Kinetic and microstructural parameters of the free-radical copolymerization of 2-hydroxyethyl methacrylate with methacrylic monomers bearing bulky polar side-groups*

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Biocompatible copolymers of *N*-(4-methacryloyloxyphenyl)-2-(4-methoxyphenyl)acetamide (OM) and *N*-[4-(4-methoxyphenylacetyloxy)phenyl]methacrylamide (MA) with 2-hydroxyethyl methacrylate (HEMA) were prepared by free-radical polymerization. The kinetic behaviour of these systems was studied gravimetrically, and the results obtained are discussed in the light of kinetic models. The reactivity ratios were determined by the application of linearization methods to the general copolymerization equation, as well as by non-linear least-squares analysis, the most correct values being $r_{OM} = 1.49$, $r_{HEMA} = 0.61$ and $r_{MA} = 0.29$, $r_{HEMA} = 1.47$. The microstructure of copolymer chains was determined statistically from the reactivity ratios, considering the terminal model for both copolymerization processes.

(Keywords: free-radical polymerization; copolymerization; 2-hydroxyethyl methacrylate; methacrylic monomers; polar side-groups; kinetics; microstructure; biocompatibility)

INTRODUCTION

Polymers and copolymers based on 2-hydroxyethyl methacrylate have found wide applications in surgery and clinical medicine because of their ability to form biocompatible hydrogels with excellent tolerance and good stability[1–6]. We are interested in the preparation of biocompatible acrylic polymers with potential pharmacological activity, following the model suggested in a pioneering work by Ringsdorf[7]. The latter basically considers the preparation of polymeric and copolymeric chains supporting molecules or residues that elicit a characteristic pharmacological effect, by means of covalent bonds that could be hydrolysed in the physiological medium (ester, amide, anhydride, urethane, carbonate, etc.). Recently, we have prepared polymeric drugs with potential anti-inflammatory activity, based on derivatives of phenylacetic and propionic acids, which are catalogued as a family of compounds known as 'non-steroidal anti-inflammatory agents'[8]. These systems were prepared by the polymerization of a methacrylic ester and a methacrylamide derivative, having identical elemental compositions and functional groups but with a structural difference arising from the position of the ester and amide groups with respect to the methacrylic double bond[9,10].

In this paper we study the behaviour of these acrylic monomers in free-radical copolymerization with 2-hydroxyethyl methacrylate. We consider that it is important to know the copolymerization parameters to prepare tailored copolymers and to control the monomer sequences along the macromolecular chains or the hydrophobic–hydrophilic balance of the copolymers, as well as the distribution of the monomeric units that support the pharmacologically active residue.

EXPERIMENTAL

Preparation of monomers

N-(4-Methacryloyloxyphenyl)-2-(4-methoxyphenyl) acetamide (OM) was synthesized in two steps as described elsewhere[9]: First, we prepared an intermediate derivative by the amidation reaction of 4-methoxyphenylacetic acid with 4-aminophenol. The monomer OM was prepared by the reaction of this intermediate with methacryloyl chloride in aqueous sodium hydroxide solution at 0°C.

N-[4-(4-Methoxyphenylacetyloxy)phenyl]methacrylamide (MA) was also synthesized in two steps[10]: The intermediate derivative was prepared by the selective amidation reaction of 4-aminophenol with methacrylic anhydride at low temperature. Then we prepared the MA monomer by reaction of the intermediate with 4-methoxyphenylacetic acid.

Both monomers were purified by fractional crystallization with methanol/water and by column chromatography (Kiesel-gel 60, Merck) using ethyl acetate as eluent, respectively. Other experimental details are given elsewhere[9,10].

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2-Hydroxyethyl methacrylate (HEMA), supplied by Hydron Europe Ltd, containing less than 0.05 wt% of ethylene glycol dimethacrylate, was distilled under reduced pressure of nitrogen and the fraction of b.p. 87–89°C/0.5 mmHg was collected.

2,2'-Azobisisobutyronitrile (AIBN) was purified by fractional crystallization from methanol, m.p. = 104°C.

N,N-Dimethylformamide (DMF) was dried over anhydrous magnesium sulphate for 2 days and later with phosphoric anhydride overnight. After drying, DMF was distilled under reduced pressure of nitrogen. Other reagents were of extra-pure grade and used without purification.

