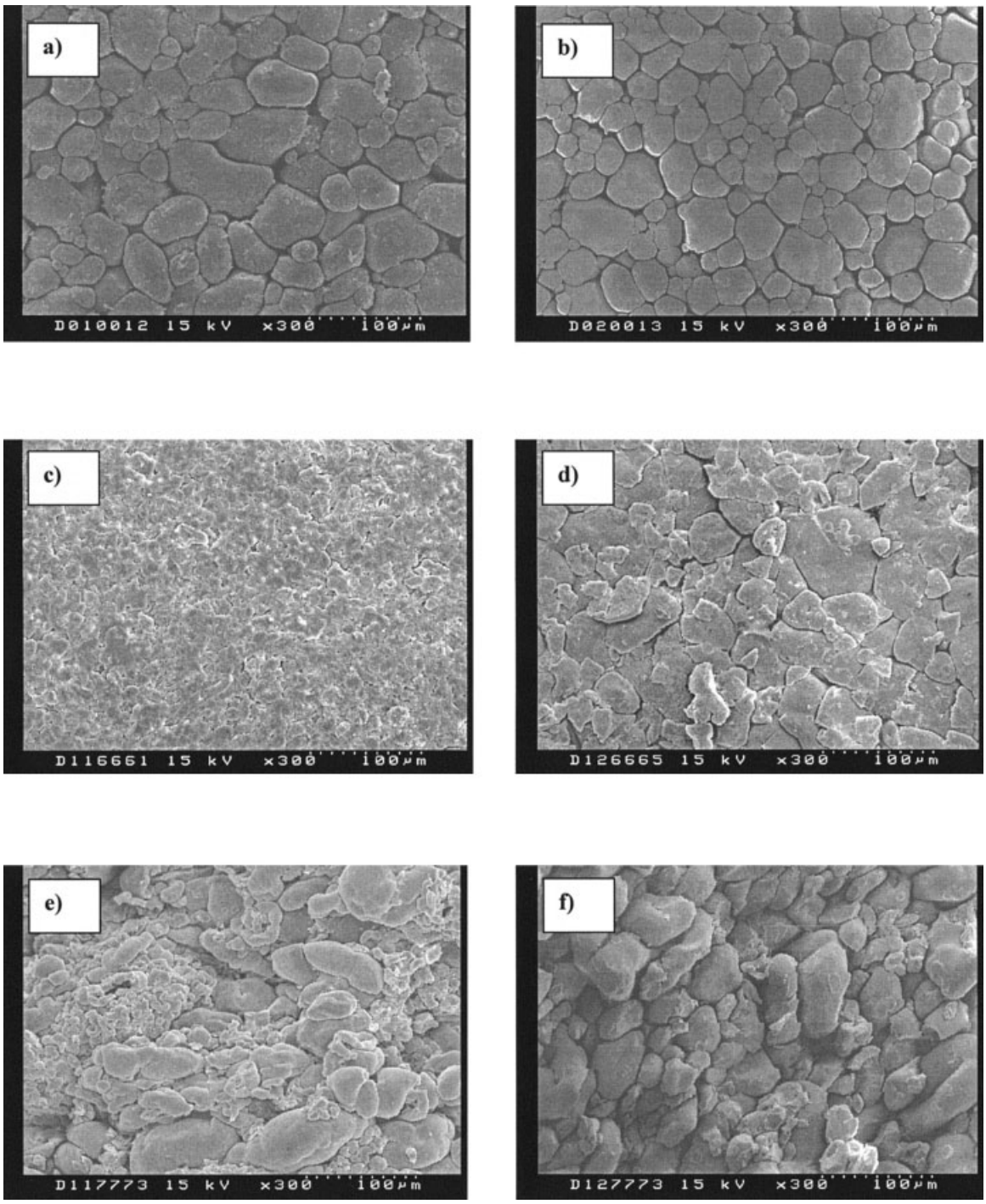

Figure 8 SEM micrographs of tablets: HS (a) and S (b) carbohydrates, the HS-EMA (c) and S-EMA (d) graft copolymers, and SEM micrographs of crushed tablets of HS-EMA (e) and S-EMA graft copolymers (f).

droxypropyl group introduced in the anhydroglucose unit, although the accessibility of the new hydroxylic groups of the HS is probably higher than the accessibility of the hydroxylic groups of the S. On the other, the native granular structure has been probably disrupted during the modification reaction. Therefore, these facts make the differences in the water affinity of the HS and S. The effect of pH is only observable in HS and its copolymer and, in both cases, the absorption is higher at alkaline pH. The hydrophobicity introduced on grafting acrylic chains is very noticeable. However, Figure 7 shows that the water uptake of HS-EMA is more than twice that of S-EMA. As we have mentioned before, both graft copolymers have approximately the same carbohydrate/acrylic ratio, hence a similar hydrophilia balance. Thus, the only reason for

HS-EMA being more hydrophilic is the higher hydrophilia of HS. In addition, water may be accommodated in the particles' surface and the HS-EMA copolymer surface presents more wrinkles or irregularities than that of the S-EMA copolymer.

