

Polyurethane nanoparticles from a natural polyol via miniemulsion technique

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Abstract

Original natural triol (castor oil) was used as a monomer for the synthesis of monodisperse polyurethane nanoparticles (size ranging from 200 to 400 nm) by miniemulsion technique in water. Various parameters such as the concentration of the reactants, the nature of stabilizers and the shear were tuned to control the particle size and its distribution. The polyaddition between the natural triol and isophorone diisocyanate (IPDI) was conducted at 60 °C, in the absence of catalyst and monitored by infrared spectroscopy. The characterization of these polyurethane latexes was carried out using light scattering measurements and transmission electron microscopy (TEM).

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1. Introduction

Miniemulsions are defined as stable aqueous dispersions of oil droplets with sizes ranging from 50 to 500 nm and are generally prepared by high shear of a system containing oil, water, surfactant and a co-stabilizer (or hydrophobe) [1]. The hydrophobe acts as a suppressor for the mass exchange between the different oil droplets by osmotic forces (the Ostwald ripening), so that the polymerization is initiated in each small stabilized droplet, also called “nano-reactor”. Appropriate formulations lead to particles that have almost the same size as the initial monomer droplets [2,3].

Polyurethanes (PUR) are widely used in many industrial applications and also for the development of biomedical devices or drug delivery systems, due to their excellent physical properties and good biocompatibility [4]. Polyurethane particles have been synthesized using several techniques such as suspension-polycondensation [5], interfacial polycondensation combined to spontaneous emulsification [6], suspension-polyaddition [7], dispersion in organic solvent and supercritical carbon dioxide [8,9]. The preparation of polyurethane nanoparticles via miniemulsion technique was also reported [10–13].

In the present paper, we report on the preparation via miniemulsion technique of PUR nanoparticles derived from a natural triol (castor oil) and isophorone diisocyanate (IPDI). Although few papers report in the literature the use of castor oil as natural triol monomer towards the synthesis of polyurethane materials [7,14–16], the synthesis of polyurethane nanoparticles via miniemulsion technique from such natural

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triol has never been described. Sodium dodecylsulfate (SDS), poly(ethylene oxide)₇₇–poly(propylene oxide)₂₉–poly(ethylene oxide)₇₇ (Pluronic F68) and poly(ethylene oxide)₂₀–sorbitane monooleate (Tween 80) were used as surfactants and olive oil as the hydrophobic agent. The objectives of this study were (i) to investigate the different routes to synthesize such polyurethane nanoparticles from a natural triol monomer in the absence of a catalyst and (ii) to study the influence of various parameters such as the type and concentration of the surfactant, the type of hydrophobic agent and the effect of shear on the particle size and its distribution and finally on the yield.

2. Materials

All chemicals – sodium dodecylsulfate (SDS, Aldrich), poly(ethylene oxide)₂₀–sorbitane monooleate (Tween 80, Beraca), poly(ethylene oxide)₇₇–poly(propylene oxide)₂₉–poly(ethylene oxide)₇₇ (Pluronic F68, BASF) isophorone diisocyanate (IPDI, Aldrich), natural triol (Kehl), polyethylene glycol, $\bar{M}_w = 400 \text{ g mol}^{-1}$ (PEG 400, Vetec), and olive oil (Yola) – were used as received without further purification.

3. Methods

3.1. Preparation of nanoparticles

A monomer mixture (10 g) containing the diisocyanate and the natural triol in a molar ratio $[\text{NCO}]/[\text{OH}] = 1.1$ and 3 wt% (vs monomer, or 5 wt%, run F18) of olive oil as a hydrophobic agent was added at room temperature under stirring to various aqueous solutions (Milli Q, Millipore[®]) containing a surfactant (i.e. SDS, Tween 80 or Pluronic F68) at concentrations ranging from 5 to 20 wt% (vs monomer). The whole monomer concentration in the polymerization medium was 5 wt% for all tested formulations.

The nanodroplets of monomers were obtained by using a homogenizer (Ultra-Turrax[®] T18, IKA[®], Germany) at 18,000 rpm for 15 min. The dispersions were maintained under mechanical stirring (800 rpm) at 60 °C for 4 h to allow the complete polyurethane formation. The polymerization was achieved with gentle mechanical stirring since the use of high-shearing mixers may destroy the stability of polymer particles during the polymerization [17].

