Development of a Suspension Copolymerization Process for Bone Cement Production

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ABSTRACT: Copolymers of MMA–STY with the suitable composition, particle size distribution, and molecular weight distribution for its medical application as bone cements have been obtained by means of suspension copolymerization. The influence of the stirring rate on the final mean particle size has been established, and the scale-up of the process has been performed with successful results. The application of a kinetic model allowed to estimate the copolymer composition during the process, which is essential to obtain polymers with adequate properties. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 76: 814–823, 2000

Key words: methyl methacrylate; styrene; suspension polymerization; scale up; Rushton stirrer; simulation

INTRODUCTION

Poly(methyl methacrylate), as a standard, has been used for decades as a synthetic filler to repair skeletal defects and affix metal implants to bone. Usually methyl methacrylate (MMA) is polymerized *in situ* at the site where additional bone is needed. The polymer hardens to become stronger than bone, and it is generally considered to be a suitable material for repairs.[1] Up to now, the average service life of a hip prosthesis cemented with it is 12 to 15 years. Bone cement suitable for clinical applications, with enhanced physical resistance properties, can be prepared by suspension copolymerization of methyl methacrylate (MMA) with styrene (STY), in the form of beads with a mean diameter of around 50 μm that can lately be handled by the surgeon.[2]

Polymer particle diameter obtained by means of a suspension polymerization usually range between 10 and 5000 μm. Particle size is critical in the workability of these bone cements. The molecular weight distribution and the ratio between the monomers units in the copolymer are also significant parameters for the use of the copolymer as bone cement.

Suspension polymerization is always a batch process that is carried out in a stirred tank. The most important issue in the practical operation of suspension polymerization is the control of the final particle size distribution. Particle size depends on the monomer type, agitation conditions in the reactor (type and geometry of the stirrer and agitation degree), the viscosity change of the suspended phase with time, and the kind and concentration of the stabilizer.[3]

In this way, Konno et al.[4,5] studied the effect of velocity on particle size in a stirred jacketed tank reactor obtaining Sauter diameters up to 800 μm for suspension polymerization of styrene, with polyvinyl alcohol as a stabilizer in the suspension

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polymerization of styrene. These authors reported the transient drop size distribution and values of Sauter diameters between 50 and 800 μm for different experimental conditions. Recently, Alvarez et al.[6] have developed a mathematical model to describe the particle size distribution for suspension polymerization of styrene. Also, Kalfas et al.[7] have devoted some attention to the influence of stirring rate on the particle size.

On the other hand, Schlegel[8] studied the design and scale-up of polymerization reactors and proposed a rule for the agitator scale-up in suspension polymerization reactors. Yuan et al.[9] have reported, in a extensive review about suspension polymerization tank reactors, some correlations for scale-up for constant mean droplet size in geometrically similar vessels. Rautzen et al.[10] established that the factor used to adjust small-scale speed to large-scale operation is the scale ratio raised to an exponent.

In this work, suspension polymerization of MMA–STY is studied using a Rushton turbine stirrer. The influence of stirring rate on particle size distribution, molecular weight distribution, polymerization rate, and polymer composition has been investigated. To predict the final composition of the copolymer, and taking into account the experimental conditions during the run, a theoretical kinetic model is employed for the simulation of changes in copolymer composition as polymerization evolves.

For the scale-up of the process, the Rushton turbine stirrer in a 10 liters reactor is used. A scale-up criteria based on an empirical correlation is tested. The properties of the scale-up copolymer are analyzed to confirm the suitability of the scale-up criteria and that the copolymer satisfies the characteristics of a qualified bone cement.

EXPERIMENTAL

Materials

Materials used in this investigation were described in a previous work.[11] Essentially, styrene and methyl methacrylate were used free from the inhibitor. Polyvinylpyrrolidone was used as dispersant agent in solution of 1 and 10% by weight to avoid drop coalescence in the samples. Benzoyl Peroxide was used as an initiator, sodium hydroxide to remove the inhibitor, methanol to pour the samples, and calcium chloride as the desiccant.
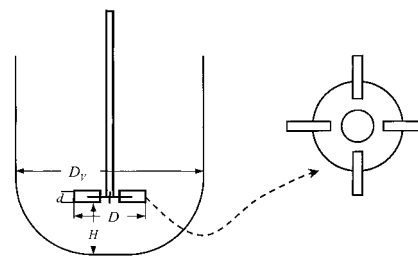
	2 l. Reactor	10 l. Reactor
D (mm)	43.3	76
D_V (mm)	130	224
d/D	1/4	1/4
H (mm)	26	45

Figure 1   Experimental setup.

