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Vinyl pyrrolidone–methacrylic monomers bearing salicylic acid derivative moieties: copolymerization parameters and microstructure analysis

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Abstract

Copolymers of vinyl pyrrolidone (VP) and the methacrylic monomers derived from salicylic acid, 2-hydroxy-4-methacrylamidobenzoic acid (4HMA) and 2-hydroxy-5-methacrylamidobenzoic acid (5HMA), were prepared by free radical polymerization in DMF solution at 50°C, using 2,2′-azobisisobutyronitrile (AIBN) as initiator. The reactivity ratios of the monomers were calculated according to the general equation using the Fineman–Ross and Kelen–Tüdös linearization methods, and also the Tidwell and Mortimer nonlinear least-squares treatment. The most probable reactivity ratio values derived from the 95% confidence diagram were the Tidwell and Mortimer ones giving $r_{4HMA} = 6.59$ and $r_{VP} = 0.03$ for the 4HMA–VP system, and $r_{5HMA} = 10.58$ and $r_{VP} = 0.02$ for the 5HMA–VP copolymer. The microstructure of the copolymer chains was analysed according to a first-order Markov statistic and to the Skeist equation for the dependence of the composition on the conversion degree.

Keywords: Vinyl pyrrolidone; Methacrylic monomers; Copolymers

1. Introduction

Copolymers of the methacrylic monomers containing salicylic acid, 2-hydroxy-4-methacrylamidobenzoic acid (4HMA) and 2-hydroxy-5-methacrylamidobenzoic acid (5HMA) (HMA) and HEMA, have been previously described as interesting drug delivery systems (DDS) for the release of the chemically bounded salicylic acid derivatives [1] The in vitro studies showed a controlled release of the drug in terms of months. However, for some specific applications, more hydrophilic and hydrosoluble materials are needed. In this sense, hydrophilic VP-based copolymers are good candidates due to the well-known hydrosolubility and biocompatibility of poly-(vinyl pyrrolidone), PVP, a polymer with many applications in the biomedical field [2].

Highly hydrophilic and water-soluble polymers bearing sodium salicylate residues, linked to polysulfonilamine backbones by azo groups have been described as very active systems for the release of 5-aminosalicylic acid in the lower bowel and the treatment of inflammatory bowel diseases [3]. Schat et al. [4] have described the preparation and the behaviour of polymeric drugs based on 5-amino salicylic acid linked to polymeric supports through azo-bonds, which are destroyed by anaerobic bacteria present in the lower bowel. In addition, an interesting characteristic of polymeric derivatives of 4- and 5-aminosalicylic acids is the strong tendency of these molecules to form very stable complexes with metals by chelating interactions [5–7]. In this sense, we have studied recently the complexation of high molecular weight polyacrylic systems derived from 4HMA and 5HMA with calcium ions, demonstrating the ability of these systems to form highly stable complexes with calcium ions, which is of practical importance from a biomedical point of view [8]. The complexation of these systems with calcium provides an interesting way for the fixation of calcium and therefore the possibility for attractive treatments of chronic diseases like osteoporosis, as well as applications in the filling of bone cavities.

Moreover, highly hydrophilic complexes of a polyacrylic derivative of 4-aminosalicylic with the natural and biodegradable polysaccharide chitosan provide excellent supports for the release of bioactive compounds, including the 4-aminosalicylic acid itself, which can be released hydrolytically in the physiological medium with the subsequent clearance of the support by the biodegradation of the chitosan counterpart [9].

In spite of the broad use of VP-methacrylates (crosslinked poly[VP-*co*-HEMA] is the most representative one in the

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Table 1
Monomer feed (F) and copolymer (f) compositions of the free radical copolymerization of 4HMA–VP and 5HMA–VP in DMF solution at 50°C.

