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Free radical copolymerization of methyl methacrylate with methacrylic monomers derived from salicylic acid. Microstructural analysis, chain flexibility and hydration behaviour of the prepared copolymers

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Abstract

Copolymers of methyl methacrylate (MMA), and the methacrylic monomers derived from salicylic acid, 2-hydroxy-4-methacrylamidobenzoic acid (4-HMA), and 2-hydroxy-5-methacrylamidobenzoic acid (5-HMA), were prepared by free radical polymerization in *N*, *N*-dimethylformamide, DMF, solution at 50°C using 2, 2′-azobisisobutyronitrile (AIBN), as initiator. Fineman–Ross and Kelen–Tüdos linearization methods, as well as the Tidwell and Mortimer non-linear least-squares treatment were used to calculate the monomers reactivity ratios, giving the Tidwell and Mortimer values from the 95% confidence diagrams, the most probable ones $r_4 = 0.83$, $r_M = 1.52$ and $r_5 = 0.29$ $r_M = 2.15$. The microstructural analysis of the prepared copolymers was performed by ^{13}C (75.5 MHz) nuclear magnetic resonance (NMR) spectroscopy, in terms of sequence distribution and stereochemistry of monomeric units along the copolymer chains. The stereochemical parameters $\sigma^* = \sigma_{4M} = \sigma_{M4} = 0.21$ and $\sigma^* = \sigma_{5M} = \sigma_{M5} = 0.19$ were determined from the ^{13}C NMR spectra of the copolymers 4-HMA–MMA and 5-HMA–MMA, respectively. Also the T_g of the corresponding homopolymers and copolymers, were analysed by differential scanning calorimetry (DSC) in terms of the Fox equation. Hydration degree of the prepared copolymers was studied in comparison to poly (4-HMA), poly (5-HMA) and poly (MMA). © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Poly(methyl methacrylate); Bone cement formulations; Hydration behaviour

1. Introduction

Poly(methyl methacrylate) (PMMA) is widely used as a biomaterial in applications such as bone cement in hip and knee prosthesis fixation due to its biocompatibility, hydrophobic character and good mechanical properties in these type of applications [1–3]. In order to improve some aspects of PMMA as bone cement, methyl methacrylate (MMA) has been copolymerized with other acrylic monomers such as 2-hydroxyethyl methacrylate and butyl acrylate, reducing volume contraction in the polymerization process, and obtaining better mechanical properties, respectively [4,5]. In this sense, the hydrophilic acrylic polymers, poly(2-hydroxy-4-methacrylamidobenzoic acid), poly(4-HMA), and poly(2-hydroxy-5-methacrylamidobenzoic acid), poly(5-HMA), exhibit the ability of forming molecular complexes with calcium ions as polycarboxylates, in which two carboxylic units are involved [6]. This fact is important if 4-HMA or 5-HMA are added to bone cement formulations to facilitate bone regeneration in this type of applications.

The radical copolymerization of MMA with the active monomers derived from salicylic acid will lead to a family of copolymers whose properties will depend on the composition, the distribution of monomeric units along the macromolecular chains and the tacticity. An indepth study of the copolymerization reaction and microstructure, and the analysis of their properties will be very helpful in order to prepare materials for specific applications in this biomedical field. The aim of this work is the study of the copolymerization reaction, the analysis of the microstructure, and the study of the hydration behaviour and chain flexibility by thermal characterization, of the prepared copolymers. The reactivity ratios of the two comonomeric pairs, 4-HMA/MMA and 5-HMA/MMA (see Scheme 1), have been determined for the free radical copolymerization using AIBN as free radical initiator. NMR spectroscopy has become the most exact characterization technique for the microstructural description of polymers and copolymers systems, including the determination of composition, stereochemical configuration and sequence length distribution [7–9].

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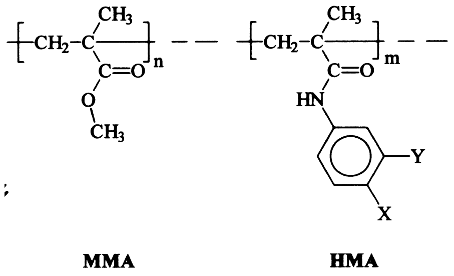

	4-HMA	5-HMA
X	COOH	OH
Y	OH	COOH

Scheme 1.

^{13}C-NMR spectroscopy has some advantages compared with ^{1}H-NMR, mainly because of their higher scale in the chemical shifts and the better resolution in folded signals. In addition, ^{13}C-NMR spectroscopy gives abundant information about the sterochemistry of acrylic and vinyl polymers and copolymers [9–11]. The microstructural characteristics are of great importance in the swelling and hydrolytic behaviour, and for these systems in the calcium complexation to the free carboxyl groups, they are very important in their osteoinductive properties in the application as bone cement substitutive [12]. Moreover, it is well known that the hydrophilic or hydrophobic characteristics of biomaterials can be controlled by preparing copolymer systems with a suitable composition and distribution of the present monomers along the copolymer chains [13,14]. In our case PMMA is a hydrophobic polymer, whereas poly(4-HMA) and poly(5-HMA) have a hydrophilic character because of the presence of polar groups such as carboxylic acid, amide and hydroxy. We have also found evidences of hydrogen bonds between HMA (4-HMA or 5-HMA) units [12] and in this way a deep microstructure analysis will help us to understand the influence of these units interactions in their “in vitro” and “in vivo” behaviour. Glass transition temperatures (T_g) of the prepared copolymers were also determined by DSC analysis. Copolymer films were prepared to carry out the study of their hydration degree and compared to those corresponding to the homopolymers poly(4-HMA) and poly(5-HMA).

2. Experimental

2.1. Monomer preparation and purification of materials

The monomers derived from salicylic acid, 4-HMA and 5-HMA, were synthesized by well-known reactions, and are described elsewhere [15].

MMA (Merck), which contains the monomethyl ether of hydroquinone, was carefully distilled under reduced pressure and used without further purification. 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 phosphorous pentoxide overnight. After drying, DMF was distilled under reduced pressure. Other reagents were extra pure grade and were used as purchased.

2.2. Copolymerization

All copolymerization reactions were carried out in DMF solutions at 50 ± 0.1°C in Pyrex glass ampoules sealed under high vacuum. The monomer and initiator concentration were 1.0 and 1.5×10^{-2} mol l^{-1}, respectively. The sealed ampoules were vigorously shaken and immersed into a water bath regulated at the polymerization temperature. After reaction, the copolymers were precipitated into a large excess of diethyl ether, washed with water and dried under vacuum until constant weight was attained.

2.3. Polymer characterization

The obtained copolymers were analysed by means of ^{1}H and ^{13}C-NMR spectroscopy in a Varian XLR-300 spectrometer. The proton spectra were recorded on 5% (w/v) solutions of a mixture CD_3OD/Cl_3CD (1:1) while the carbon spectra were recorded on 15% (w/v) deuterated dimethylsulfoxide DMSO-d$_6$ solutions at 70°C with the spectrometer operating at 75 MHz, and using a flip angle of 90° (pulse with of 13 μs), a relaxation decay of 4 s and with inverse-gated decoupling in the acquisition to ensure the complete relaxation of all the ^{13}C nuclei analysed. The relative peak intensities were determined from peak areas calculated by means of an electronic integrator or by triangulation and planimetry. Deconvolution was done by using the computer program PEAKFIT version 3.11.