Polymerization Procedures

Suspension copolymerizations were carried out in a 2-L double-jacketed glass reactor equipped with digital control of stirring rate and temperature. To avoid coalescence of droplets for examination, small aliquots of the suspension were periodically taken and poured in a 10% solution of polyvinylpyrrolidone before the identity point. The scale-up study was carried out in a geometrically similar jacketed tank reactor of 10 L of capacity.

The experimental set up are shown schematically in Figure 1. Rushton turbine stirrers with four vertical blades were used in both reactors. Dimension parameters of the equipment are also shown in Figure 1.

The suspension copolymerization mixture composition in wt % was: styrene (4.55%), methylmethacrylate (18.13%), water (77.04%), benzoyl peroxide (0.23%), and polyvinylpyrrolidone (0.07%).

Temperature was not maintained in a fixed value during the experiments. Reaction mixture was charged into the reactor and heated until reaching 60°C. This point was considered as zero time. Then, the set point of the temperature controller was raised to 80°C for 2 h. After that, the temperature set point was maintained at 90°C for 2 h and finally at 100°C during the last 3 h.

The real temperature profile in the laboratory reactor was published in a previous work,[11] where the experimental procedure was established.

Measurements

The change of particle size distribution during the copolymerization process was determined from

several microphotographs of stabilized samples after a statistical treatment.[11] Number-average diameter, Sauter diameter, and weight-average diameter (only for the final samples) were calculated using the following expressions:

Number average diameter

$$d_n = \frac{\sum n_i d_i}{\sum n_i}$$

Sauter diameter

$$d_{32} = \frac{\sum n_i d_i^3}{\sum n_i d_i^2}$$

Weight average diameter

$$d_w = \frac{\sum n_i \rho \frac{\pi}{12} d_i^3}{\sum n_i} \quad (1)$$

The weight-average diameter of final solid copolymer particles as measured by a Sedigraph 5100 (Micromeritics) apparatus, corroborates the values obtained from microphotographs.

Number- and weight-average molecular weights (M_n and M_w, respectively) and polydispersity (M_n/M_w) of the copolymer were determined by gel-permeation chromatography (GPC) at 38°C as described in the literature.[11] ^{1}H-NMR spectra were recorded on a Varian Unity 300 operating at 299.89 MHz using deuteroacetone and tetramethyl-silane as the solvent and internal standard, respectively.

RESULTS AND DISCUSSION

Results with the Rushton Stirrer

The evolution of the number-average diameter of droplets produced during the polymerization for different stirring rates ranging between 400 and 600 rpm is shown in Figure 2. It can be seen that particle size increases as reaction progresses, until reaching a certain maximum value. This final value is attained at a certain time, the identity point, in our case between 180 and 210 min from the beginning of the experiment. The higher the agitation rate, the lower the particle size is attained with time.
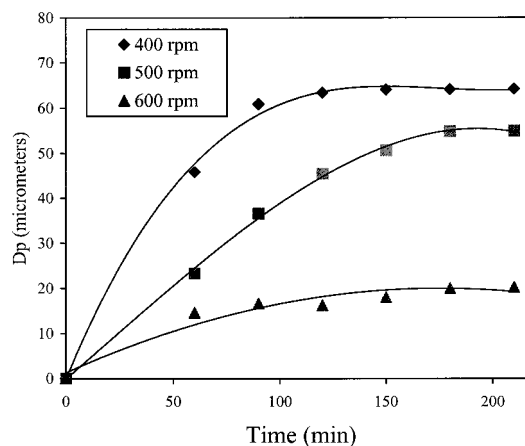

Figure 2 Evolution of number average diameter of droplets during the polymerization for different stirring rates. Laboratory reactor.

The increment of particle size during a suspension polymerization has been reported and explained by several authors.[12–14] There are basically two kinds of behaviors in a suspension polymerization[15]: (a) systems, type A, in which the final particle size is already established at very low conversion. Polymerizing droplets maintain their identity during the experiment, and subsequent reduction in a stirring speed has no influence on particle size. (b) Systems, type B, in which the particles reach the so-called identity point only at high conversion. With these systems it is apparently necessary to take into account the time and conversion dependence of the parameters affecting the polymerization. In certain systems of this kind, the time at which the unpolymerized emulsion reaches its final diameter is longer than the time needed to reach 50% of its conversion.