F_4^*	f_4^*	F_5^*	f_5^*
0.05	0.45	0.02	0.36
0.10	0.57	0.05	0.53
0.15	0.64	0.10	0.42
0.20	0.70	0.15	0.73
0.30	0.78	0.20	0.78
0.40	0.84	0.30	0.83
0.50	0.88	0.40	0.89

contact lens area), it is well described in the literature that VP presents a relatively low reactivity with methacrylates in free radical polymerization [10]. However, we have demonstrated that uncrosslinked VP–HEMA copolymers are very interesting as resorbable supports for the controlled release of pharmacologically active compounds [11]. For this reason, an in-depth study of the reaction in controlled conditions to avoid crosslinking, is included in this work; this study has been focussed on the variation of the microstructural copolymer parameters with the conversion, in order to characterize and predict the high conversion uncrosslinked materials which are the most interesting from a practical point of view.

2. Experimental

2.1. Monomer preparation and purification of materials

The methacrylamides 2-hydroxy-4-methacrylamidobenzoic acid (4HMA), and 2-hydroxy-5-methacrylamidobenzoic acid (5HMA), were synthesized by a one-step route involving well known organic reactions [12].

Vinyl pyrrolidone, VP, was distilled under reduced pressure and used without further purification. 2-2′-azobisisibutyronitrile, AIBN, was purified by fractional crystallization from methanol, mp 104°C. *N*,*N*-dimethylformamide, DMF, was dried over anhydrous magnesium sulphate for 2 days and later with phosphorus pentoxide overnight. After drying DMF was distilled under reduced pressure. Other reagents were extra pure grade and were used as purchased.

2.2. Copolymerization

Copolymerization reactions were carried out in DMF solutions at 50 ± 0.11°C in Pyrex glass ampoules sealed under high vacuum. The monomer and initiator concentrations were 1.0 and 1.5×10^{-2} mol l^{-1}, respectively. The sealed ampoules were shaken vigorously and immersed in a water-bath maintained at the polymerization temperature. After reaction, the ampoules were immediately poured into

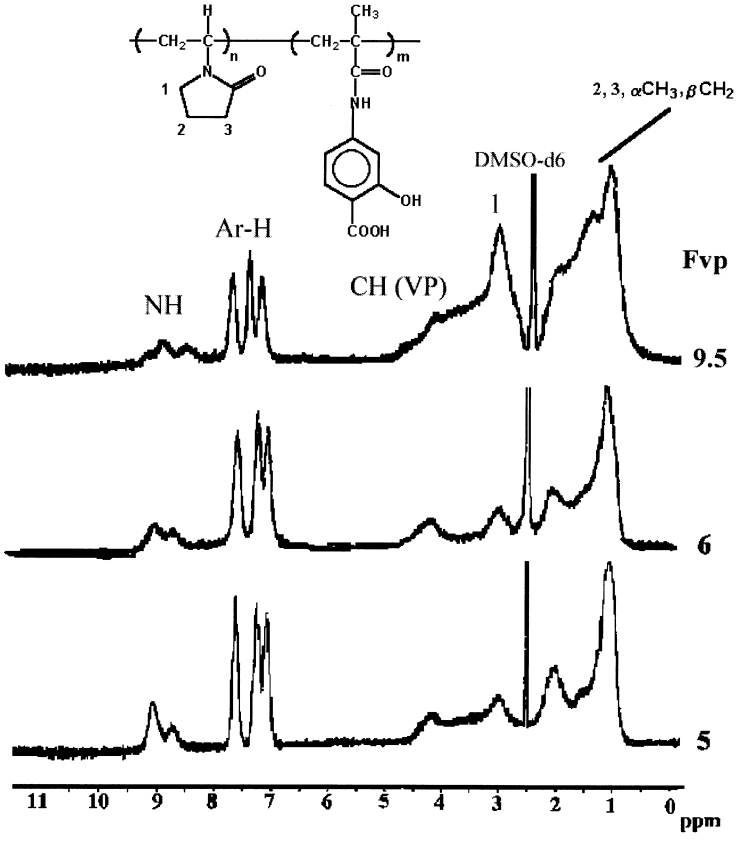

Fig. 1. ^{1}H NMR (200 MHz) spectra of 4HMA–VP copolymers prepared with the molar composition of monomer feed indicated.