2.4. Differential scanning calorimetry

The T_g values of the corresponding homopolymers and prepared copolymers were determinated with a Perkin–Elmer DSC-7 calorimeter. Measurements and calibration were carried out at a heating rate of 10°C min^{-1}. T_g was taken as the midpoint of the transition region. Samples (∼40 mg weight) were introduced into the aluminium pan, heated at 450 K, compressed and quenched at room temperature before carrying out the measurements. T_g values determined at 5 and 15°C min^{-1} heating rates, gave a deviation of <2% with respect to those obtained at 10°C min^{-1}.

2.5. Preparation of films

Films of 0.4–0.5 mm thickness were prepared by slow evaporation of a solution of 0.5 g of the copolymer samples in 5 ml of DMF/methanol (1:1). Copolymers prepared with 5, 10 and 20 wt.% of 4-HMA and 5-HMA were used. In order to obtain homogeneous discs, a cylindrical mould of Teflon (20 mm diameter and 8 mm depth) was prepared. After evaporation and drying at reduced pressure, transparent and clear films were obtained. Homopolymers

Table 1
Molar and weight composition in the feed and in the copolymer systems. Conditional probability data of the free radical copolymerization of 4-HMA and 5-HMA with MMA in DMF solution at 50°C. T_g's of 4-HMA–MMA and 5-HMA–MMA prepared copolymers determined by differential scanning calorimetry

$F_{4\text{-HMA}}$ feed	$f_{4\text{-HMA}}$ copolymer	P_{4M}	P_{M4}	$w_{4\text{-HMA}}$ copolymer	T_g (K)
0.00	0.00	—	—	0.00	375
0.20	0.14	0.828	0.141	0.26	439
0.40	0.33	0.644	0.305	0.52	475
0.60	0.52	0.445	0.497	0.70	496
0.80	0.76	0.231	0.725	0.81	500
1.00	1.00	—	—	1.00	504
$F_{5\text{-HMA}}$ feed	$f_{5\text{-HMA}}$ copolymer	P_{5M}	P_{M5}	$w_{5\text{-HMA}}$ copolymer	T_g (K)
0.00	0.00	—	—	0.00	375
0.20	0.09	0.932	0.104	0.20	433
0.40	0.22	0.838	0.236	0.38	463
0.60	0.38	0.696	0.411	0.57	490
0.80	0.60	0.463	0.650	0.77	506
1.00	1.00	—	—	1.00	534

poly(4-HMA) and poly(5-HMA) films were also prepared to carry out comparative studies.

2.6. Hydration degree

The study of the hydration degree of films was followed gravimetrically by measuring the weight with the time of immersion in 10 ml of distilled water at 37°C. Measurements were taken until the equilibrium was reached, which was considered when three consecutive measurements gave the same value.

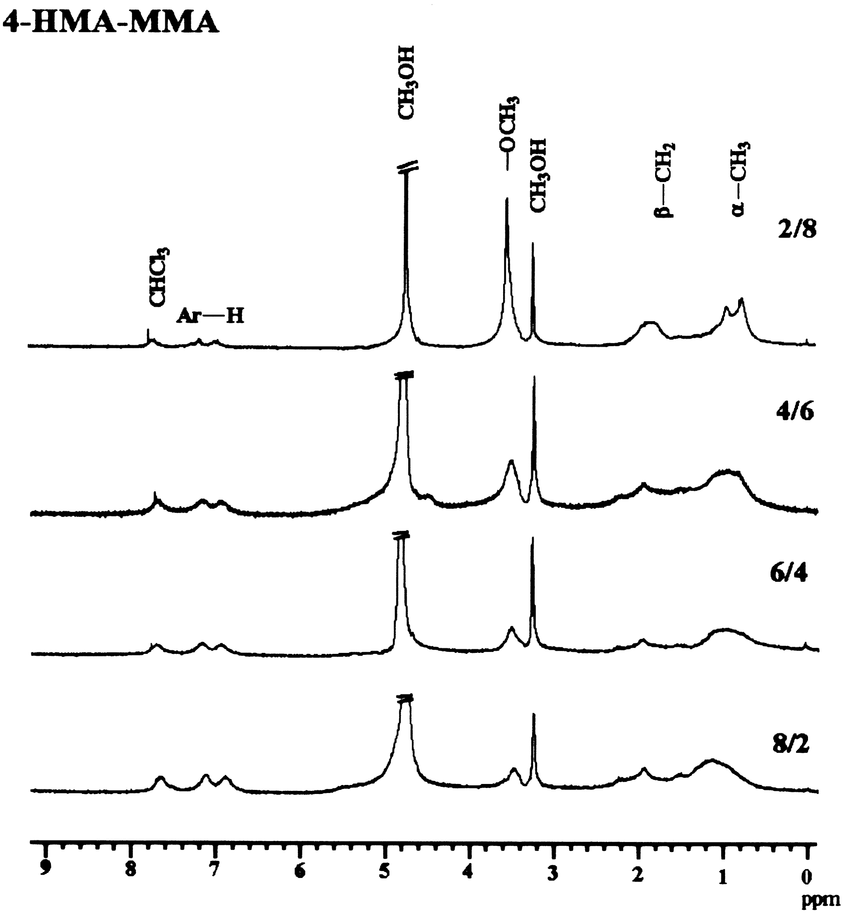

Fig. 1. ^{1}H NMR spectra of the 4-HMA–MMA copolymer system, registered in a mixture of CD_3OD and $CDCl_3$. N°/N° corresponds to the molar ratio of monomers 4-HMA/MMA in the monomer feed.

Table 2
Copolymerization parameters of the free radical copolymerization of 4-HMA and 5-HMA with MMA

	Method		
Parameter	Fineman–Ross [18]	Kelen–Tüdos [19]	Tidwell–Mortimer [17]
4-HMA–MMA			
r_{M}	1.56 ± 0.29	1.57 ± 0.07	1.52
r_4	0.85 ± 0.03	0.85 ± 0.15	0.83
$r_{\mathrm{M}} \times \mathrm{r}_4$	1.33	1.33	1.26
$1/r_{\mathrm{M}}$	0.64	0.64	0.66
$1/r_4$	1.18	1.18	1.2
5-HMA–MMA			
r_{M}	2.33 ± 0.11	2.42 ± 0.10	2.15
r_5	0.34 ± 0.01	0.37 ± 0.11	0.29
$r_{\mathrm{M}} \times r_5$	0.81	0.91	0.62
$1/r_{\mathrm{M}}$	0.42	0.41	0.46
$1/r_5$	2.87	2.65	3.44

3. Results and discussion

The radical copolymerization of MMA with the methacrylic monomers derived from salicylic acid 4-HMA and 5-HMA in anhydrous DMF, was studied over a wide composition interval with molar fractions in the monomer feed, $F_{4\text{-HMA}}$ and $F_{5\text{-HMA}}$, from 0.20 to 0.80 as it is shown in Table 1. The reaction time was initially regulated to reach conversions of <5 wt.% in order to satisfy the differential copolymerization equation [16]. The molar fraction of monomer units in the copolymer chains was determined from the ^{1}H NMR spectra of the copolymer samples prepared with different monomer feed. The analysis was carried out by comparison of the integrated intensities of resonance signals with chemical shifts of 8.0–6.5 ppm assigned to the aromatic protons of the methacrylic monomers 4-HMA and 5-HMA, and from the signals with chemical shifts of 3.5 ppm corresponding to the MMA methoxy groups as can be observed in Fig. 1 for the 4-HMA–MMA copolymer system.

