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Hydrogels based on graft copolymerization of 2-hydroxypropyl methacrylate/acrylate mixtures on amylose: swelling behaviour

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Hydrogels were prepared by simultaneous graft copolymerization on amylose of 2-hydroxypropyl methacrylate with different acrylates (methyl acrylate, ethyl acrylate and butyl acrylate) using ceric ammonium nitrate as initiator. Similarly, another series of grafted samples with a 50/50 (mol/mol) composition of hydroxylic/non-hydroxylic monomers with 34 mol% of ethylene glycol dimethacrylate were prepared. Percentages of crude grafting (%CG), polymerized monomer (%PM) as well as equilibrium water content (%EWC) were analysed as a function of the monomer composition in the initial mixture and the degree of crosslinking. As the proportion of hydroxylic monomer in the copolymers increased, a slight rise in %EWC was observed and a higher increase as the alkyl side-group length of acrylates decreased. The swelling behaviour had only an appreciable variation at basic pH, even achieving similar values to those of amylose when diethylene glycol dimethacrylate was added.

(Keywords: amylose hydrogels; graft copolymers; swelling behaviour)

INTRODUCTION

Hydrogels are a broad class of hydrophilic materials formed by a three-dimensional network held together by crosslinks of covalent bonds and weak cohesive forces in the form of hydrogen or ionic bonds. These crosslinked macromolecular structures are able to take up large quantities of water and biological fluids without dissolution. The biocompatibility of hydrogels is attributed to their ability to simulate natural tissues due to their high water content and their special surface properties. As a result of the resemblance between the synthetic and natural materials, these gels have been used in a wide variety and growing number of biomedical applications such as drug delivery[1], orthopaedic[2] and medical devices[3].

Composite materials consisting of natural macromolecules and synthetic polymers have attracted much interest from the viewpoint of improving the tissue tolerance of synthetic polymers and the mechanical properties of natural polymers. One method used to obtain this type of biomaterial is graft copolymerization on natural macromolecules.

This work reports on the synthesis of hydrogels from graft copolymerization on amylose (the linear component of starch) using 2-hydroxypropyl methacrylate (HPMA) as hydroxylic monomer, due to its high biocompatibility, copolymerized with various non-hydroxylic monomers: methyl acrylate (MA), ethyl acrylate (EA) and butyl acrylate (BA). The influence of the hydroxylic/non-hydroxylic ratio of the feed composition on the final grafting yields as well as on the final water content was the purpose of our study.

Finally, graft copolymers were obtained with 34 mol% of ethylene glycol dimethacrylate (EGDMA) because of the greater values of water content obtained for similar materials in a preceding paper[4].

EXPERIMENTAL

Materials

The amylose used (linear starch fraction), potato amylose-V, was supplied by AVEBE, Holland. The hydroxylic methacrylate HPMA (Merck) was purified as described previously[5] and the non-hydroxylic acrylates MA, EA and BA were purified by washing and distillation under suitable conditions.

All the other products were reagent grade or equivalent.

Grafting procedure

The graft copolymerization on amylose of HPMA with different acrylates (MA, EA and BA) was carried out using Ce(IV) as initiator. As we have mentioned before, these monomers were selected in order to study the influence of the size of alkyl side group on the grafting yields and on the equilibrium water content.

The mixtures of hydroxylic/non-hydroxylic monomers (HPMA/MA, HPMA/EA and HPMA/BA) were obtained with a feed composition ratio ranging from 100/0 to 0/100. On the other hand, taking into account the results obtained in previous work[4], another series of grafted samples was prepared with a monomer ratio of 50/50 with 34 mol% of a bifunctional monomer (EGDMA),

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*To whom correspondence should be addressed because this proportion was the only one that produced a high variation in %*EWC* (percentage equilibrium water content).

Graft copolymers were obtained by the method described in an earlier work[6]. First, 2 g of amylose was suspended in 290 ml of water in a three-necked separable flask under constant light source[7]. After purging with nitrogen for 30 min, the required amount of monomers (0.047 mol) was added, and 5 min later the initiator solution with 0.5482 g of ceric ammonium nitrate in 10 ml of 1 N nitric acid. Graft copolymerization was allowed to proceed for 4 h at 30°C by stirring under a stream of nitrogen. At the end of this period, the solid obtained was filtered, exhaustively washed with 1 N nitric acid and distilled water, and then dried at 50°C under vacuum until constant weight.

Characterization of products

The yields of the graft copolymerization are readily determined by a gravimetric technique using the following parameter[8]:

$$\%CG = \frac{\text{total weight}}{\text{weight of polysaccharide}} \times 100$$

where %*CG* is the percentage crude grafting.