Table 2
Copolymerization parameters of the free radical copolymerization of 4HMA–VP and 5HMA–VP

Method	r_{VP}	r_4	$r_{VP} \times r_4$	$1/r_{VP}$	$1/r_4$
F–R	$0.03 \pm 2 \times 10^{-3}$	6.59 ± 0.06	0.20	33.33	0.15
K–T	$0.03 \pm 3 \times 10^{-3}$	6.64 ± 0.05	0.20	33.33	0.15
T–M	0.03	6.59	0.20	33.33	0.15
	r_{VP}	r_5	$r_{VP} \times r_5$	$1/r_{VP}$	$1/r_5$
F–R	$0.02 \pm 1 \times 10^{-3}$	10.68 ± 0.72	0.21	50.00	0.09
K–T	0.02 ± 0.01	10.45 ± 0.69	0.21	50.00	0.10
T–M	0.02	10.58	0.21	50.00	0.09

a large excess of diethyl ether. The precipitated samples were washed with a mixture of chloroform and diethyl ether and dried under vacuum until constant weight was attained.

2.3. Polymer characterization

The copolymers obtained from different mixtures of 4HMA and 5HMA with VP, were analysed by ^{1}H NMR spectroscopy with a Bruker AM-200 NMR spectrometer operating at 200 MHz. The spectra were recorded on 5% (w/v) deuterated dimethylsulphoxide, DMSO-d_6, solutions.

3. Results and discussion

The copolymerization of the methacrylic monomers derived from salicylic acid, 4HMA and 5HMA, with VP, was studied over a wide composition range with molar fractions of 4HMA and 5HMA in the range 0.02–0.50 in the monomer feed as shown in Table 1. The reaction time was initially regulated to reach conversions of <5 wt% in order to satisfy the differential copolymerization equation [13]. The molar fractions of monomer units incorporated in the copolymer systems 4HMA–VP and 5HMA–VP were determined from the ^{1}H NMR spectra of copolymer samples prepared with different monomer feeds and registered in DMSO-d_6 solutions. The analysis was performed 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 4HMA and 5HMA methacrylic monomers, and from signals with chemical shifts 4.5–2.6 ppm assigned to protons 1 and CH of VP, as shown in Fig. 1 for the 4HMA–VP copolymers with different molar fractions of the corresponding monomers in the monomer feed.

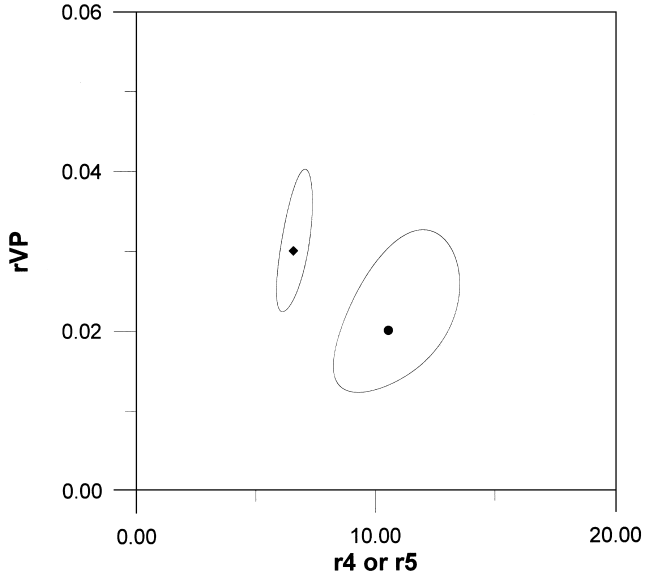

Fig. 2. The 95% confidence diagram for the reactivity ratios of 4HMA and VP, r_4 and r_V (◆), and 5HMA and VP, r_5 and r_V (●), determined by the nonlinear least-squares method (Tidwell–Mortimer).

Table 1 shows the molar fractions of the initial mixtures of comonomers used and the resulting composition of the 4HMA–VP and 5HMA–VP copolymer systems obtained under the mentioned conditions. It can be observed that it is very difficult (if not impossible) to prepare with accuracy and reproducibility copolymer samples of f_{4HMA} and f_{5HMA} <0.30 since it would be necessary to use feeds with F_{4HMA} and F_{5HMA} molar fractions of <0.02.