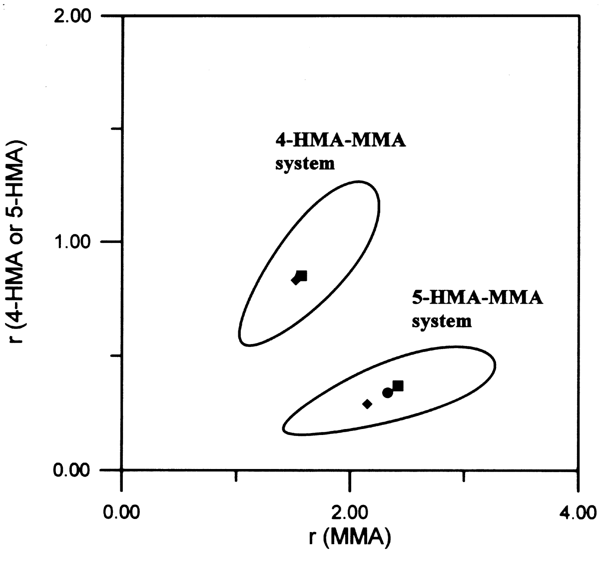

Fig. 2. 95% confidence diagram for the reactivity ratios of 4-HMA, 5-HMA and MMA, determined by the non-linear squares method suggested by Tidwell and Mortimer. Reactivity ratios determined by the methods: ●—Fineman–Ross; ■—Kelen–Tüdos; ◆—Tidwell–Mortimer.

The reactivity ratios of the monomers were determined according to the general copolymerization equation by application of the non-linear least squares treatment proposed by Tidwell and Mortimer [17]. To this end, initial approximated values of r_4, r_{M} and r_5, r_{M}, were obtained by means of the Fineman–Ross [18] and Kelen–Tüdos [19] linearization methods. The results are shown in Table 2. It must be pointed out that r_4, r_{M} and r_5, r_{M} reactivity ratios values obtained by the linearization methods are somewhat different with respect to the non-linear least squares method. In this sense, the Tidwell and Mortimer reactivity ratios are suggested to be the most probable ones of the copolymer systems. The 95% confidence limit gives an idea of the experimental error and the accuracy of the experimental conditions used to generate the composition data. When the experimental error is reasonably small and the data have been taken under the appropriate conditions, the approximation can be remarkably good. This is illustrated by applying the mathematical treatment suggested by Behnken [20] and Tidwell and Mortimer [17]. The application of this treatment to the copolymerization data reported in Table 1, and the r values quoted in Table 2, provides the 95% confidence limits defined by the area of the elliptical diagram exhibited in Fig. 2 for both copolymer systems. This diagram confirms the good approximation of the r_4 and r_{M}, r_5 and r_{M} values as indicated by the reduced dimensions of the ellipse.

In both copolymer systems, the fact that the reactivity ratio values of 4-HMA and 5-HMA are smaller than unity, which indicates that the homopropagation constants of these monomers are lower than the cross-propagation constants, 5-HMA inferior to 4-HMA, with 4-HMA and 5-HMA being more reactive to MMA than to themselves. In contrast, MMA propagation constants are higher than the cross-propagation ones, r_{M} being higher than 2 in the 5-HMA–MMA system. The $1/r_4 \backsim 1.2$, and $1/r_5 > 2$ values indicate

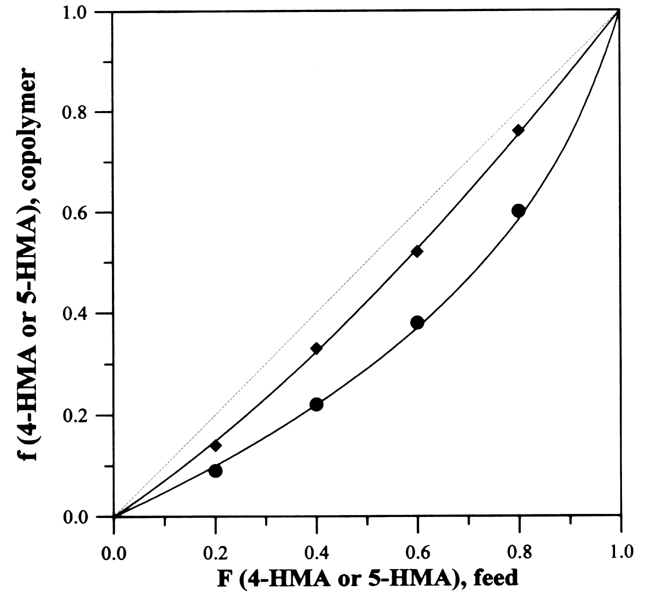

Fig. 3. Composition diagrams of the 4-HMA–MMA and 5-HMA–MMA copolymer systems. The solid lines correspond to the theoretical diagrams deduced from the reactivity ratios given in Tables 3 and 4. (◆) 4-HMA–MMA, (●) 5-HMA–MMA.

that the growing radicals with 4-HMA and 5-HMA ends, are more reactive to MMA than to their respective monomer units, whereas $1/r_M = 0.6$ (for 4-HMA–MMA) and $1/r_M = 0.4$ (for 5-HMA–MMA) values point to a higher reactivity of the growing radicals with MMA ends to MMA than to 4-HMA or 5-HMA. Therefore, the tendency of MMA sequences formation is relatively higher than 4-HMA or 5-HMA ones for a fixed composition of the reaction media.

The $r_4 \times r_M \backsim 1.3$, being r_4 and r_M relatively close to unity, indicates that the 4-HMA–MMA copolymers prepared under these conditions will have a random distribution of the monomer units along the copolymer chains. However, the $r_5 \times r_M < 1$ value gives rise to a random distribution of the monomer units with a higher tendency of MMA blocks formation along the copolymer chains. The reactivity ratios of both copolymer systems are in the range of those reported for the free radical copolymerization of MMA with other methacrylamides [21].

Using the Tidwell and Mortimer reactivity ratios values, the copolymer 4-HMA–MMA and 5-HMA–MMA theoretical composition diagrams were determined using the Mayo and Lewis [16] equation and these are exhibited in Fig. 3. The experimental composition data fit adequately the theoretical diagrams represented by solid lines, indicating the random character of these copolymer systems with compositions richer in MMA with respect to the feed.

