Production of Poly(acrylic acid) Particles Dispersed in Organic Media

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Summary: A process for preparation of poly(acrylic acid) particles dispersed in oil is presented. The process comprises two steps: the first step involves the preparation of a poly(acrylic acid) solution, while the second step consists in the preparation of the polymer particles by dispersing the polymer solution in an organic phase. During the second step, modification of the polymer chain structure can be performed through chemical reactions. One of the advantages of the proposed process is the possibility to produce particles loaded with drugs or other chemical compounds. Besides that, if the continuous phase is vegetable oil, purification of the reaction medium may not be necessary.

Keywords: controlled release; emulsion polymerization; hydrogel; poly(acrylic acid)

Introduction

Polymer micro- and nanoparticles have been widely used in the veterinary and biomedical fields as drug carrier vehicles. The use of these particles as drug carriers usually allows for reduction of the rates of drug degradation in the body, for reduction of collateral effects and increase of the drug bioavailability, leading to lower frequencies of administration.[1–2] In the veterinary field, for example, the development of pharmaceutical formulations that can lead to reduction of the total number of drug administrations is extremely necessary because of the difficult administration of medicines to animals. Moreover, treatments are frequently time demanding and the quick excretion of the drug makes daily applications necessary to maintain a minimum concentration of the compound in the animal blood.[3–4]

Materials used as drug carriers should be easy to prepare, present low cost, be biodegradable (although this certainly depends on the particular analyzed application), have small size, absorb the desired drug efficiently, lead to gradual release of the drug and, at least ideally, present local action, only affecting the tissues or regions where the treatment is desired.[1]

Poly(acrylic acid) - PAA - presents many of the advantages mentioned previously. Moreover, it is biocompatible, being widely used in the synthesis of dental cements and cosmetics, among other applications.[5–6] PAA is also a super absorbent polymer and water soluble, characteristics that permit the use of this polymer in applications involving the incorporation of water-soluble drugs.[7]

The present study describes a process for production of poly(acrylic acid) particles intended for use as drug carriers. It is important to mention, though, that such polymer particles are not used only in the pharmaceutical area. These particles can also be used as carriers of other chemicals, such as urea, for the fertilizer industry. The process comprises two steps: the first step involves the preparation of a poly(acrylic acid) solution, while the second step

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consists in the preparation of the polymer particles by dispersing the polymer solution in an organic phase. During the second step, modification of the polymer chain structure can be performed through chemical reactions. The continuous phase used in the second step can be a vegetable oil, making the separation and purification of the final PAA particles unnecessary in some real medical applications.

Experimental – First Step (Synthesis of the Hydrogel)

Materials

In the first step of the experimental procedure, which involves the synthesis of hydrogels, the following chemicals were used: acrylic acid (monomer), glycerol and ethylene glycol dimethacrylate (EGDMA) (cross-linking agents) and potassium persulfate (initiator). All chemicals were supplied by Vetec with minimum purity of 99%, except EGDMA, which was supplied by Sigma-Aldrich with a minimum purity of 98%. Reagents were used as received, without any further purification.

Experimental Procedure

First of all, an initiator solution was prepared by dissolving potassium persulfate (final concentration of 1/100 w/w) in a specified amount of distilled water (final concentrations ranged from 59/100 w/w to 79/100 w/w). Then a mixture of acrylic acid (final concentration of 20/100 w/w) and glycerol (final concentration ranging from 0/100 w/w to 20/100 w/w) was prepared. The initiator solution was poured into the monomer mixture and the reaction vessel was placed in a thermal bath at 70–80 °C for 2 hours under stirring. At the end of the reactions, hydrogels with different properties were obtained.

Similar experiments were performed in presence of EGDMA (final concentration of 3/100 w/w), used as a cross-linking agent. At the end of the reaction, solid rubbery blocks were always obtained. Therefore, EGDMA cannot be used for production of PAA resins intended for posterior processing, which justifies the utilization of glycerol as an appropriate cross-linking agent for the analyzed system. It must be emphasized that glycerol has not been used yet as cross-linking agent in PAA polymerizations aiming at particles synthesis.

Analytical Procedure

Different techniques were used to characterize the properties of the synthesized gels. All characterization tests were performed with dried samples, except the rheological analyses, due to the high viscosity of the samples reached after the drying process.