In some experiments and for comparison, the PEG 400 was added as a co-monomer in substitution to 50 mol% of natural triol.

3.2. Fourier transform infrared spectroscopy (FTIR)

The polyurethane formation was followed by Fourier transform infrared spectroscopy (FTIR) in the attenuated total reflection (ATR) mode. For that purpose, the latexes were deposited on an ATR crystal to form a film and spectra were recorded using a Bruker – Tensor 27 spectrometer.

3.3. Particle size determination

The particle size and its distribution were measured in aqueous suspension, using light scattering equipment (Zetasizer 3000 HSA, Malvern, and ALV-5000E, ALV). The samples were prepared by dilution of the formulation in Millipore water without filtration.

In the case of scattering measurements performed with Zetasizer, a single 90° scattering angle was used. When using the ALV-5000 set-up, the scattered light was measured at different angles in the range of 60°–120°. In both cases, the temperature was set to $25 \pm 0.1 \text{ °C}$. The intermediate dynamic scattering function $I(q,t)$ is related to the measured homodyne intensity–intensity time correlation function by the Siegert-relation [18]:

$$G^2(q,t) = B[1 + \alpha|I(q,t)|^2]$$

where B is the baseline and α is the spatial coherence factor, which depends on the geometry of the detection and the ratio of the intensity scattered by the particle to that scattered by the solvent. For a Brownian motion, the autocorrelation function is generally described by a single relaxation, i.e. $I(q,t) \sim e^{-\Gamma t}$. Γ is the relaxation frequency ($1/\tau$) and is related to the diffusion coefficient D by the relation $\Gamma = Dq^2$. The autocorrelation function of the scattered intensity was analyzed by means of the cumulant method and CONTIN analysis to yield the effective diffusion coefficient and the corresponding size $R = (k_B T / 6\pi\eta D)$ where $k_B T$ is the Boltzmann energy and η is the viscosity of the medium ($\eta = 0.89 \text{ cP}$ at 25 °C).

3.4. Particle morphology

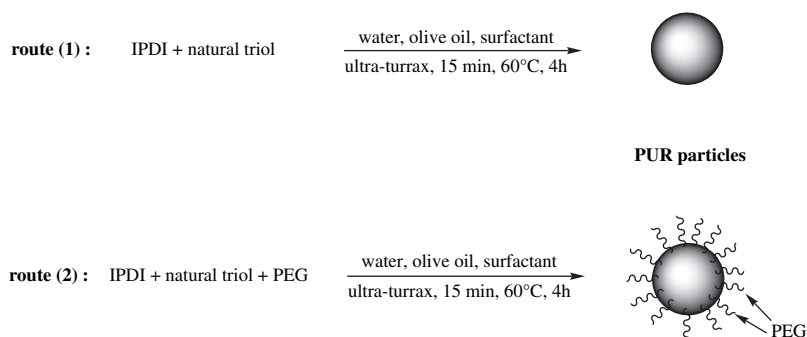
The morphology of the nanoparticles was investigated by transmission electron microscopy (TEM) using JEOL – JEM – 2000FX equipment. The samples were prepared by deposition of PUR latex droplets on copper grids with Formvar film.

4. Results and discussion

4.1. Preparation of nanoparticles

For the successful synthesis of PUR particles via miniemulsion, a few requirements are necessary: (a) low water solubility of the reactants; (b) the reaction between the isocyanate and the alcohol functions has to be inhibited during the time required for the miniemulsion preparation; (c) the side reaction of the diisocyanate with water in the dispersed state has to be slower than the reaction with the triol actually used. In the latter case, the ratio of the diisocyanate molecules located at the droplet/water interface to the molecules inside the droplets should be small [10]. Precisely, isophorone diisocyanate (IPDI) is a monomer of choice since it has been shown to react slowly with water during polyurethane synthesis [11].

Polyadditions were conducted between IPDI and the natural triol or a mixture of natural triol and PEG 400 in the presence of olive oil as the hydrophobe and various surfactants



Scheme 1.

