

Graft Copolymerization of Different Mixtures of Acrylic Monomers on Amylopectin. Swelling Behavior

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SYNOPSIS

Hydroxylic and nonhydroxylic acrylates—methyl acrylate (MA), ethyl acrylate (EA), butyl acrylate (BA), hydroxypropyl methacrylate (HPMA), ethylenglycol dimethacrylate (EGDMA), and mixtures of HPMA–MA, HPMA–EA, HPMA–BA in a 50/50 feed composition—were grafted onto amylopectin with different amounts of crosslinking agent, EGDMA. Percent of total conversion, percent crude grafting, and influence of pH in water content were studied. In this sense it was only at pH 10 when a real variation in the water content could be seen. It was also proved that the highest values were obtained when one of the comonomers was EGDMA with a 34 mol % of the initial feed composition. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Hydrogels are known as biomaterials due to their similar physical properties to those of living tissues. This resemblance is based on their high water content, soft and rubbery consistency, and low interfacial strength. In particular, hydrophilicity is one of the most important factors for hydrogels in medical use; however, this hydrophilicity may lead to poor mechanical properties thereby limiting their use in biomedical applications.

It has been demonstrated that these types of compounds have the capacity to absorb great amounts of water, and it is believed that this water content is intrinsically related to their biocompatibility.¹ Considering the possibility of using these types of materials as drug delivery systems, the water content measurements are of great importance since there is a possible correlation between the rate of drug release and water swelling properties of hydrogels. In this field, owing to the different pH regions existent in the gastrointestinal tract [pH 1–2 (stomach), pH 4–6 (duodenum), pH 6.5–7 (mouth), and pH 6–8 (intestine)], it would be interesting to

characterize the compounds obtained by their water retention content at different pHs.

In this work we intend to obtain new hydrogels with, on the one hand, improved mechanical stability and, on the other hand, with improved biocompatibility. This last property will be attained by the incorporation of natural macromolecules (collagen, gelatin, starch, etc.).² With this goal we obtained acrylic copolymers of well-known mechanical stability grafted on carbohydrate.

Hydrogels were synthesized by graft copolymerization into amylopectin of different acrylic monomers: 2-hydroxypropyl methacrylate (HPMA), methyl acrylate (MA), ethyl acrylate (EA), butyl acrylate (BA), and ethylenglycol dimethacrylate (EGDMA). In the same way, graft copolymers of HPMA in combination with MA, EA, and BA with a 50/50 feed composition, to study the influence of the side alkyl group length, and a variable amount of crosslinking agent, EGDMA, were synthesized and the grafting yield and swelling behavior were studied.

EXPERIMENTAL

Materials

The amylopectin used was a commercial product, amylopectin UG (AVEBE Holland). All the mono-

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mers methyl, ethyl, and butyl acrylate, ethyleneglycol dimethacrylate, and hydroxypropyl methacrylate (Merck) were purified by distillation in previously described conditions.³

All the other products were reagent grade or the equivalent.

Method

The graft copolymers were obtained by the method described in previous studies.^{4,5} Amylopectin (2 g) was dispersed in 290 mL of bi-distilled water under a constant light. After purging the medium with nitrogen for 30 min, the required amount of both monomers and crosslinking agent (0.047 mol total) were added, and 5 min later, 10 mL of ceric ion solution was added. Grafting was allowed to proceed for 4 h at 30°C by stirring under a stream of nitrogen.

The grafting reactions of various acrylic monomers: MA, EA, BA, HPMA, EGDMA, and three different monomer mixtures HPMA-MA, HPMA-EA, and HPMA-BA in a 50/50 feed composition were studied. In the last case the proportion of 50/50 was selected because of the yields obtained at the same conditions in previous works⁵ were carried out. Different amounts of EGDMA, 0–7 mol %, with respect to the total monomer concentration in the initial feed composition (0.047 mol) were added to the monomer mixture, as a crosslinking agent, with the end of controlling the water content.

