Polym. Bull. (2012) 68:931–948
DOI 10.1007/s00289-011-0583-z

ORIGINAL PAPER

Acrylic polymers derived from high solid emulsions as excipients to pharmaceutical applications: synthesis and characterization

J. C. O. Villanova · E. Ayres · M. O. Reis ·
R. L. Oréfice

Received: 14 May 2011 / Revised: 13 July 2011 / Accepted: 16 July 2011 /

Abstract Novel polymeric excipients need to be designed to allow for the controlled delivery of many drugs to treat a variety of diseases. In this work, two polymers based on different proportions of ethyl acrylate, methyl methacrylate, and butyl methacrylate were synthesized by multistage emulsion polymerization using a redox initiator system to yield excipients for the manufacture of prolonged release tablets by the coating or compression technique. Fourier Transform Infrared spectrometer (FTIR) indicated that the polymerization reaction of the monomers was complete without carbon double bond absorption bands. Differential Scanning Calorimetry (DSC) analysis indicated that the glass transition temperature (T_g) of the polymers was around 50 °C. The dispersions obtained were characterized in terms of particle size and particle size distribution (PSD) using Dynamic Light Scattering (DLS), and the particle charge (zeta potential) was measured by electrophoretic mobility. The measurements showed particle diameters of approximately 200 nm and a zeta potential close to −60 mV. The low viscosity obtained for the polymers was attributed to bimodal PSD. The dispersions were freeze dried and the particles were submitted to in vitro cell tests to make a preliminary check of the toxicity of the materials. The low viscosity of the polymers, the absence of volatile solvents, and the high solid content (>50%) are ideal for these polymers to

---

J. C. O. Villanova
Universidade de Mogi das Cruzes—UMC, Campus Villa-Lobos, Núcleo de Saúde-Farmácia,
São Paulo, SP, Brazil

E. Ayres
Departamento de Materiais, Tecnologia e Processos, Escola de Design,
Universidade do Estado de Minas Gerais—UEMG, Belo Horizonte, MG, Brazil

M. O. Reis · R. L. Oréfice (✉)
Departamento de Engenharia Metalúrgica e de Materiais, Universidade Federal de Minas
Gerais—UFMG, Av. Antônio Carlos, 6627, sala 3551, Bloco 2, Pampulha,
CEP: 31270-901 Belo Horizonte, MG, Brazil
e-mail: rorefice@demet.ufmg.br

be used as coatings and matrices pharmaceutical excipients for prolonged release tablets. In vitro MTT tests suggested that the materials can be considered nontoxic.

Keywords Emulsion polymerization · Sonification · Multistage process · Low viscosity · Pharmaceutical excipients · Tablets

Introduction

The design of drug delivery systems with advanced therapeutic performance has recently become a major issue in both Pharmaceutical and Materials Sciences. However, traditional tablets for conventional or modified release of drugs are still the most important medications prescribed by physicians and used by patients. It is a remarkable fact that tablets still account for more than 80% of all dosage forms administered to patients. The main reasons for their continued popularity include the fact that tablets contain a single dose of the drug, allow for self-medication, display good stability, and are produced and controlled by very well-known techniques [1].

Most of the modified release tablets contain cellulose or its by-products as excipients to modulate drug release. A main limitation of the use of cellulose by-products is the high viscosity of the dispersion after dissolution in water since the viscosity must remain sufficiently low to facilitate atomization in coating process or wet granulation in compression process [2, 3]. In this view, the objective of this work was to produce excipients based on acrylic and methacrylic monomers using the emulsion polymerization technique as a pharmaceutical agent for the production of prolonged release tablets by the coating or compression processes (wet granulation or direct compression).

Excipients are defined as any compound, except the drug and prodrug, which has its safety checked and can be included in medications to promote stability, processability, increase treatment acceptability, modify the drug delivery, and enhance drug bioavailability. The coatings on tablets can be functional or nonfunctional. In the latter, the excipients are employed to improve the appearance of the tablets as well as the increase stability and mechanical properties. For functional coatings, the excipients are used to modify the drug delivery. In all cases, the solid content and viscosity of the polymer dispersion affect the processing and film thickness, which must be between 20 and 100 μm. Polymeric dispersions can also be used to wet the particles in the compression processes. The viscosity and solid content of the polymer dispersions are also used to determine the degree of wetness of the particles. When the dispersions are dried, the solid particles can be used in direct compression processes [4].

Emulsion polymerization is one of the most useful methods for the preparation of acrylic ester polymers used as excipients. The main reasons are economy, the ease of temperature control, and the rate and completeness of reaction. The use of water as a dispersant instead of organic solvents is also a major advantage [5, 6]. The increasing use of solvent-coatings in the pharmaceutical industry has led to an increased concern about environmental contamination and operator safety. Those aspects have motivated research related to the replacement of the organic solvent with water to produce waterborne polymers. It is well known that organic solvent residues can be toxic and restrict the use of these materials in pharmaceutical and biomedical applications. The development of techniques using water as a polymerization medium is highly desirable [1, 2].

In conventional emulsion polymerizations, the main ingredients are monomer(s), water, a surfactant, and an initiator. The surfactant confers stability against sedimentation (or creaming). When the concentration of surfactant exceeds its critical micelle concentration (CMC), the excess surfactant molecules self-assemble to form small colloidal clusters referred to as micelles. In general, high surfactant content leads to more stable lattices with smaller particle size but high viscosity, which is disadvantageous for many applications, including pharmaceutical ones [5, 6].

In most applications in which lattices are used, it is very useful to reach high polymer concentrations since increasing the polymer content can improve certain characteristics, e.g., high productivity, short film-forming time, and low storage and transportation costs [5–7]. High solid content (HSC) lattices refer to aqueous polymer dispersions, the solid content of which is more than 60% [8]. In the specific case of pharmaceutical applications, commercially available products have a solid content of 30–40% [9, 10]. Thus, polymer dispersions with solid content values of higher than 50% can offer many advantages, such as control over the process of wetting the particles to allow for the use of wet granulation. Lower amounts of dispersions with high solid contents can also be used to produce coatings that can lead to higher levels of productivity and lower costs [1–3].