Differential scanning calorimetry analyses (DSC) were performed with DSC-7 equipment, from Perkin-Elmer. Thermograms were recorded during the second heating/cooling cycle. Temperature ranged from 0 to 260 °C, using a constant cooling/heating rate of 10 °C.min^{-1} under nitrogen atmosphere. DSC analyses of polymer samples were used to determine the characteristic transition temperatures.

Thermogravimetric analyses (TGA) were performed on a TGA-7 equipment, from Perkin-Elmer. Samples were heated until 700 °C, under a constant heating rate of 10 °C.min^{-1} in a nitrogen atmosphere. These analyses are important to evaluate the thermal stability of the polymer samples.

Fourier Transform Infrared analyses (FTIR) were performed on a Nicolet 6700 model from Thermo Scientific. Analyses were performed under ambient conditions, using 128 scans with a resolution of 4 nm in transmittance mode. Wave numbers ranged from 500 to 4000 cm^{-1}.

Water absorption data were obtained with the help of gravimetrical analyses.

Viscosity analyses of polymer solution samples were performed in an Ares-TA rheometer to evaluate the effect of glycerol on the viscosity of the polymer solution. The strain controlled rheological properties of all solution samples were measured from 0.01 to 500 s^{-1} at 25 °C, using a cone-plate system.

Results (Synthesis of the Hydrogel)

FTIR spectra do not show the insertion of glycerol into the polymer chains unequivocally, since the bands present in the spectra of PAA resins obtained in the presence of glycerol and that are not present in the spectrum of pure PAA (1109 cm^{-1}, 1038 cm^{-1}, 922 cm^{-1}), are also present in the spectrum of pure glycerol. Therefore, it is not possible to discriminate the PAA material from a mixture of pure PAA and glycerol based solely on the FTIR spectra. However, DSC analyses show that the introduction of glycerol into the reaction medium causes the disappearance of the Tg of the final polymer resin, as usually expected in cross-linked materials. Therefore, it seems reasonable to assume that glycerol causes the cross-linking of the PAA chains, as might be expected because of the multifunctional character of glycerol. Figure 1 illustrates the disappearance of the Tg.

The thermal analyses of the obtained polymer resins show that the thermal stability of the produced materials increases with the addition of glycerol, probably due to cross-linking, as shown in Figure 2. The water absorption data corroborate this assumption, since increasing of the glycerol concentration causes the

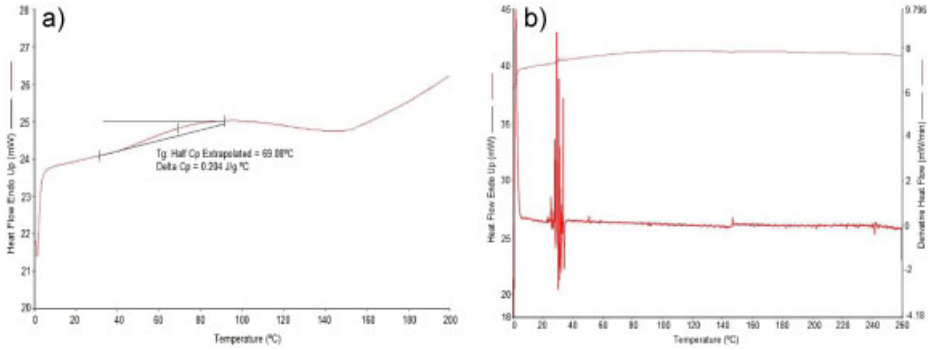

Figure 1.
DSC of dried (a) pure PAA and (b) PAA prepared in presence of glycerol (20/100 w/w).

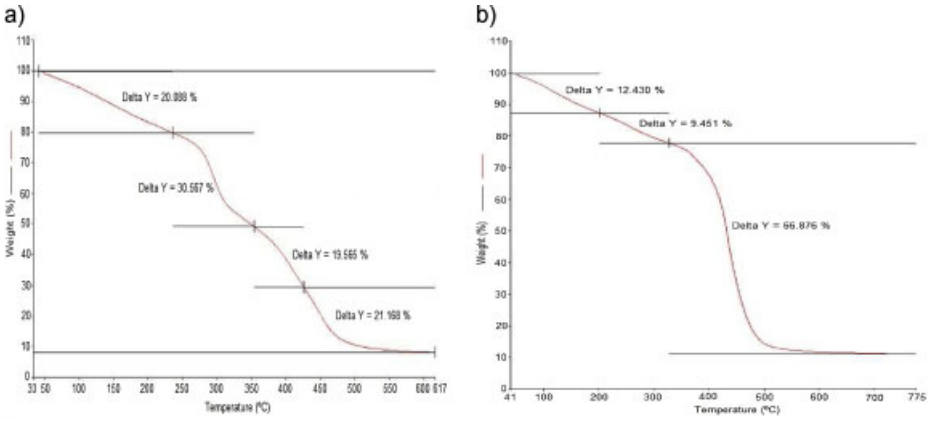

Figure 2.
TGA of dried (a) pure PAA and (b) PAA prepared in presence of glycerol (10/100 w/w).