The reactivity ratios (r values) of the monomers were determined according to the general copolymer composition equation by applying the linearization methods suggested by Fineman and Ross [14] and Kelen and Tüdös [15] as well as by the nonlinear least-squares analysis proposed by Tidwell and Mortimer [16]. The results are shown in Table 2 for both copolymer systems. It must be pointed out that the reactivity ratios values obtained by the linearization and nonlinear least-squares methods are very similar in both copolymer systems. The r_{VP} values are the same independent of the method used for both 4HMA–VP ($r_{VP} = 0.03$) and 5HMA-VP ($r_{VP} = 0.02$) copolymer systems, whereas r_{4HMA} is 6.59 for the Fineman–Ross and Tidwell–Mortimer methods, and r_{5HMA} is in the range 10.45–10.68 (see Table 2). In any case, the r values determined by the application of the analysis suggested by Tidwell and Mortimer have been considered the most probable ones because of the well-known higher accuracy of the non-linear method. Fig. 2 shows the 95% confidence limits defined by the area of the elliptical diagram together with the points of the reactivity ratios values obtained by the TM method. The 95% confidence diagrams give an idea of the experimental errors 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 good conditions, the approximation can be acceptable. This is illustrated by applying the mathematical treatment suggested by Behnken [17] and Tidwell and Mortimer [16]. 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 diagrams represented in Fig. 2. These diagrams confirm the good approximation

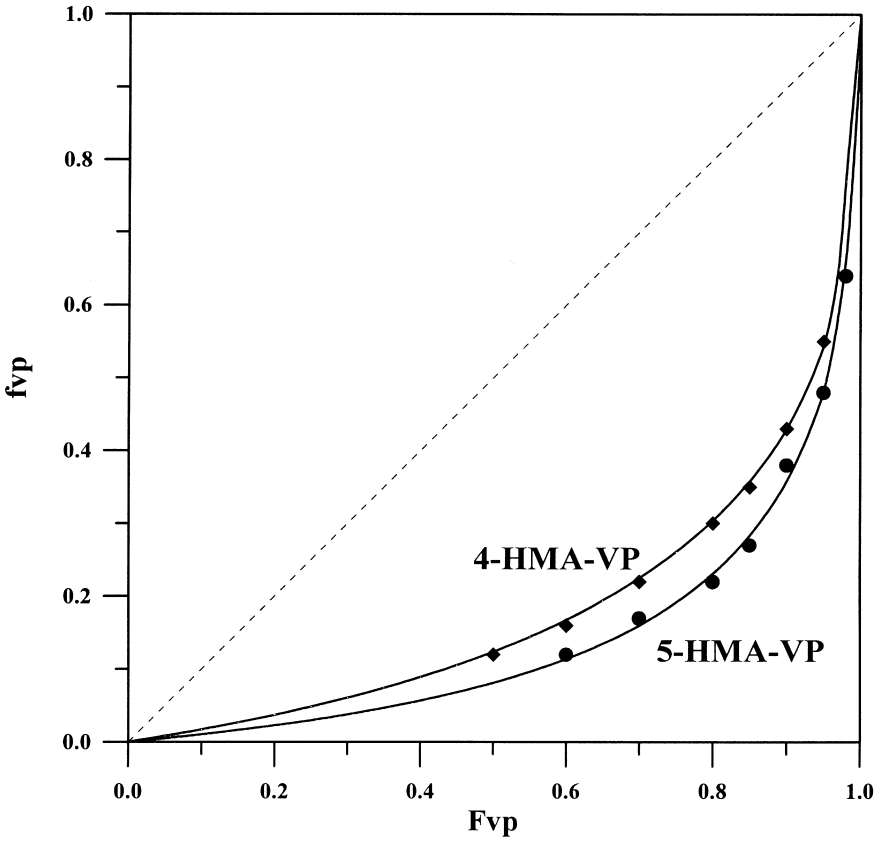

Fig. 3. Composition diagrams of the 4HMA–VP (◆) and 5HMA–VP (●) copolymer systems. The curve lines correspond to the theoretical diagrams deduced from the *r* values given in Table 2.

of the r_{VP}, r_{4HMA} and r_{VP}, r_{5HMA} values, as indicated by the reduced dimensions of the ellipses.