Another factor to be taken into consideration is the use of tablets to perform the test of the copolymers. This makes compaction one more factor to be taken into account. Figure 8 shows the morphology of tablets obtained from the four products studied in this work. We can say that compaction of S and HS is very similar (Figs. 8a and b), hence the water uptake depends mainly on chemical structure. However, Figures 8c and d are very different. Figure 8c shows a very extended and fine porosity while Figure 8d shows fewer voids. SEM photographs of crushed surfaces (Figs. 8e and f) help us to understand these morphologies. Moreover, if we compare these photographs with those of Figure 4, we can see that in none of the cases can we distinguish the single particle shape. There are lobules of the particles that compact, giving rise to a very good particle–particle interaction. Again, the more irregular forms of the HS-EMA particles give rise to the formation of bigger amount of voids or channels to lodge water. We can say that particle surface morphology takes more importance in compaction than particle size distribution. Nevertheless, in both cases the copolymers are hydrophilic matrix systems.

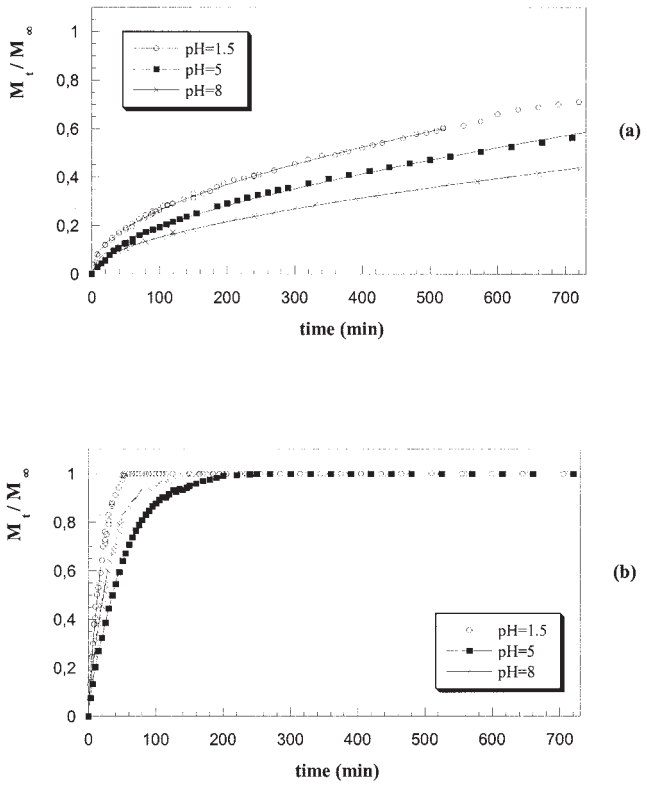

Figure 9 Anhydrous theophylline and procaine hydrochloride fraction released (M_t/M_∞) from a-formulation with HS-EMA graft copolymer, (a) aHETh and (b) aHEPr, at 37°C and at three pHs.

In vitro dissolution tests

Drug release can be modified by the selection of the polymer and this selection should depend on the solubility characteristics of the drug. Accordingly, hydrophilic matrices are generally used to prolong the release of highly water-soluble drugs. In the case of these drugs, the fastest hydrating derivatives are indicated to prevent rapid initial dissolution of the surface particles.[28] Matrices containing drugs of lesser solubility may be prepared from polymers hydrating more slowly to limit the gel layer thickness. For nearly insoluble drugs, tablets must be formulated to allow erosion because dissolution of the drug becomes the rate-limiting factor.

As we have explained before, two kinds of drugs have been used in this work, one slightly soluble in water and the other highly soluble. The solubility of both substances does not appreciably change with changes in pH. Also, we have seen that the graft copolymers are hydrophilic, but to a moderate degree. The well-known exponential relationship proposed by Ritger and Peppas[22] is today universally accepted. This equation may be used to describe the Fickian and non-Fickian release behavior of swelling-controlled release systems that swell to a moderate degree (up to 25 vol %) when prepared by incorporation of a drug in an initially glassy hydrophilic polymer, as in our case.