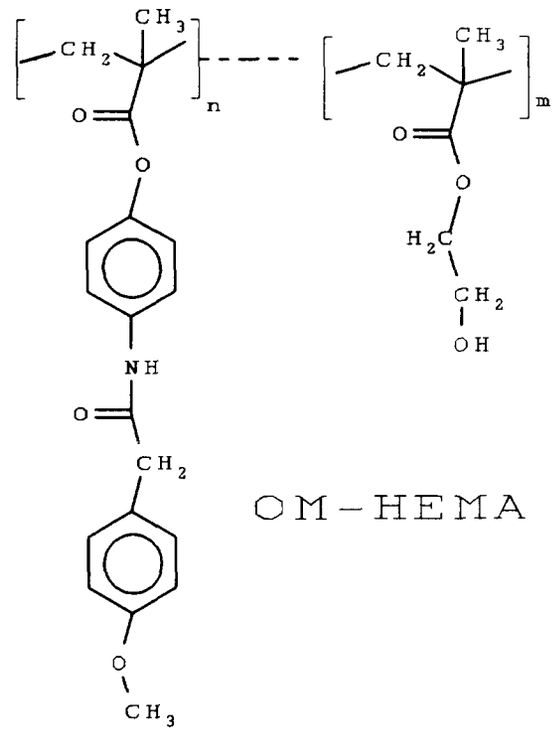
Polymerization

Copolymerization reactions were carried out in DMF solution at 50 ± 0.1°C, in Pyrex glass ampoules sealed off under high vacuum. Monomer and initiator concentrations were 1 mol l^{-1} and 1.5×10^{-2} mol l^{-1}, respectively. The sealed ampoules were shaken vigorously and immersed in a water bath held at the required temperature of polymerization. After the proper reaction time, the ampoules were removed from the bath and at once the contents were poured into a large excess of diethyl ether/chloroform 1/1 mixture. The precipitated samples were washed with the precipitant mixture and dried under vacuum until constant weight was attained.

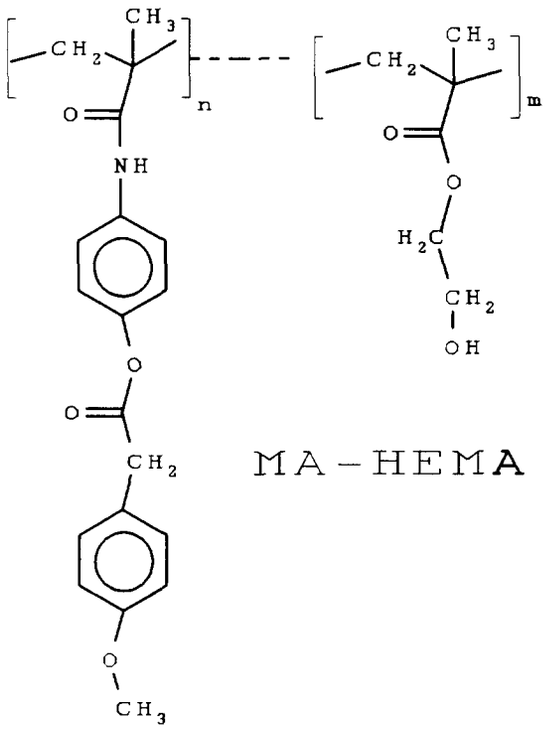
The copolymers obtained from different mixtures of OM or MA and HEMA were analysed by ^{1}H n.m.r. spectroscopy with a Varian XLR-300 spectrometer (300 MHz). The spectra were recorded at 80°C on 5% (w/v) deuterated dimethylsulphoxide (DMSO-d_6) solutions.

RESULTS AND DISCUSSION

As indicated above, the most interesting characteristic of OM and MA from a chemical point of view is that both compounds are methacrylic derivatives with identical elemental compositions and functional groups, but with a structurally different position of the ester and amide groups with respect to the methacrylic double bond. Following the model suggested by Ringsdorf[7], we prepared these acrylic monomers by introducing a spacer group between the methacrylic double bond and the pharmacological residue (4-methoxyphenylacetic acid). From a practical point of view we selected the 4-aminophenoxy group as spacer (this is also an interesting metabolite with pharmacological applications). The synthetic route followed for the preparation of OM[9] afforded a methacrylate ester in which the 4-aminophenyl group is linked to the methacrylic residue through the carboxylic function and to the phenylacetic residue through an amide group (see *Scheme 1*). On the contrary, the methacrylamide derivative MA presents the 4-aminophenyl spacer oriented in the opposite direction, being linked to the methacrylic residue through the amide group and to the phenylacetic residue through the ester function (see *Scheme 2*). We have found that the reactivity of the methacrylic double bond is rather different for both monomers, which has been explained by the polar effects of the corresponding bulky and polar side substituents[11]. Therefore, the study of the copolymerization behaviour is interesting from theoretical as well as practical points of view.



