 DOI: 10.1002/masy.200551129

Use of Natural Monomer in the Synthesis of Nano- and Microparticles of Polyurethane by Suspension-Polyaddition Technique

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Summary: Polyurethane nano- and microparticles were synthesized by suspension-polyaddition technique, using aqueous polymerization medium. Castor oil, a vegetable triglyceride possessing hydroxyl groups was used as natural polyol and methylene diphenyl diisocyanate (MDI) as isocyanate. The levofloxacin, an antibacterial drug was used as model drug to measure the particles encapsulation efficiency. The effect of the addition of a second polyol, the poly(ethylene glycol) (PEG), and the stirring rate on the mean diameter and morphology of particles was also investigated. The poly(ethylene glycol) has an important effect in the reduction of particles size and their porosity. On the other hand, the poly(ethylene glycol) reduced the yield of encapsulation from 70% for the formulation without PEG to 20% for formulations with PEG. FTIR analysis confirmed the polyurethane formation. Dynamic light scattering study, transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were used to determine the nanoparticles size and shape. Spectrofluorimetric analysis was used to detect the levofloxacin.

Keywords: castor oil; microparticles; poly(ethylene glycol); polyurethanes; suspension-polyaddition

Introduction

Many techniques for the micro- and nanoparticles preparation involve synthetic polymers such as poly(ethylene oxide), poly(lactic acid), chitosan using several methods of preparation. In this paper we use the technique of suspension-polyaddition to synthesize polyurethane's micro- and nanoparticles. Polyurethanes (PU) are present in many aspects of modern life. They represent a class of polymers that have found a widespread use in medical, automotive and industrial fields.[1] This polymer has been employed as biomaterials due to its excellent physical properties and relatively good biocompatibility. Polyurethanes are obtained from the polycondensation or polyaddition of diisocyanates (hard segments with –N=C=O groups) and di- or polyols (soft segments with –OH groups).[2]

Efforts have been made to replace the expensive polyols with low cost natural vegetable oils or others derivatives in the production of urethane products. In this work, a natural vegetable oil, castor oil (CO), was used in the synthesis of polyurethane nano- and microparticles. Castor oil, a vegetable triglyceride possessing hydroxyl groups, extracted from *Ricinus communis L.* beans, appears to be a good polyol for the urethane synthesis. This oil contains 87–90% of ricinoleic acid (cis-12-hydroxyoctadec-9-enoic acid), the only common fatty acid bearing an OH group.

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CO is thus one of the few almost pure natural glycerides. The other minor non-hydroxylated fatty acids include: linoleic (9,12-octadecanoic ~ 4%) oleic (9-octadecenoic ~ 3%), stearic (octadecanoic ~ 1%) and linolenic (9,12,15-octadecatrienoic ~ 0,3%) acids. The triol group is responsible for the crosslinking in the tridimensional polyaddition of CO with diisocyanates.[3]

Degradability problems have incited researchers to investigate possible modification or production of chemically degradable polyurethanes. The results have shown that variations in the degradation patterns of polyurethanes are the results of the different properties of these polymers such as their topology and chemical composition.[1] The polyurethane used in this study is interesting because it was synthesized with a natural monomer and its potentiality to degradation aspects will be examined.

In suspension polyaddition, the monomer phase (which contains the monomers) is suspended in an immiscible polymerization medium in the form of small droplets. The polymerization medium may be an aqueous or organic liquid, and may contain the stabilizer. Following the formation of the desired droplet suspension, the polyaddition reaction is allowed to proceed and the monomer droplets are directly converted to the corresponding polymer particles.[4] In our case, the polymerization medium was water and it is a great advantage because it excludes the use of organic solvents. Polymerization in water is better for the environment, is more safe for many applications and the cost is low. The average size of particles produced by suspension polyaddition is controlled by stirring rate, type and concentration of stabilizer, volume ratio of the monomer to suspension medium and type of mixing.[4] In this work, we have also observed an important effect in the reduction particles size when the poly(ethylene glycol) was added as second polyol in the reaction. This will be also discussed in this contribution.

Materials

The monomers, methylene diphenyl diisocyanate (MDI) was obtained from BAYER (Germany), castor oil (Kehl Ind. LTDA, Brazil), poly(ethylene glycol) (PEG 400, Vetec LTDA, Brazil), DABCO 120 Catalyst (Air Products, USA). Levofloxacin, the model drug, was obtained from Henrifarma LTDA, Brazil. The surfactants sorbitan monooleate (Span 80) and poly(oxyethylene)(20)-sorbitane monooleate (Tween 80) were obtained from Beraca LTDA, Brazil. The solvents were distilled and ultra-pure water (Milli Q filter systems – Millipore, USA).