The products obtained were filtered and the solid washed with water and nitric acid solution and dried to constant weight under vacuum at 50°C to obtain the xerogel. In contrast with previous works, the unreacted amylopectin and homopolymers were not removed because it has not been found that a solvent removed the ungrafted material without dissolving part of the grafted product, as we proved through the infrared spectroscopy of the residue solutions. Only in the graft copolymers with a 34 mol % of EGDMA in the initial feed composition was it possible to separate the ungrafted homopolymers due possibly to the crosslinked network formed by this difunctional monomer, which favors no dissolution of the product obtained. In these cases the grafting efficiency was about 91–94%.

Characterization of Graft Copolymers

In order to characterize the products obtained two parameters are defined: percent of total conversion (%CT)⁶ and percent of crude grafting (%CG)⁷:

$$\%CT = \frac{\text{weight of grafted and ungrafted monomer}}{\text{weight of initial monomer}} \times 100$$

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

In the same way, the water content of rehydrated xerogels was determined after the adequate equilibration time in water solution (a week). This water content was calculated by a gravimetric technique using the following relationship⁸:

$$\begin{aligned} \% \text{ equilibrium water content (EWC)} \\ = \frac{W_{\text{hyd}} - W_{\text{dry}}}{W_{\text{hyd}}} \times 100 \quad (3) \end{aligned}$$

where W_{hyd} is hydrated gel weight and W_{dry} is initial xerogel weight.

As we have said before, the compounds that are capable of imbibing larger quantities of water without dissolving, hydrogels, have been employed as drug delivery systems because of their biocompatibility, their ability to release imbibed drugs in aqueous medium, and the ease of regulating such drug release by controlling water swelling and crosslinking density. So, to this end, it would be interesting to study the influence of pH on the swelling behavior of the hydrogels obtained due to the pH variations throughout the gastrointestinal tract. In this work the solutions of different pHs used are the following: pH 1 (hydrochloric acid 0.1N), pH 4 (buffer, Panreac), pH 7 (bidistilled water), pH 10 (buffer, Panreac).

All the absorptions were carried out at room temperature.

RESULTS AND DISCUSSION

Effect of a Crosslinking Agent on the Grafting Parameters

First of all, graft copolymers of one monomer (MA, EA, BA, HPMA and EGDMA) onto amylopectin have been studied.

The %CT parameter gives an idea of the monomer reactivity because the higher the conversion the higher the reactivity of the monomer. As can be seen in Table I, reactivity of the acrylates are higher as length of the side alkyl group increases, which agrees

Table I Yields of the Graft Copolymerization of Different Monomers on Amylopectin

Monomer	Total Weight (g)	Total Conversion (%)	Crude Grafting (%)
MA	3.3	33	66
EA	3.9	40	94
BA	6.6	77	232
HPMA	7.5	81	274
EGDMA	8.2	68	309

with the values found in the literature: HPMA > BA > EGDMA > EA > MA. In the same way, it would be expected that this sequence would be repeated in the %CG parameter. However, in this parameter it has to take into account the molecular weight of added monomer so, in spite of the reactivities found through the %CT parameter, the highest value of %CG is obtained for the EGDMA graft copolymer because its lower reactivity is compensated for by its higher molecular weight.

The yields obtained for the different mixtures are listed in Tables II–IV.

If we observe the results of all the mixtures, we can prove that by increasing the amount of added crosslinking agent, both parameters, the %CG and the %CT, increase too. That is an expected behavior if we take into account that when EGDMA is added, we are introducing a difunctional monomer, which in addition has higher molecular weight and can be grafted in a higher proportion than the other monomer of each mixture.

Making a comparative analysis, it can be seen that there are no big differences between the three mixtures. However, it should be pointed out that in the HPMA–BA mixture the variation of %CT with

Table II Yields of the Graft Copolymerization of HPMA–MA (50/50 mol %) on Amylopectin with Different Amounts of EGDMA

%EGDMA	Total Weight (g)	Total Conversion (%)	Crude Grafting (%)
7	5.9	69	196
2	5.3	60	166
1	4.8	51	139
0	4.7	50	135

Table III Yields of the Graft Copolymerization of HPMA–EA (50/50 mol %) on Amylopectin with Different Amounts of EGDMA

%EGDMA	Total Weight (g)	Total Conversion (%)	Crude Grafting (%)
7	6.2	70	205
2	5.3	57	165
1	4.9	51	145
0	4.9	51	145

the addition of crosslinking agent is less important. This is a logical behavior if we take into account the reactivity sequence found in literature data: HPMA > BA > EGDMA > EA > MA. In the other two mixtures, HPMA–MA and HPMA–EA, in contrast, as the reactivity of the average monomeric unit increases when we add the crosslinking agent the influence of added crosslinking agent is higher.

