The physico–chemical characterization of poly (2-hydroxyethyl methacrylate-co-methacrylic acid): 1. Effect of PEG 400 on the tacticity and reactivity ratios

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A series of copolymers of 2-hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAA) were selected as possible carrier systems for controlled drug delivery. The tacticity of these copolymers averaged 60% syndiotacticity and 40% heterotacticity when prepared with 2,2,azobisisobutyronitrile (AIBN) at 70°C (pH *c.* 3.5). The presence of poly(ethylene glycol)400 (PEG 400) in the reaction mixture seemed to have only a minimal effect (at a low pH) on the polymerization reaction. In contrast, an increase in the pH gave a tendency towards heterotacticity and had an enormous effect on the reactivity ratios. The *r* values change from *r*(1) 1.50 and *r*(2) 0.67 to *r*(1) 13.8 and *r*(2) 0.07 for HEMA and MAA respectively. These changes affect the copolymer composition and thus the rate of drug release from the polymeric drug delivery systems made from these copolymers.

(Keywords: drug delivery system; poly(2-hydroxyethyl methacrylate-co-methacrylic acid); reactivity ratios; tacticity; PEG 400; h.p.l.c.; ^{13}C n.m.r.)

INTRODUCTION

Today there is widespread interest in the so-called hydrogels[1] in medical sciences. Part of this interest originates from their potential to control the rate of release of drugs when they are exposed to water. It is well known that changes in the composition of the hydrogels do affect the rate of release of the incorporated drug. Secondly, these hydrogels appear to be compatible with biological membranes.

An important parameter in the controlled-release of drugs from hydrogels is the glass transition temperature (T_g). There is practically no diffusion of drug in the dry hydrogel. The incorporated drug can diffuse through the polymeric network only in the rubbery state. Factors that affect the T_g and thus might affect the drug release include, for example, the chemical composition and the tacticity of the (co)polymer. To study these phenomena we synthesized a series of copolymers of 2-hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAA).

Both the tacticity and the glass transition temperature[2] were measured as a means of studying, respectively, the effects of the monomeric feed on the product and the effects of solvents (like water and PEG 400) on the behaviour of the product. The effect of the plasticizer PEG 400 on the tacticity was checked because PEG polymers have been described in the literature as able to change the distribution of the different monomeric units along the polymeric chain (matrix polymerization or template effect)[3]; affect the tacticity of the polymer[3]; act as an initiator for the polymerization[4]; and increase the rate of polymerization[5]. In the crosslinked polymeric network, PEG polymers also will have an effect based on the formation of association complexes between the oxyethylene units and the carboxylic groups of the polymer[6]. These complexes, which have been described, for example, for polyacrylic acid and PEG in solution, are influenced by the pH. Above pH 12 only polyoxyethylene is precipitated from the solution. Below pH 4 the complex itself precipitates from the solution. Furthermore the stability and solubility of these complexes are affected by the presence of salts (or drugs).

Next, the chemical composition was checked by measuring the reactivity ratios in dilute solutions using a new h.p.l.c. assay. This was done because the measurement of monomer concentrations in concentrated solutions (especially in the presence of a crosslinker) is technically not possible. The collected data were then used to describe the conditions in the crosslinked system.

Subsequently, the reactivity ratios were calculated according to Macret *et al.*[7], where *r*(1) and *r*(2) were defined as the reactivity ratios of HEMA and MAA, respectively. In order to check if our results from the h.p.l.c. method were correct, i.e. whether ideal copolymerization occurs in our system, we also determined the reactivity ratios by ^{13}C-n.m.r. analysis[9]. The polymerization technique described earlier was then used to study the effects of changes in the reaction mixture, such as pH and the addition of PEG 400, on the copolymer.

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MATERIALS

The monomers used were 2-hydroxyethyl methacrylate (Serva p.a.) and methacrylic acid (Fluka p.a.). The monoethyl ether of hydroquinone was removed from the MAA by Amberlyst A26 (Serva). The HEMA was purified from traces of MAA over an activated basic alumina column. As initiator 2,2-azobisisobutyronitrile (AIBN, Polysciences p.a.) was used. All solvents were of h.p.l.c. grade and were distilled before use. All other chemicals were of analytical grade.