The results of the dissolution tests for a-formulations in different media are shown in Figures 9 and 10. These figures illustrate the differences in the dissolution profiles of both graft copolymers depending on the drug and the pH. Figure 9a shows very slow release of theophylline, the drug of poor solubility, at the three pHs, at which less than 60% of the drug was released in 12 h. The influence of the solubility of the drug is clearly demonstrated if we compare Figures 9a and b. In the latter, for the aHEPr formulation, the soluble drug is released very quickly and reaches the steady state at approximately 2 h in all the dissolution media. The differences in the behavior attributed to the different solubilities of the tested drugs and to the moderate hydrophobicity of both copolymeric matrices are in keeping with the findings of other authors, who showed that an increase in drug solubility resulted in an increase in the dissolution rate.[29,30] Another aspect that cannot be forgotten is the effect of pH. Surprisingly, the sequence of the maximum dissolution attained at the three pHs is different from that of the water uptake. We could attribute these differences to changes in the diffusion of the drug through the swelled matrix; however, we must avoid that at

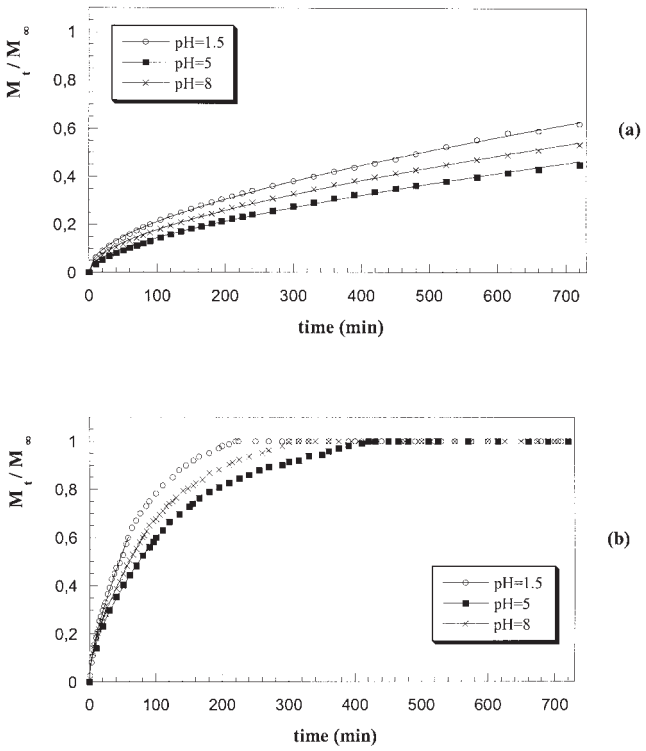

Figure 10 Anhydrous theophylline and procaine hydrochloride fraction released (M_t/M_∞) from a-formulation with S-EMA graft copolymer, (a) aSETh and (b) aSEPr, at 37°C and at three pHs.

the end of the tests run at pH 1.5 the tablets appear damaged. Thus, we can say that the small disintegration of the tablets prevails over that of the diffusion.

Similar behavior is observed in Figure 10, where the dissolution kinetics of the copolymers obtained from starch are plotted. However, we can point out one main difference between these graft copolymers and those of HS: although the pattern of release of theophylline is very similar, that of procaine attains a steady state more slowly. In this case, it must be recognized that the pH sensitivity is negligible, although the effect of the tablet disruption at acid pH is also observed. Again, the matrices perform in a way that is more suitable to the release of less soluble drugs, just like poor hydrophilic matrices.

Therefore, we have seen that in the case of the more soluble drug we obtain fast release and in the other case extremely slow release. For a specific dose of drug, varying the polymer concentration is probably the most efficient way for the formulator to adapt the release characteristics to a specific criterion. Moreover, adjuvants are often necessary for the tableting operation. On the other hand, the role of diluents is very pronounced, and actually an increase in dissolution is noticed with both insoluble and soluble fillers.[28]

The dissolution profiles of anhydrous theophylline and procaine hydrochloride from tablets prepared from b-formulation (Figs. 11 and 12) show that the presence of Emcompress as a filler and stearic acid in the granules results in a quick increase in drug release compared with tablets prepared from a-formulations.[15] So, the faster release of all the b- or standard formulations compared to their respective a-formulations at the three pHs used can only be attributed to the dilution of the polymer in the tablet composition. However, by comparing the figures related to the a- and b-formulations we can find two similarities: (1) the release of the theophylline drug (Figs. 11a and 12a) is much faster at the most acid pH and (2) the release of procaine hydrochloride (Figs. 11b and 12b) from the standard formulation tablets occurs almost instantaneously. The effect of the pH on the release of the drugs from the b-formulations is exactly the same, although higher, as in the a-formulations, confirming the considerable influence of the graft copolymer matrix and the best tablet compaction obtained with the copolymer alone.