(Scheme 1). The miniemulsions were formed by adding the monomers and the hydrophobic agent mixture onto an aqueous solution of surfactant at room temperature, with the use of a homogenizer (Ultra-Turrax[®]) at shearing rate ranging from 10,000 to 22,000 rpm. It is worth mentioning that attempts to form stable initial monomer droplets by ultrasound was ineffective, leading systematically to the formation of several particle distributions with different sizes. Indeed, this phenomenon was attributed to the high viscosity of the natural triol which was rather difficult to emulsify. Surprisingly, the homogenizer (Ultra-Turrax[®]) proved to be effective in these specific experimental conditions, with respect to the control and distribution of the particle size.

Following this procedure, the turbidity of the preparation increased rapidly during the first minutes of homogenization, became milky and then remained constant. Then the polymerization was allowed to continue for 4 h under gentle mechanical stirring at 60 °C. Table 1 summarizes data that correspond to the experiment runs with different mixtures of monomers and various types of surfactants.

Generally the PUR particle size was between 200 and 300 nm and the polydispersity index was between 0.3 and 0.4.

The amount of surfactant was shown to slightly affect the particle size. Indeed, the particle diameter slowly decreases from 292 to 261 nm as the amount of Tween surfactant increases from 5 to 20 wt% vs monomer (see F10–F12). The best results

Table 1
PUR particles based on natural triol synthesized by miniemulsion using 3 wt% of olive oil (vs monomers) as a hydrophobic agent

Latex	Monomers (g)	Surfactant (wt% vs monomers)	Yield ^a (%)	Particle average diameter ^b (nm)	PI ^c
F10	Polyol (3.6) PEG (3.1) IPDI (3.3)	Tween (20.0)	97	261 (100%) ^d	0.39
F11	Polyol (3.6) PEG (3.1) IPDI (3.3)	Tween (10.0)	97	282 (100%)	0.37
F12	Polyol (3.6) PEG (3.1) IPDI (3.3)	Tween (5.0)	88	292 (100%)	0.35
F13	Polyol (7.0) IPDI (3.0)	Tween (5.0)	58	297 (100%)	0.36
F16	Polyol (7.0) IPDI (3.0)	Tween (20.0)	96	246 (100%)	0.40
F18 ^e	Polyol (3.6) PEG (3.1) IPDI (3.3)	Tween (10.0)	92	194 (59%) 661 (41%)	0.42
F19	Polyol (3.6) PEG (3.1) IPDI (3.3)	SDS (10.0)	53	463 (53%) 2473 (47%)	0.94
F20	Polyol (3.6) PEG (3.1) IPDI (3.3)	Pluronic (10.0)	86	285 (100%)	0.31

^a Measured by gravimetry.

^b Measured by light scattering (Zetasizer/Malvern).

^c Polydispersity index, determined by Malvern.

^d Percentage value of each size distribution mode.

^e Formulation prepared with 5 wt% of hydrophobic agent (olive oil).

in terms of particle size distribution were obtained when using Tween and Pluronic as surfactants (see F10–F16 and F20).

It is noteworthy that the use of hydrophilic PEG 400 as a co-monomer leads to a slight increase in the particle diameter from 246 to 261 nm (see runs F10 and F16). This result is in contradiction with the data reported from hydrophilic macrodiol [7,10,19]. The reactivity of the two polyols (PEG 400 and natural triol, respectively) with IPDI must be different. Indeed, the natural triol bears a secondary alcohol function, known to be less reactive than primary alcohol, which can favor the reactivity with water. However, the higher hydrophobicity of the natural triol should be more effective to avoid this secondary reaction, as discussed further in the paper.

4.2. Polyurethane characterization by FTIR

The formation of polyurethane was monitored by FTIR using an ATR method. The completion of the polyaddition reaction between IPDI and natural triol or IPDI and natural triol/PEG 400, without any catalyst, was confirmed by ATR-FTIR analysis. This is illustrated by ATR-FTIR spectra of the final polyurethane particles presented in Fig. 1 together with the spectra of the initial IPDI and natural triol monomers. The intensity of isocyanate vibration band located at 2235 cm^{-1} was used to follow the polyurethane formation. Indeed, as shown in Fig. 1, this band has completely disappeared (samples F10 and F16). Moreover, the NH vibration at 3300 cm^{-1} , the carbonyl vibration at 1743 cm^{-1} and the C–N vibration at 1550 cm^{-1} are strong evidence for the formation of polyurethane [10,20].