From the reactivity ratio values and taking into consideration well known statistical relationships, we have determined the "run number", *R*, defined by Harwood and Ritchey [22] as the average number of monomer alternations in a copolymer per 100 monomeric units. This parameter provides a useful picture of the sequence distribution in a copolymer chain and can be used to estimate the variation of the physical properties of copolymers with the

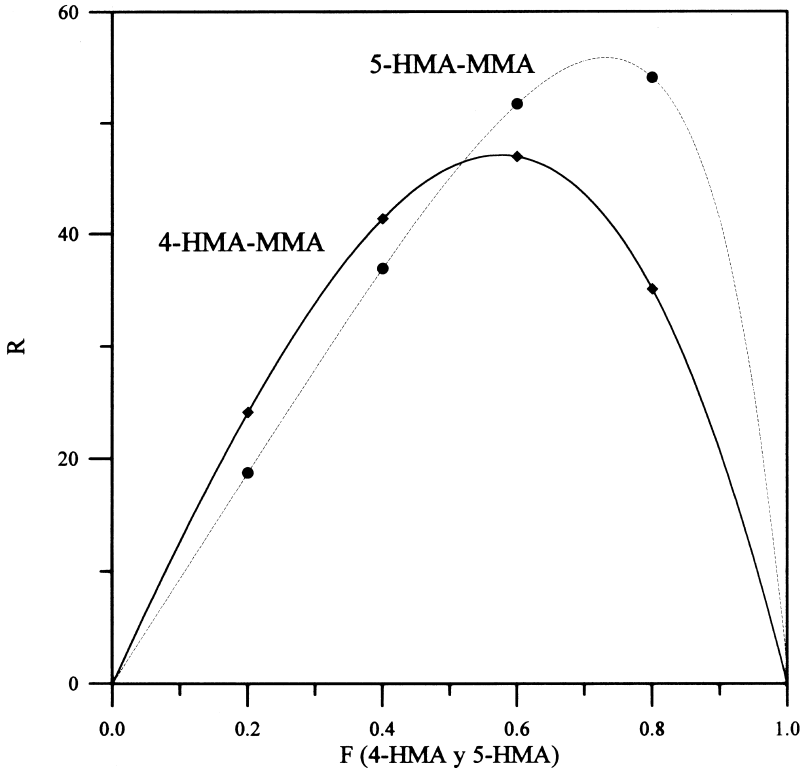

Fig. 4. Variation of the "run number", *R*, with the feed composition F_4 and F_5 for the 4-HMA–MMA and 5-HMA–MMA copolymer systems.

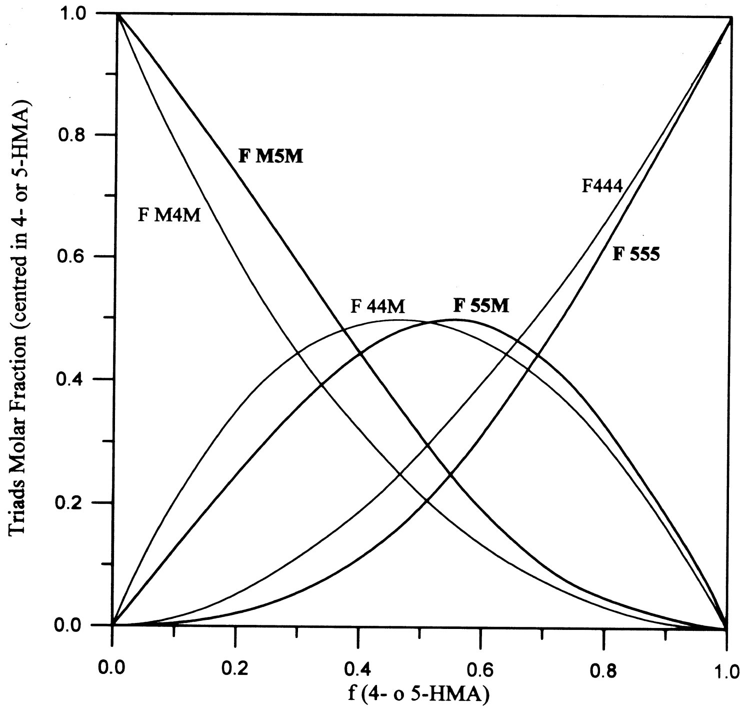

Fig. 5. Variation of the molar fraction of 4-HMA and 5-HMA centred triads with the molar fraction of 4-HMA and 5-HMA in the respective copolymers.

composition. Values of R have been determined in terms of r values and probability statistics for different values of the monomer feed, covering a wide range of composition. Fig. 4 shows the variation of R with the molar fractions $F_{4\text{-HMA}}$ and $F_{5\text{-HMA}}$ in the feed. The maximum values of R are ≈47 for $F4 = 0.59$ for the 4-HMA–MMA system, and ≈56 for $F5 = 0.7$ for the 5-HMA–MMA copolymers.

The statistical distribution of HMA centred triads was determined considering the equation for the first-order Markovian transition probabilities P_{4M}, P_{M4}, P_{5M}, P_{M5} (see Table 1) according to the following equation [23]:

$$P_{HM} = 1 - P_{HH} = \frac{1}{1 + r_H X},$$

$$P_{MH} = 1 - P_{MM} = \frac{1}{1 + r_M/X},$$

where $X = [\text{HMA}]/[\text{M}]$ is the ratio of the concentration of HMA and MMA units in the monomer feed. These can be clearly seen in Fig. 5, where the variation of HMA centred triads as a function of HMA molar fraction in the copolymer chains is shown. The concentration of homotriads 444 or 555 (4 = 4-HMA, 5 = 5-HMA) increases with f_{HMA}, whereas the concentration of alternating triads (M4M and M5M) decreases, and the concentration of heterotriads M44* or M55* present a maximum at values of 0.49 and 0.58, respectively. It is clear from this figure that the relative concentration of M and H centred sequences can be regulated by controlling the composition of the monomer feed.

We have found that the stereochemical distribution of the side group of acrylic monomers in free-radical copolymerization in general follows Bernoullian statistics [24,25]. On this basis, we assume that the configurational sequence distribution of HMA–MMA copolymers may be described according to Bernoullian statistics with the isotacticity and co-isotacticity parameters σ_{ii}, σ_{jj}, σ_{ij} and σ_{ji} defined by Bovey [7] and Coleman [26], where σ_{ij} is the probability of generating a meso dyad between an i ending growing radical and incoming j monomers, σ_{ii} and σ_{jj} correspond to the isotacticity parameters of the free radical polymerization of HMA and MMA in the experimental conditions used for the preparation of copolymers, giving values of $\sigma_{4\text{-HMA}} = 0.17$, $\sigma_{5\text{-HMA}} = 0.20$ [15] and $\sigma_{\text{MMA}} = 0.22$ [27]. The coisotacticity parameter is not directly accessible, but it can be assumed that $\sigma_{ij} = \sigma_{ji} = \sigma^*$ as it has been assumed for similar systems [28–30]. This parameter can be determined from the analysis of the stereochemical distribution derived from NMR data. Statistically, according to the models considered for the copolymerization process, i.e. the first-order Markov statistics for the addition of the comonomeric units to growing radical, and the randomly Bernoullian model for the distribution of the stereochemical configuration of the acrylic units along the copolymer chains, it is possible to obtain the equations necessary to determine the concentration of HMA and MMA centred sequences of triads with a particular stereochemical configuration.