Scheme 1



Scheme 2

The copolymerization reactions were carried out in anhydrous DMF solutions with different compositions of OM or MA in the monomer feed. The reaction time was initially regulated to reach conversions lower than 10 wt% (*Table 1*), in order to satisfy the differential copolymerization equation[12]. The data on molar composition of the initial mixture of comonomers used and the resulting copolymers are quoted in *Tables 1* and *2*. The conversion weight percentages of the corresponding polymerization experiments were determined gravimetrically after exhaustive drying of the isolated

Table 1 Average molar composition of OM–HEMA copolymers and overall rate of copolymerization for the free-radical copolymerization in DMF at 50°C

Feed, F_{OM}	Copolymer, f_{OM}	$R_p \times 10^5$ (mol l^{-1} s^{-1})	Amount (wt%)
0.00	0.00	4.80	15.9
0.20	0.29	4.48	4.5
0.40	0.50	4.57	4.0
0.60	0.71	5.02	2.6
0.80	0.85	6.72	7.8
1.00	1.00	9.21	12.2

Table 2 Average molar composition of MA–HEMA copolymers and overall rate of copolymerization for the free-radical copolymerization in DMF at 50°C

Feed, F_{MA}	Copolymer, f_{MA}	$R_p \times 10^5$ (mol l^{-1} s^{-1})	Amount (wt%)
0.00	0.00	4.80	15.9
0.20	0.13	2.88	7.5
0.40	0.27	2.07	4.9
0.60	0.43	1.32	2.8
0.80	0.61	1.56	2.8
1.00	1.00	2.75	15.0

copolymer samples. Representative chemical structures of OM–HEMA and MA–HEMA are drawn in *Schemes 1* and *2*.

We have also analysed the variation of the degree of conversion with reaction time up to 60 min in order to study the effect of the feed composition on the kinetics of copolymerization. In all the experiments, the conversion–time diagrams were straight lines without any apparent inhibition or induction period. From the slope of the corresponding diagrams, the values of the overall polymerization rate, R_p, quoted in the third column of *Tables 1* and *2* were determined. *Figure 1* shows the variation of the whole polymerization rate, R_p, with the OM or MA molar fraction in the monomer feed. It is clear from this figure that the rate of copolymerization decreased with the composition with respect to the corresponding homopolymerization. This behaviour has been described for several copolymerization reactions of polar vinyl and acrylic monomers[13–17] and it has been ascribed to a considerable increase of the rate of termination step as a consequence of the contribution of bimolecular cross-termination processes, with respect to the homopolymerization of the corresponding monomers.

The rate of copolymerization depends not only on the propagation step, but also on the rate of initiation and termination. In general, a clear decrease of the overall rate of copolymerization with respect to that of the corresponding homopolymerization reactions is observed[12,13,18,19]. It is considered that the rate of initiation, R_i, changes little with the composition of the reaction medium if the copolymerization system is constituted by monomers that polymerize easily[13]. Therefore, the variation of R_p with the feed composition has been ascribed to the influence of reaction medium in the termination step[39].

A typical copolymerization scheme according to the Mayo–Lewis terminal model[12] considers three bimolecular termination reactions, each one characterized by the corresponding rate coefficients, i.e. termination