On the other hand, we thought it would be interesting to copolymerize each monomer and the above-mentioned monomer mixtures with EGDMA (Table V), usually used as a crosslinking agent. For all the reactions we have chosen the amount of EGDMA used for graft copolymerization of mixtures of three monomers, which contains a 34 mol % of EGDMA as comonomer.

If we compare first the values obtained for MA, EA, BA, and HPMA graft copolymers with and without EGDMA as comonomer (Tables I and V), it can be seen that in the case of the monomers that are less reactive than EGDMA, the introduction of this difunctional monomer causes an increase in both parameters and a decrease for the monomers that are more reactive than EGDMA.

Finally, if we compare the graft copolymers of the

Table IV Yields of the Graft Copolymerization of HPMA–BA (50/50 mol %) on Amylopectin with Different Amounts of EGDMA

%EGDMA	Total Weight (g)	Total Conversion (%)	Crude Grafting (%)
7	6.1	63	205
2	5.9	61	199
1	5.7	58	188
0	5.5	55	177

Table V Yields of the Graft Copolymerization of Various Monomers, with a 34 mol % of EGDMA as Comonomer, on Amylopectin

Monomers	Total Weight (g)	Total Conversion (%)	Crude Grafting (%)
MA-EGDMA	4.7	47	135
EA-EGDMA	4.9	48	149
BA-EGDMA	6.1	58	208
HPMA-EGDMA	6.4	65	222
HPMA-MA-EGDMA	5.8	57	190
HPMA-EA-EGDMA	6.1	60	208
HPMA-BA-EGDMA	6.2	58	209

mixtures of three monomers, it can be seen that there are no big differences between the reaction yields. In the way the length of alkyl side group increases, owing to higher molecular weight average of structural grafted unit, the %CG increases slightly. On the other side, as Table V shows, the %CT values are similar. All of this means that it is the EGDMA comonomer that determines final yield in these terpolymeric graft reactions.

Effect of Crosslinking Agent on Swelling Behavior

These types of materials, hydrogels, are being extensively studied for biomedical applications such as implants and drug delivery systems. As we know, for this kind of applications it is very important to determine the water absorption capacity of these materials at different pHs.

To start with, it would be interesting to know the water content of the ungrafted polysaccharide. Several factors contribute to its high and practically constant water content value, at the different pHs. This value is of approximately 63%. We assume that this high water content is owing to the branched structure and the great amount of hydroxilic groups of the amylopectin in which the water molecules can be retained.

After that, swelling behavior of graft copolymers of one monomer were studied. In light of the results given in Table VI it can be said that the graft copolymerization produces an important decrease of water content that can be attributed to the partial rupture of the carbohydrate structure.

In general, it can be said that the water content value of each graft copolymer hardly changes at the different pHs except for the HPMA copolymer.

The HPMA graft copolymer has a very different behavior at low and high pH. At pHs under 7 the

water content remains practically constant, but at high pH the hydroxilic groups of HPMA graft copolymer are ionized (hydrogen bonds and hydrophobic interactions are broken), and the higher electrostatic interactions and hydration of ions increase the water content. This behavior is in agreement with the results obtained by Kopecek et al.⁹ They found that although the more hydrophilic the gel the lower the pH sensitivity, some hydrophilic monomers, for example, because of the strong intramolecular hydrogen bonding ability they have, at low pH give a lower swelling degree than expected from their hydrophilicity.

In the same way, the water content (%EWC) of HPMA-MA, HPMA-EA, and HPMA-BA (50/50) graft copolymers onto amylopectin with different amounts of crosslinking agent were measured as a function of pH (Figs. 1, 2, and 3, respectively).