3.1. *Stereochemical analysis of poly (4HMA-co-MMA) and poly (5HMA-co-MMA) copolymers.α-CH3 groups*

As it is shown in Fig. 6, the α-methyl signals split into

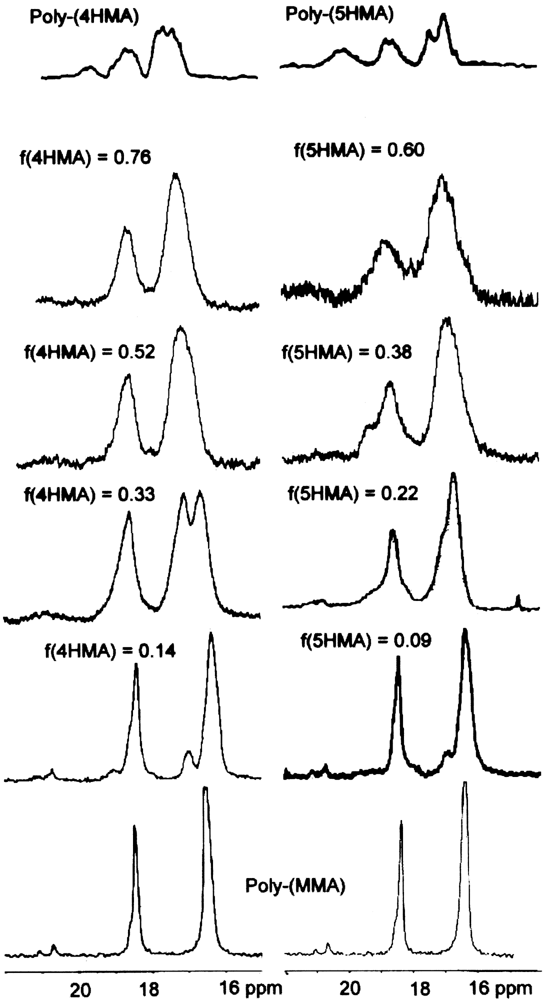

Fig. 6. ^{13}C NMR signals of the α-CH_3 of the corresponding 4-HMA–MMA and 5-HMA–MMA copolymer systems.

two clearly different signal groups for both copolymer systems, which can be tentatively assigned to heterotactic (mr + rm, 18–19 ppm) and syndiotactic triads (rr, 16–17 ppm) in order of increasing field, according to the homopolymer analysis of sequences [15]. Moreover, at lower field there is a wide, low intensity group of signals which has been assigned to isotactic triad sequences (mm, 19–20 ppm). Fig. 6 shows the homopolymer splitting of this group as reference. The splitting of each signal group has to be related to the contribution of the compositional sequences and to larger stereochemical effects. From this tentative assignment, we have calculated the coisotacticity parameter σ_{12} that gave a better fitting of the data according to a Bernoullian statistics. Tables 3 and 4 show the determined σ_{12} values next to the area of the different signals. The good agreement between the different σ_{12} values and the fact that they are very close to the isotacticity parameters of homopolymers confirm the given assignments. Therefore, the stereochemical nature of the copolymer chains is very similar to that of the homopolymers, that is, they are highly syndiotactic being the average coisotacticity parameters $\sigma_{4\text{HMA-MMA}} = 0.21$ and $\sigma_{5\text{HMA-MMA}} = 0.19$. The poly(4-HMA-co-MMA) system is stereochemically very close to PMMA and the poly(5-HMA-co-MMA) system is slightly more syndiotactic than homopolymers.

Table 3
Molar fractions of isotactic (mm) heterotactic (mr + rm) and syndiotactic (rr) triads of the 4-HMA–MMA copolymer system determined from the α-CH_3 ^{13}C NMR signals

f(4-HMA) (copolymer)	rr	mr + rm	mm	σ_{4M}
1.0-poly-4-HMA	0.68_9	0.28_2	0.02_9	(0.17)[a]
0.76	0.66_7	0.30_4	0.03_0	0.20
0.52	0.63_2	0.32_7	0.04_1	0.22
0.33	0.62_7	0.33_4	0.03_9	0.21
0.14	0.61_0	0.34_9	0.04_1	0.22
0.0 (poly-MMA)	0.60_8	0.34_3	0.04_8	(0.22)[a]
Average σ_{4M}				0.21

[a] Correspond to the coisotacticity parameter of the corresponding homopolymers.

3.2. –C– quaternary group

Figs. 7 and 8 show the quaternary carbon resonance pattern of homo- and copolymers of both systems next to the Lorentzians obtained by using the PEAKFIT computer program which gives us the best fit of the real spectrum. The homopolymers poly(4-HMA) and poly(MMA) gives well separated signals with a clear shift of at least 2.0 ppm of the quaternary carbon of poly(4-HMA) respect to that of poly(MMA) as shown in Fig. 7. From this figure, it is clear that the copolymer system presents both group of signals with a variation of the intensities according to the average composition of the copolymers and in addition, a more complicated pattern in each group of signals as a consequence of the cotacticity effects. This supports the independent analysis of both resonance signals because of the high reliability of nonexistence of cross-peaks due to compositional effects which is confirmed by the agreement of the intensities with the molar fractions values obtained from ^{1}H-NMR (see Table 5). These considerations have also been taken into account in the analysis of the 5-HMA–MMA copolymer system because of their similarity and the agreement on molar fractions (Table 5) although in this case the resonance signals of both units are closer in the spectrum. It can be seen that the hyperfine signal resolution increases when the copolymer becomes richer in MMA units.

The analysis of the spectra have been done in terms of the composition and stereochemical configuration sequences, as it has been drawn in the Schemes 2 and 3, assuming as predominant the compositional effect in terms of triad sequences because of the similar shielding in the syndiotactic arrangement for both neighbouring units (assumption supported by the pattern of the homopolymer signal, and chemically coherent because the quaternary carbon is part of the backbone and it is affected by the different inductive

Table 4
Molar fractions of isotatic (mm) heterotactic (mr + rm) and syndiotactic (rr) triads of the 5-HMA–MMA copolymer system determined from the α-CH_3 ^{13}C NMR signals

f(5-HMA) (copolymer)	rr	mr + rm	mm	σ_{5M}
1.0-poly-5-HMA	0.64_0	0.32_0	0.04_0	(0.20)[a]
0.60	0.64_6	0.31_6	0.03_8	0.19
0.38	0.63_4	0.32_7	0.03_9	0.19
0.22	0.62_9	0.33_4	0.03_7	0.20
0.09	0.62_0	0.33_6	0.04_4	0.18
0.0 (poly-MMA)	0.60_8	0.34_3	0.04_8	(0.22)[a]
Average σ_{5M}				0.19

[a] Correspond to the coisotacticity parameter of the corresponding homopolymers.

effects of the ester or amide present in the neighbouring units, but it will be shielded by the α-CH_3 groups spatially close to the neighbouring units in a similar way, independent of the different chemical nature of the other pendant group).

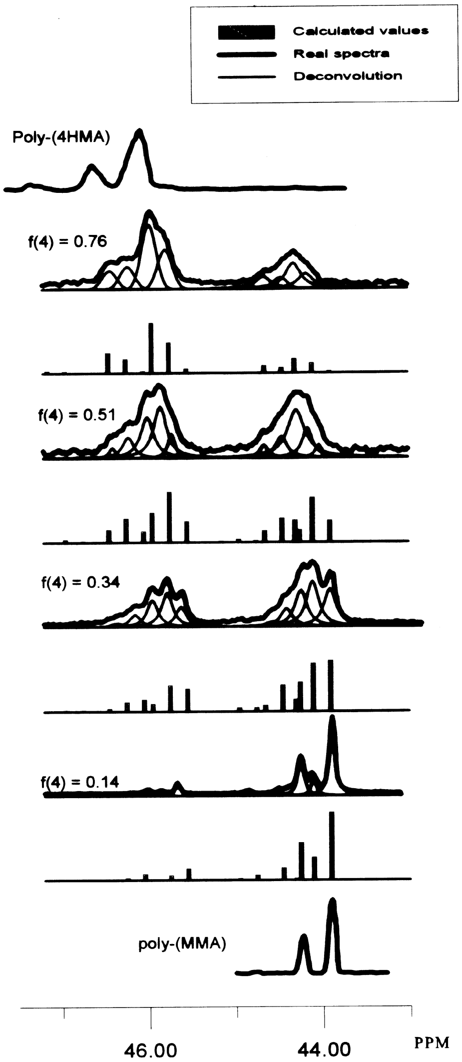

Fig. 7. ^{13}C NMR signals, calculated values and spectra deconvolution of the quaternary carbons of the 4-HMA–MMA copolymer systems.