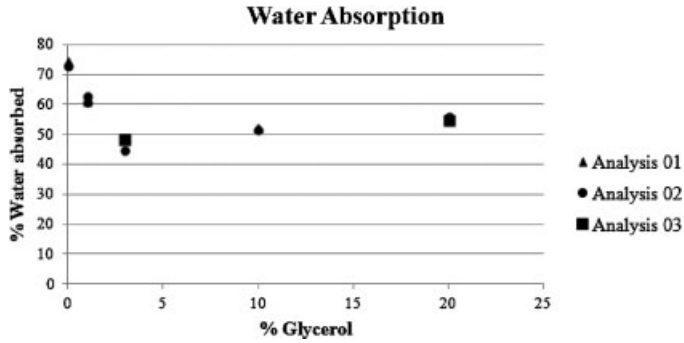

Figure 3.
Water absorption by dried polymer samples.

decrease of water absorbency of the dried samples, as shown in Figure 3. The initial reduction of water absorption can probably be related to the lower mobility of the chains in the presence of the cross-linking agent. The subsequent increase is probably related to the increase of the free hydroxyl group concentration due to the higher concentration of glycerol.

As TGA and DSC analyses indicated that the dried samples were probably cross-linked, it was expected that the addition of glycerol would cause the increase of the hydrogel viscosity. However, as illustrated in Figure 4, rheological analyses of polymer solutions obtained at the end of the first process step showed that the introduction of glycerol causes the reduction of the hydrogel viscosity. So, the reaction mechanism can involve glycerol molecules in different steps simultaneously, as shown in Figure 5 and 6.

First, glycerol can be incorporated into polymer chains through direct esterification, as shown in Figure 5. However, it is unlikely to happen because the presence of large excess of water is expected to shift the equilibrium towards the monomer. This hypothesis is supported by the relatively low viscosity of the hydrogels produced in the presence of glycerol. Glycerol can also be incorporated into the polymer chain through a chain transfer mechanism, as described in Figure 6. The open literature

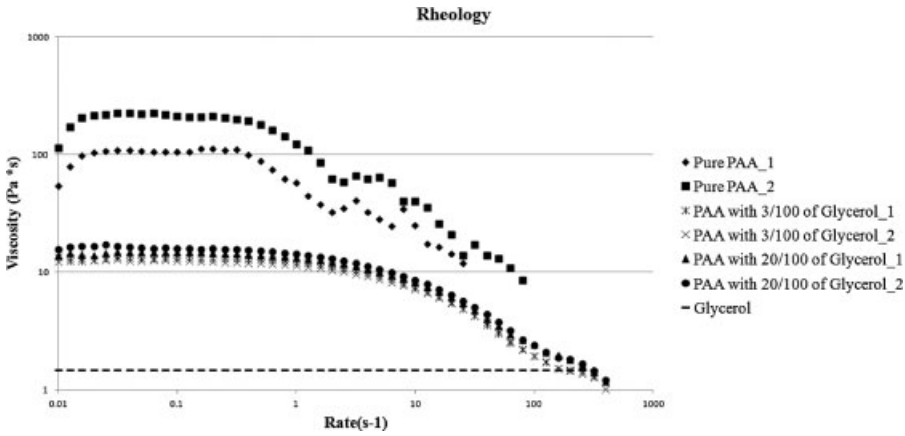

Figure 4.
Rheological analyses of obtained PAA solutions.