Using the Tidwell and Mortimer reactivity ratio values (r_{4HMA}, r_{VP} and r_{5HMA}, r_{VP}), the average composition diagrams of both copolymeric systems have been drawn considering the classical Lewis–Mayo equation, and they are represented in Fig. 3. The experimental composition data fit adequately the theoretical diagram represented by the curve lines of the corresponding 4HMA–VP and 5HMA–VP copolymers, as is indicated in Fig. 3.

In both copolymer systems the VP reactivity ratios are near to zero (0.02 and 0.03) indicating that the homo-propagation constants of VP in free radical copolymerization with 4HMA and 5HMA, are smaller than cross-propagation constants, and VP will tend to react with the salicylic monomers rather than with other VP molecules. On the other hand, 4HMA and 5HMA reactivity ratios r_{4HMA} and r_{5HMA} are 6.59 and 10.58, respectively, indicating that the homo-propagation constants are higher than the cross-propagation ones, and 4HMA and 5HMA will react preferentially with 4HMA and 5HMA units, respectively, rather than with VP molecules.

The reactivity of growing radicals with 4HMA ends, as measured by the ratio $1/r_{4HMA}$ is somewhat higher for 4HMA than VP monomer molecules. In the case of 5HMA growing radicals, $1/r_{5HMA}$ is more pronounced with respect to 4HMA, but of similar order to 5HMA units than VP. However, the reactivity of the growing radical with VP ends is much higher towards 4HMA or 5HMA in both copolymer systems, even higher in the 5HMA–VP case. In this sense, it can be considered that the growing radicals ending in vinyl pyrrolidone units exclusively add to 4HMA or 5HMA monomers during the radical process. Therefore, there is an initial tendency towards the formation of 4HMA or 5HMA sequences, and copolymers with long blocks of 4HMA or 5HMA will be obtained in the first steps of the reactions, this tendency being slightly more pronounced for the 5HMA–VP copolymers.

Similar *r* values have been obtained for these copolymerization systems being in the range of those reported for the free radical copolymerization of methacrylic monomers and vinyl pyrrolidone [11,18–20].

From a practical point of view, reactions at high conversion have to be considered and a correct microstructure description of the final copolymers need an in-depth analysis of the microstructure variation with the conversion. In this respect, the theoretical study of the variation of the different variables with conversion is included in this work. The instantaneous statistical distribution of triads centred on one monomer unit, or on the other, can be determined for each copolymer system considering the first-order Markov statistics corresponding to the classical terminal