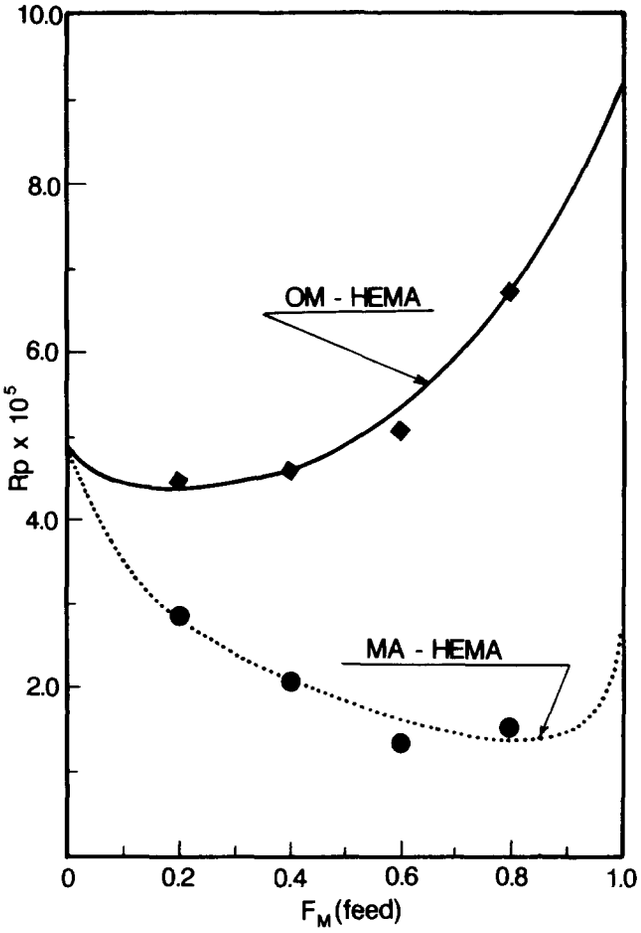


Figure 1 Kinetic diagrams of the free-radical copolymerization of OM–HEMA and MA–HEMA systems in DMF at 50°C

between like radicals (k_{t11}, k_{t22}) and cross-termination between unlike radicals (k_{t12}).

On this basis Melville[20] and Walling[21] suggested the so-called 'chemical-controlled termination model', which considers that the rate of copolymerization is described by the equation:

$$R_p = \frac{(r_1[M_1]^2 + 2[M_1][M_2] + r_2[M_2]^2)R_i^{1/2}}{(r_1^2\delta_1^2[M_1]^2 + 2\phi r_1 r_2 \delta_1\delta_2[M_1][M_2] + r_2^2\delta_2^2[M_2]^2)^{1/2}} \quad (1)$$

where

$$\phi = \frac{k_{t12}}{2(k_{t11}k_{t22})^{1/2}}$$

The δ_1 and δ_2 terms are simply the reciprocal of the familiar $k_p/(2k_t)^{1/2}$ ratios for the homopolymerization of the individual monomers. The term ϕ represents the ratio of half the cross-termination rate constant to the geometric mean of the rate constants for self-termination of like radicals[18]. Kinetic studies have shown that, for the copolymerization of monomers with rather similar chemical structure, $\phi = 1$ (ref. 22). However, the copolymerization of monomers with dissimilar molecular structure in general presents ϕ values greater than unity[20,23], i.e. cross-termination is favoured in comparison with termination of homoradicals. This phenomenon has been explained in terms of polar factors in the transition state as those responsible for the alternating tendency of the propagation reactions in such systems[22]. The

interpretation of ϕ values from a chemical point of view is valid if the rate of termination is not strongly influenced by physical effects. According to North's approach, it is clear that termination reactions in radical homopolymerization and copolymerization are, at least partially, diffusion-controlled[24,25] and physical parameters like the flexibility of polymer chains and the viscosity of the reaction medium can play an important role in the control of termination reactions. In this way, Atherton and North[24] considered that the cross-termination coefficient k_{t12} is determined by the composition of the growing copolymer radicals and may be considered as a linear combination of the rate coefficients of homopolymerization. However, this consideration does not hold adequately for many copolymerization systems[22]. More recently, Russo *et al.*[26,27] have suggested a scheme that involves both physical and chemical aspects, by considering that it is only the flexibility, and hence the composition, of the segment end that is active physically, rather than the overall chain composition and overall flexibility. Therefore, they obtained relatively good results considering that the rate coefficients for the cross-termination reactions were given by the geometric means of appropriate homo-termination reactions. Rudin *et al.*[23] also reported an empirical formulation for the overall termination rate coefficient in terms of monomer concentrations and reactivity ratios and a cross-termination factor, as an extension of the diffusion-controlled model suggested by North *et al.*[24].

As is clearly shown in *Figure 1*, the kinetic behaviour of the copolymerization systems studied here is rather different. The curves in this figure have been determined by equation (1) using the values of $k_p/k_t^{1/2}$ of the corresponding homopolymerization reactions, i.e. 0.722 for OM, 0.216 for MA and 0.378 for HEMA, and values of $\phi = 3$ for the system OM–HEMA and $\phi = 14$ for MA–HEMA. As might be expected from the rather chemical structures of OM and HEMA (both are methacrylic esters), the best value of ϕ to fit the experimental points to equation (1) is rather close to unity, $\phi = 3$. However, in the case of the copolymerization of MA with HEMA, it is necessary to consider a value of $\phi = 14$ to fit the experimental points, as a consequence of the great dipolar differences associated with the amide nature of the MA-ended radicals with respect to the carboxylic ester structure of HEMA-ended radicals. It is noteworthy that the ϕ value considered here is similar to that reported for the free-radical copolymerization of methyl methacrylate with styrene, $\phi = 13$ (refs 12, 14, 23), in which the dipolar interactions between the carboxylic ester group of methyl methacrylate units and the π aromatic ring of sytrene units are important[28].