The absorption band between 1000 and 1300 cm^{-1} was used to identify the PEG 400 in the F10 formulation [5]. When the PEG was added as a co-monomer (F10), reaction with water occurred and urea formation was evidenced (see peak at 1635 cm^{-1}). In the absence of PEG (F16), the vibration at 1635 cm^{-1} (carbonyl of urea) is less intense indicating that the reaction of isocyanate with water is secondary. Urea formation in the case of F10 can be explained by the hydrophilicity of PEG which favors the reaction between isocyanate and water molecules.

4.3. Effect of the surfactant type

For the miniemulsion formulations, a wide range of anionic, cationic and nonionic surfactants could be used resulting in differently charged and stable polymeric dispersions. Anionic and cationic surfactants have been reported for the formation of monodisperse droplets between 30 and 200 nm while nonionic oligomeric or polymeric surfactants are suitable for the formation of droplets between 100 and 800 nm [21]. The majority of the recipes described in the literature are based on anionic SDS as a model system.

In this study, SDS and two nonionic surfactants namely Tween 80 and Pluronic F68 were used. The surfactant SDS was found to be not efficient in our system, resulting in some coagulation and in low latex yield (around 50%) with the formation of two particle size distributions (see Table 1, F19). This result was attributed to the poor affinity of the ionic

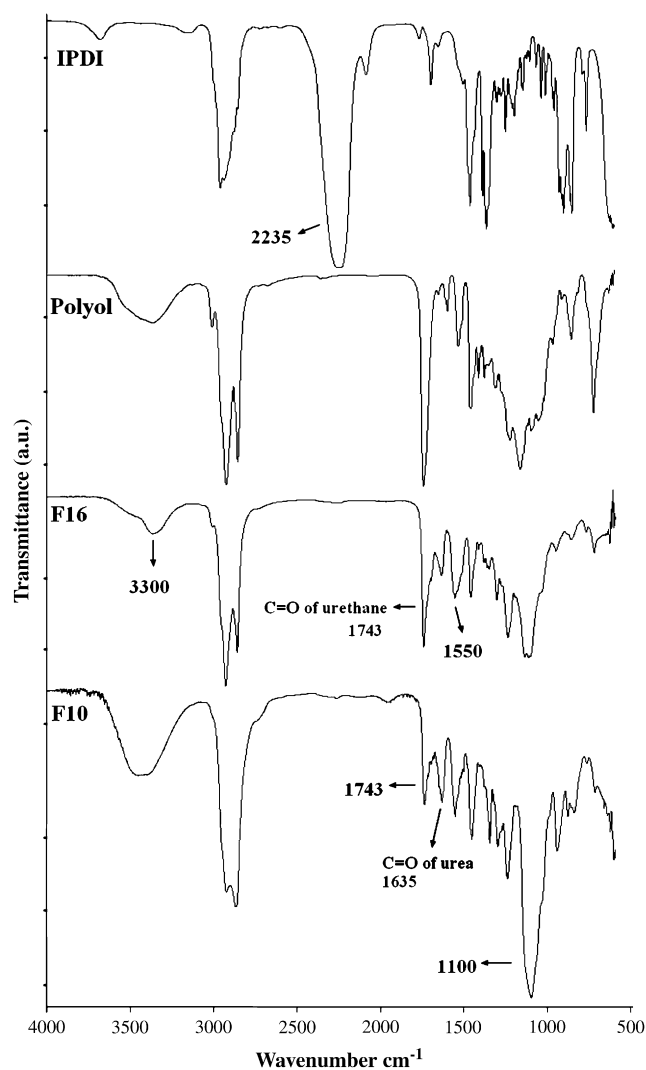


Fig. 1. FTIR spectra of IPDI, natural triol, F16 (triol and IPDI) and F10 (triol, PEG and IPDI).

surfactant with the neutral triol. Conversely, the nonionic surfactants gave monomodal particle size distribution and good yields. The particles synthesized with Tween 80 or Pluronic F68 were very similar to each other in terms of yield and particle size distribution. Tween 80 and Pluronic F68 can be considered as polymeric surfactants that stabilize the miniemulsion by steric effect. This behavior seemed to be more appropriate for the stabilization of the viscous natural triol.