As shown in Figure 3, the behavior of this system is consistent with the characteristics of the above-mentioned group B: the time needed to reach the identity point (around 180 min) is longer than that necessary to reach 50% of polymer yield (around 150 min). The same results were obtained by the authors with a vertical four-blade stirrer under the same agitator speed.[11]

Number-average diameter, Sauter diameter, and weight final-average particle diameter are shown in Table I. At a stirring rate of 600 rpm, the diameter size is similar to the value obtained by the authors[11] for a vertical four-blade agitator. Higher stirring rates (>600) are expected to have no effect on the particle diameter, because the breakup of the individual drops is the controlling
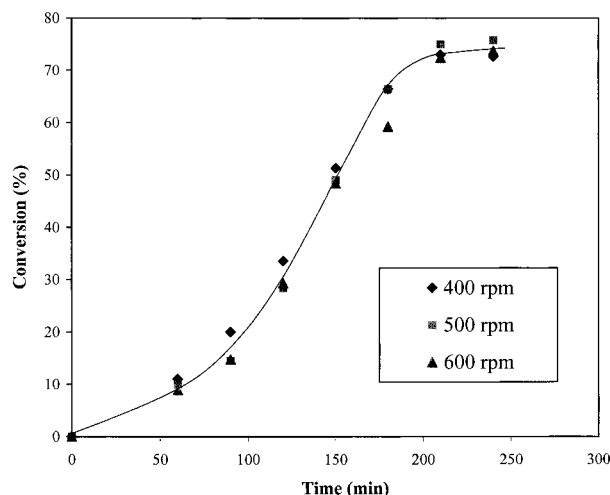
Figure 3 Evolution of conversion for different stirring rates. Laboratory reactor.

step for the droplets size during the polymerization process.

Particle size distribution vs. time for 400 and 600 rpm are shown in Figure 4(a) and (b), respectively. The mean value of particle size increases with time, for the slower stirring rate, undergoing from a unimodal distribution at the beginning of the experiment to a multimodal distribution as time progresses, with a high percentage of small particles. For higher stirring rates, the evolution of particle size is less pronounced. Unimodal distribution remains along the run, slightly rising the mean particle size during the experiment.

On the other hand, the conversion during the polymerization process is not affected by the stirring rate. As expected, our system exhibits the typical behavior of a suspension polymerization. Each bead may be regarded as a small isolated reactor, and the observed copolymerization kinetics corresponds directly to that for bulk polymerization.
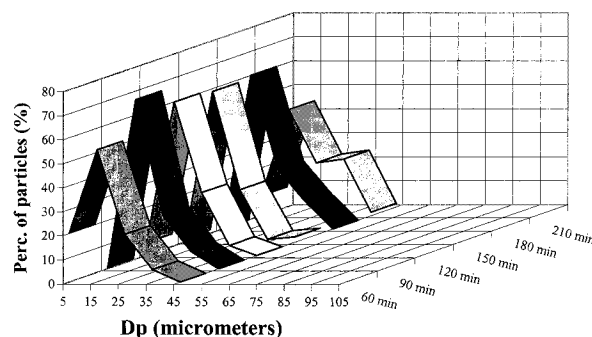
As was mentioned in the Introduction, for its surgical application the mean particle size of the

Table I Particle Size Evolution with Stirring Rate

Stirring Rate (rpm)	D_n (μm)	D_{32} (μm)	D_w (μm)
400	64.21	102.45	116.87
500	54.95	72.48	78.88
550	31.91	50.82	61.77
600	27.5	45.14	53.29
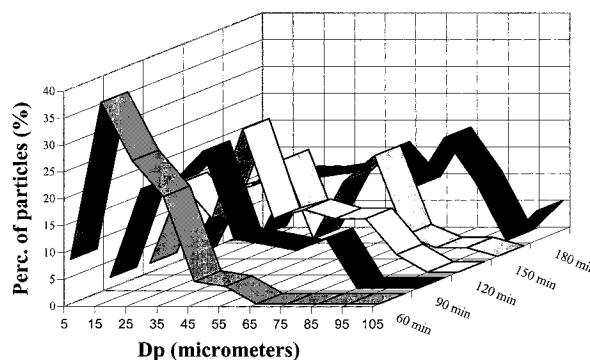
a)

b)

Figure 4 Particle size distribution vs. time for the laboratory reactor at: (a) 400 rpm; (b) 600 rpm.

copolymer beads must be about 50 μm. This value guarantees an optimal workability of the slurry formed by mixing the copolymer beads with a small amount of methyl methacrylate, to be applied as adhesive for the fixation of metal endoprostheses.