METHODS

The polymerization reactions were performed in a 500 cm^3 flask equipped with a reflux condenser and thermostated at 70°C. De-aerated solutions with a total amount of 5 g of monomer (HEMA/MAA 50:50 mol%) in 250 cm^3 water were polymerized under continuous stirring and under a nitrogen gas flow to keep oxygen out. The polymerizations were initiated with 7.5 mg AIBN in 100 μl acetone. Because we performed the polymerization in the presence of water (to prevent vitrification) we developed an h.p.l.c. assay to measure the reactivity ratios directly from water solutions. We used a 60 min interval for collecting samples. Monomer concentrations were determined on a Waters Associated h.p.l.c. system (column: Z-module RP C18-μBondapak, 10 μm, 100 × 8 mm; eluens: 40% v/v methanol in phosphate buffer (0.05 M, pH 6.8) + tetrabutylammonium (0.01 M) + hydroquinone (10 mg/l); flow rate 1.0 ml/min; internal standard: methoxyphenol; detection: model 440 u.v. detector (254 nm)).

The retention times were 4.7 min for MAA, 6.8 min for HEMA and 8.8 min for methoxyphenol. The sample preparation was as follows. A 1.0 cm^3 sample was taken at regular time intervals and cooled immediately on ice. The samples were then filtrated over a small paper-packed column to remove the precipitated polymer. Exact volumes of filtrate were diluted with mobile phase. After the addition of the internal standard, 25 μl were injected on the h.p.l.c. column. The reactivity ratios were determined according to the method of Macret and Hild[7]. This method has one definite drawback: it includes the determination of first-order reactivity constants for both monomers by making log-concentration *versus* time plots of the monomer feed concentrations. The reactivity ratios are then calculated from the Fineman–Ross plot[8], which is derived from these constants. As we discussed[9] previously, this method will always give reactivity constants that indicate an ideal copolymerization. Thus, only in the case of ideal copolymerization correct values will be obtained.

The ^{13}C-n.m.r. spectra were recorded at 75.4 MHz on a Bruker WM-300 spectrometer equipped with an Aspect-200 data system. The assays were run at 67°C in DMSO. The required copolymers were prepared by the former method. The reactions were carried out at 70°C for 24 h. The copolymers with a high percentage of MAA were precipitated with hydrochloric acid. After centrifugation, the polymers were washed with demineralized water and were then freeze-dried. The polymers were then dissolved in DMSO. The tacticity was calculated by measuring the area of the different α-methyl peaks (*Figure 1*). Polymers prepared in a solution of pH 5.5 and in a solution of 10% w/w PEG 400 were also analysed.

RESULTS AND DISCUSSION

The tacticities of the different polymers, prepared by radical initiation with AIBN, are presented in *Table 1* and *Figure 2*. The results from these data are an average of 60% syndiotacticity and 40% heterotacticity. There is a slight tendency towards an increase in heterotacticity at increasing amounts of MAA in the copolymer. The effect of the addition of PEG 400 and an increase of the pH (6.75) on the tacticity are shown in *Table 2*. We observe that PEG, in particular, tends to increase the number of syndiotactic sequences. In addition, the ^{13}C-n.m.r. spectra reveal minimal amounts of isotactic sequences, which we estimate at 0–3%. Russel *et al.*[10]