However, making high solid content lattices involves many difficulties. At concentrations of 50%, the aqueous dispersions obtained by emulsion polymerization have relatively high viscosities [5, 7, 8]. At low solid content, the particles have relatively weak interactions, therefore, the viscosity remains low. As the solid content increases, the viscosity increases slowly at first, then increasingly faster as the particles begin to interact very strongly [8, 11]. It is important to keep the viscosity of the polymer dispersions low to enable their use as coatings, since systems with low viscosity are easier to atomize and dry.

More recently, a few authors have successfully explored the possibilities of increasing the solid content of an emulsion while maintaining the viscosity at as low of a level as possible, offered by the miniemulsion polymerization technique [12, 13]. Miniemulsions are relatively stable emulsions of oil nanodroplets in water, prepared by the intense shearing of a mixture of monomer, water, a stabilizer, and a highly water insoluble compound, the so-called hydrophobe. This compound suppresses the mass exchange between the oil droplets, the Ostwald ripening, whereas the stabilizer prevents the coalescence of droplets. The small droplet size of nanoemulsions (also referred to as miniemulsions, ultrafine emulsions, and submicron emulsions) confers stability against sedimentation (or creaming), given that the Brownian motion and, consequently, the diffusion rate are higher than the sedimentation rate induced by the gravity force [6, 13]. Since most hydrophobes are not covalently bonded to the polymer, they are prone to phase separation or leaching from the polymer [14]. This gap is highly undesirable for pharmaceutical miniemulsions if the desorption occurs.

In the present study, ultrasound was used as an energetic homogenization of reaction mixture to reduce the size of the monomer droplet and was associated with the multistage polymerization process using a redox initiator system. The energetic homogenization generated by sonifiers is generally attributed to a cavitation mechanism. The ultrasound waves in liquid macroscopic dispersion result in a sequence of mechanical depressions and compressions, generating cavitation bubbles, which tend to implode. Subsequently, this shock provides sufficient local energy to increase the surface area gained with emulsification corresponding to nanometric-scaled droplets [15, 16].

Reduction–oxidation systems (redox systems) for polymerization of acrylic esters do not require the application of heat to initiate polymerization. As soon as the initiators are introduced into the kettle, the polymerization promptly begins, and the temperature rises to the *peak* temperature, calculated according to Hess's law [15]. In redox polymerizations, the monomer concentration should be kept low enough so that there is sufficient water present to absorb the heat and prevent the batch from boiling [6, 17, 18].

Such an emulsion polymerization technique was adapted from Sullivan and Mallios [19]. Later, Gehman et al. [20] used a multistage polymerization process to produce internally plasticized polymer lattices. The first stage was highly water soluble, whereas the second stage was less hydrophilic and of higher T_g than the first stage and was polymerized in the emulsion in the presence of the first stage. The internally plasticized polymer lattices had a minimum film temperature of more than 5 °C below the calculated T_g.

In this perspective, the main objective of this study was to synthesize acrylic polymers with low viscosity and high solid content using the proposed technique, with the intention of using them as excipients for the formation of tablets by coating or compression (wet or direct process) to control drug release.

Experimental

Materials

Ethyl acrylate (EA), methyl methacrylate (MMA), butyl methacrylate (BMA), and cumene hydroperoxide were supplied by Aldrich, USA. Span® 85 (Sorbitan trioleate, a trademark of Croda International PLC), ferrous sulfate, ammonium persulfate, sodium dithionite, and ascorbic acid with analytical purity were purchased from Synth. Sodium dodecyl sulfate (SDS) and Renex® 300 (obtained through the reaction of nonylphenol and ethylene oxide with degree of ethoxylation of 30) were kindly donated by Cognis (Brazil) and Oxiteno (Brazil), respectively. All reagents were used as received without prior purification. Since high temperatures are to be employed, the monomer inhibitor was not removed.

Polymerization procedure

Two types of polymers, named A and B, were prepared by varying the composition of monomers. To prepare polymer A, a 250-mL three-neck glass flask equipped with heating mantel, mechanical stirrer, thermometer, and nitrogen gas inlet system were used. The selection of monomers was based on the composition of commercial pharmaceutical polymer dispersions, included in monographs of the Pharmacopeias and in monographs of the Handbook of Pharmaceutical Excipients [21, 22]. The Pharmacopoeias contain descriptions of the polymers used in the preparation of matrix tablets prepared from the monomers EA, MMA, and BMA. However, there are no specific monographs for the monomers. Span® 85, ascorbic acid, Renex® 300, and sodium lauryl sulfate also have monographs included in the Pharmacopoeias and in the Handbook of Pharmaceutical Excipients.

First, a mixture of monomers and water containing the surfactants (first stage of pre-emulsion) was subjected to 15 min of pulsed sonication (5.0 s on, 5.0 s off) at a 50% amplitude with a Branson Sonifier W 450 Digital. To avoid any polymerization due to the heating of the sample, the mixture was ice-cooled during homogenization. The obtained pre-emulsion was transferred to the kettle, to which the initiators, under slow agitation (250 rpm), were added. After a few minutes, the temperature began to rise, starting from 20 °C, until it reached 90 °C. The batch was then cooled to about 25 °C. Simultaneously, another portion of pre-emulsion (second stage) was subjected to 15 min of pulsed sonication (5.0 s on, 10.0 s off) at a 40% amplitude, and the second stage was then added to the kettle. The entire mass was shaken, and the initiators were introduced. Shortly thereafter, the temperature began to rise, starting from 20 °C, until it reached 85 °C. When the temperature dropped to 40 °C, the set of adjuvant initiators was added to polymerize the residual free monomer. The solid content calculated for polymer A was 57%.

To prepare polymer B, the same procedure used to prepare polymer A was followed. The polymerization temperature in the first stage should reach 90 °C, starting from 20 °C, and in the second stage, it should reach 80 °C. The solid content calculated for polymer B was 55%. The lattices of polymer A and polymer B were cast on polyethylene plates and dried in an oven at 40 °C for 24 h to form thin films (about 1 mm thick). Before characterization, the dry films were exhaustively washed with distilled water to remove unreacted products and left in an oven at 40 °C overnight. The recipes for the preparation of polymer A and polymer B are shown in Table 1.