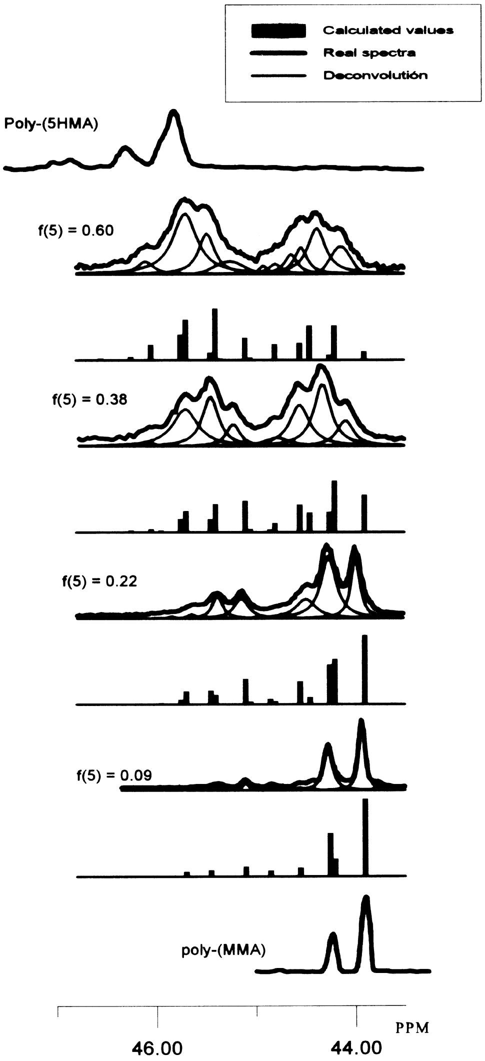

Fig. 8. ^{13}C NMR signals, calculated values and spectra deconvolution of the quaternary carbons of the 5-HMA–MMA copolymer systems.

From the resonance signals of the triad sequences of the homopolymers, (444 or 555 and MMM), we have considered empirically some shielding contributions of the neighbouring units: ±0.2 and ±0.3 ppm for the 4-HMA–MMA and 5-HMA–MMA systems respectively; one MMA unit shifts the resonance signal of HMA central unit to upper field and one HMA neighbouring unit shifts the MMA central unit to lower field. For instance, the 444 syndiotactic triad in the homopolymer poly(4-HMA), shifts to 45.95 ppm, and the $M44_{rr}$ or $44M_{rr}$ unit (inclusion of one MMA neighbouring unit) will shift to 45.75 ppm, and the $M4M_{rr}$ sequence (inclusion of two MMA neighbouring units) will shift to 45.55 ppm. These simple considerations are drawn in the Schemes 2 and 3 where the theoretical values of molar fractions of the different triad (compositional and stereochemical) sequences are quoted. These values were determined by using the Bernoullian statistics for the stereochemical arrangement (with the obtained σ_{12}), and the first-order Markov statistic in the compositional

Table 5
Integration of the quaternary and carbonylic HMA carbons signals obtained from the ^{13}C NMR spectra of 4-HMA–MMA and 5-HMA–MMA copolymer systems

f(HMA) (copolymer)[a]		Integration $HMA_{quarter}$		Integration $HMA_{C=O}$	
4-HMA	5-HMA	4-HMA	5-HMA	4-HMA	5-HMA
0.76	0.60	0.70	0.57	0.73	0.63
0.52	0.38	0.52	0.47	0.54	0.47
0.33	0.22	0.39	0.26	0.36	0.25
0.14	0.09	0.12	0.09	0.13	0.09

[a] Obtained from ^{1}H-NMR [6].

distribution (using the reactivity ratios mentioned before). Figs. 7 and 8 show these theoretical fractions as filled rods under the corresponding spectrum; there is a good prediction of the splitting evolution with composition as well as a good correlation in intensities.

3.3. Thermal transitions of 4-HMA–MMA and 5-HMA–MMA copolymers

It is well recognised that the intrinsic flexibility of polymeric chains is related to the glass transition temperature in amorphous macromolecules, being the measure of the T_g a good way to know the segmental mobility of polymer and copolymer chains of high molecular weight, in which the influence of chain ends is negligible.

The T_g of polymethylmethacrylate was determined to be 375 K, a value lying in the range of those reported in the literature [31]. However, T_g's of poly(4-HMA) and poly(5-HMA) have been previously reported by our research group being 504 and 534 K, respectively [15]. These high values of the homopolymers T_g's were justified by the rigidity of the amide bonds present in the side chains, and mainly by the capability of forming intra- and intermolecular hydrogen bonds through the amide, hydroxy and carboxylic groups of these macromolecules (see Scheme 1), supported by the FTIR data of both homopolymers [15]. Table 1 shows the T_g experimental values of the 4-HMA–MMA and 5-HMA–MMA copolymers, and the molar and weight fractions of the monomers in the feed and in the copolymer samples. Fig. 9(a) exhibits the diagrams of the $1/T_g$ versus the weight

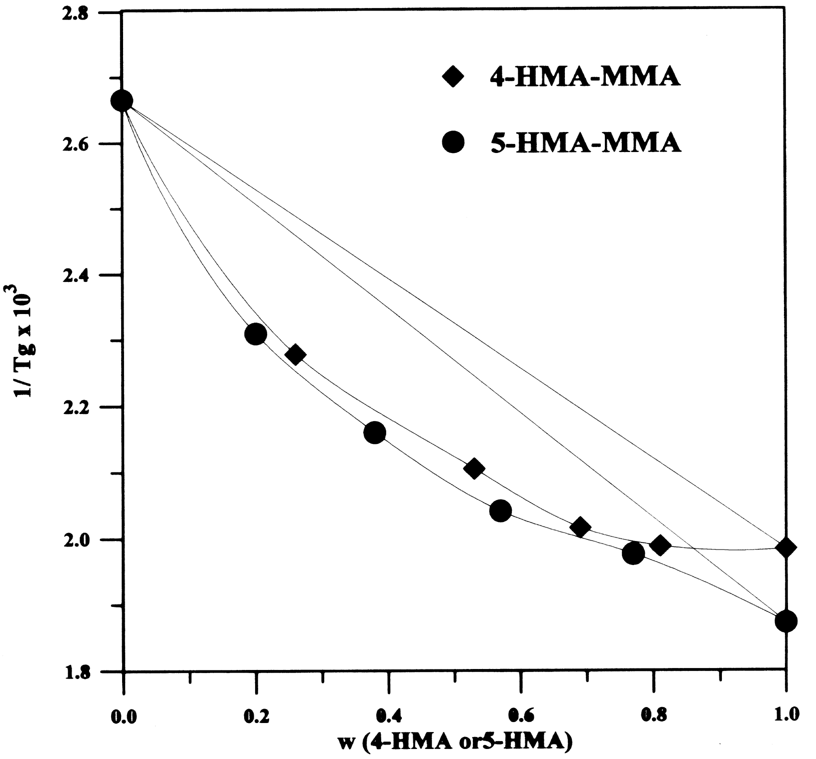

Fig. 9. Variation of the T_g inverse versus monomer weight fraction in the copolymer of the prepared copolymer systems. (◆) 4-HMA–MMA, (●) 5-HMA–MMA.