Therefore, the effect of surfactant concentration was tested only with Tween 80. The latter is widely used for the formulation of pharmaceutical and cosmetic products, owing to its attractive cost and low toxicity [22]. On the other hand, the SDS surfactant that is used in miniemulsion shows some toxicity problems [23].

4.4. Effect of Tween 80 concentration

The concentration of Tween 80 was varied from 5 to 20 wt% (as compared to the monomer amount). It is worth

noting that a minimal concentration of 5 wt% of Tween 80 was required to favor the colloidal stability and to avoid aggregation. Generally, the surfactant concentration should be below the CMC (critical micellar concentration) upon formation of the miniemulsion in order to prevent any side micellar polymerization [17]. As expected [2,17,24–27], the particle size was decreased as the surfactant concentration was raised from 5 to 20 wt% (see Table 1 and Fig. 2). Nevertheless, this trend is rather weak in our experimental conditions. In addition, the formulation yield was increased using higher surfactant concentrations (see Table 1).

Formulations containing PEG as a co-monomer and Tween 80 at the concentration of 5 wt%, gave yield of 88% (F12). At same Tween 80 concentration and in absence of PEG, the yield of formulation fell down to 58% (F13). This phenomenon was attributed to the co-surfactant effect of PEG.

4.5. Effect of the hydrophobic agent

The crucial role of the hydrophobic agent in miniemulsion polymerization is to prevent Ostwald ripening. The effectiveness of the hydrophobe increases with decreasing water solubility in the continuous phase [3]. Olive oil has been described in the literature as a substance model for oil/water suspension [28] and as a carrier in ointments and cosmetics [29,30] but there are few reports concerning the use of olive oil as hydrophobic agent in miniemulsion. We have chosen olive oil as the hydrophobic agent because of its low solubility in water and its compatibility with the natural triol (castor oil). Monomodal PUR particles were obtained in the presence of olive oil used at a concentration of 3 wt% vs monomers (see Table 1). The bimodal particle size distribution only observed in run F18, when the concentration of olive oil was increased to 5 wt% vs monomers, is in agreement with the results observed by Landfester [3] who described that droplets with high hydrophobic agent content increase in size until the osmotic pressure in all droplets is equilibrated. In an ideal case, a bimodal dispersion can be favored.

Finally, it is interesting to mention that hexadecane, usually used as a hydrophobic agent in colloidal stabilization, led to ill-defined materials when used in our system (data not shown).

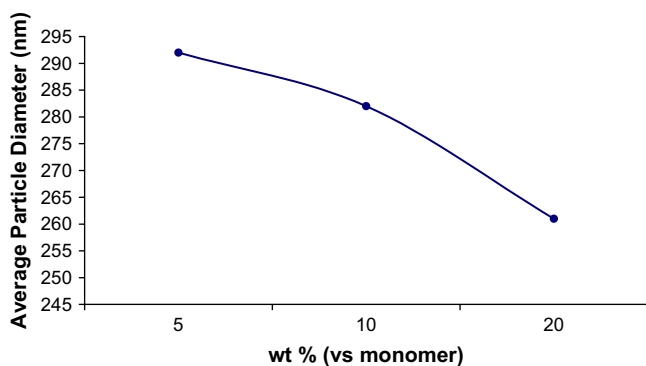


Fig. 2. Effect of Tween 80 concentration on average PUR particle diameter (nm).

4.6. Effect of shear

Contrary to what is described in the literature [3,31], we have observed that the Ultra-Turrax[®] is an efficient tool to obtain well-defined PUR nanoparticles using miniemulsion route. In order to investigate the effect of shear on the formation and stability of the monomer droplets, we performed different miniemulsions at various shear rates, from 10,000 to 22,000 rpm during the same time period (15 min). Data are summarized in Table 2.

Monomodal and particle size distribution could be readily prepared, provided the shear rate was higher or equal to 14,000 rpm [7,32–34]. Below this value, bimodal particle distributions were obtained after polymerization (run F21). Above this shear rate threshold, monomodal particle size distribution was obtained with an average particle diameter of 290 nm, without any significant effect of shear rate on the particle size (F11, F22–F23).