Graft copolymers were also characterized by ^{13}C n.m.r. spectroscopy. The spectra of graft copolymers were registered after swelling the samples in d-dimethylsulfoxide using tetramethylsilane as an internal reference until a homogeneous gel was obtained. The ^{13}C n.m.r. measurements were carried out at 20–25°C on a Varian VXR 300 MHz spectrometer operating at 75.4 MHz. The conditions of operation were: pulse width 14 μs, acquisition time 1 s, delay time 3 s, taking about 30 000 transients. From the n.m.r. spectra, the composition of the grafted polymer can be calculated by taking a representative peak of each monomer unit. In these mixtures the selected peaks were the CH_3 carbon of the HPMA unit, CH_3O carbon of the MA unit, CH_3 carbon of the EA unit and CH_3 carbon of the BA unit, appearing at 20, 52, 14.05 and 14.31 ppm respectively. By calculating the copolymer composition from spectra with different compositions, another parameter could be calculated:

$$\%PM = \frac{(\text{total weight} - \text{weight of polysaccharide})/M}{m_t} \times 100$$

where %*PM* is the percentage polymerized monomer, M is the molecular weight of structural grafted unit and m_t is the total number of moles in the feed composition (0.047).

Swelling behaviour

In recent years, hydrogels have attracted considerable interest as useful biomaterials. Particularly, in uses like controlled-release devices for pharmacological compounds[1], attributes such as permeability to small molecules, soft consistency and low interfacial tension between the gel and aqueous solution are some of the important properties that have helped to generate this interest.

Therefore, a further object of our research was to characterize graft copolymers on amylose as hydrogels; so the water sorption capacity was determined. The water absorbed by a hydrogel network could be represented quantitatively by the equilibrium water content (%*EWC*). This parameter can be calculated from the ratio of the weight of water in the hydrogel to the weight of the hydrogel at equilibrium hydration, expressed as a percentage[9]:

$$\%EWC = \frac{W_{\text{hyd}} - W_{\text{dry}}}{W_{\text{hyd}}} \times 100$$

%*EWC* was determined by weighing samples in a dry state (W_{dry}) and in a swollen state (W_{hyd}) calculated after placing the dry samples in aqueous solutions, and maintaining them during an adequate equilibration time.

Also, because of possible applications as drug delivery systems, the products were characterized by the equilibrium degree of swelling as a function of the pH of the solutions, since the pH changes through the gastrointestinal (GI) tract: neutral pH (mouth), acid pH (stomach) and slightly basic pH (intestine). The influence of pH was determined by placing the products in buffers of different pH, ranging from 1 to 10. Owing to the potential application of these materials as biomaterials, all the measurements were carried out at body temperature (37°C).

RESULTS AND DISCUSSION

Synthesis of graft copolymers

Before starting the study of the graft copolymer mixtures, we tested the behaviour of graft copolymers using only one monomer. The results are listed in *Table 1*. As the molecular weight of the grafted monomer increases, %*CG* increases too, following the sequence MA < EA < BA < HPMA < EGDMA. In addition, the %*PM* results, considering only the acrylates, increase in the same way as the size of the alkyl side group. So, based upon the %*PM* parameter, it could be assessed that the increase is also related to the reactivity of the monomers, because the higher the %*PM* the higher the reactivity.

Synthesis of graft copolymer mixtures

Effect of hydroxylic/non-hydroxylic monomer ratio. The variation of reaction yields with the feed composition for the three mixtures studied, HPMA/MA, HPMA/EA and HPMA/BA, is collected in *Tables 2, 3* and *4* respectively. Comparing the results in these tables it can be seen that the graft copolymerization yields of monomer mixtures have a similar tendency. In spite of the fact that no big difference can be noted, the %*CG*

Table 1 Grafting yields for different acrylic monomers grafted on amylose

Monomer	Total weight (g)	%*CG* (wt/wt) Grav.[a]	%*CG* (wt/wt) ^{13}C[b]	%*PM* (mol/mol)
MA	3.75	187	193	43
EA	5.65	282	278	78
BA	6.80	340	328	80
HPMA	7.58	379	388	83
EGDMA	7.78	389	–	65

[a] Data obtained gravimetrically
[b] Data obtained from ^{13}C n.m.r.