The release kinetics were fitted to the equation of Ritger and Peppas,[22] obtaining the diffusion (k_1) and relaxation (k_2) mechanism constants, which can be observed in Table IV. In all of them, the diffusional mechanism contribution is higher than the relaxational contribution ($k_1 > k_2$), as corresponds to diffusion in a glassy polymer well below T_g. However,

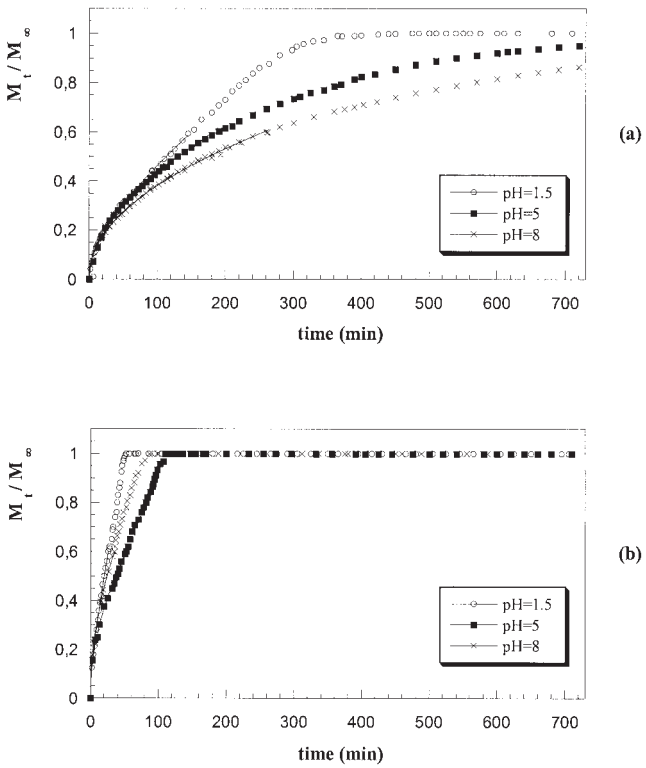

Figure 11 Anhydrous theophylline and procaine hydrochloride fraction released (M_t/M_∞) from b-formulation with HS-EMA graft copolymer, (a) bHETh and (b) bHEPr, at 37°C and at three pHs.

these differences are more noticeable when the less soluble drug is delivered, i.e., when we have a slow dissolution process. With procaine both contributions are closer. This kind of comparison is not so clear when we analyze the b-formulation, where the presence of the polymer is smaller. The fact of the small disintegration of tablets at pH 1.5 makes any comparison difficult. Nevertheless, if we compare data at pH 5 and 8, we can say that S copolymers show approximately the same plots but, HS copolymers show a clear slower release at basic pH. These differences must be attributed only to the carbohydrate backbone, since the highest swelling at pH 8 is due to this part of the copolymer. The lesser hydrophilia of the S-copolymers gives rise to a different behavior in the release of the poor soluble drug. We can see that procaine hydrochloride shows a slower release from the S copolymers than from the HS copolymers.

CONCLUSIONS

Brazel and Peppas[31] demonstrated that solute transport in swellable hydrophilic polymers was affected by a variety of structural and physical characteristics in the polymers and by the nature of the solutes used.