4.7. Dynamic light scattering

All the samples were diluted 400 times and analyzed using dynamic light scattering (ALV or Zetasizer apparatus) with and without filtration. Fig. 3 shows the correlation function obtained at the scattering angles $\theta = 60^\circ$, 90° and 120° at 25°C for samples F10 and F16. They are essentially represented by a single exponential decay.

For both formulations (F10 and F16), the hydrodynamic radii of the particles were determined using Stokes–Einstein relation and the results are 131 and 113 nm, respectively (Fig. 4).

Additionally, the angular variation of the frequency $\Gamma = 1/\tau_s$ shows a q^2 behavior, indicating a diffusive motion [35] (see Fig. 5).

Table 2
Particle average diameter, polydispersity index and yield as a function of the shear (Ultra-Turrax[®] apparatus)

Latex	Monomers (g)	Shear rate ^a (rpm)	Yield ^b (%)	Particle average diameter ^c (nm)	PI ^d
F21	Polyol (3.6) PEG (3.1) IPDI (3.3)	10,000	98	245 (48%) ^c 1016 (52%)	0.86
F23	Polyol (3.6) PEG (3.1) IPDI (3.3)	14,000	97	279 (100%)	0.39
F11	Polyol (3.6) PEG (3.1) IPDI (3.3)	18,000	97	282 (100%)	0.37
F22	Polyol (3.6) PEG (3.1) IPDI (3.3)	22,000	97	306 (100%)	0.39

^a In a Ultra-Turrax[®] device (time of shear: 15 min).

^b Measured by gravimetry.

^c Measured by light scattering (Zetasizer/Malvern).

^d Polydispersity index, determined by Malvern.

^e Percentage value of each size distribution mode.

4.8. Morphology analysis

TEM images of polyurethane latexes synthesized by mini-emulsion polymerization are presented in Figs. 6 and 7. The particle size observed using TEM is in good agreement with the results obtained by dynamic light scattering.

Fig. 7 shows the TEM image of PUR nanoparticles prepared with PEG as a co-monomer in the formulation. In this case, it is speculated that a fraction of PEG (hydrophilic diol) can migrate at the interface of the PUR particle–water forming a protecting layer around the particle, as observed in the TEM image. The covering of nanoparticles by PEG is very important in order to avoid immunoresponse (“stealth particles”) and to increase circulation time in the blood stream