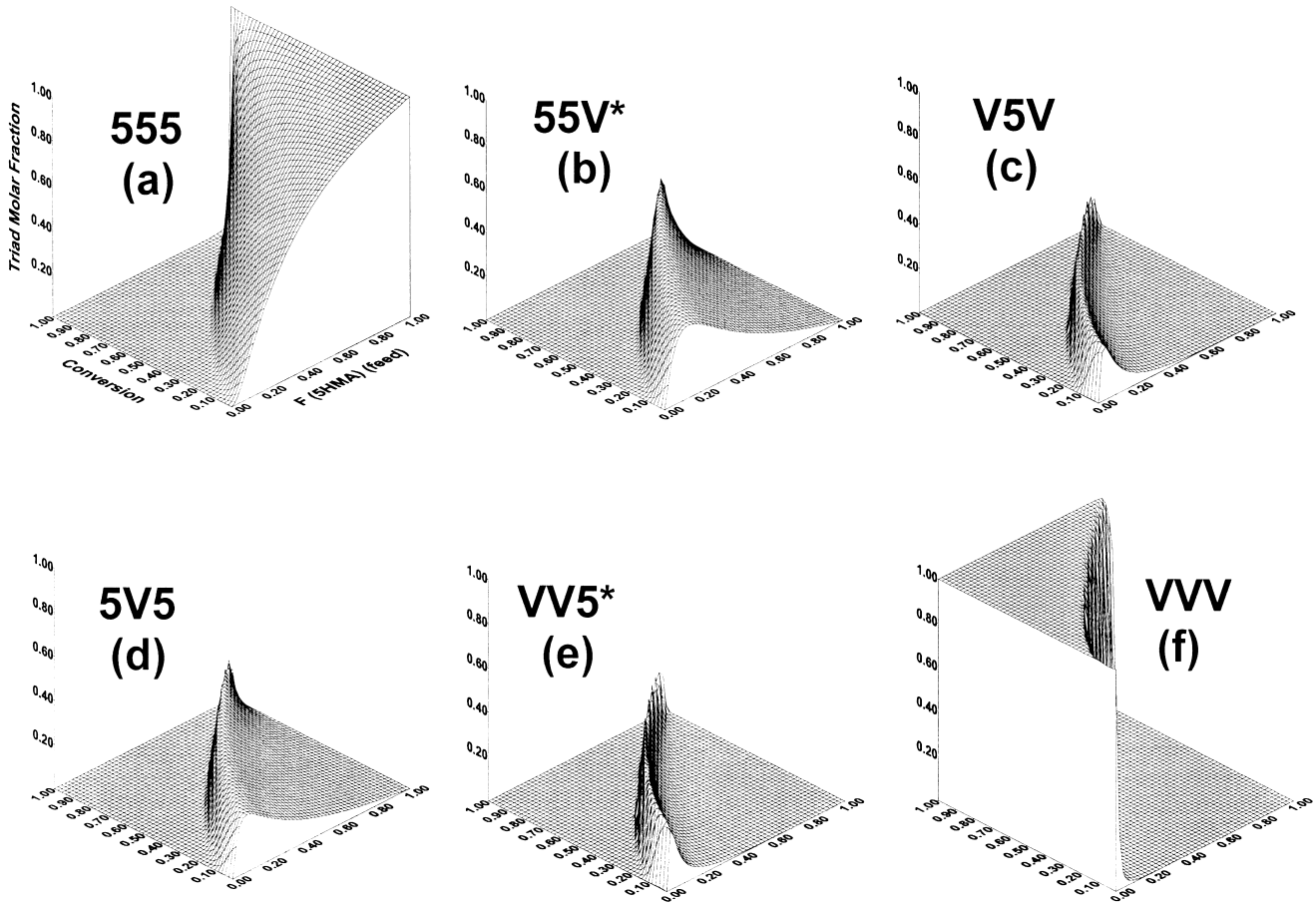

Fig. 4. Instantaneous triad molar fraction surfaces versus conversion and initial feed composition for the 5HMA–VP system. $55V^{*} = 55V + V55$, $VV5^{*} = VV5 + 5VV$.

model, and from the reactivity ratios and instantaneous monomer feed concentrations according to the following equations [21]:

$$P_{12} = 1 - P_{11} = \frac{1}{1 + r_1 X}$$

$$P_{21} = 1 - P_{22} = \frac{1}{1 + r_2/X} \tag{1}$$

where $X = [M_1]/[M_2]$ is the ratio of the concentration of $[M_1] = [HMA]$ (4HMA or 5HMA in this case) and $[M_2] = [VP]$ in the monomer feed, r_1 and r_2 are the reactivity ratios, and P_{ij} $(i, j = 1, 2)$ is the conditional probability of the monomer j to be added to a growing chain with radicals with i ends.

Moreover, using the Skeist treatment for the progress of the reaction with conversion, some surface plots of the variation of the instantaneous triad molar fractions with the initial feed compositions and the conversion can be obtained (Fig. 4).