If we observe the results obtained in each mixture, it can be said that the water content values are approximately the same for pHs under 7, and it is only at pH 10 when a real variation can be observed. This behavior could be due to that at this basic pH, the hydroxyl groups of HPMA monomer are ionized, and hydrophobic interactions and intramolecular hydrogen binding present at low pH are interrupted.⁹

Table VI Equilibrium Water Content (%EWC) of Different Graft Copolymers of One Monomer, at Various pHs

Monomer	pH = 1	pH = 4	pH = 7	pH = 10
MA	42	41	42	45
EA	38	41	37	41
BA	31	30	33	35
HPMA	40	38	38	60
EDGMA	48	47	47	47

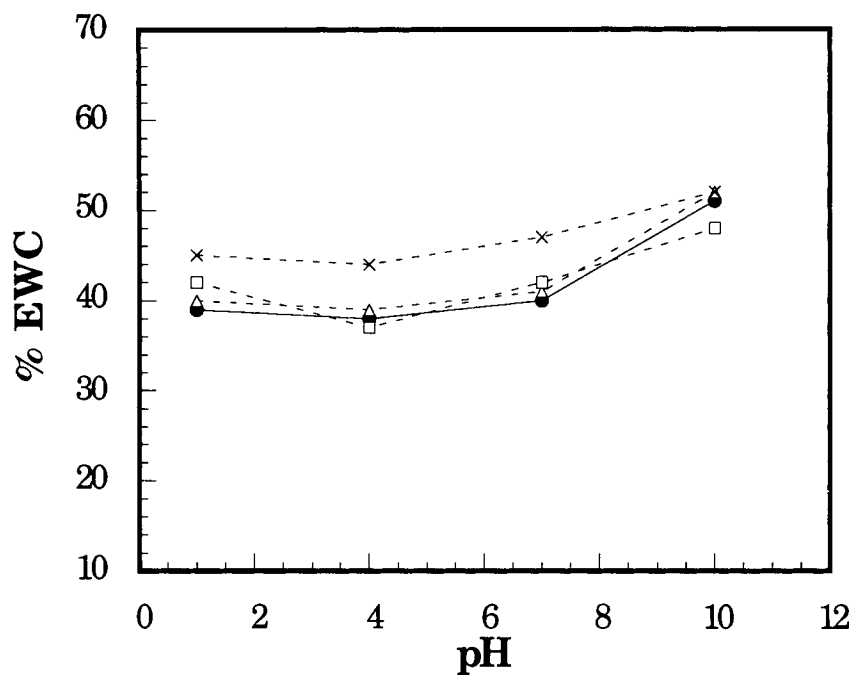


Figure 1 Equilibrium water content (%EWC) of HPMA-MA (50/50)-amylopectin graft copolymers, with different amounts of EGDMA: (●) 0%, (△) 1%, (□) 2%, (×) 7%, as a function of pH.