According to the structural composition of OM and MA units incorporated into the growing polymeric chains, it can be assumed that the diffusion of OM and MA chains might be similar considering exclusively steric contributions, since the side substituents have the same volume in both cases (similar functional groups in OM and MA units). Therefore, according to the diffusion model, similar cross-termination constants for both systems should be expected, which is not the case according to the experimental data obtained.

Recently, we have found that the reactivity of OM and MA monomers in free-radical polymerization is strongly affected by the polarizability of the acrylic double bond, associated with the ester or amide nature of the carboxylic acrylic function[11]. As has been assumed, in general, the polarity of monomer molecules associated with the nature of the side substituents is similar to that of the corresponding growing radicals[18]. Therefore, we consider that the differences in the kinetic behaviour of OM–HEMA and MA–HEMA systems are related to the different dipolar interactions associated with the relative position of the amide and ester functional groups of OM and MA units rather than with a net diffusion control of the termination step. On the other hand, Rudin *et al.*[23] considered that an appropriate value of ϕ can be approximated from the experimental values of reactivity ratios r_1 and r_2, to determine the overall termination coefficient, since high polar effects (i.e. large values of ϕ and preference of cross-termination) may be expected to result in a tendency towards the formation of alternating sequences and a low product r_1r_2, in such a way that an inverse relation between ϕ and r_1r_2 could be considered. This was suggested in pioneering work by Walling[29] and Melville *et al.*[30].

As has been reported by North[25], if the factor ϕ is interpreted in terms of the growing radical polarities similar to the Q–e scheme, it should be similar to $(r_1r_2)^{-1/2}$, but it can be easily seen from values of ϕ reported in the literature that this relation does not yield good agreement between calculated and experimental ϕ parameters except for values rather close to unity. As shown in the seventh column of *Tables 3* and *4* a value of $\phi = 2$ is obtained from the diagram reported by Rudin *et al.*[23] with the value of $r_1r_2 = 0.91$ for the copolymerization of OM–HEMA, in fairly good agreement with the value of $\phi = 3$, shown by the application of equation (1). However, as quoted in the seventh column of *Table 4*, a value of $\phi = 8.4$ would be obtained from diagram of ϕ *versus* r_1r_2 for a value of $r_1r_2 = 0.43$, corresponding to the copolymerization of MA–HEMA, in clear disagreement with the value $\phi = 14$ determined by the application of equation (1) to the experimental data, which supports the considerations indicated above, pointed out by North[25].

The copolymer compositions (*Tables 1* and *2*) were calculated from the relative intensities ratio of various ^{1}H n.m.r. signals, characteristic of each kind of unit. Thus we considered (see the chemical structure of the copolymer chains represented in *Schemes 1* and *2*) the integrated intensities of the amido (–NH–) signal at

Table 3 Reactivity ratios, relative reactivities and cross-propagation ratio, ϕ, of the free-radical copolymerization of OM–HEMA

Method	r_{OM}	r_{HEMA}	$r_{OM}r_{HEMA}$	$1/r_{OM}$	$1/r_{HEMA}$	ϕ^a
Fineman–Ross	1.37	0.53	0.73	0.73	1.89	3.4
Kelen–Tüdös	1.43 ± 0.28	0.58 ± 0.07	0.83	0.70	1.72	2.6
Tidwell–Mortimer	1.49	0.61	0.91	0.67	1.64	2.0

[a]Calculated from the diagram $\phi = f(r_1r_2)$ reported by Rudin *et al.*[23]

Table 4 Reactivity ratios, relative reactivities and cross-propagation ratio, ϕ, of the free-radical copolymerization of MA–HEMA

Method	r_{MA}	r_{HEMA}	$r_{MA}r_{HEMA}$	$1/r_{MA}$	$1/r_{HEMA}$	ϕ^a
Fineman–Ross	0.28 ± 0.01	1.47 ± 0.07	0.41	3.57	0.68	8.8
Kelen–Tüdös	0.31 ± 0.07	1.52 ± 0.05	0.47	3.23	0.66	7.6
Tidwell–Mortimer	0.29	1.47	0.43	3.45	0.68	8.4

[a]Calculated from the diagram $\phi = f(r_1 r_2)$ reported by Rudin *et al.*[23]

$\delta = 9.93$ ppm (OM) or 8.80 ppm (MA) and the signals of the aromatic protons ($\delta = 6.5$–8.0 ppm) to determine the molar fraction of OM or MA in the copolymer chains, whereas for the HEMA units we considered the hydroxy (–OH) signal at $\delta = 4.60$ ppm and oxymethylene signals at $\delta = 3.91$ ppm (OM–HEMA) and at 3.65 ppm (MA–HEMA). The values obtained are quoted in *Table 1* for the OM–HEMA system and in *Table 2* for the MA–HEMA system, the OM and MA content being higher and lower respectively than the corresponding monomer feed.