Table 2 Variation of grafting yields with feed composition in graft copolymers of HPMA/MA mixtures on amylose

HPMA/MA (mol/mol)	Total weight (g)	%*CG* (wt/wt)		%*PM* (mol/mol)
		Grav.[a]	^{13}C[b]	
0/100	3.7	187	193	43
20/80	3.2	161	164	22
40/60	5.0	250	238	53
50/50	5.3	264	262	55
60/40	5.5	273	275	57
80/20	6.2	312	315	65
100/0	7.6	379	388	83

[a] Data obtained gravimetrically
[b] Data obtained from ^{13}C n.m.r.

Table 3 Variation of grafting yields with feed composition in graft copolymers of HPMA/EA mixtures on amylose

HPMA/EA (mol/mol)	Total weight (g)	%*CG* (wt/wt)		%*PM* (mol/mol)
		Grav.[a]	^{13}C[b]	
0/100	5.6	282	278	77
20/80	4.1	202	210	36
40/60	5.1	254	251	48
50/50	5.6	282	280	56
60/40	6.7	336	340	71
80/20	7.3	366	375	81
100/0	7.6	379	388	83

[a] Data obtained gravimetrically
[b] Data obtained from ^{13}C n.m.r.

Table 4 Variation of reaction yields with feed compositions in graft copolymers of HPMA/BA mixtures on amylose

HPMA/BA (mol/mol)	Total weight (g)	%*CG* (wt/wt)		%*PM* (mol/mol)
		Grav.[a]	^{13}C[b]	
0/100	6.8	340	328	80
20/80	6.5	326	334	72
40/60	6.8	339	342	74
50/50	7.1	356	361	79
60/40	7.5	378	374	84
80/20	7.6	382	379	84
100/0	7.6	379	388	83

[a] Data obtained gravimetrically
[b] Data obtained from ^{13}C n.m.r.

values are larger following the sequence HPMA/MA, HPMA/EA, HPMA/BA, which is clearly related to the molecular weights of the structural unit, which increases in the same sequence. The evolution of %*CG* and %*PM* for each mixture, excluding the values for pure monomers, shows a gradual increase with the enrichment of the feed composition in hydroxylic monomer. This increase can be attributed, according to earlier studies[10], to the greater capacity of HPMA to graft and homopolymerize, compared to acrylates.

The results were also corroborated by ^{13}C n.m.r. spectroscopy analysis. In *Figure 1* can be seen the spectra of the three graft copolymer mixtures. In previous papers similar spectra of a number of graft copolymers have been analysed[11,12], and the characteristic peaks identified. In addition, if we register the spectra under specific conditions, %*CG* can be calculated directly from the n.m.r. spectrum without previous degradation of the products, as we have reported in a preceding paper[11]. Thus, %*CG* was calculated by comparing representative peaks of each component of the grafted products: Am (amylose), acrylate and HPMA. As can be seen in *Tables 2, 3* and *4*, the results obtained gravimetrically and by ^{13}C n.m.r. are almost the same by both methods.

Moreover, making a comparative analysis from these spectra with different feed compositions, the molar composition of the grafted copolymer chains could be calculated taking a representative peak for each component. The results collected in *Table 5* show that, in all cases, the ratio between HPMA and acrylate signals is greater than those of their corresponding feed composition ratios, a higher molar fraction of HPMA always being obtained in the copolymer than in the feed. Similar results have been obtained by Gaddam *et al.*[13] with HPMA/acrylate copolymers synthesized at low conversion. So, graft copolymerization does not influence, to a great extent, the copolymer chain obtained by radical polymerization and the results corroborate the higher reactivity of HPMA compared to that of the acrylates.

Effect of addition of EGDMA. One method to obtain a wide variety of hydration degrees and different swelling behaviours is based on obtaining a crosslinked copolymer with bi- or tetrafunctional monomers, because the hydration of this kind of material is mainly controlled by the crosslink density. The introduction of a bifunctional monomer, EGDMA, would produce a crosslinked structure. Thus, based on previous results[4], it seemed to be interesting to study the influence on the final grafting yields of the addition of 34 mol% of EGDMA in the feed.

By comparison of the results listed in *Tables 1* and *6*, we can observe that the %*CG* of graft copolymer using EGDMA changed in the same way as in graft copolymers of one monomer without it. Only in the case of MA is an increase in %*CG* produced when the third monomer is added, principally due to the greater molecular weight of EGDMA.

Graft copolymers with EGDMA as comonomer are not soluble because of the possibility of formation of a crosslinked structure; so, it is not possible to study them by n.m.r. analysis. Thus, taking into account that in all

Table 5 Monomer ratio of HPMA/acrylate (mol/mol) in the feed and in the grafted copolymer calculated by ^{13}C n.m.r.