P4HMA	f(4) / δ (ppm)	0.76	0.52	0.33	0.14	PMMA
	43.80					
	43.85					
	43.90	1	7.3	19	38	MMM_{rr}
	43.95					
	44.00					
	44.05					
	44.10	5.9	15	18	13	$MM4^{*}_{rr}$
	44.15					
	44.20					
	44.25	0.6	4.1	11	21	$MMM_{mr^{*}}$
	44.30	8.4	7.4	4.5	1.1	$4M4_{rr}$
	44.35					
	44.40					
	44.45	3.2	8	10	6.9	$MM4^{*}_{mr^{*}}$
	44.50					
	44.55					
	44.60					
	44.65	4.4	3.9	2.3	0.59	$4M4_{mr^{*}}$
	44.70					
	44.75		0.6	1.5	3	MMM_{mm}
	44.80					
	44.85					
	44.90					
	44.95	0.4	1.1	1.4	0.99	$MM4^{*}_{mm}$
	45.00					
	45.05					
	45.10					
	45.15	0.6	0.5	0.3	0.99	$4M4_{mm}$
	45.20					
	45.25					
	45.30					
	45.35					
	45.40					
	45.45					
	45.50					
$M4M_{rr}$	45.55	2.6	7.1	8.6	6.5	
	45.60					
	45.65					
	45.70					
$M44^{*}_{rr}$	45.75	18	17	9.8	2.6	
	45.80					
	45.85					
	45.90					
444_{rr}	45.95	30	10	2.8	0.3	
	46.00					
$M4M_{mr^{*}}$	46.05	1.4	3.8	4.5	3.5	
	46.10					
	46.15					
	46.20					
$M44^{*}_{mr^{*}}$	46.25	8.4	8	3.5	1.2	
	46.30	8.4				
	46.35					
	46.40					
$444_{mr^{*}}$	46.45	12	4.2	1.1	0.099	
	46.50					
	46.55					
	46.60					
	46.65					
	46.70					
$M4M_{mm}$	46.75	0.5	0.5	0.61	0.5	
	46.80					
	46.85					
	46.90					
$M44^{*}_{mm}$	46.95	1	1	0.51	0.099	
	47.00					
	47.05					
	47.10					
444_{mm}	47.15	1.3	0.4	0.1		
	47.20					
	47.25					

Scheme 2.

	f(5)	0.6	0.38	0.22	0.09	PMMA
	δ (ppm)					
	43.85					
	43.90	2.9	13	26	43	MMM_{rr}
	43.95					
	44.00					
	44.05					
	44.10					
	44.15					
	44.20	12	18	17	9.7	$\mathrm{MM5}^{*}_{rr}$
	44.25	1.7	7.1	15	24	MMM_{mr+}
	44.30					
	44.35					
	44.40					
	44.45	12	6.8	2.7	0.58	$\mathrm{5M5}_{rr}$
	44.50					
	44.55	5.9	9.6	8.7	5	$\mathrm{MM5}^{*}_{mr+}$
	44.60					
	44.65					
	44.70					
	44.75					
	44.80	5.4	3.2	1.2	0.29	$\mathrm{5M5}_{mr+}$
	44.85	0.19	0.96	3.2	3.4	MMM_{mm}
	44.90					
	44.95					
	45.00					
	45.05	0.87	1.2	1.1	0.67	$\mathrm{MM5}^{*}_{mm}$
$\mathrm{M5M}_{rr}$	45.10	7.7	11	9.7	5.6	
	45.15					
	45.20					
	45.25					
	45.30					
	45.35	0.68	0.38	0.19		$\mathrm{5M5}_{mm}$
$\mathrm{M55}^{*}_{rr}$	45.40	18	9.8	3.6	0.77	
$\mathrm{M5M}_{mr+}$	45.45	2.6	4.6	5.2	3.6	
	45.50					
	45.55					
	45.60					
	45.65					
$\mathrm{555}_{RR}$	45.70	14	7.4	4.9	2.8	
$\mathrm{M55}^{*}_{mr+}$	45.75	8.8	4.7	1.8	0.39	
	45.80					
	45.85					
	45.90					
$\mathrm{M5M}_{mm}$	45.95	0.39	0.57	0.57	0.29	
	46.00					
$\mathrm{555}_{mr+}$	46.05	5.3	1.1	0.19		
	46.10					
	46.15					
	46.20					
$\mathrm{M55}^{*}_{mm}$	46.25	1.1	0.57	0.19		
	46.3					
	46.35					
	46.4					
	46.45					
	46.5					
$\mathrm{555}_{mm}$	46.55	0.68	9.6E-2			
	46.6					
	46.65					
	46.7					
	46.75					
PSHMA						

Scheme 3.

fraction of 4-HMA and 5-HMA. The straight lines correspond to the application of the Fox equation based on the free volume theory [32].

The experimental points of both copolymer systems deviate negatively with respect to the Fox equation, indicating that the T_g's of the copolymers prepared are higher than the average weight values of the corresponding homopolymer T_g's. Several studies [33–35] describe the strong effect of the hydrogen bonds on the glass transition temperature giving rise to important deviations with respect to average weight values of the T_g of the hompolymers. In some cases, the T_g of complexes strongly bonded by hydrogen bonding exceed the value of the component of highest T_g. The presence of polar groups such as amide, hydroxy and carboxylic of the 4-HMA and 5-HMA units, as well as the carbonyl group of MMA, contribute to a considerable T_g deviation of the copolymer samples with respect to the average weight contribution of the homopolymers T_g's, as can be observed in Fig. 9 which is because of the possibility of intra- and intermolecular hydrogen bonds between these

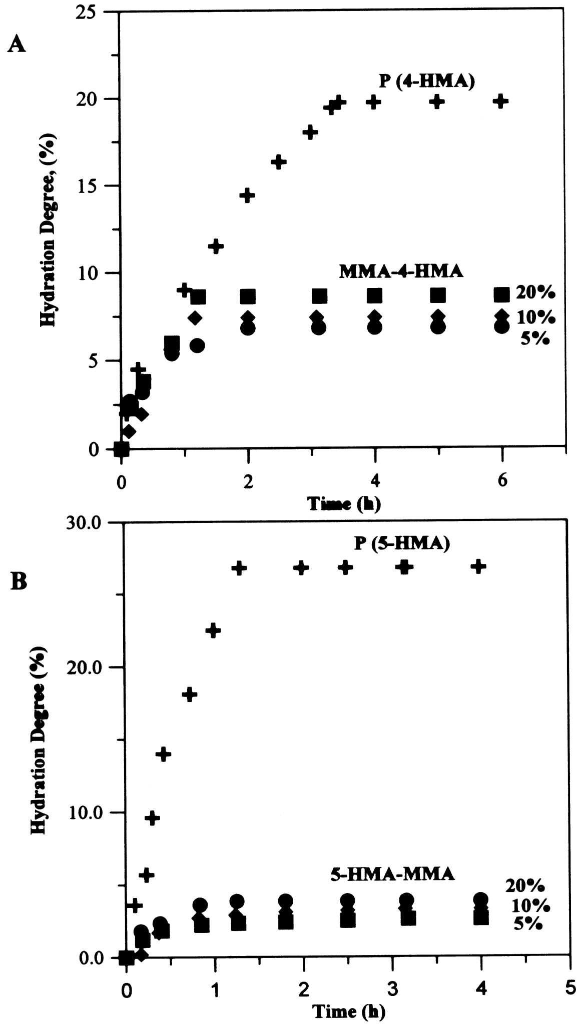

Fig. 10. Swelling isotherms (37°C) of films prepared from: (A) poly(4-HMA) and 4-HMA–MMA copolymers; (B) poly(5-HMA) and 5-HMA–MMA copolymers.

groups. Microstructural treatments based on the T_g of the alternating dyads [36–38] could not be applied to these copolymers due to the T_g's high deviations promoted by the hydrogen bonding present in these copolymer systems.