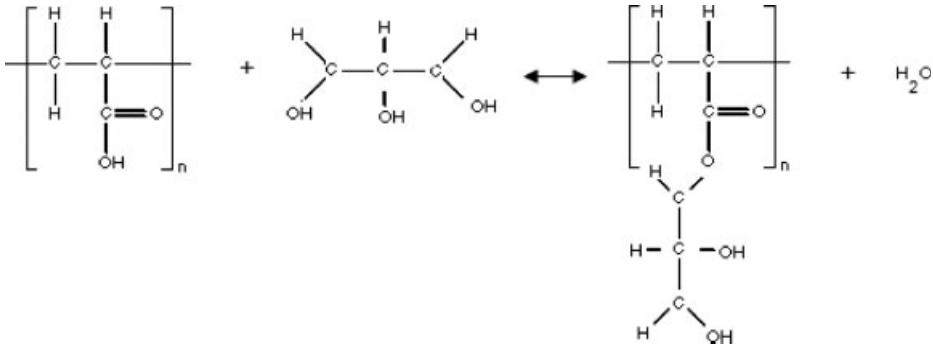

Figure 5.
Glycerol incorporation through direct esterification.

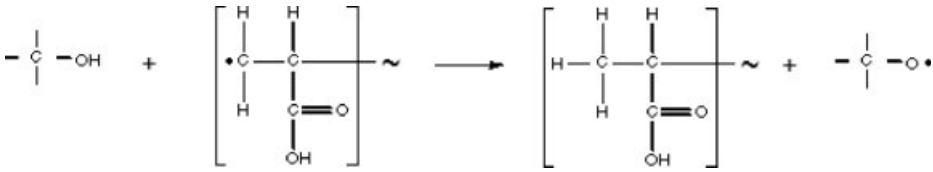

Figure 6.
Glycerol incorporation through chain transfer.

has reported the use of different alcohols as chain transfer agents in acrylic acid polymerizations, including methanol, ethanol, n-propanol and isopropanol.[8] Chain transfer to glycerol can lead to products with relatively lower molecular weights, causing the decrease of the hydrogel viscosity, as observed experimentally. Finally, esterification can occur during the drying stage, due to the continuous removal of water, shifting the equilibrium towards the polymer product. The lower degree of polymer swelling after drying and the decrease of the polymer solubility in aqueous medium seem to confirm this hypothesis. Therefore, glycerol seems to be a chain transfer agent during the reaction step and a cross-linking agent during the drying step. This is indeed a very interesting effect, as the polymer load can be increased significantly during the first process step, given the lower viscosities of the polymer solution prior to drying.

Table 1 summarizes the results obtained after the first process step, emphasizing the changes that glycerol causes on the final properties of the produced polymer resins.

Experimental – Second Step (Synthesis of PAA Particles)

Materials

In order to produce the PAA particles, a standard aqueous polymer solution containing PAA (15/100 w/w) donated by Dentsply and the hydrogel solutions synthesized in the first process step were used. The initiator, potassium persulfate, was provided by Vetec with minimum purity of 99%. The cross-linking agent, ethylene glycol dimethacrylate (EGDMA), and the surfactant, sorbitan monooleate (Span 80), were supplied by Sigma-Aldrich, with a minimum purity of 98%. The vegetable oil used was refined sunflower oil, manufactured by Liza and provided as a commercial grade. Produced particles were loaded with the antibiotic doxycycline, provided by CEVET as a commercial

Table 1.
Summary of results obtained after the first process step.

Analysis	Pure PAA	PAA with glycerol
FTIR	Characteristic bands of PAA (2933 cm^{-1}, 1698 cm^{-1}, 1162 cm^{-1}).	New bands that are not present in the spectrum of pure PAA. However, they are present in the spectrum of glycerol (1109 cm^{-1}, 1038 cm^{-1}, 922 cm^{-1}).
DSC	Tg at 70 °C.	Disappearance of Tg.
TGA	Three characteristic bands. The wider band corresponds to the higher temperature (350–600 °C), leading to mass loss of approximately 41%.	The mass loss of the third band increases continuously as the glycerol concentration increases.
Water absorption	Water absorption around 75% of the initial weight of dry polymer.	Water absorption capacity decreases to around 55% of initial weight of dry polymer.
Rheology	High viscosity (100 Pa.s)	Pronounced decrease of the solution viscosity at the end of the first step (around 10 Pa.s).

grade. The reagents were used as received, without any further purification.

Experimental Procedure

Initially an initiator solution (final concentration of 1/100 w/w in the aqueous phase) of potassium persulfate was prepared. An aqueous mixture of commercial PAA (final concentration of 10/100 w/w in the aqueous phase) and EGDMA (final concentration of 5/100 w/w in water in the aqueous phase) was also prepared. Then, the initiator solution was poured into the polymer solution and the medium was homogenized. When the hydrogel containing glycerol prepared in the first step was used, no additional manipulation of the PAA hydrogel was performed.