We have determined the reactivity ratios of monomers according to the general copolymer composition equation, using the linearization methods suggested by Fineman and Ross[31] and Kelen and Tüdös[32] as well as the non-linear least-squares analysis suggested by Tidwell and Mortimer[33]. The values obtained for the OM–HEMA system are reported in *Table 3* and those of the MA–HEMA system in *Table 4*. The values of r_{OM}, r_{MA} and r_{HEMA} determined by the three methods are very close for each copolymerization system. In order to check the experimental error of the composition data used to determine these parameters, we have tested the dimensions of the ellipse generated by the treatment suggested by Bechnken[34] and Tidwell and Mortimer[33]. *Figures 2* and *3* show the elliptical diagrams of the 95% confidence limits for the OM–HEMA and MA–HEMA systems, respectively. As expected, non-linear least squares gives the best estimation of the reactivity ratios, although the linearization methods also give a good approximation to the real values for both systems.

The values of reactivity ratios indicate a rather different behaviour of both systems in free-radical copolymerization. Although OM and HEMA are methacrylic esters, the corresponding reactivity ratios are rather different, $r_{OM} > 1$ whereas $r_{HEMA} < 1$. However, the product $r_{OM}r_{HEMA}$ is very close to unity, which indicates that the copolymerization of OM with HEMA gives rise to the formation of random copolymers, predominantly.

The values of $1/r_{OM}$ and $1/r_{HEMA}$ give an idea of the relative reactivity of radicals. According to the data collected in the fifth and sixth columns of *Table 3*, growing radicals ending in a HEMA unit have a relatively higher tendency towards addition of OM whereas radicals ending in OM present a relative tendency towards homopropagation. This means that long sequences of OM units can be expected for copolymers prepared in a relatively wide composition interval. This characteristic may be interesting for the preparation of copolymers for specific applications, like hydrogels for local or transdermal activity. On the other hand, these values are in the range of reactivity ratios reported for

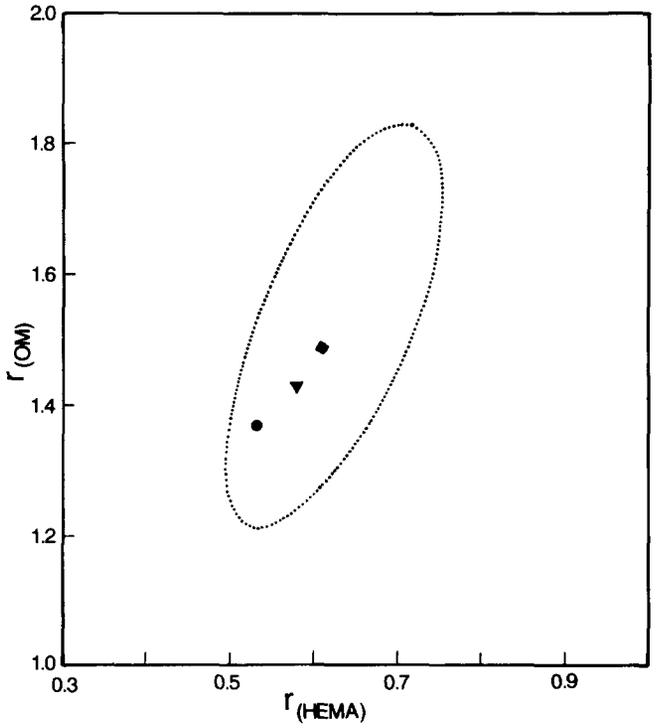


Figure 2 The 95% confidence limits for the free-radical copolymerization of OM with HEMA in DMF solution at 60°C: (●) Fineman–Ross; (▼) Kelen–Tüdös; (◆) Tidwell–Mortimer