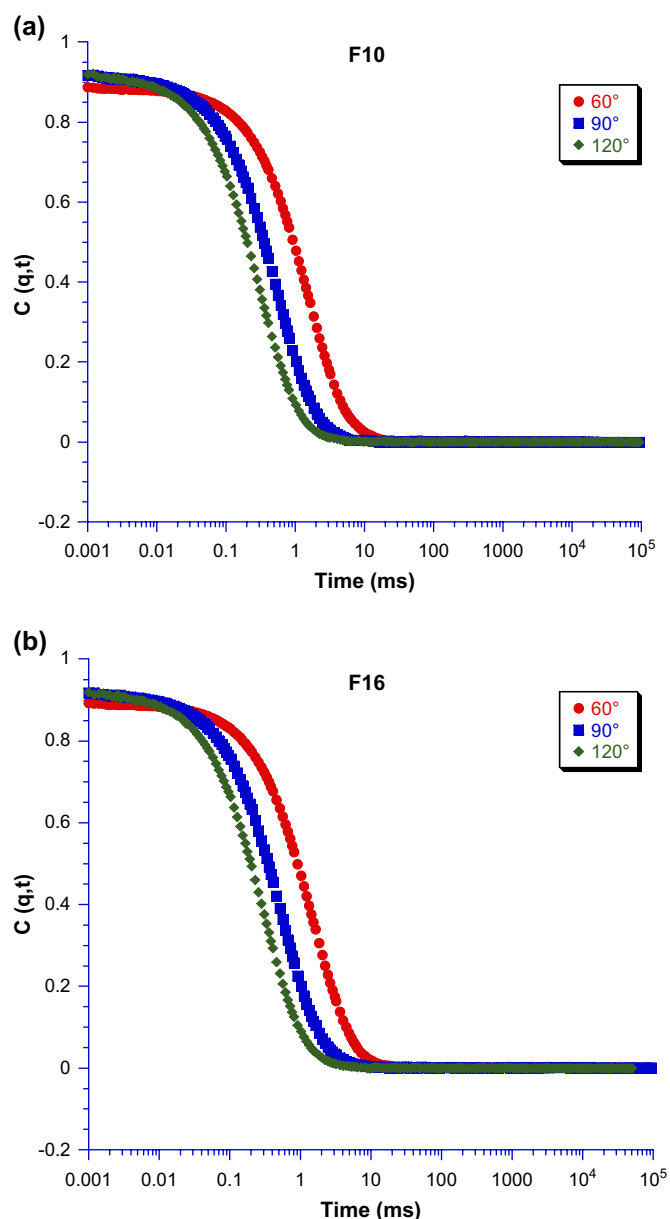


Fig. 3. Correlation functions measured at the scattering angles $\theta = 60^\circ$, 90° and 120° for (a) F10 and (b) F16 formulations, respectively, at the temperature of 25°C .

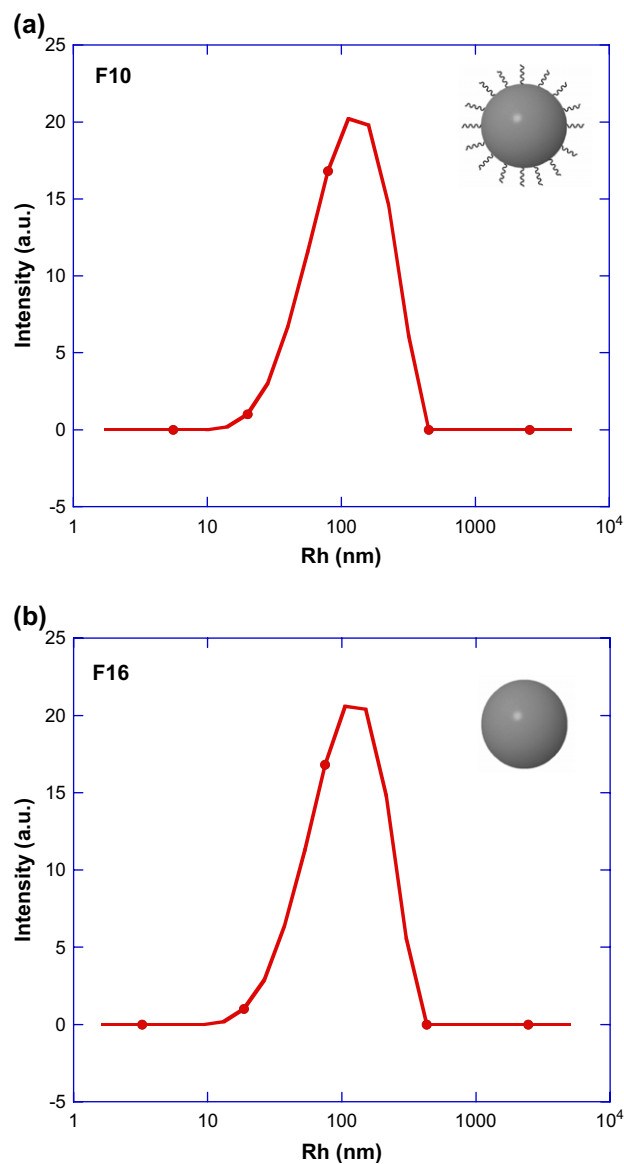


Fig. 4. Determination of hydrodynamic radius R_h (nm) for formulations (a) F10 and (b) F16.

[36,37]. Therefore, such latexes could be very useful for drug encapsulation and intravenous applications.