In this way, it would be important to find a relationship between the agitation speed and the particle size. By means of dimensional analysis, Hopff et al.[16] derived a simplified potential equation relating both parameters, in the case of a suspension polymerization of methyl methacrylate. The weight-average particle size, d_w (cm), vs. the agitation rate, N (s^{-1}), in logarithmic scales has been drawn out in Figure 5. The values has been fitted to a potential equation with the following form:

$$d_w = 0.483 \, N^{-1.96} \tag{2}$$

The value of the exponent is higher than other previously reported in the literature,[9] which is an expected behavior because the agitator employed
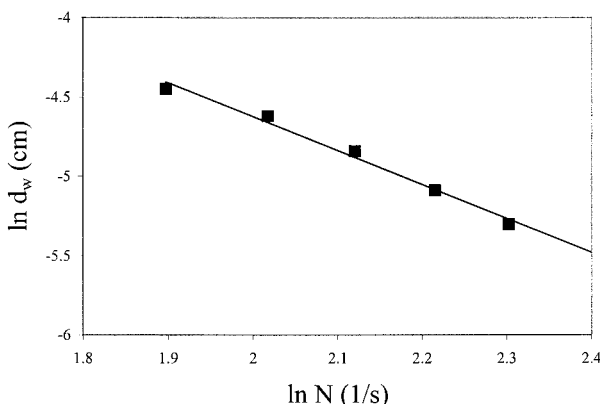
Figure 5 Dependence of the average particle diameter d_w (weight) on the stirring rate in the suspension copolymerization of methyl methacrylate and styrene.

has four and not six blades, and the reactor has no baffles as those described in the literature. However, the general trend of particle diameter variations with agitator and speed changes are in good agreement with some of the results previously reported in the bibliography for these kind of systems.[4]

Scale-Up

The scale-up of an agitated tank reactor for a suspension polymerization process should not alter the molecular weight distribution, particle size, and composition of the polymer product, if the recipe and operating conditions are the same. The problem is reduced to the scale-up of a liquid–liquid dispersion in agitated vessels.[9]

As previously mentioned, in liquid–liquid dispersion a steady state is required, in which the droplets continuously coalesce into larger ones, and are broken up by the stirrer into new droplets.

According to Yuan et al.,[9] if the physical characteristics of the suspension system and the droplet size are constant, the scale-up problem can be simplified to keep constant the turbulence fluctuation force (τ_t, kg/ms^2). In geometrically similar vessels, τ_t, is given by:

$$\tau_t \propto c' N^{(m+3)} D^2 d_n^{(m-1)} \qquad (6)$$

The value of the exponent m in the previous expression depends on the different ranges of the energy spectrum function. It takes the value of 5/3 in the inertial subrange. In the Taylor subrange, corresponding to the transition regimen,

m, takes a value equal to 2. Finally, in the viscous dissipation subrange it is equal to 3.

To estimate the operating regime, the Reynold's number must be determined. The Reynold's number of agitator, N_{Re}, is given by the following expression,

$$N_{Re} = \frac{\rho_S N D^2}{\mu_S} \qquad (3)$$

where $D(m)$ is the impeller diameter and ρ_S (kg/m^3) and μ_S (kg/ms) are the mean suspension density and viscosity that change during the copolymerización process. For density, the use of a weighted arithmetic mean is recommended,

$$\rho_S = o\rho_o + w\rho_W \qquad (4)$$

where o and w are the volumetric fractions of the organic ($_o$) and the aqueous ($_W$) phases.