Characterization

Fourier transform infrared (FTIR)

A Thermo Scientific Nicolet 6700 spectrometer provided with a Centaurus microscope was used to characterize lattices A and B. FTIR-ATR spectra of the films in the region of 650–4,000 cm^{-1} using germanium crystal were obtained in the absorption mode with dry nitrogen purge; resolution of 4 cm^{-1} and 64 scans was recorded and averaged.

Determination of percent total solids by gravimetric method

The total solid content of the polymer lattices was determined by gravimetric method through moisture weight loss [18]. Samples (200 μL) were loaded onto a

Table 1 Batch recipes (all values in grams/100 g total)

Reagents	First stage	Second stage
Polymer A		
MMA	13.53	19.47
BA	4.20	6.79
EA	4.20	6.79
SDS (25% w/v)	1.75	0.88
Renex® 300 (70% w/v)	0.17	0.41
Span® 85	***	0.58
Deionized water	29.12	11.59
Ferrous sulfate	0.009	0.002
Ammonium persulfate	0.047	0.064
Sodium dithionite	0.047	0.064
Cumene hydroperoxide	0.058	0.197
Ascorbic acid	***	0.032
Polymer B		
MMA	10.60	15.89
BA	6.36	9.54
EA	4.28	6.31
SDS (25% w/v)	1.69	0.845
Renex® 300 (70% w/v)	0.112	0.563
Span® 85	***	0.45
Deionized water	28.21	14.65
Ferrous sulfate	0.009	0.002
Ammonium persulfate	0.045	0.062
Sodium dithionite	0.045	0.062
Cumene hydroperoxide	0.056	0.187
Ascorbic acid	***	0.032

pan and the weight determined. Triplicate determinations were made with each sample and were then put into an oven at high temperature (105 °C) for 1 h to remove all volatiles. At the end of this time, the pans were removed from the oven, cooled until room temperature in a desiccator, and reweighed. Total solids were then calculated, and the results from these triplicate determinations must agree within 0.5% relative.

pH Measurement

The pH was verified by direct measurement using a digital pHmeter Marconi (model MA PA 200). Measurements were made in triplicate.

Viscosity measurement

The apparent viscosity of the synthesized lattices was determined using the Brookfield viscometer (model RV-DVII+Pro). Measurements were performed using the adapter for small amounts of sample (Sample Adapter, model 13 R), thermostatically maintained at 25 °C. Spindle SC4-28 was used and readings were taken at 200 and 100 rpm. The results were an average of five measurements taken every 10 s with periods of balance of 60 s.

Determination of particle size, size distribution, and zeta potential (ξ)

The particle size and particle size distribution were measured by dynamic light scattering (DLS) (Malvern Zetasizer nano series). For the measurement, samples were diluted by a factor of 500 in Milli-Q® water and sonified for 5 min at 40% amplitude. The mean particle size was characterized by z-average diameter (D_z), and the particle size distribution was characterized by the polydisperse index (PDI), together with the particle size distribution curve (PSD). Measurements were evaluated by performing three readings for each sample. The zeta potential (ξ) was measured at constant pH of 6.5 with no variation of ionic strength by electrophoretic mobility using Malvern Zetasizer Nano Series. The dielectric constant of the medium was 78.5.

Study of lattices particles and dried particles by scanning electron microscopy (SEM)

The particles of the lattices were analyzed by scanning electron microscopy (SEM, JEOL JSM 6360, Japan) using a voltage of 15 kV, in combination with energy-dispersive X-ray spectroscopy (EDX) from Thermo Noran model Quest, and attached to a sputtering device (Bal-Tec model MCS 010). Prior to investigation, a drop of lattices was deposited on the silicon wafer and allowed to dry at room temperature overnight. The dry film was sputter-coated with gold. The morphology of freeze-dried polymers was observed by SEM (JEOL JSM 5410, Japan) using a voltage of 15 kV. Prior to investigation, the samples were sputter-coated with gold.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed on samples of polymer A and polymer B. Tests were performed using a TA 2920 MDSC from room temperature (25–30 °C) to 300 °C at a heating rate of 20 °C/min. Nitrogen gas with a flow rate of 50 mL/min was purged through the sample.

Thermogravimetry (TG)

The measurement of weight loss as a function of temperature in the sample of lattices was analyzed via thermogravimetry (TG) using a Shimadzu DTG 60 thermobalance in a nitrogen flow at a rate of 100 mL/min. Samples of 5–10 mg were heated in an aluminum crucible from room temperature up to 600 °C (1,112°F) with a heating rate of 10 °C/min (50°F/min).

Cellular viability by MTT in vitro test

To evaluate preliminarily the toxicity of the potential excipients, solid particles from polymer A and B were freeze dried. Cytotoxicity of the solid excipients was assayed using the cell viability test based on the MTT colorimetric assay, using cells from human gingival fibroblasts. The culture and isolation of the cells was described in detail by Villanova et al. [23], according to methodology developed by Carvalho et al. [24]. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) is a water soluble tetrazolium salt, which is converted into an insoluble purple formazan by cleavage of the tetrazolium ring by succinate dehydrogenase within the mitochondria. The formazan product is impermeable to the cell membranes and, therefore, accumulates in healthy cells. The MTT assay was tested for its validity in various cell lines. In the test, the amount of formazan that is produced can be correlated with the amount of living cells in the sample [25].

Briefly, 1×10^4 cells well^{-1} were previously seeded in a 24-well plate and cultivated for 24 h. Samples were sterilized by UV radiation. After, samples of the solid excipients (10 mg mL^{-1}) were placed on the same plates and incubated for 24 h. Later, the entire medium was aspirated, and 210 μL of culture medium with serum were added to each well. Next, 170 μL of MTT (5 mg mL^{-1}) was added to each well and incubated in a 5% CO_2 incubator at 37 °C. After 4 h, 210 μL of HCl solution (4% in volume of isopropanol) was added. After 10 min, aliquots of 100 μL were withdrawn from each well and transferred to a 96-well flat plate. After 2 h, the cell morphology and formazan salts were viewed with an inverted optical microscope. The formazan salts were solubilized for 12 h with 10% sodium dodecyl sulfate (SDS)–HCl and the metabolic activity was determined from the optical density at 595 nm by using a spectrophotometer (ADAP 1.6). The cell viability was determined by comparing the optical densities of samples and controls of cultures with a standard curve of 10^3–10^6 cells well^{-1}. The controls used included: (1) cells and Dulbecco's modified Eagle's medium (DMEM) with 10% of fetal bovine serum (FBS), (2) cells and DEMEM medium without FBS, (3) phosphate buffered saline solution (PBS) as the positive control, and (4) 10 mg mL^{-1} of orthodontic wire as the negative control. All experiments were performed with triplicate assays ($n = 3$), and the data were presented as means ± standard deviation. Statistical comparisons were performed using one-way analysis of variance (ANOVA) and Bonferroni's post hoc test (GraphPad, San Diego, CA). Differences were considered statistically significant for $P \leq 0.05$.