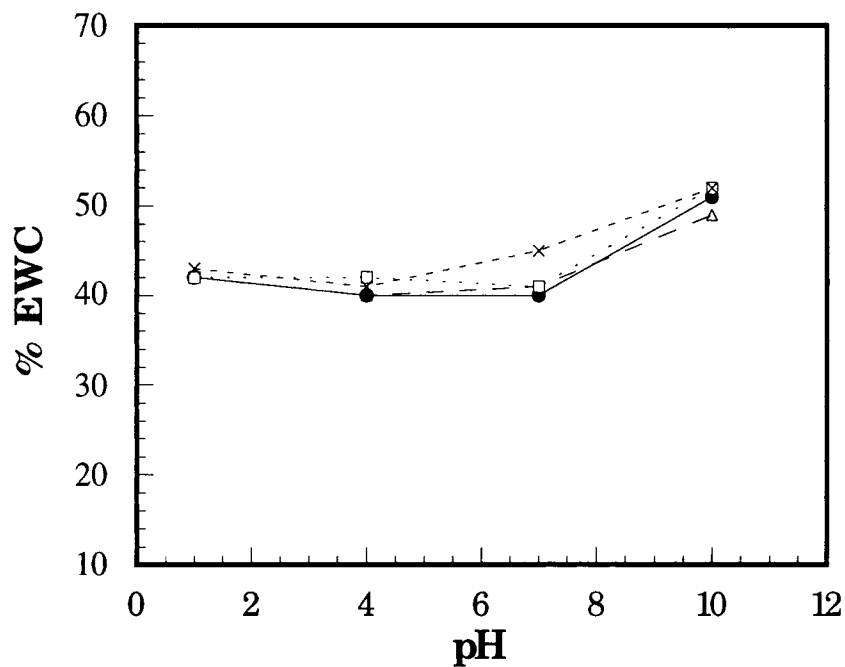


Figure 2 Equilibrium water content (%EWC) of HPMA-EA (50/50)-amylopectin graft copolymers, with different amounts of EGDMA: (●) 0%, (△) 1%, (□) 2%, (×) 7%, as a function of pH.

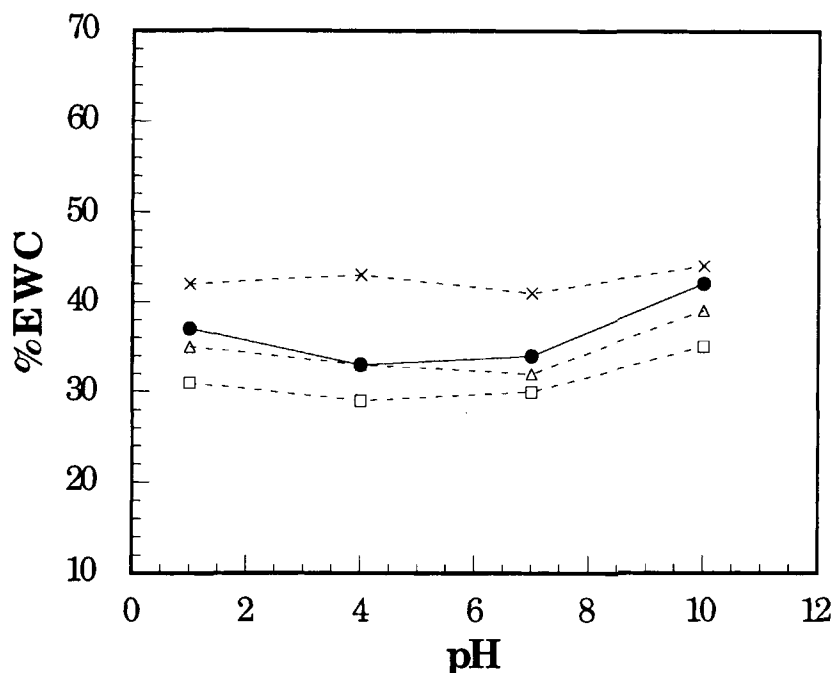


Figure 3 Equilibrium water content (%EWC) of HPMA-BA (50/50)-amylopectin graft copolymers, with different amounts of EGDMA: (●) 0%, (△) 1%, (□) 2%, (×) 7%, as a function of pH.

Besides, as we have mentioned before, the interaction and repulsion of ions and solvation of these ions produce an increase in the water absorption parameter.

It is also found that generally, if we add 1–2% of crosslinking agent, EGDMA, to the feed composition, the %EWC values remain practically constant (even for the HPMA-BA graft copolymer, water absorption decreases), but when we add a 7% of EGDMA to the feed composition, an increase in the water content is observed. That behavior at high crosslinking concentrations may presumably be due to a decrease of hydrogen bonds and the formation of covalent crosslinked network where water could be retained, increasing the %EWC value.

As it is known, absorption depends on the ratio

of the hydrophilic/hydrophobic regions that exist in the graft copolymer. In this sense, and for the mixture HPMA-BA, since the length of the butyl radical and the %CG (with different amount of EGDMA) are higher than in the other mixtures, there will be more hydrophobic areas that will repel water molecules and therefore the water content

Finally, the swelling behavior of graft copolymers with a 34 mol % of EGDMA in the feed composition were studied. If we compare the results of graft copolymers of one monomer with and without EGDMA (Tables VI and VII), it can be seen that the introduction of a 34 mol % of a bifunctional monomer produces an increase in the water content. For example, for MA-EGDMA, EA-EGDMA, and BA-EGDMA mixtures, an increase of 50% in the