3.4. Hydration behaviour of copolymer systems

In order to study the hydration process and the influence of the copolymers composition in the kinetics of swelling, copolymer systems with 5, 10 and 20 wt.% of the monomers derived from salicylic acid were used for the preparation of thin films by slow evaporation of the solvent as reported in the experimental section. The dry films of the 4-HMA–MMA and 5-HMA–MMA copolymers were brittle, with glass transition temperatures well above the temperature of the experiments. Films of the homopolymers poly(4-HMA) and poly(5-HMA) were also prepared to carry out comparative studies. After immersions in water at 37°C, the homopolymers films readily swell whereas the copolymer ones became hydrated slowly, according to their composition.

The hydration degree was determined by measuring the weight of films at different times, by the equation [39]

$$H = \frac{W_w - W_0}{W_w} \times 100$$

where W_0 is the weight of the dry sample and W_w is the weight of the wet sample at different times of treatment. The maximum degree H_{max}, was considered as the equilibrium hydration degree, H_∞. Fig. 10(a) and (b) show the variation of the hydration degree as a function of the swelling time for films prepared form homopolymers and copolymers with the composition indicated in the figures. In all cases, except for poly(4-HMA), the equilibrium hydration degree is reached in a short period of time (<100 min) for all compositions studied. However, there is a noticeable effect of the copolymer composition on the equilibrium hydration degree reached in the experiments, H_∞, ranging from 6.8 for films prepared with copolymers with a 5% of 4-HMA to 8.6 for films with copolymers of 20% of 4-HMA, and from 2.6 for films with copolymers of 5% of 5-HMA to 3.8 for films with 20% of 5-HMA. This is a consequence of the strong hydrophilic character of the monomers derived from salicylic acid as can be observed in Fig. 10(A) and (B), where the homopolymers poly(4-HMA) and poly(5-HMA) reach equilibrium hydration degrees of 19.7 and 26.8, respectively.

The dependence of the equilibrium swelling degree on the copolymer composition was previously reported for other copolymer systems [14]. In Fig. 11, the equilibrium hydration degree is plotted against the mole fraction of the hydrophilic components, 4-HMA and 5-HMA, of both copolymers systems. As the hydrophilic components mole fraction increases, the hydration degrees also increases, lying in between homopolymers hydration degree, 1% for PMMA [40], 19.7 for poly(4-HMA) and 26.8 for poly(5-HMA).

There are some differences between both systems arising from their microstructural characteristics. As it was previously discussed, the 5-HMA–MMA copolymer system has a higher tendency to MMA blocks formation along the macromolecular chains with respect to 4-HMA–MMA system. This makes that the hydrophilic character of 5-HMA–MMA copolymers is lower than the 4-HMA–MMA ones, for systems rich in MMA units, probably because of the lower accessibility of water molecules to the hydrophilic units, being the hydrophobic MMA units forming longer blocks than in the case of 4-HMA–MMA copolymer systems. However, the thermal analysis demonstrated that the copolymer systems are homogeneous, without any segregation of micro domains of 4-HMA or 5-HMA sequences rich in MMA systems. Probably, the distribution of 4-HMA or 5-HMA units is relatively short together with the reduced flexibility or stiffness of copolymer segments,

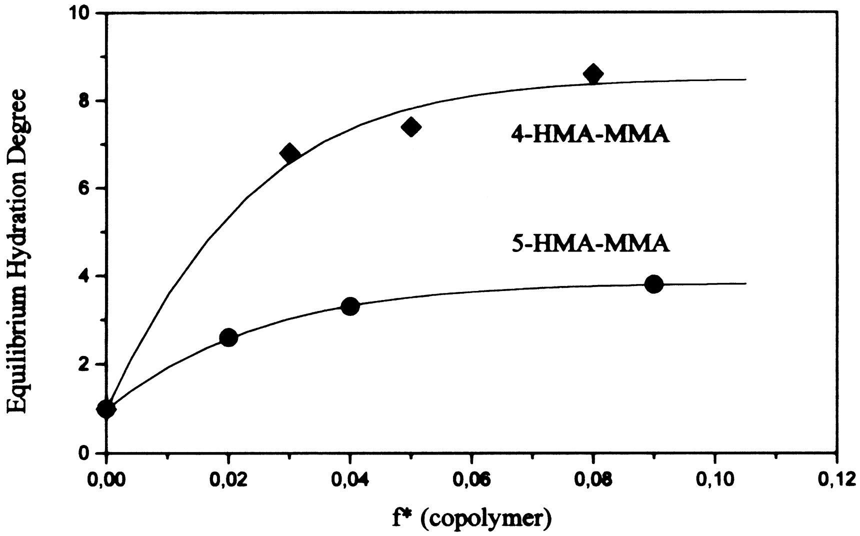

Fig. 11. Variation of the equilibrium hydration degree with the composition of the copolymer systems (◆) 4-HMA–MMA and (●) 5-HMA–MMA copolymers. $f^* = f_{4\text{-HMA}}$ or $f_{5\text{-HMA}}$.

makes difficult the diffusion mechanism of water molecules into the bulk mass of both copolymer systems.

4. Conclusions

Two new acrylic formulations based on modified PMMA have been prepared by copolymerization with two methacrylic monomers derived from salicylic acid, which have been proposed to stimulate bone regeneration by forming molecular complexes with Ca^{++}.

Some important aspects of the relative reactivity of the salicylic acid derivatives have been studied by the analysis of the free radical copolymerization with methyl methacrylate, considering the terminal model and giving rise to reactivity ratios of $r_4 = 0.83$, $r_M = 1.52$ and $r_5 = 0.29$ $r_M = 2.15$.

The stereochemical arrangement (which could influence the Ca complexation) fit to Bernoullian statistics with a coisotacticity parameters of $\sigma^* = \sigma_{4M} = \sigma_{M4} = 0.21$ and $\sigma^* = \sigma_{5M} = \sigma_{M5} = 0.19$.

The high T_g values of the copolymeric samples demonstrate the strong unit interactions which is related to the mechanical properties of the applied acrylic formulation for bone cements.

The swelling studies demonstrated the higher water uptake of this derivative with respect to PMMA, because of their higher hydrophilic character. This is interesting in applications as bone cement because it will compensate the intrinsic volume reduction associated to the polymerization process and promotes strong interactions with natural components of the bone tissue.

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