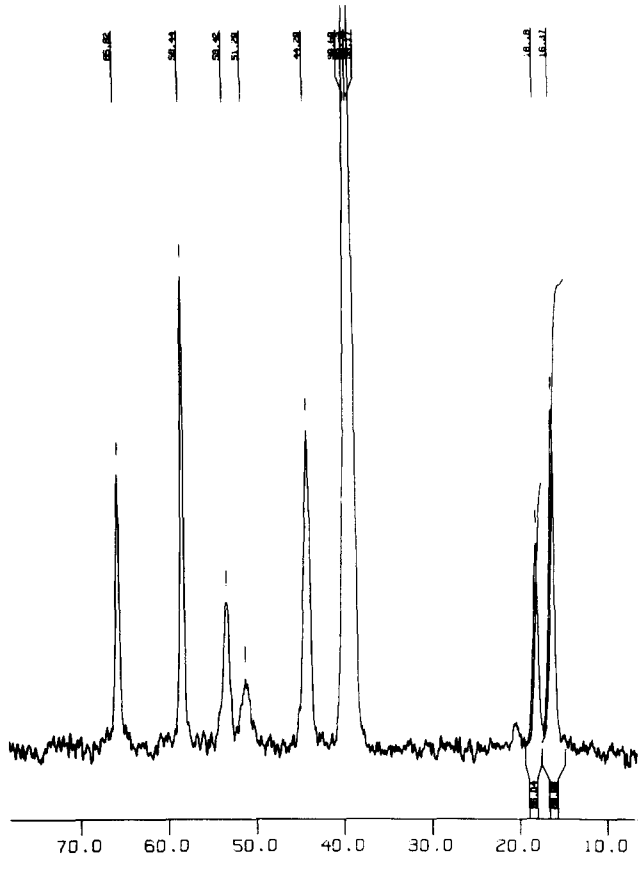

Figure 1 A ^{13}C-n.m.r. diagram of 50/50 poly-(HEMA-co-MAA) at 67°C in DMSO (see methods). The response at 16.4, 18.2 and at approximately 21 ppm is due to the methyl group in the heterotactic, syndiotactic and isotactic sequences

Table 1 Tacticity measurements by ^{13}C-n.m.r. analysis on different (co)polymers of HEMA and MAA

Composition (mol% MAA)	% Heterotactic	% Syndiotactic
0	35.0	65.0
10.1	36.4	63.6
20.1	36.8	63.2
30.2	36.4	63.6
40.2	39.4	60.6
50.2	37.5	62.5
60.2	39.6	60.4
70.2	34.6	65.4
90.1	39.6	60.4
100.0	42.2	57.8

Table 2 The tacticity of different polymers formed in the presence of 10% w/w PEG400 in the polymerization mixture

Composition	% Heterotactic	% Syndiotactic
p-HEMA	34.7	65.3
50/50 co-pol	36.1	63.9
p-MAA	31.2	68.8

Table 3 The tacticity of different polymers formed at a pH of 6.75 in the polymerization mixture

Composition	% Heterotactic	% Syndiotactic
p-HEMA	36.5	63.5
50/50 co-pol	38.6	61.4

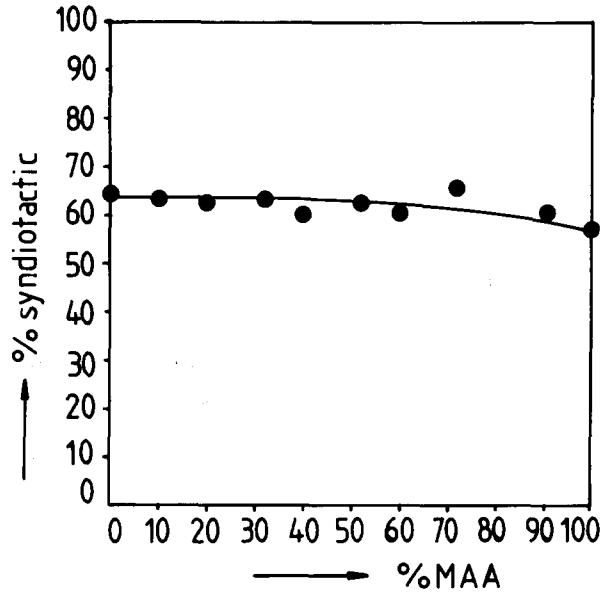

Figure 2 The tacticity of poly-(2-hydroxyethyl methacrylate-co-methacrylic acid) as a function of the composition

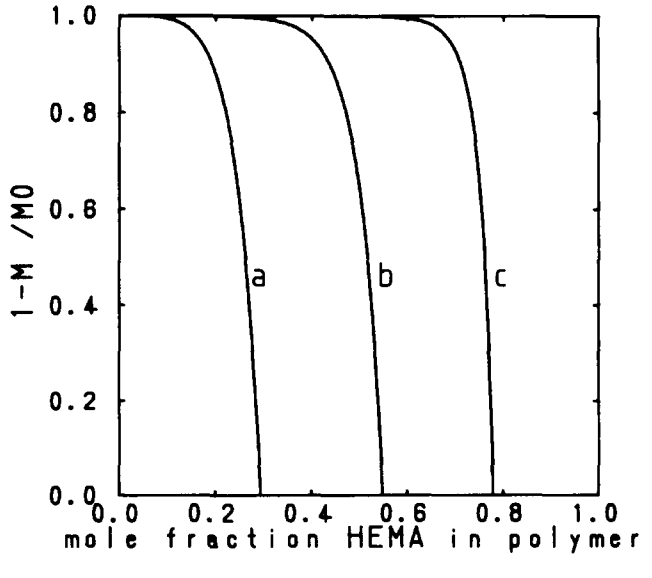

Figure 3 The composition of the copolymer during the conversion of the monomers into the copolymer based on $r(1)=1.14$ and $r(2)=0.75$ at three different starting conditions: curve a, 25 mol% HEMA and 75 mol% MAA; curve b, 50 mol% HEMA and 50 mol% MAA; curve c, 75 mol% HEMA and 25 mol% MAA