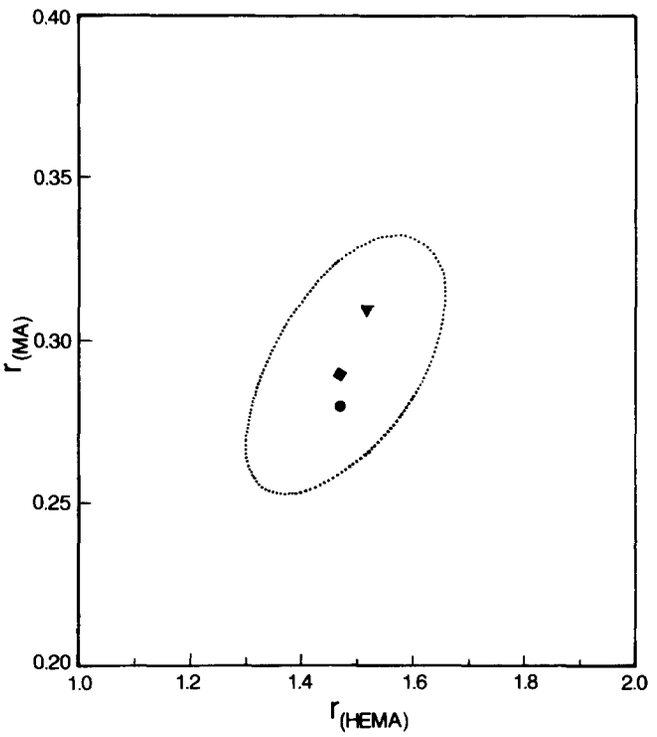


Figure 3 The 95% confidence limits for the free-radical copolymerization of MA with HEMA in DMF solution at 60°C: symbols have the same meaning as in *Figure 2*

the copolymerization of a rather similar system, i.e. 4-methacryloyloxyacetanilide (MOA)–HEMA, which in the experimental conditions used in the present work presents values of $r_{MOA} = 2.15$ and $r_{HEMA} = 0.90$ (ref. 35), and also are close to those of the copolymerization of glycidyl methacrylate (GMA)–HEMA, $r_{GMA} = 1.00$ and $r_{HEMA} = 0.74$ (ref. 36).

The data quoted in *Table 2* show that the behaviour of the more dissimilar system MA–HEMA is rather different, with $r_{MA} < 1$ and $r_{HEMA} > 1$ as well as a product $r_{MA}r_{HEMA} = 0.43$, which indicates a higher tendency towards the formation of alternating sequences. It is clear from the values of the relative reactivity of radicals, expressed by the ratios $1/r_{MA}$ and $1/r_{HEMA}$, that MA-ended radicals have a clear tendency to incorporate HEMA molecules, whereas HEMA-ended radicals present a relative tendency towards homopropagation rather than cross-propagation. This behaviour has been reported for the free-radical copolymerization of other methacrylamide derivatives with polar side-groups and HEMA[37] as well as for the copolymerization of dodecylacrylamide with methyl methacrylate[38].

Figure 4 shows the composition diagram of both systems. The lines correspond to the theoretical diagrams according to the Mayo–Lewis equation with the values $r_{OM} = 1.49$, $r_{HEMA} = 0.61$ and $r_{MA} = 0.29$, $r_{HEMA} = 1.47$, respectively. The experimental data fit adequately the composition diagrams, which correspond to the classical terminal model of copolymerization.

According to these results, it is possible to determine the statistical distribution of M-centred triads by considering the equations for the first-order Markovian