The continuous phase was prepared independently, by mixing the vegetable oil with the surfactant (final concentration of 1/100 w/w in oil). The hydrophilic phase (final concentration of 20/100 w/w of the emulsion) was then poured into the hydrophobic phase (final concentration of 80/100 w/w of the emulsion). The mixture was submitted to emulsification with the help of a Ultra-Turrax disperser, T25 basic model, by IKA, operating at 6500 min^{-1} for 2 minutes.

The emulsion was finally heated at a constant heating rate of 17 °C.min^{-1} until it reaches the temperature of 110 °C. The mixture was kept at 110 °C for 5 minutes, for removal of water.

It is important to mention that dispersion of the hydrogel in oil is significantly affected by the hydrogel viscosity. If the viscosity is sufficiently high, efficient emulsification is not possible with the Ultra-Turrax. For this reason, hydrogel emulsions were produced only with materials containing glycerol or with the commercial PAA hydrogel.

Analytical Procedure

The synthesized particles were analyzed by microscopy to determine the shape and average size of the produced particles. The microscopy analyses were performed on a binocular microscope, a SMZ 800 model, by Nikon, equipped with a digital camera. Analyses of particle size distribution were also performed with the help of a light scattering equipment, Turbiscan Lab Expert model, by Formulaction. Analyses were performed at 24 °C and scans were performed every 1 min for 25 min, in order to obtain the average diameter of the particles.

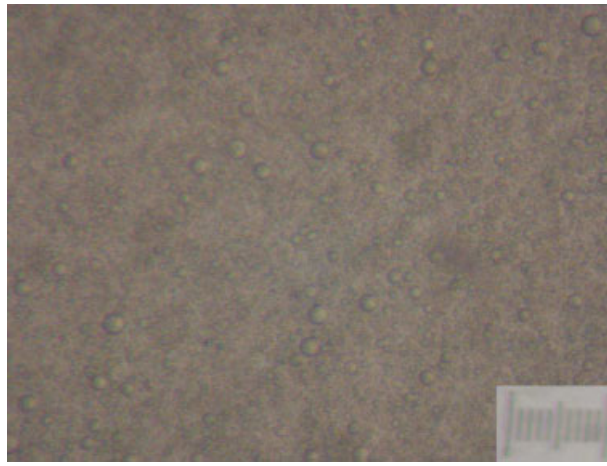

Figure 7.
Optical microscopy of the particles synthesized with the PAA hydrogel. The smallest graduation of the ruler equals 10 micrometer.

Results (Synthesis of PAA Particles)

The proposed methodology resulted in the synthesis of PAA particles with some desired characteristics, such as spherical morphology and average particle diameters of 830 nm (ranging from 600 to 1000 nm, according to light scattering analyses). All results obtained with all samples prepared in the first step (with the exception of the hydrogel prepared without glycerol, which led to inefficient emulsification and massive coagulation of the polymer phase) led to very similar results, probably due to the efficient dispersion provided by the Ultra-Turrax. Figure 7 shows a typical optical micrograph of the produced particles. It is important to note that drugs can be added to the hydrophilic phase during the second step, for incorporation into the PAA particles.

The average particle diameters obtained by light scattering analyses were approximately equal to 830 nm after 5 min of analysis in all cases. However, Figure 7 suggests larger particle diameters because the particle size distributions were broad and because particle coalescence could be observed during the microscopic analyses. Nevertheless, it is important to note that the prepared emulsions were stable for long periods when left at rest in oil, as observed through repetition of light scattering characterizations after several days.

Conclusion

A process for preparation of poly(acrylic acid) particles dispersed in oil was presented. The process comprises two steps: the first step involves the preparation of a poly(acrylic acid) solution, while the second step consists in the preparation of the polymer particles by dispersing the polymer solution in an organic phase. During the second step, modification of the polymer chain structure can be performed through chemical reactions. One of the advantages of the proposed process is the possibility to produce particles loaded with drugs or other chemical compounds.

The results presented here showed that glycerol can be incorporated into PAA hydrogels, causing chain cross-linking during drying, although chain transfer reactions are likely to occur during the first reaction step. In addition, the proposed process leads to successful preparation of particles in the submicron range, which can be used for incorporation of drugs or other hydrophilic compounds and posterior medical or veterinary use.

Acknowledgements: The authors thank CEVET (Brazil) for the financial support.

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