Feed composition HPMA/acrylate (mol/mol)	Grafted copolymer composition (mol/mol)		
	HPMA/MA	HPMA/EA	HPMA/BA
0.25	1.27	1.13	0.49
0.67	1.42	5.06	1.36
1	2.41	5.25	1.57
1.5	7.33	10.11	2.35
4	10.11	9.0	4.88

Table 6 Grafting yields for different acrylic monomers grafted on amylose with 34 mol% of EGDMA

Monomer	Total weight (g)	%*CG* (wt/wt)	%*PM* (mol/mol)
MA	5.05	252	52
EA	5.53	276	57
BA	5.84	292	54
HPMA	6.52	326	59

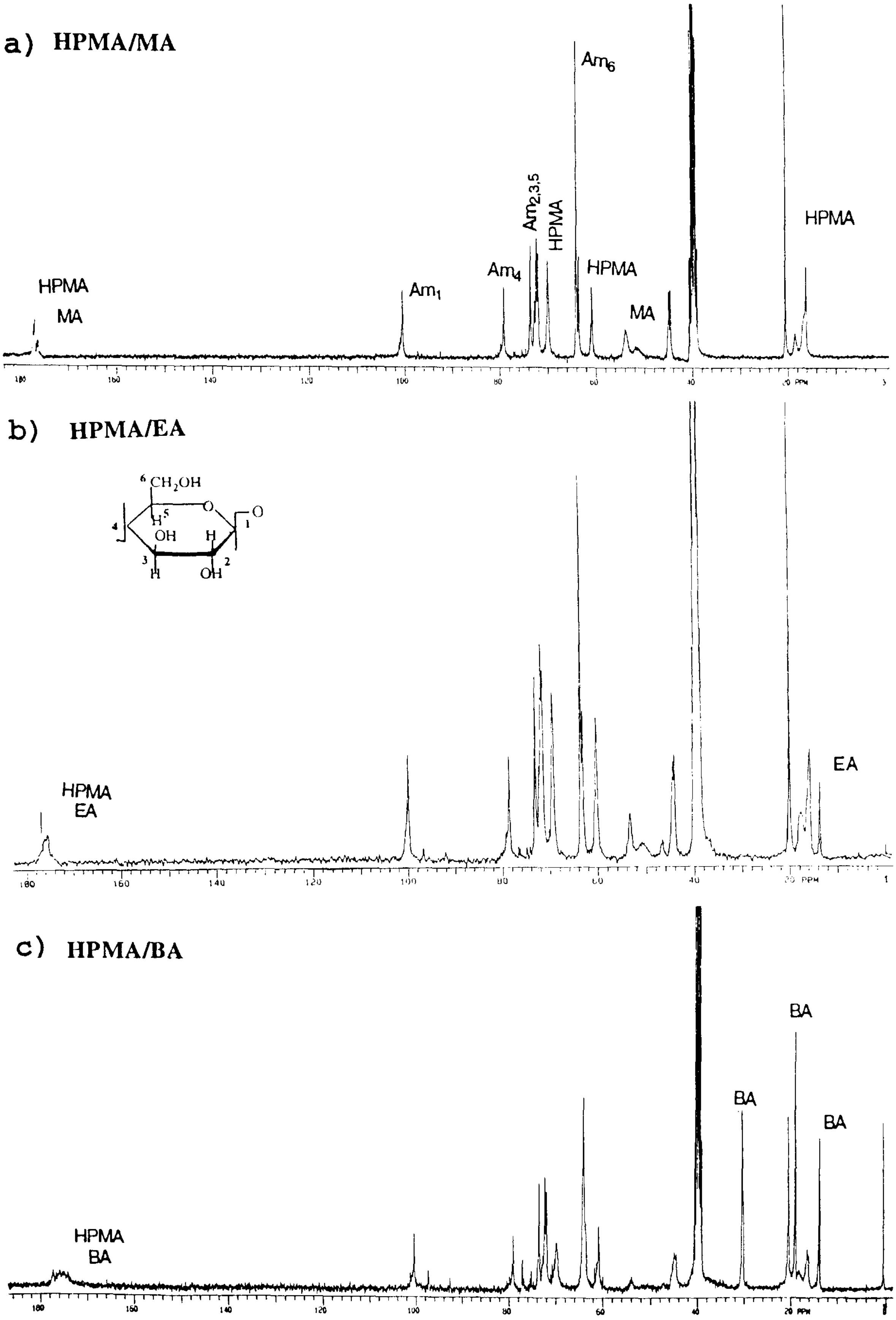

Figure 1 ^{13}C n.m.r. spectra of graft copolymer mixtures of HPMA/acrylate with 50/50 (mol/mol) of feed composition on amylose

cases the grafting efficiency was about 90%, the %*PM* can be calculated. In spite of the results of %*CG*, an important variation can be observed in %*PM* parameter, leading to practically the same results in all the graft copolymers, independently of the acrylic monomer. This could be due to the higher ability of EGDMA to react, because of its bifunctionality. This confirms that the influence on the grafting yields of the nature of the