Results and discussion

Achieving high solid content lattices through simple processes constitutes a challenge [5, 6]. In this work, no costabilizers (hydrophobes) were required, since the high shear forces around the cavitation bubbles acted to restrict Ostwald ripening by fragmenting larger oil droplets into smaller ones [6, 13], and each pre-emulsion stage was quickly polymerized. The new method demonstrated a good potential to produce high solid lattices obtained by conventional emulsion polymerization.

The initiators can be located either in the continuous phase (water) or in the dispersed phase (monomers). The main system of initiators used included ammonium persulfate as the oxidizing agent and sodium dithionite as the reducing agent, both of which are located in the continuous phase. The pair of initiators consisting of cumene hydroperoxide and ascorbic acid (located in the dispersed phase) was used to polymerize the residual free monomers. With persulfate–dithionite redox systems, small amounts of metallic salts, in the range from 0.1 to 100 ppm, increase the polymerization rate [6, 18]. In this case, ferrous sulfate was used.

The nature of the surfactant determines the size of particle and the stability of lattices. A wide variety of surfactants have been used in emulsion polymerization of monomeric acrylic esters [6, 18]. Anionic surfactants have been the most commonly used because they produce lattices with a relatively small particle size, whereas nonionic surfactants generally provide lattices with good stability but large particle size. In this work, a mixture of anionic surfactant (SDS) and nonionic surfactants (Renex® 300 and Span® 85) was used.

The particle size of the polymer lattices is also influenced by the amount of surfactant. With an initially high quantity of surfactant, a large number of micelles are formed and a large number of polymer particles are produced. The greater the number of particles formed for a particular quantity of monomer, the smaller the particle size of the lattices. In contrast, if the amount of surfactant present is initially very small, the number of micelles formed is small, relatively few polymer particles are produced, and the particle size is large. The larger particle size favors low viscosity and thus allows higher solid concentrations. However, with low surfactant content, the lattices may be too unstable, resulting in excessive coagulation.

In the synthesis of polymers A and B, the content of surfactant used was 3%, based on the weight of monomer. Compared to conventional microemulsion polymerization, in which large amounts of surfactants are essential for the formation of microemulsion droplets [26, 27], the amount of surfactant used may be considered small. According to the above reference, surfactants can also have adverse effects on lattice properties. The nonpolymerizable surfactants adsorbed onto the surfaces of the lattices may desorb, resulting in lattice destabilization when subjected to freeze and thaw cycles, applied shear stress, or high levels of electrolyte. In the case of pharmaceutical application, this can lead to potential toxicity.

In addition, Zhenxing et al. [28] added a surfactant at submicellar level to produce highly monodispersed polystyrene nanospheres by emulsion polymerization. No SDS micelles were formed; only the homogeneous nucleation process occurred in this polymerization system. Thus, the authors chose to call this modified method a quasi-emulsifier-free emulsion polymerization. However, the solid content of the lattices prepared by such a method was still low, unlike the lattices produced in the current study. The behavior during polymerization of both polymers A and B is described in Table 2.

As shown in Table 2, the temperature before adding the initiators was adjusted to 20 °C. In the first stage, for both polymers A and B, the temperature did not reach the theoretically calculated value. This result may be attributed to the presence of the inhibitor added to the monomers to prevent polymerization during shipping and

Table 2 Peak temperatures reached by polymer A and polymer B

Temperature change	Polymer A [ΔT = 70 °C] [15]	Polymer B [ΔT = 69 °C] [15]
1st stage		
Initial temperature	20 °C	20 °C
Final temperature calculated	90 °C	89 °C
Final temperature observed	74 °C	74 °C
Temperature change	Polymer A [ΔT = 66 °C] [15]	Polymer A [ΔT = 61 °C] [15]
2nd stage		
Initial temperature	20 °C	20 °C
Final temperature calculated	86 °C	81 °C
Final temperature observed	88 °C	92 °C

storage. The inhibitor was not previously removed before using the monomers. Unlike the first stage, the temperatures in the second stage exceeded the theoretically calculated temperatures. It is believed that some residual monomers from the first stage should have polymerized along with the monomers of the second stage. In others words, the temperatures did not reach the theoretical values in the first stage, thus leading to an accumulation of free monomers, which polymerized in the second stage. Evidence for this hypothesis is found in the fact that the lattices produced were free of monomer odor.

The lattices obtained were coagulum-free and without phase separation. They were stored at room temperature and, after 12 months, presented no change in their visual aspect. The films produced remained homogeneous, smooth, and transparent for the same storage period. The FTIR spectra shown in Fig. 1 indicate the details of functional groups present in the synthesized polymer A and polymer B.

A sharp intense band at 1,720–1,738 cm^{-1} appeared due to the presence of the ester carbonyl group's stretching vibration. Furthermore, the two strong C–O stretching bands at 1,238 and 1,140 cm^{-1} characterize the ester groups. The absence at 1,635 cm^{-1} associated with C=C double bond stretching indicated the conversion of C=C into C–C bonds and suggests that the polymerization reaction was successful. Other well-evidenced bands included 1,447 cm^{-1} (CH_2 symmetric bending, CH_3 asymmetric bending), 1,386 cm^{-1} (CH_3 symmetric bending), and 748 cm^{-1} due to rocking CH_2 [29].

Conversions of the monomers were measured by the percentage of total solids. For polymer A, the value was 54.70% (57.0% theoretical), while for polymer B, the value was 52.40% (55.0% theoretical). The values found are in agreement with the low temperatures reached during polymerization in the first stage, indicating a residual free monomer content of about 2% for both polymers.