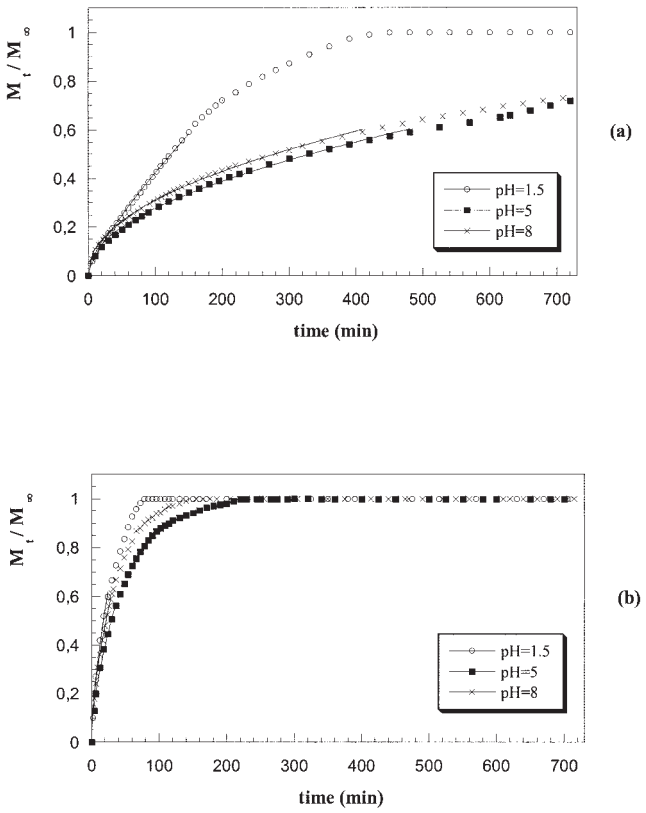

Figure 12 Anhydrous theophylline and procaine hydrochloride fraction released (M_t/M_∞) from b-formulation with S-EMA graft copolymer, (a) bSETh and (b) bSEPr, at 37°C and at three pHs.

TABLE IV
Peppas' Equation-Fitting Parameters at Three Different pHs

Formulation	pH	k_1 (min^{-n})	k_2 (min^{-2n})	k_2/k_1	r
aHETh					
	1.5	3.16×10^{-2}	5.23×10^{-4}	0.017	0.9994
	5	2.13×10^{-2}	6.85×10^{-4}	0.032	0.9972
	8	1.69×10^{-2}	4.69×10^{-4}	0.028	0.9995
aHEPr					
	1.5	4.44×10^{-2}	3.70×10^{-2}	0.833	0.9973
	5	2.70×10^{-2}	1.67×10^{-2}	0.619	0.9996
	8	4.39×10^{-2}	2.23×10^{-2}	0.508	0.9996
aSETh					
	1.5	2.32×10^{-2}	7.20×10^{-4}	0.031	0.9997
	5	1.42×10^{-2}	7.04×10^{-4}	0.050	0.9989
	8	1.88×10^{-2}	6.97×10^{-4}	0.037	0.9995
aSEPr					
	1.5	4.13×10^{-2}	1.05×10^{-2}	0.254	0.9982
	5	4.65×10^{-2}	4.68×10^{-3}	0.101	0.9992
	8	4.90×10^{-2}	6.00×10^{-3}	0.122	0.9995
bHETh					
	1.5	3.56×10^{-2}	2.67×10^{-3}	0.075	0.9950
	5	4.41×10^{-2}	1.16×10^{-3}	0.026	0.9985
	8	4.47×10^{-2}	2.93×10^{-4}	0.007	0.9991
bHEPr					
	1.5	5.99×10^{-2}	1.73×10^{-2}	0.298	0.9993
	5	8.66×10^{-2}	2.04×10^{-3}	0.024	0.9984
	8	1.06×10^{-1}	2.63×10^{-3}	0.025	0.9992
bSETh					
	1.5	1.41×10^{-2}	4.74×10^{-3}	0.337	0.9995
	5	3.20×10^{-2}	2.81×10^{-4}	0.009	0.9990
	8	3.75×10^{-2}	1.10×10^{-4}	0.003	0.9996
bSEPr					
	1.5	7.84×10^{-2}	1.59×10^{-2}	0.203	0.9955
	5	6.79×10^{-2}	8.72×10^{-3}	0.128	0.9977
	8	8.92×10^{-2}	8.79×10^{-3}	0.098	0.9985

In this work, we have demonstrated that the polymer is the most responsible element of the drug release in the formulation. So, the use of different percentages of polymer represents a potential way of achieving the required release profile. As expected, the drug was released more slowly from tablets with a higher polymer content. Therefore, changing the polymer content in the tablets can modify the release rate of the drug. And, consequently, increases in polymer concentration slow down drug release, because the increasing levels of disintegrant change the dissolution profile by accentuating the "burst" effect, as Alderman reported.[15]

The graft copolymers, HS-EMA and S-EMA, obtained in this work act as efficient matrices to release drugs of slight water solubility, but they are not hydrophilic enough to perform slow release of the highly water-soluble drug. In light of these results we propose obtaining graft copolymers with higher carbohydrate content to produce polymeric matrices that exhibit higher hydrophilia.

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