Table 7 Grafting yields of graft copolymerization of 50/50 (mol/mol) of HPMA/acrylate on amylose with 34 mol% of EGDMA

Mixture	Total weight (g)	%*CG* (wt/wt)	%*PM* (mol/mol)
HPMA/MA	5.48	174	52
HPMA/EA	5.84	192	55
HPMA/BA	5.91	195	53

monomers is less important when there is a bifunctional monomer in the feed.

In the same way, graft copolymer mixtures with 50/50 feed composition (HPMA/MA, HPMA/EA, HPMA/BA) were obtained using 34 mol% of EGDMA. These polymers were also characterized by %*CG* and %*PM*, and the results are listed in *Table 7*. It is clear from this table that %*PM* reached practically the same values in the three mixtures, independently of the other grafted monomer, just like the graft copolymers of a single monomer.

All in all, we can assess that the addition of a bifunctional monomer (EGDMA) is the main factor to determine the final yields in graft polymerization. Similar behaviour has been obtained in an earlier work using another carbohydrate, amylopectin[4].

Swelling behaviour

The maximum amount of water that can be maintained in a polymeric gel depends on the hydrophilicity, and thus on the hydrophilicity of the monomer or, in a more general way, on the balance of hydrophobicity/hydrophilicity of the components of the hydrogel. Then, previously to the study of water absorption capacity of graft copolymer mixtures, we have found it interesting to analyse the swelling behaviour of the different components of these graft copolymers separately. Thus, we start with homopolymers, then amylose, graft copolymers of a single monomer, graft copolymer mixtures and finally graft copolymers using EGDMA.

First, we studied %*EWC* for the acrylic homopolymers, whose results are plotted in *Figure 2*. It is known that the swelling, in addition to the hydrophobicity of the constituents, depends upon the balance of contributing steric and polar effects. In our case, the polar contribution arises predominantly from the hydroxyl groups (HPMA and amylose) and to a lesser extent from the ester group, whereas the steric effect arises from the combined contribution of the α-methyl group and alkyl side chain of the hydrophobic monomers. In the light of these results, the influence of the alkyl group size is, obviously, noticeable. The %*EWC* values are strongly affected by the amount of hydrophobic groups in the side chain, obtaining values of 5% for BA and 32% for MA.

Regarding the swelling behaviour of amylose, it has an equilibrium water content of 60%, which does not change with pH. Two main factors contribute to this high value: one is the great amount of hydroxylic groups in this structure (which favours the process of absorption by the formation of hydrogen bonds with water) and the other is the fact that amylose was formed by a 'network' constituted by a helicoidal conformation, and able to retain inside a high amount of water[14].

On the other hand, in graft copolymers of a single monomer, the degree of swelling is influenced by the two components: the polysaccharide and the grafted acrylic polymer, as can be seen in *Figure 3*. It is important to point out that the differences in %*EWC* found on the acrylic homopolymer are not so noticeable when they are grafted, reaching a similar value in all cases.

Therefore, we can assess that carbohydrate is the main factor responsible for water absorption, and this water absorption capacity decreases in comparison with amylose, owing to the partial rupture of the helicoidal structure, caused by the graft copolymerization.

Besides, focusing on the evolution of equilibrium swelling content throughout the acid–alkali range, only HPMA homopolymer and HPMA graft copolymers show pH dependence. The maximum is obtained at basic pH, changing from 30% at neutral pH to 53% at pH = 10. This behaviour could be ascribed to a sharp transition of extended polymeric chains at pH > 7 to a compact morphology in acidic media. Siegel[15] and Grigon[16] show similar characteristic transitions in specimens based on polyelectrolyte gels of poly(acrylic acid) or copolymer bearing carboxylic groups as side substituents. Firestone[17] reported the behaviour of weak carboxylic acid pendent groups introduced in solutions at several pH values, and found an increase in the swelling with an increase of the pH of the solutions. A similar pH dependence had been observed in a methacrylic polymer by Vazquez[18]. Poly(ethyoxytriethylene