Table VII Equilibrium Water Content (%EWC) of Different Graft Copolymers of One Monomer with 34 mol % of EGDMA, at Various pHs

Monomer	pH = 1	pH = 4	pH = 7	pH = 10
MA-EGDMA	62	62	62	66
EA-EGDMA	61	60	60	62
BA-EGDMA	48	46	47	52
HPMA-EGDMA	40	36	40	47

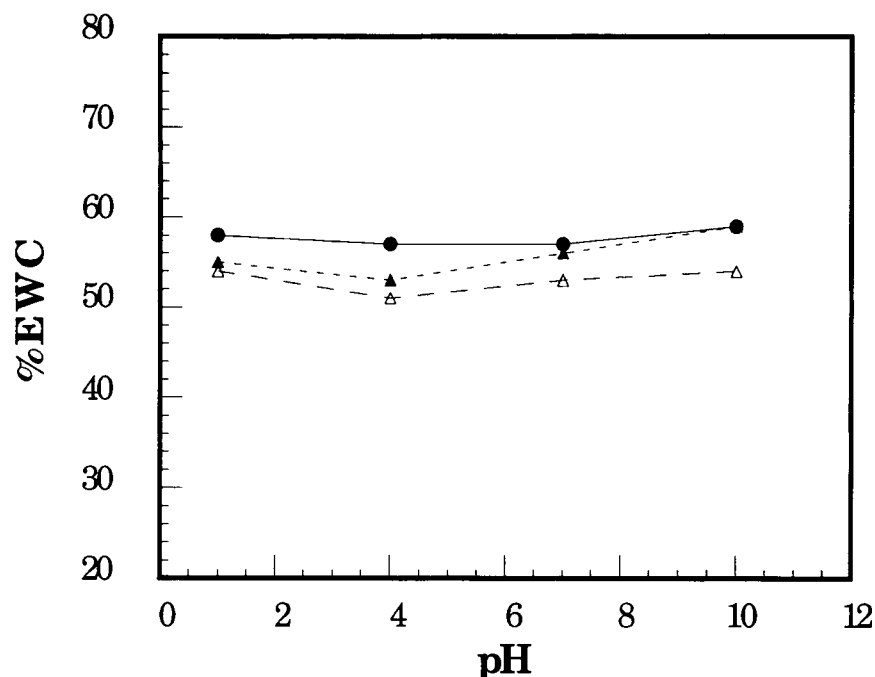


Figure 4 Equilibrium water content (%EWC) of different graft copolymer mixtures: (●) HPMA-MA, (△) HPMA-EA, (▲) HPMA-BA (50/50) with a 34 mol % of EGDMA in the initial feed composition at various pHs.

%EWC is attained. In addition, there are less differences between the different pHs than without EGDMA in the feed composition. On the other hand, the %EWC increase observed at high pH in HPMA-EGDMA graft copolymer with a 34 mol % of EGDMA is less important than in HPMA graft copolymer without EGDMA. This behavior could be due to the fact that the hydrogen bonds present at low pH are broken by crosslinks, and at high pH the ions of hydroxylic groups have less ability to be solvated.

In the same way the swelling behavior of graft copolymers of three monomers (containing a 34 mol % of EGDMA as comonomer) are shown in Figure 4. As can be seen, with the three mixtures similar values are obtained, and, besides, with regards to the results achieved with less than 7% of EGDMA, the %EWC values attained are higher and practically independent of pH. With all of these, it can be concluded that in these cases, the bifunctional comonomer governs the water absorption due to the formation of a covalent crosslinked network where water can be retained increasing %EWC values.

In conclusion, considering the water content values, we can resume that in spite of the obtained graft, copolymers do not absorb more water than

the ungrafted amylopectin. By grafting copolymerization of different acrylic mixtures with a variable crosslinking degree, we will improve the poor mechanical properties of the amylopectin maintaining a high capacity of water absorption giving rise to partial biodegradable materials. So on the whole, these materials could be designed for favorable interactions in their intended environment to be used in a number of applications as drug delivery, implants, and so forth.

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