The treatment initially suggested by Skeist [22] represents the progress of the reaction by the equation

$$\ln\left(\frac{M}{M_0}\right) = \int_{F_1^0}^{F_1} \frac{dF_1}{f_1 - F_1} \tag{2}$$

where M and M_0 represent the total number of moles present in the monomer feed at a given time t and at time 0, respectively. Meyer and Lowry [23] have shown that Skeist's equation can be readily integrated provided that f_1, the instantaneous copolymer composition, is expressed in terms of F_1, the corresponding instantaneous monomer composition, and the monomer reactivity ratios by means of the Mayo–Lewis instantaneous copolymer composition equation. For $r_1 \neq 1$ and $r_2 \neq 1$ is obtained:

$$\frac{M}{M_0} = \left(\frac{F_1}{F_1^0}\right)^{\alpha}\left(\frac{F_2}{F_2^0}\right)^{\beta}\left(\frac{F_1^0 - \delta}{F_1 - \delta}\right)^{\gamma} \tag{3}$$

where

$$\alpha = \frac{r_2}{1 - r_2} \qquad \beta = \frac{r_1}{1 - r_1} \qquad \gamma = \frac{1 - r_1 r_2}{(1 - r_1)(1 - r_2)}$$

$$\delta = \frac{1 - r_2}{2 - r_1 - r_2}$$

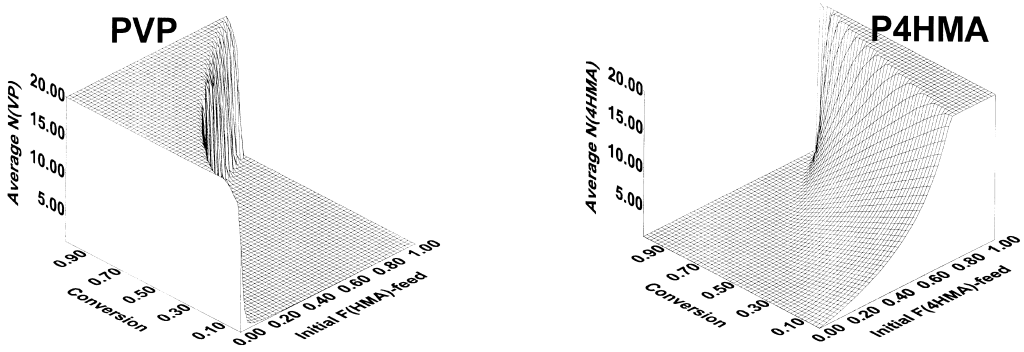

Fig. 5. Average instantaneous sequence length of the 4HMA–VP copolymers versus conversion and initial feed composition.

From a simple mass balance consideration, it has been shown [24] that the mole fraction of monomer 1 in the feed at a given time of reaction, f_1, is related to the cumulative average mole composition of the copolymer F_1 (cumulative) by:

$$f_1 = \frac{f_1^0 - XF_1\ (\text{cumulative})}{1 - X} \tag{4}$$

where X is the molar degree of conversion defined as:

$$X = 1 - \frac{M}{M_0} \tag{5}$$

Eqs. (1) and (3)–(5) have been used to generate theoretical points of the different variables as a function of the conversion in order to predict the course of the reaction, by means of a computer program tailored by the algorithm described elsewhere [11].

Fig. 4 well illustrates the characteristics of this copolymerization reaction and it can be used to predict the microstructure of the final macromolecular chains for the 5HMA–VP system (the 4HMA–VP system has a similar behaviour). As it has been discussed, when $r_{VP} \simeq 0$ and $r_{HMA} \gg 1$, at low conversions the reaction preferentially incorporates HMA units (4 or 5) to the copolymeric chains leading to chains with a high content of homotriads 444 or 555 (Fig. 4a; in the forthcoming discussion 4HMA and 5HMA will be substituted in the triad nomenclature by 4 or 5 and VP by V). At this point of the reaction there are some populations of triads 44V or 55V and 4V4 or 5V5 (which in general incorporate a VP unit isolate in HMA blocks), specially at high VP initial feed content (Fig. 4b and d).