The main effect of pH on the emulsion polymerization of acrylic esters is concerning the degree of hydrolysis of the monomer. Investigations have shown that at pH of 7 or less, hydrolysis is quite low and would be negligible in emulsion

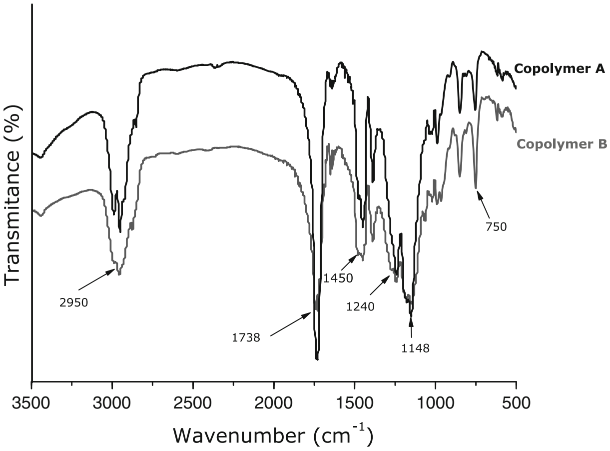

Fig. 1 FTIR spectra of polymers A and B

polymerization, whereas under alkaline conditions, saponification is fairly rapid at room temperature [6, 18]. The pHs of polymers A and B were 4.28 ± 0.02 and 4.98 ± 0.02, respectively. The viscosity values for polymers A and B were 59 cP and 48 cP, respectively. However, one must take into account that the polymers produced here have a higher solid content when compared with their commercial counterparts.

Dynamic light scattering (DLS) provides a relatively fast and simple method for submicron particle sizing [30–32]. DLS—also known as photon correlation spectroscopy (PCS) or quasi-elastic light scattering (QELS)—uses scattered light to measure the Brownian motion of nanoparticles and relates this movement to an equivalent hydrodynamic diameter, with the motion of smaller particles being overestimated. The results of DLS are summarized in Table 3. PDI (polydispersity index) is a dimensionless number that describes the heterogeneity of the sample, which can range from 0 (monodisperse) to 1 (polydisperse).

As can be observed, polymer dispersions A and B showed particles with submicrometric diameters, and the PDI values indicated a relatively wide range of distributions.

In recent years, nearly all the low viscosity high solid content lattices were prepared by broadening the PSD [8]. Increasing the solid content in a reproducible manner entails the strict control of a complex particle size distribution (PSD) [33, 34]. According to the above references, the particles in a perfectly

Table 3 Data obtained from DLS and zeta potential analysis of copolymers A and B

	Size average (nm)	Polydispersity index (PDI)	Zeta potential (mV)
A	175.20 (±2.71)	0.151 (±0.11)	−65.13 (±1.48)
B	173.5 (±3.42)	0.191 (±0.15)	−62.01 (±2.31)

$n = 3$ ± standard deviation of the average size

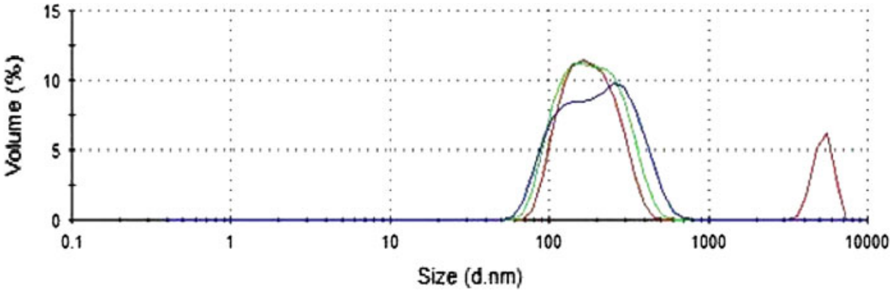

Fig. 2 Particle size distribution (PDS) by volume of polymer A

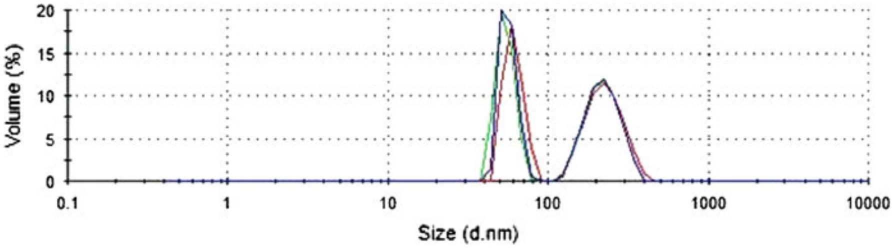

Fig. 3 Particle size distribution (PDS) by volume of polymer B

monodisperse lattices will enter into contact with solid contents of approximately 64 wt%. In a bimodal particle size distribution, if the difference in particle sizes is significantly high, small particles will efficiently pack into the voids left by the large particles, thus increasing the maximum packing factor (maximum volume fraction of particles in the dispersion). This is well illustrated in Fig. 2 in the work by Guyot et al. [35]. The graphs shown in Figs. 2 and 3 are the results of the volume distribution of polymers A and B, respectively. The bimodal particle size distribution may have contributed to the low viscosity presented by them.

The use of larger amounts of anionic surfactant in the first stage may have produced particles with smaller sizes. On the other hand, using a larger amount of nonionic surfactant in the second stage may have produced particles with larger size, thus causing a multimodal distribution of particle size. In addition, there may have been some contribution corresponding to small drops of residual monomer.