The viscosity can be calculated by means of using the weighted geometric mean viscosity:

$$\mu_S = (\mu_o)^o (\mu_W)^w \qquad (5)$$

Taking into account that polymer density is not very different from water; the water density can be used to estimate N_{Re}. On the other hand, the viscosity of the suspended phase varies from 1 to 10,000 cP, as calculated previously by Konno et al.[5] for styrene polymerization, and it can be expected that viscosity varies in a similar way for the copolymerization of styrene and methyl methacrylate. At the identity point the viscosity takes a value between to 1000–3000 cP, as can be seen in the graphics proposed by Konno et al.[5] For these values of viscosity of the suspended phase, the value of the Reynold's number calculated from eq. (3) ranges between 1115 and 2330.

According to Zlokarnik and Judat,[17] the transition regime arises only in vessels without baffles and for Reynolds ranging between 10 and 5×10^4. As the working interval is in the transition zone, the exponent that has to be applied to the scale-up of the process must be 2. In this way, the expression for the turbulence fluctuation force takes the form

$$\tau_t \propto (D/D_V)^{0.45} N^{(2.5)} D^2 d_n \qquad (7)$$

and the scale-up criterion for the agitation rate, for geometrically similar vessels,

Table II   Scale-Up Results in Taylor Subrange with Four Vertical Blades Rushton Turbine

Vol. (1)	d/D	N (rpm)	D (cm)	d_p (μm)	τ_t (Kg/cm $\cdot$ s^2)	Av. Dev. τ_t (%)
2	1/3	520[a]	4.38	0.0050	$1.293 \, 10^{-5}$	3.16
10	1/3	330	7.60	0.0053	$1.324 \, 10^{-5}$	

[a] Interpolated value.

$$\frac{N_2}{N_1} = \left(\frac{D_1}{D_2}\right)^{0.8} \tag{8}$$

where subscripts $_1$ and $_2$ refer to the bench and pilot plant scales, respectively.

Using eq. (8), a stirring rate of 330 rpm was calculated for the scale-up experiment in the 10-liter batch reactor. Table II shows the results obtained in the scale-up experiment. Experimental data prove that particle diameter remains unchanged in the scale-up, showing that the choice of the scale-up criterion was the correct one. The turbulence fluctuation force, τ_t, remains invariable for model and prototype (less than 4% of difference), confirming again that the process is in the Taylor subrange and the rightful of choice.

Figure 6 shows the difference between the evolution of the mean particle diameter during the experiment for the model and prototype experiments. Initially, d_n values are lower in the laboratory reactor because the power per unit volume delivered is higher when using this reactor. Nevertheless, the final mean particle sizes are the same in both experiments, showing that the scale-up is a strong influenced of the stirring rate than the power delivered.

Conversion vs. time for the scale-up experiment and the bench scale reactor at 500 rpm is shown in Figure 7. The conversion is lower in the prototype reactor due to the lower temperature profile. Because the Reynold's numbers are higher in the laboratory reactor (in the outer and in the inner part of the jacket) than in the scale-up reactor, necessarily, the overall heat transfer coefficient must be inferior in the latter reactor leading to a lower heat transfer rate.

Molecular weight distribution of the copolymers obtained in the laboratory and the scale-up experiments were determined by GPC chromatography. The values, shown in Table III, indicates that the average molecular weight is quite similar to those reported in the bibliography for STY–MMA copolymers obtained under similar conditions.[18] Polydispersity of the copolymer in the scale-up experiment is lower than that obtained in the laboratory experiment, probably due to the difference in temperature profile.
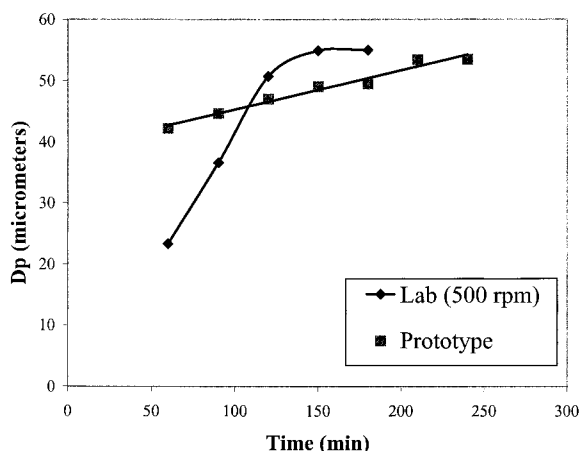