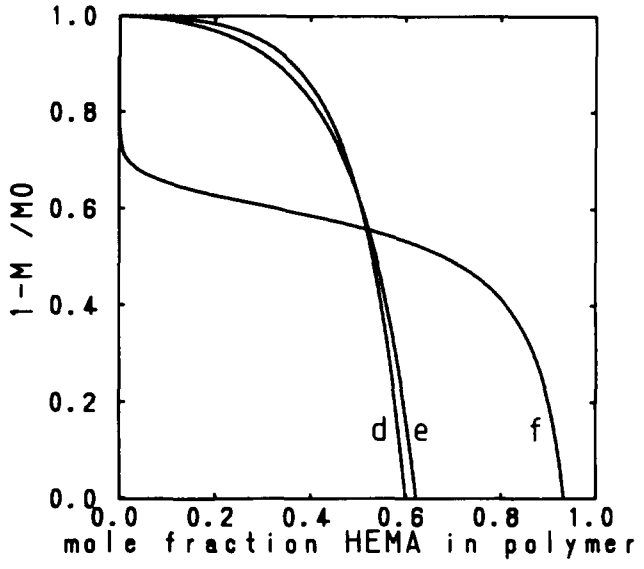

Figure 4 The composition of the copolymer during the conversion of the monomers into the copolymer based on $r(1)=1.14$ and $r(2)=0.75$. The starting mixture contains 50 mol% HEMA and 50 mol% MAA. Three different starting conditions are presented: curve d, no additions; curve e, the addition of 10 m/m % PEG 400; curve f, like curve e but at pH 6.75 (potassium borate/boric acid buffer)

presented similar data for *p*-HEMA prepared by free-radical polymerization: 33% heterotacticity, 66% syndiotacticity and less than 1% isotacticity.

The reactivity ratios were $r(1)$ 1.50 ± 0.13 ($n=5$) and $r(2)$ 0.67 ± 0.06 ($n=5$) for the polymerization in water at 70°C, resulting in a product of 1.01. This could be expected using the method of Macret and Hild[7]. In practice, plasticizers, salts and drugs will often be added to the reaction mixture. We therefore performed some pilot studies which revealed the necessity of using this kind of approach. The addition of, for example, PEG 400 shows only a slight increase in $r(1)$ to 1.65 and an unchanged value of 0.61 for $r(2)$. In contrast, an increase of the pH to 6.75 gives an enormous effect: $r(1)$ 13.8 and $r(2)$ 0.07. Ionization of the methacrylic acid shows an enormous decrease in the radical reactivity, especially when the polymer also ionizes (pKa 6–7). Similar data have been described also by Blauer for *p*-MMA[11]. These effects are presented schematically in *Figures 3* and *4*. *Figure 3* shows the composition of the copolymer during the polymerization reaction for the 'n.m.r. values' of 1.14 and 0.77 (see below) for different starting concentrations. At first, there is a slightly higher incorporation of HEMA in the copolymer, in the end there is a sharp increase in the MAA incorporation. *Figure 4* shows the enormous effect of the changing of the pH after an initial 75% conversion of pure *p*-MAA is synthesized. These 'blended' copolymers can be expected to have totally different physico-chemical properties, resulting in a change in the rate of drug release from these copolymers.

Because the method of Macret and Hild[2] always results in an ideal copolymerization, we used the n.m.r. method described earlier for comparison. This resulted in $r(1)=1.14$ and $r(2)=0.77$, giving a product of 0.88. Although there is a discrepancy, both methods show similar results. The last data set also seems to approach ideal copolymerization conditions. So, if we now assume this copolymerization to be ideal, we have a good

alternative to the Macret and Hild[2] method for studying the effects of changes in the polymerization mixture.

CONCLUSIONS

The radical copolymerization, using AIBN as an initiator, results in a (co)polymer with approximately 60% syndiotactic and 40% heterotactic sequences. This ratio is fairly constant at changing amounts of both monomers. The presence of PEG 400 during the polymerization reaction seems to have little effect. In glaring contrast, an increase in the pH shows a tendency towards more heterotactic polymers and has an enormous effect on the reactivity ratios. These effects should be considered both in the design and manufacturing of hydrogels for drug delivery systems.

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