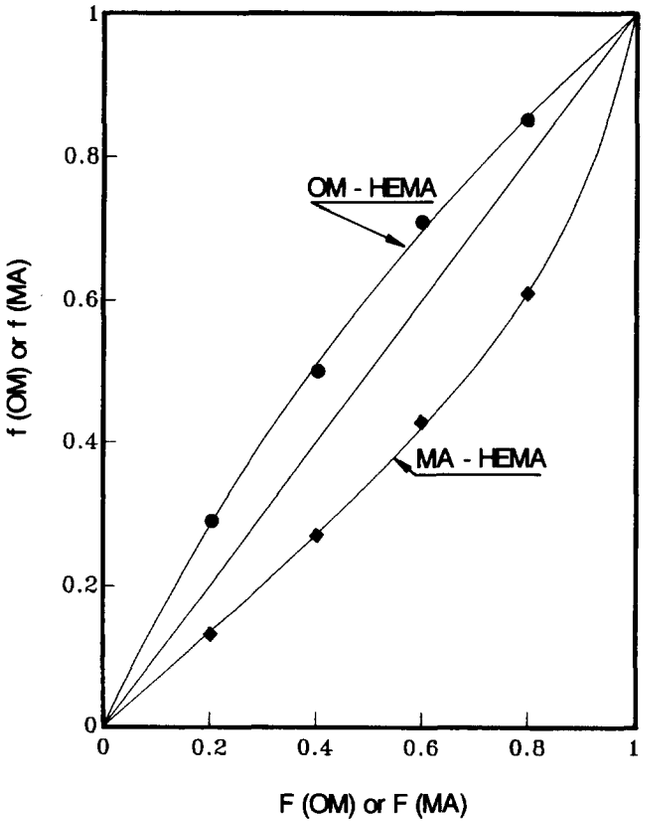


Figure 4 Composition diagrams of OM–HEMA and MA–HEMA copolymerization systems

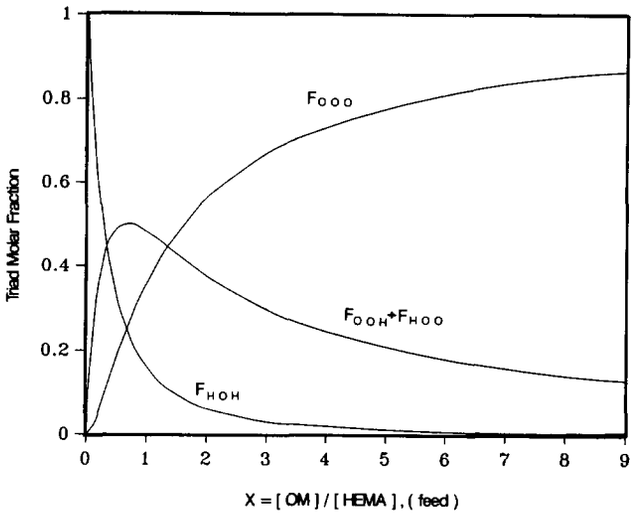


Figure 5 Variation of the molar fraction of OM-centred triads with the composition of monomer feed. For the sake of clarity in the figure, OM = O and HEMA = H

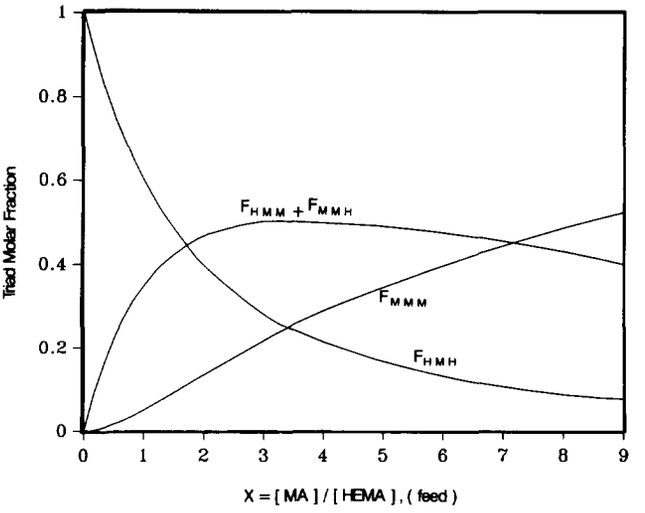


Figure 6 Variation of the molar fraction of MA-centred triads with the composition of monomer feed. For the sake of clarity in the figure, MA = M and HEMA = H

transition probabilities, P_{12}, P_{11}, P_{21} and P_{22}:

$$P_{12} = 1 - P_{11} = 1/(1 + r_1X)$$

$$P_{21} = 1 - P_{22} = 1/(1 + r_2/X)$$

where $X = [M_1]/[M_2]$ is the ratio of the concentration of OM or MA and HEMA in the monomer feed. *Figure 5* shows the variation of OM-centred triads with the ratio X. It is clear from this figure that the molar fraction of alternating triads with two HEMA units (HOH) decreases drastically with increasing X, whereas the concentration of heterotriads (OOH + HOO) presents a maximum for a value of X very close to unity and the molar fraction of homotriads (OOO) increases monotonically with X.

Finally, *Figure 6* shows the same kind of diagrams for the system MA–HEMA. In this case, the concentration of alternating triads (HMH) decreases and that of triads (MMM) increases smoothly with increasing X, whereas the molar fraction of heterotriads (MMH + HMM) does not present a sharp maximum, most probably being in a relatively wide composition interval from $X \simeq 1.5$ to $X \simeq 7.0$.

The results obtained provide a deep insight into the microstructure of copolymer chains of both systems, which will be useful to interpret the hydrolytic behaviour of copolymers prepared with known composition in physiological conditions as well as physical properties and swelling in hydrated media.

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