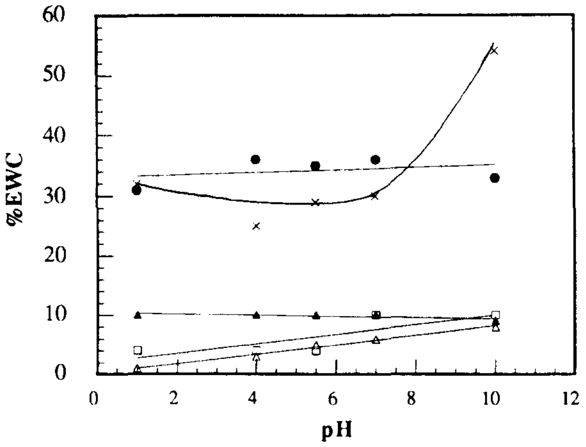

Figure 2 Equilibrium water content (%*EWC*) at different pH values of several acrylic homopolymers: (●) MA, (□) EA, (△) BA, (×) HPMA, (▲) EGDMA

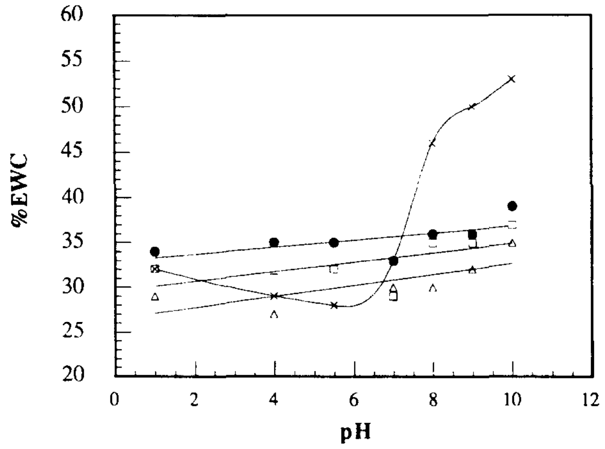

Figure 3 Equilibrium water content (%*EWC*) at different pH values in graft copolymers on amylose: (●) MA, (□) EA, (△) BA, (×) HPMA

glycol monomethacrylate) showed high swelling capacity at basic pH, the oxyethylene side residues being responsible for this particular behaviour, due to their strong hydrophilic character, which favours the formation of the compact coil arrangement at low pH. An increase in %*EWC* had also been found in graft copolymers of HEMA in gelatin[19].

Therefore, taking these results into account we could say that, in our graft copolymers, at physiological and slightly acid pH, most of the hydrophobic segments of the chain tend to be aggregated, and therefore the water that is hydrogen-bonded with the polar groups is preferentially accumulated on the periphery, giving rise to a less swollen hydrogel. However, high pH allows an extended conformation of the polymer chain and a higher hydration of hydrophilic groups is obtained by orientation around the hydrogen-bonding group of the chain. Thus the influence of the hydroxylic groups is more noticeable, as has been reported in other works[20].

In order to obtain more information about the method of absorption of water and to confirm the formation of hydrogen bonds in HPMA graft copolymers, we have studied the effect of the addition of a strong hydrogen-bond disruptor, the aketone. A decrease from 30 to 20% was observed on the swelling in water in the presence of low amounts of such ketone. This fact could be ascribed to the rupture of the hydrogen bonds formed between the hydroxylic groups and water. This behaviour is not perceptible when these measurements are carried out with graft copolymers, which do not contain HPMA.

Effect of grafted hydroxylic/non-hydroxylic monomer ratio. In order to study the effect on the equilibrium water content of the hydroxylic/non-hydroxylic ratio, graft copolymers containing varying proportions of hydrophobic monomers (ranging from 0% to 100%) were analysed. In *Figures 4, 5* and *6* are plotted the variation of %*EWC* as a function of pH in the three graft copolymer mixtures studied in this work, leading to a %*EWC* of approximately 30% for all products. These data point out again a remarkable decrease with regard to that of amylose, just like graft copolymers of a single monomer, which is attributed to the partial rupture of the amylose structure, as we have mentioned above.