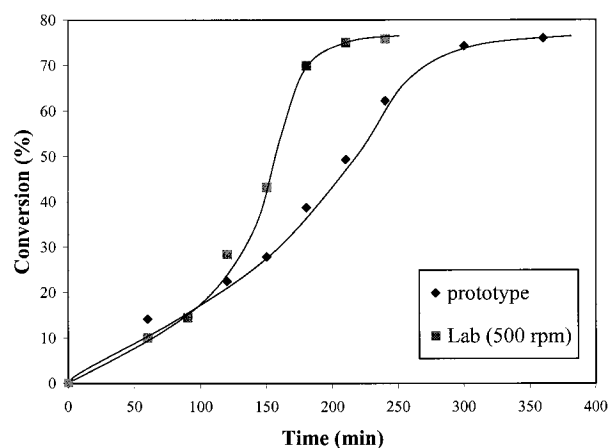**Figure 6**   Evolution of mean particle diameter for the model and prototype experiments.

Figure 7   Conversion vs. time for the scale-up and the laboratory.

Table III Copolymers Properties

Properties	Base Copolymer	Prototype Copolymer
Mole fraction in the feed	0.8(MMA) 0.2(STY)	0.8(MMA) 0.2(STY)
Final copolymer composition	0.818(MMA) 0.182(STY)	0.816(MMA) 0.184(STY)
Average molecular weight (weight)	297,200	263,600
Average molecular weight (number)	147,800	140,400
Polydispersity	2.01	1.88
Temp. of thermal degradation (°C)	401	390

Reactor Simulation

Considering the following assumptions: (a) free radical polymerization of two monomers; (b) reaction probabilities depending on the composition of the polymer chain already formed; and (c) the initiation and termination steps may occur in several varieties, but they have little effect on overall chain composition provided the chains are long; then, the following equation can be applied[19]:

$$\frac{x_p}{y_p} = \frac{x}{y}\left(\frac{r_x x + y}{x + r_y y}\right) = \frac{dx}{dy} \quad (9)$$

where r_x, r_y are the copolymer reactivity ratios (0.52 for styrene and 0.46 for methylmethacrylate); x, y are the concentration of both monomers in the suspension; and x_p, y_p are the concentration of both monomers in the polymer.

This equation can be integrated analytically, but a numerical solution is adequate for the present purpose. The molar fraction of both monomers in the copolymer is shown in Figure 8 vs. the conversion. It should be noted that the identity point is reached at about 75% of polymer yield, which corresponds to $x_p = 0.82$ and $y_p = 0.18$, in good agreement with the experimental findings ($x_p = 0.818$, $y_p = 0.182$), obtained from ^{1}H-NMR measurements (Table III).

The solution does not require explicit knowledge of the polymerization rate. However, if more information about the reaction is required, a rate expression is needed. A suitable one for a free radical copolymerization is[19]:

$$-\frac{d(x+y)}{dt} = \frac{\sqrt{R_I \bullet / k_t g_t}\, k_{xx}(r_x x + 2xy + r_y y)^2}{r_x x + (k_{xx}/k_{yy})r_y y} \quad (10)$$

where $R_I \bullet$ denotes the generation rate for primary radicals. k_t represents the termination process including coupling, disproportionation, and chain transfer to monomer. k_{xx} and k_{yy} are the constants for the homopolymerization propagation reactions. The termination mechanisms require pairwise interactions between large molecules, and these become increasingly difficult at high polymer concentrations due to chain entanglements. The propagation reaction is less affected and the net rate of polymerization increases. This phenomenon of the rate increasing as the concentration of monomers decrease is a form of autoacceleration known as the gel or Trommsdorf effect. In this work, the gel effect correlation with monomer conversion from Hamer[20] has been employed:
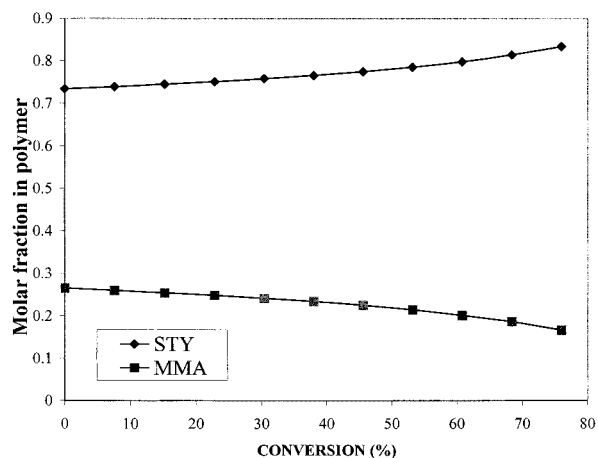
$$g_t = \exp(-0.4404X - 6.362X^2 - 01704X^3) \quad (11)$$