On the other hand, the population of triads with 2 VP units, VHV and VVH*, presents a sharper surface (Fig. 4c and e), which reflects the low probability of incorporating 2 VP units to a growing chain before 4 or 5 have been consumed. In this sense, we should compare the three-dimensional surfaces of VV4 or VV5 and V4V or V5V (2 VP units) with the 44V or 55V and 4V4 or 5V5 surfaces (1 VP unit). The first are sharp peaks but the latter show a smooth slope in the right-hand side of the graphs; the global balance of this analysis is that the reaction incorporate first the 4 or 5 units and it introduces some VP units isolated in the 4 or 5 blocks. Depending on the feed composition, the molar fractions of 555, 55V* ($=$55V + V55) and 5V5 change as shown in Fig. 4. At certain conversion which depends of the feed composition, the HMA in feed decreases and there is a sharp formation of V5V and VV5* ($=$VV5 + 5VV) triads (where the last HMA units are consumed) and finally, at the end of the reaction, a true homopolymer of PVP is formed in the course of the polymerization at high conversion, as observed in Fig. 4f. The homotriad VVV appears drastically at certain conversion (when 4 or 5 are consumed) in the form of a vertical cliff, reaching a molar fraction of 1 (PVP is formed).

Therefore, the analysis shows that the copolymerization reaction leads to the formation of 2 mean species in the course of the reaction: HEMA-rich copolymer (mainly blocks of 4 or 5 which include isolated VP units) and PVP. Fig. 5 give us an useful picture of the sequence distribution for the 4HMA–VP system (5HMA–VP system has a similar behaviour). In this graph, the average instantaneous sequence length of the copolymers calculated according to well-known expressions [25], are quoted versus conversion and initial feed composition. The differences in slopes and plateaus are directly related with differences in the reactivity ratios. r_{HMA}s are one order of magnitude or less far from the unity and there is a broad region where the average sequence length of HMA increases from 1 to $>$20 (it can be considered as homopolymer PHMA), showing a high but measurable slope. Moreover, the upper plateau, an artefact that represents the region with sequences $>$ 20, is quite narrow. However, r_{VP}s, are two orders of magnitude far from the unity and as a consequence, the slope of the average instantaneous sequence length is almost vertical and there is a broad plateau at $N > 20$. As it has been discussed before, VP is introduced in between HMA blocks (isolated VP units) until this monomer is consumed and then PVP homopolymer is formed.

In conclusion, the reaction products can be considered as compatible blends of PVP and HEMA-rich copolymer. The conversion, X, and the initial feed composition, F_0, control in some way the ratio between both species and the length of the 4HMA or 5HMA blocks.

On the other hand, the material has to be considered as

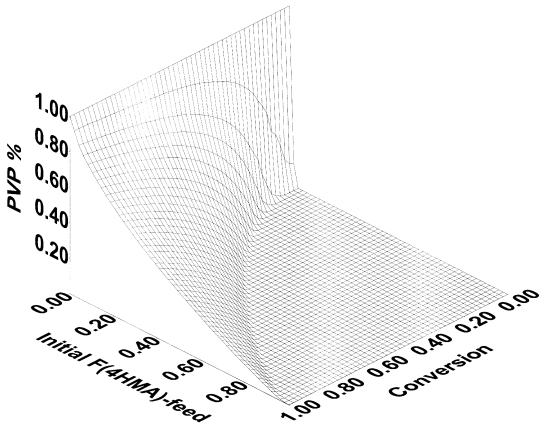

Fig. 6. Theoretical PVP molar content surface for the 4HMA–VP system versus conversion and initial feed composition.

entirely resorbable because the hydrolysis of 4HMA or 5HMA units leads to ionic carboxylate residues which in addition to PVP are water-soluble. From a biomedical point of view, this is an obvious advantage for their use as DDS in parenteral routes because the copolymers will disappear after some time. Moreover, as it has been shown for similar systems [26], the resorption rate and the hydrophilic character of the systems depend on the composition, mainly on the PVP percentage. Fig. 6 shows the theoretical PVP molar content surface for the 4HMA–VP system, considered as forming copolymer chains richer than 95% in VP units. In this case, the hydrolytic behaviour and the release rate which are intimately related to the hydrophilic character (and to the PVP content) can be tailored to some extent by adjusting the parameters of the reaction.

Acknowledgements

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