The authors' main concern was to control the polymerization process under realistic conditions rather than increase the solids' content above 55%. For this reason, it was not the aim of this work to control the process for obtaining bimodal or multimodal particle size distributions. Future research will certainly involve greater control over the distribution of particle size to achieve higher solid lattices. The bimodal size distribution was also confirmed by SEM photos. From Figs. 4 and 5, the morphology of lattice particles clearly demonstrates the existence of particles of small size, along with larger size particles, which most likely formed in the second stage of polymerization process. One disadvantage of the coating and wet granulation is the slow drying rate due to the high water content in commercially

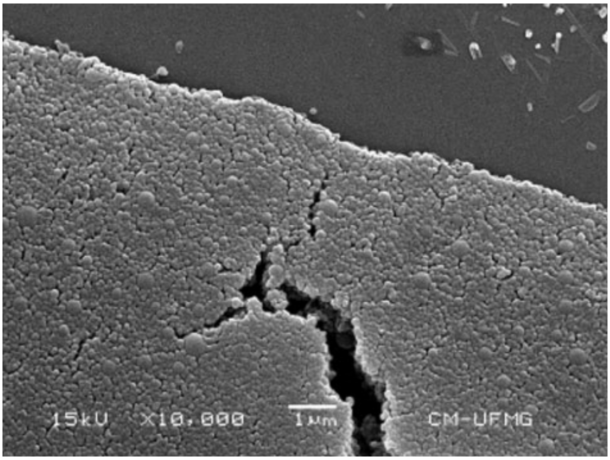

Fig. 4 SEM micrograph of latex particles of polymer A (magnification 10,000×)

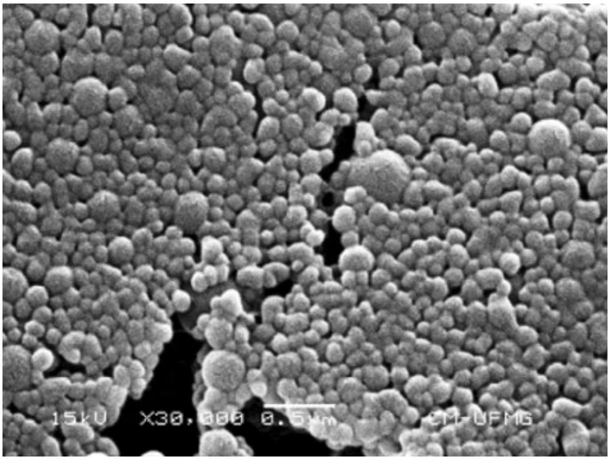

Fig. 5 SEM micrograph of latex particles of polymer A (magnification 30,000×)

available polymeric dispersions for pharmaceutical use. The high values of the solid contents and low viscosity of the polymer dispersions obtained in this work can be useful in overcoming these disadvantages [4, 36].

The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles in suspension have a large negative or positive zeta potential, then they will tend to repel each other and there is no tendency to flocculate. However, if the particles have low zeta potential values, then there is no force to prevent the particles from coming together and flocculating. The general dividing line between stable and unstable suspensions is generally taken at

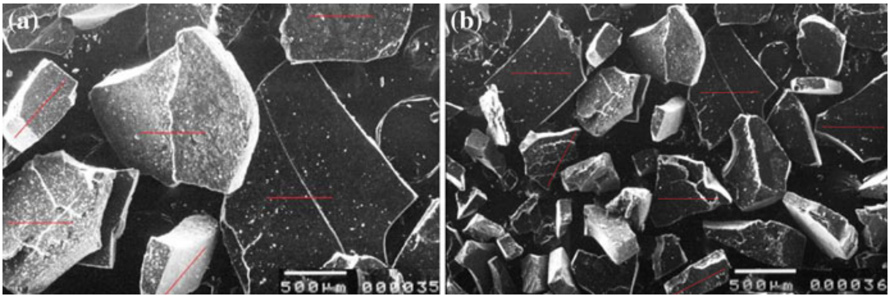

Fig. 6 SEM of freeze-dried polymer A (**a**) and feeze-dried polymer B (**b**) (Magnification of 35×)

either +30 or −30 mV. Particles with zeta potentials more positive than +30 mV or more negative than −30 mV are normally considered stable [32, 37, 38].

The zeta potential, related to the surface potential of particles in polymers A and B showed high negative values (Table 3), possibly due to the structural characteristics of the interface of the particles, especially the presence of sodium lauryl sulfate. According to the authors [39], SDS is one of the ionic emulsifiers that produces SO_4^- groups on the microsphere surface in lattice solutions, and the electrostatic repulsive forces, originated from these groups, prevent coagulation. The presence of ions from the initiators may also have contributed to the observed values. Du et al. reported that the use of persulfate as an initiator can result in the incorporation of sulfate groups at the end of the polymer chains, making them negative and inducing colloidal stability by steric effect [5, 6, 38].

The proposed polymerization process led to the production of lattices with characteristics suitable for pharmaceutical use: high content of solids, low viscosity, and colloidal stability. The presence of a high concentration of solid particles and, at the same time, low viscosity, will allow for the use of a smaller amount of lattice in coating or wet granulation. Both processes occur more rapidly, and the end products will present a reduced cost. Finally, the use of water to replace solvents provides benefits to the environment, the organism, as well as the cost of the tablets. However, the freeze-dried emulsions gave rise to nonspherical particles as observed by SEM (Fig. 6). In this case, there are many sites of contact with greater cohesiveness between the irregular particles and, therefore, lower flowability. This behavior suggests that the present emulsions are more useful as coatings or wet compression. Further investigations on size and shape of the particles after freeze-drying and grinding are needed to optimize the use of these polymers as excipient by the direct compression.

Figure 7 shows the DSC curves of polymer A and polymer B films. The endothermic step (ΔC_p) in the heat flux, which should correspond to the glass transition, is observed below 50 °C. For aqueous dispersions used in coatings, recommendations are to keep the coating temperature at 10–20 °C above the minimum film-forming temperature to ensure that optimal conditions for film formation are achieved [40].