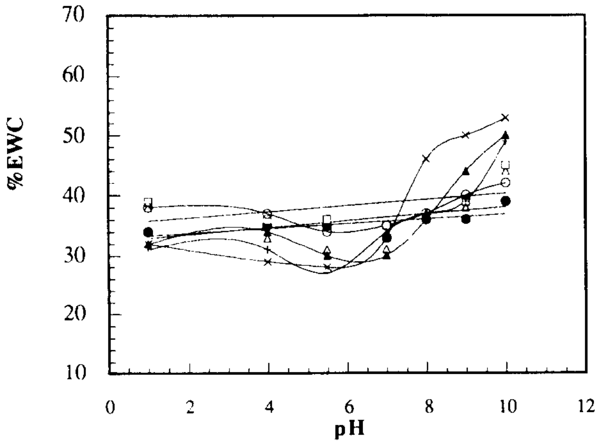

Figure 4 Equilibrium water content at different pH values in graft copolymers of HPMA/MA on amylose as a function of the proportion of HPMA (mol%) in the feed: (●) 0%, (△) 20%, (□) 40%, (▲) 50%, (+) 60%, (○) 80%, (×) 100%

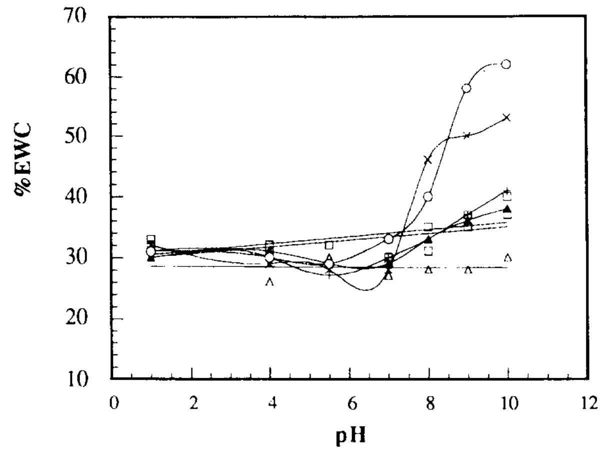

Figure 5 Equilibrium water content at different pH values in graft copolymers of HPMA/EA on amylose as a function of the proportion of HPMA (mol%) in the feed: (□) 0%, (△) 20%, (□) 40%, (▲) 50%, (+) 60%, (○) 80%, (×) 100%

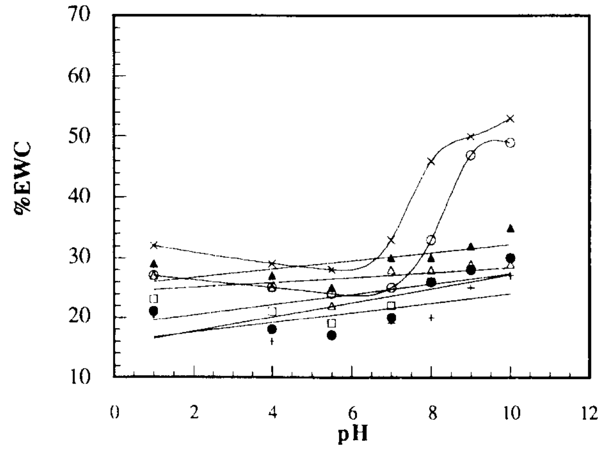

Figure 6 Equilibrium water content at different pH values in graft copolymers of HPMA/BA on amylose as a function of the proportion of HPMA (mol%) in the feed: (▲) 0%, (△) 20%, (□) 40%, (●) 50%, (+) 60%, (○) 80%, (×) 100%

The effect of the hydrophobic component on %*EWC* can also be shown in these figures. It can be observed that the equilibrium swelling values increase with the increase of the percentage of hydrophilic monomer in the graft copolymer. In copolymers where the acrylate is the major component, the %*EWC* of the hydrated copolymer is virtually independent of the pH, the values fitting a straight line. In these compositions the hydrophobic interaction of alkyl side chains is the dominant factor controlling the water absorption of the graft copolymers. Therefore, comparing the results of %*EWC* in the three synthesized mixtures, the lowest values are obtained when using a more hydrophobic monomer, such as BA.

Moreover, when the hydrophilic monomer is the major component, the overall hydrophilicity increases, controlling %*EWC*, and then a higher pH dependence can be seen. Besides, a slight increase in the swelling can be observed as the HPMA content in the gel increases, probably due to the higher amount of hydroxylic groups. Thus, the higher swelling found at basic pH could be attributed to the presence of the HPMA monomer in the graft copolymer.

Summarizing, we could say that all copolymers obtained can be considered as hydrogels because all of them have a %*EWC* > 20%[1]. All the gels obtained with different amounts of HPMA and different acrylates are obtained with almost the same values of %*EWC*. Therefore, the ratio between the hydroxylic and non-hydroxylic groups is not a critical factor to control the final water content in these hydrogels, since the carbohydrate is mainly responsible for the absorption. However, this ratio is responsible for the observed swelling changes of behaviour at high pH. This kind of material also shows excellent biocompatible behaviour due to the composition and high water content.