5. Conclusions

We have shown that a natural triol (castor oil) can be used as a monomer for the synthesis of polyurethane nanoparticles via miniemulsion technique. The specific features of our system are the use of Ultra-Turrax[®] device, the requirement of nonionic surfactants (Tween 80 or Pluronic F68) and of olive oil as co-stabilizer (hydrophobe). FTIR spectroscopy allowed us to confirm the completion of the polymerization. The polyurethane particle size was measured by light scattering measurements and transmission electron microscopy (TEM). The average particle diameter was measured around 300 nm. Studies of drug encapsulation and enzymatic degradation of such

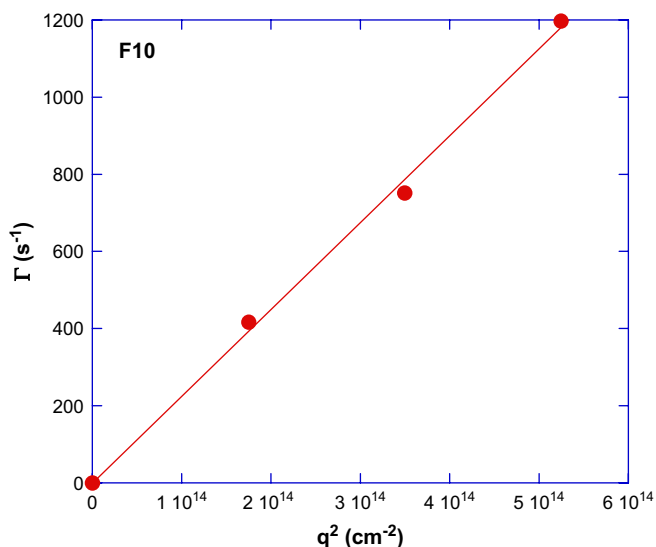


Fig. 5. I vs q^2 for F10 formulation – diffusive behavior.

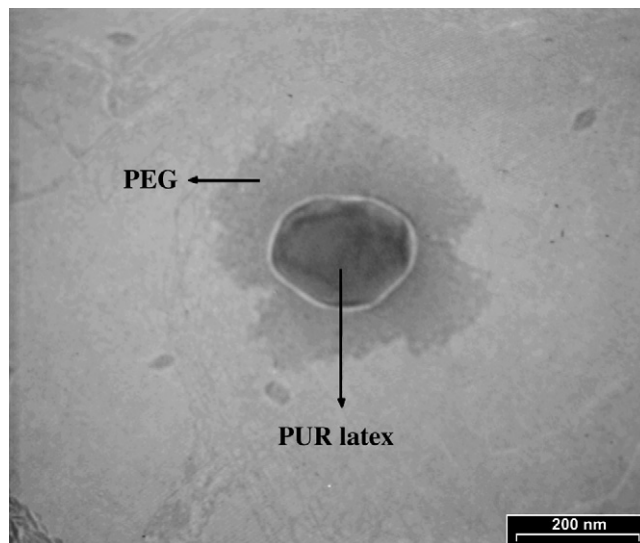


Fig. 7. TEM image of F10 formulation, prepared with PEG as co-monomer.

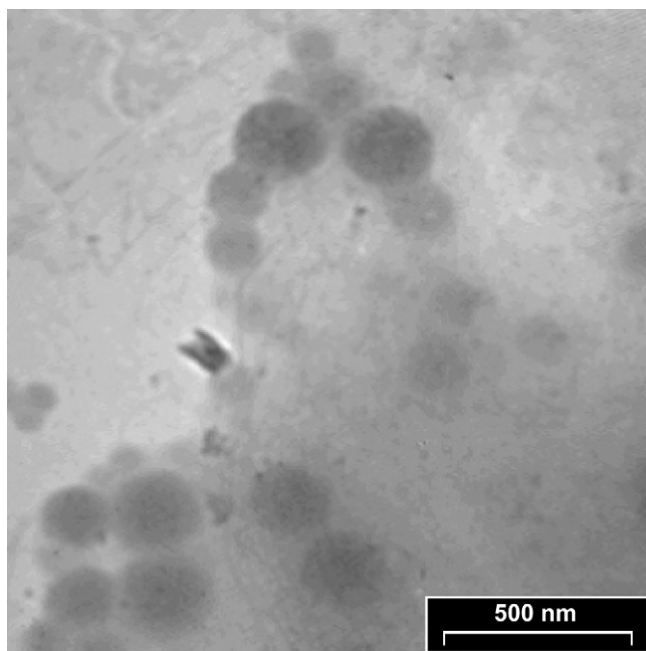


Fig. 6. TEM image of the polyurethane particles (F16) obtained by miniemulsion polymerization.

particles are in progress and the potentiality for encapsulation and degradation will be described in a forthcoming paper.

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