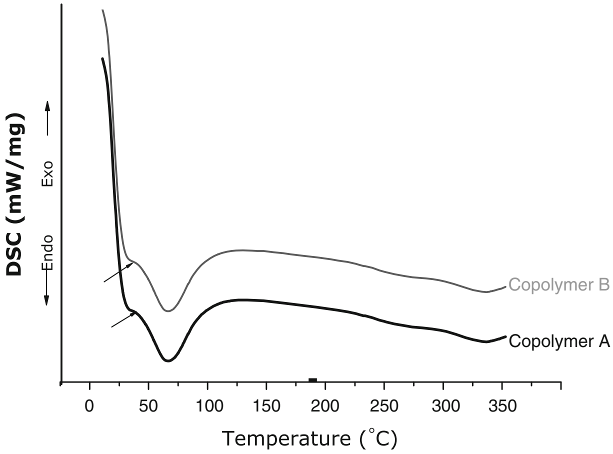

Fig. 7 DSC curves of polymers A and B films

Table 4 Glass transition temperatures (T_g) of homopolymers

Homopolymers of	T_g (°C)	T_g (K)
MMA	104	377
BMA	20	293
EA	−22	251

Values obtained from [16]

The T_g of polymers A and B was calculated assuming the Fox equation valid [40, 41]. The theoretical value of glass transition temperature of each polymer was calculated from those of the MMA, BMA, and EA homopolymers that exhibit glass transition as shown in Table 4, according to Eq. 1:

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}} \tag{1}$$

where T_g is the glass transition temperature of the blend, T_{g1} that of polymer 1, T_{g2} that of polymer 2, and W_1 and W_2 weight fractions of polymers 1 and 2, respectively. The theoretical values of glass transitions of polymers A and B obtained for the MMA:BMA:EA 60:20:20 and 50:30:20 monomer compositions are 53 and 45 °C, respectively. The values of T_g above room temperature may well explain the brittle surface of the films as shown by SEM micrographs presented in Fig. 6.

Figure 8 shows the weight loss and the weight loss rate as a function of temperature of polymers A and B, respectively. The obtained TG/DTG curves are similar for both polymers A and B. Any small observed differences can be assigned to the differences in composition (proportion of the monomers) of the polymers.

Finally, cellular viability studies showed that gingival fibroblasts were viable in cultures that came in contact with the freeze-dried polymers A and B (Fig. 9). No statistical difference in cell viability, when compared to the control groups after 24 h, could be observed. It is also possible to observe that, in the control groups

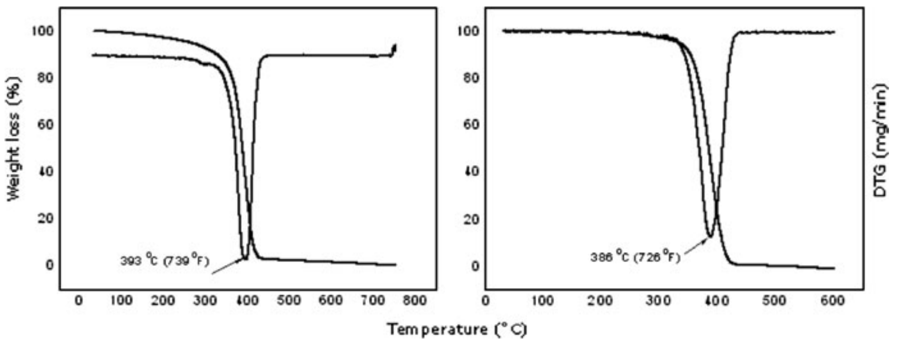

Fig. 8 TG and DTG curves of polymers A (**a**) and B (**b**)

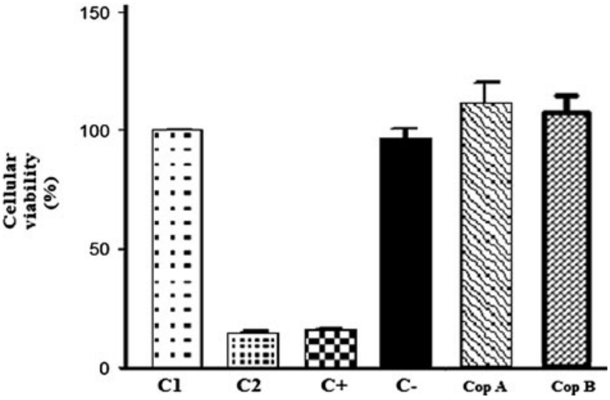

Fig. 9 Cellular viability of polymers A (Cop A) and B (Cop B) obtained by MTT assay after 24 h ($n = 3$; $p \leq 0.05$)

(control and 1 negative control), cell viability was approximately 100%. These results indicate that both polymers A and B can be suitable for use as excipients in pharmaceutical applications.

Conclusions

In the present study, two polymers based on different proportions of acrylic and methacrylic monomers were successfully prepared using a multistage polymerization process. Polymerization using a redox initiator system and sonification has proven to be useful for multimodal lattices with high solids and low viscosity. The influence of the mixed surfactant system (anionic/nonionic) on particle size distribution, and thus on viscosity, was hypothesized herein. The experimental results are consistent with those required for pharmaceutical applications. The lattices obtained were coagulum-free and without phase separation. They were stored at room temperature and after 12 months, no change in their visual aspect could be observed. The films produced remained homogeneous, smooth, and transparent for the same storage period. The dispersions produced can be used as granulating agents and matrix formers in the compression process by the wet method. The low viscosity, high solid content, and small particle size allow for researchers to obtain a coating material that would lead to a more rapid coating process. The high proportion of solids also allows for the use of small quantities of polymer dispersions for coating and during the wet granulation, with a subsequent reduction in the cost of the final product. The result of cellular viability demonstrates that gingival fibroblast viability is not modified in the presence of the polymers, which indicates their nontoxicity.

Acknowledgments The authors wish to acknowledge financial support from the National Council for Scientific and Technological Development (CNPq), a foundation linked to the Ministry of Science and Technology (MCT) of the Brazilian Government and the Research Foundation of the State of Minas Gerais (FAPEMIG).