Effect of addition of EGDMA. In graft copolymers obtained by grafting a single monomer together with 34% of EGDMA, the water absorption increases significantly as can be seen by comparing *Figures 3* and *7*. As we know, the introduction of a bifunctional monomer forms a crosslinked network able to retain greater amounts of water inside. Another factor contributes to this difference: this is the fact that these materials have a minor %*PM* and a minor %*CG*; therefore, the higher content of carbohydrate will also favour the increase in %*EWC*.

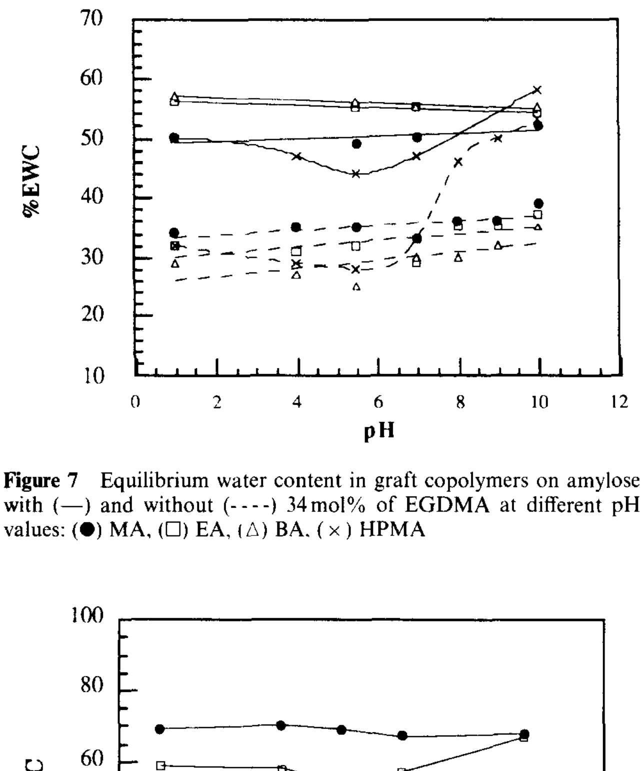

Figure 7 Equilibrium water content in graft copolymers on amylose with (—) and without (----) 34 mol% of EGDMA at different pH values: (●) MA, (□) EA, (△) BA, (×) HPMA

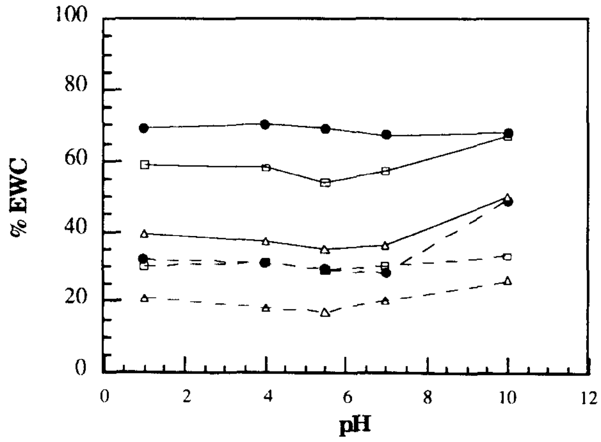

Figure 8 Equilibrium water content in different graft copolymer mixtures 50/50 (mol/mol) on amylose with (—) and without (----) 34 mol% of EGDMA at different pH values: (●) HPMA/MA, (□) HPMA/EA, (△) HPMA/BA

A similar behaviour can be observed in *Figure 8* for graft copolymers obtained from a 50/50 monomer mixture, with and without EGDMA. In the three mixtures higher values of %*EWC* are obtained, reaching values of approximately 70% for HPMA/MA mixture. In this case the influence of basic pH on the swelling behaviour is less important, since now the factor that controls the swelling behaviour is mainly the crosslinked structure and not the amount of polar groups.

It can be concluded that the introduction of a bifunctional comonomer governs the water absorption, due to the formation of a covalent crosslinked network, where water can be retained, increasing the %*EWC* values.

These results suggest that the incorporation of a different proportion of acrylic monomers with different nature allows the control of %*EWC* in hydrogels that could be obtained with a predictable amount of water. In this sense, the graft copolymers obtained in this work may have improved mechanical and biodegradability properties and can be designed to be used as polymeric supports for drug delivery systems.

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