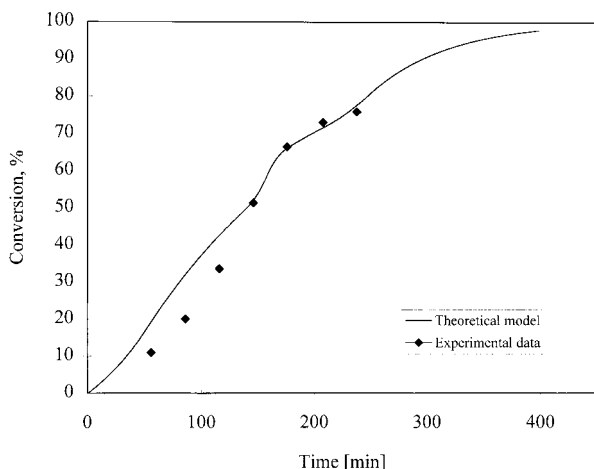**Figure 8** Molar fraction of both monomers in the copolymer vs. conversion.

Figure 9 Evolution of conversion in the laboratory reactor: model predictions and experimental data.

Equations (9) and (10) have been solved simultaneously by including the temperature profile and the gel effect. A self-developed application in Excel using the Runge-Kutta method has been used. The values of all the constants were taken from Kalfas et al.[7] Results obtained from the model predictions and experimental data are shown in Figures 9 and 10 for the laboratory and the scale-up reactor, respectively. Model predictions are in good agreement with experimental results in both kind of reactors. Small bumps in the model fittings, at about 180 min, are due to the corresponding jumps in the temperature profile that has been reported in a previous work.[11] Because the droplets size of the polymer is controlled by the conversion, a model able to reproduce experimental data as a function of the temperature and composition of the initial mixture is essential to obtain polymers with adequate properties.

When high values of monomer conversion have been reached (around 75%), the reaction does not progress, due to the high viscosities and low diffusivities typical of concentrated polymer solutions.

Final copolymer composition were determined by ^{1}H-NMR. Figure 11 shows the ^{1}H-NMR spectrum of the copolymer obtained at 500 rpm at the laboratory. The intensities of the resonances in the 6.5–7.5 ppm range due to the phenyl proton of the styrene unit, and the resonances in the 0–4 ppm range corresponding to the rest of proton of the copolymer were employed for the determination of the copolymer compositions.

The compositions calculated from ^{1}H-NMR are shown in Table III. As commented on above, the values obtained are in good agreement with model predictions for both scales. This means that the final composition of the copolymer obtained can be accurately calculated from experimental conditions (initial composition and conditions during the run).

Finally, it is worth to say at this point that copolymers of MMA–STY obtained by the procedure described in this work have been tested in a medical application as bone cements in a clinical center in Cuba, with some satisfactory results.

CONCLUSIONS

1. Copolymers of MMA–STY obtained by the procedure described in this work have suitable composition, particle size distribution, and molecular weight distribution for medical application as bone cements.
2. An empirical equation relating stirring speed and the mean particle size has been established at a bench scale. An agitation rate equal to 520 rpm provides the suitable mean particle size (50 μm).
3. The scale-up procedure, based in that procedure proposed by Yuan et al.,[9] gave adequate results for suspension polymerization in a stirred tank reactor without baffles.
4. The use of a kinetic model allows the prediction of copolymer composition during the polymerization process from the tem-
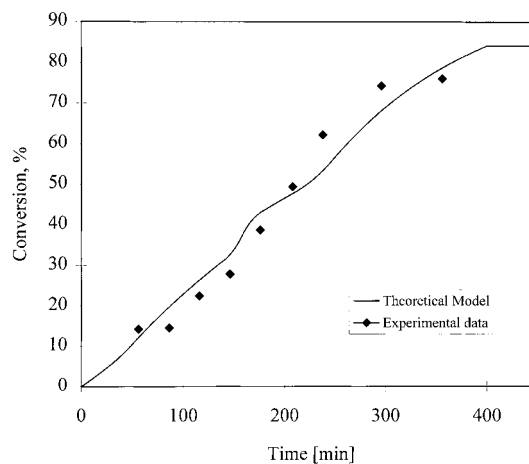