References

1. Jivraj M, Martini LG, Thomson CM (2000) An overview of the different excipients useful for the direct compression of tablets. PSST 3(2):58–63
2. Sangalli MA, Maroni A, Foppoli A, Zema L, Giordano F, Gazzaniga A (2004) Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: a study on process parameters and in vitro performances. Eur J Pharm Sci 22:469–476
3. Barkley A, Levine S, Signorino C (2011) The evolution and evaluation of tablets coating. Tablets & Capsules. Available at: http://online1.ispcorsp.com/en-US/Media/Articles/The%20Evolution%20and%20Evaluation%20of%20Tablet%20Coatings.pdf. Accessed February, 18, 2011
4. Swarbrick J (2007) Encyclopedia of pharmaceutical technology, 3rd edn. Informa Healthcare, New York
5. Du Y, Ma G, Nagai M, Omi S (2002) Synthesis of high solid lattices by thermally initiated emulsion polymerization. J Appl Polym Sci 85:2478–2483
6. Anderson CD, Daniels ES (2003) Emulsion polymerisation and latex applications. Rapra Rev Rep 14(4):3–31
7. Sajjadi S (2006) Effect of mixing protocol on formation of fine emulsions. Chem Eng Sci 61:3009–3017
8. Ai Z, Deng R, Zhou Q, Liao S, Zhang H (2010) High solid content latex: preparation methods and application. Adv Colloid Interface Sci 159:45–59
9. Cao X, Gao Q, Gao P, Ding P, Gao Z, Sun X (2002) Preparation and characterization of a novel aqueous dispersion of Eudragit® E for coating. Asian J Pharm Sci 2(1):29–37
10. Ojoe E, Consiglieri VO, Cobo TV, Miyauchi EM (2005) Formulation and in vitro evaluation of theophylline Eudragit® sustained-release tablets. Braz J Pharm Sci 4(3):377–384
11. Boutti S, Graillat C, McKenna TF (2005) High solids content emulsion polymerisation without intermediate seeds. Part III. Reproducibility and influence of process conditions. Polymer 46:1189–1210
12. Asua JM (2002) Miniemulsion polymerization. Prog Polym Sci 27:1283–1346
13. Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ (2005) Nano-emulsions. Curr Opin Colloid Interface Sci 10(3–4):102–110
14. Quintero R, Mendon SK, Smith OW, Thames SF (2006) Miniemulsion polymerization of vegetable oil macromonomers. Prog Org Coat 57:195–201
15. Teo BM, Prescott SW, Ashokkumar M, Grieser F (2008) Ultrasound initiated miniemulsion polymerization of methacrylate monomers. Ultrason Sonochem 15:89–94
16. Anton N, Benoit JP, Saulnier P (2008) Design and production of nanoparticles formulated from nano-emulsion. J Control Rel 128:185–199

17. Florence AT, Attwood D (2005) Physicochemical principles of pharmacy, 4th edn. Pharmaceutical Press, New York
18. Riddle EH (1954) Monomeric acrylic esters. Reinhold Publishing Co, New York
19. Sullivan CI, Mallios PD (1996) Polymer latex. United States Patent 3244655
20. Gehman DR, Owens JM, Zdanowski RE (1979) Internally plasticized polymer latex. United States Patent 4150005
21. United States Pharmacopeia 32, National Formulary 27 (2009) US Pharmacopoeia, Rockville. CD-Rom version
22. American Pharmacists Association (2006) In: Rowe RC, Sheskey PJ, Owen SC (eds) Handbook of pharmaceutical excipients, 5th edn. American Pharmaceutical Society of Great Britain, Washington. Eletronic version. CD-Rom version
23. Villanova JCO, Ayres E, Carvalho SM, Patrício PO, Vargas FP, Oréfice RL (2011) Pharmaceutical acrylic beads obtained by suspension polymerization containing cellulose nanowhiskers as excipient for drug delivery. Eur J Pharm Sci 42:374–385
24. Carvalho S, Oliveira A, Andrade V, Leite MF, Goes A, Pereira MM (2009) Comparative effect of the ionic products from bioactive glass dissolution on the behavior of cementoblasts, osteoblasts and fibroblasts. Key Eng Mater 396(398):55–59
25. Mossmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 65:55–63
26. Richards JR, Congalidis JP (2006) Measurement and control of polymerization reactors. Comput Chem Eng 30:1447–1463
27. Xu XJ, Gan LM (2005) Recents advances in the synthesis of nanoparticles of polymer lattices with high polymer-to-surfactant ratios by microemulsion polymerization. Curr Opin Colloid Interface Sci 10:239–244
28. Zhenxing H, Xiaowei Y, Junliang L, Yuping Y, Ling W, Yanwei Z (2011) An investigation of the effect of sodium dodecyl sulfate on quasi-emulsifier-free emulsion polymerization for highly monodisperse polystyrene nanospheres. Eur Polym J 47:24–30
29. Silverstein RM, Webster FX, Kiemle D (2005) Spectrometric identification of organic compounds, 7th edn. Wiley, New York
30. Xu R (2008) Progress in nanoparticles characterization: sizing and zeta potential measurement. Particuology 6:112–115
31. Brar SK, Verma M (2011) Measurement of nanoparticles by light-scattering techniques. Trends Anal Chem 30(1):4–17
32. Zeta Sizer Nano Series—User Manual (2004) Malvern Instruments, England. Available at: http://www.nbtc.cornell.edu/facilities/downloads/Zetasizer%20Manual.pdf. Accessed Jan 23, 2011
33. Mariz IFA, Cal JC, Leiza J (2010) Control of particle size distribution for the synthesis of small particle high solids content lattices. Polymer 51:4044–4052
34. Moyaed SH, Shohreh F, Pourmahdian S (2007) Synthesis of a latex with bimodal particle size distribution for coatings applications using acrylic monomers. Prog Org Coat 60:312–319
35. Guyot A, Chu F, Schneider M, Graillat C, McKenna TF (2002) High solid content lattices. Prog Polym Sci 27(8):1573–1615
36. Petereit HU, Weisbrod W (1999) Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. Eur J Pharm Biopharm 7(1):15–25
37. Sinko PJ (2006) Martin's physical pharmacy and pharmaceutical sciences, 5th edn. Lippincott Williams and Wilkins, Baltimore
38. Du YZ, Hu FQ, Yuan H, Omi S (2006) Thermal emulsion polymerization without any conventional initiators and emulsifiers. Chin Chem Lett 17(4):553–556
39. Quental AC, Carvalho FP, Tada ES, Felisberti MI (2010) Blendas de PHB e seus copolímeros: miscibilidade e compatibilidade. Quím Nova 33(2):438–446
40. Cole G (1995) Pharmaceutical coating technology. Taylor & Francis, London
41. M'Bareck CO, Nguyen QT, Metayer M, Saiter JM, Garda MR (2004) Poly(acrylic acid) and poly(sodium styrenesulfonate) compatibility by Fourier transform infrared and differential scanning calorimetry. Polymer 45:4181–4187