Figure 10 Evolution of conversion in the scale-up reactor: model predictions and experimental data.
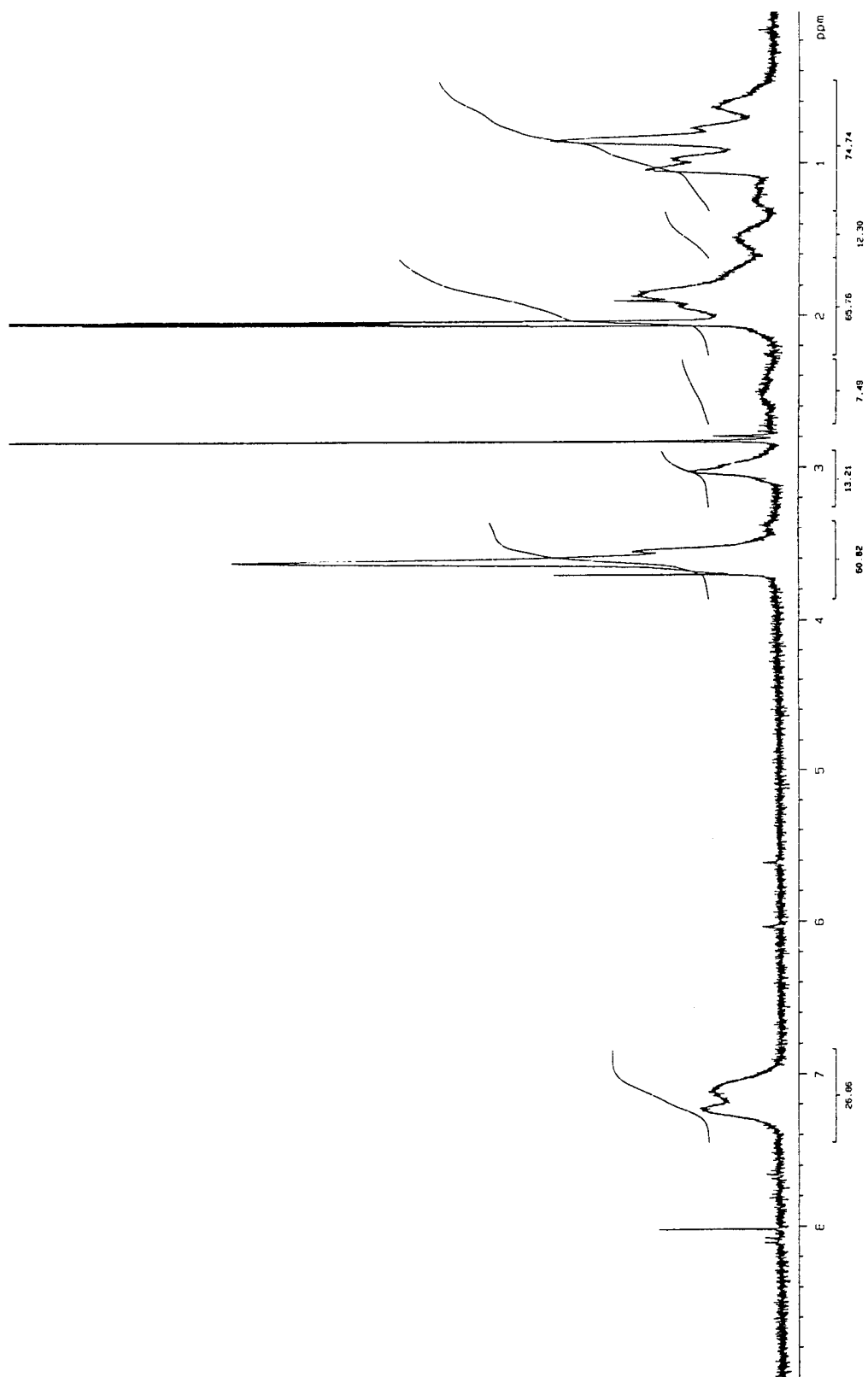
Figure 11 ¹H-NMR spectra of the copolymer obtained a 500 rpm at the laboratory.

perature profile and initial composition, which is essential to obtain polymers with adequate properties.

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