Methods

Synthesis of Polyurethane Particles

Polyurethane nano- and microparticles were synthesized by suspension-polyaddition technique in two steps (Figure 1): in the first step, a monomer phase was constituted by methylene diphenyl diisocyanate (4 g), a natural polyol, castor oil (6 g), a catalyzer organo-metalic (0.1 g) and Span 80 (1 g) as a lipophilic surfactant. When levofloxacin was encapsulated, it was added in the monomer phase (500 mg). The polymerization medium was the same for all formulations and it was constituted by 200 mL of distilled water containing Tween 80 (1 g), a hydrophilic surfactant. We used two surfactants, a lipophilic in the monomer phase and other hydrophilic in the polymerization medium to guarantee the emulsion stability. One notes that Tween 80 and Span 80 are approved for use in specific food products and are generally recognized as safe. They are well tolerated upon oral administration and are practically non-irritating, possessing very low potential toxicity. The use of two surfactants in the synthesis of polyurethane nanocapsules by interfacial polycondensation combined to spontaneous emulsification was described by Bouchemal and collaborators.[2]

In the second step, the monomer phase was suspended in the polymerization med-

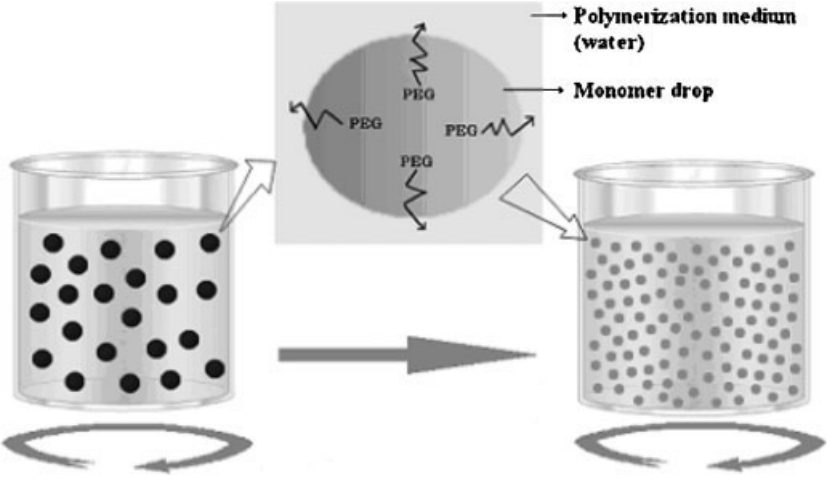

Figure 1.
Mechanism of particles preparation. Effect of poly(ethylene glycol) in the reduction of particles size.

ium under stirring at 1 000 rpm (magnetic stirring), 12 000, 16 000 or 20 000 rpm (Dispersor Extratur® -Mod. Q252, Quimis, Brazil). The magnetic stirring of 1 000 rpm was maintained during 3 h at room temperature in order to ensure the particles stability and formation.

The whole monomer concentration in the polymerization medium was 5% for all the tested formulation (about 10 g), MDI/Polyol (4:6). Also, the MDI to polyol ratio was unchanged, but PEG 400 ($M_w = 400$) was added as a second polyol in suspension varying from 0 to 30% (w/w), in concentration.

After suspension, the polymerization was followed for 3 h at room temperature under stirring. The stirring rate used during the preparation of particles was 1 000 rpm (magnetic stirring), 12 000, 16 000 and 20 000 rpm (Dispersor Extratur® stirring, for 5 min). The obtained formulations are listed in Table 1.

Table 1.
Composition, formulations parameters and yields of polyurethane particles.

Formulation	Monomeric phase	Polymerization medium	PEG %	Stirring rate	Yield %
F1	MDI:Polyol (4:6)	Water + Tween 80	0	1 000	94
F2	MDI:Polyol:PEG (4:5:1)	Water + Tween 80	10	1 000	96
F3	MDI:Polyol:PEG (4:4:2)	Water + Tween 80	20	1 000	95
F4	MDI:Polyol:PEG (4:3:3)	Water + Tween 80	30	1 000	90
F5	MDI:Polyol (4:6)	Water + Tween 80	0	12 000	93
F6	MDI:Polyol:PEG (4:5:1)	Water + Tween 80	10	12 000	97
F7	MDI:Polyol:PEG (4:4:2)	Water + Tween 80	20	12 000	96
F8	MDI:Polyol:PEG (4:3:3)	Water + Tween 80	30	12 000	98
F9	MDI:Polyol (4:6)	Water + Tween 80	0	16 000	90
F10	MDI:Polyol:PEG (4:5:1)	Water + Tween 80	10	16 000	92
F11	MDI:Polyol:PEG (4:4:2)	Water + Tween 80	20	16 000	97
F12	MDI:Polyol:PEG (4:3:3)	Water + Tween 80	30	16 000	98
F13	MDI:Polyol (4:6)	Water + Tween 80	0	20 000	95
F14	MDI:Polyol:PEG (4:5:1)	Water + Tween 80	10	20 000	94
F15	MDI:Polyol:PEG (4:4:2)	Water + Tween 80	20	20 000	93
F16	MDI:Polyol:PEG (4:3:3)	Water + Tween 80	30	20 000	98

Characterization

Fourier Transformed Infrared Spectroscopy (FTIR)

The polymer structure was confirmed by using Fourier transformed infrared spectroscopy (FTIR) in the attenuated total reflection (ATR) mode. The suspension of particles was deposed on an ATR crystal to form film and spectra were recorded using a Bruker – Tensor 27 spectrometer.

Particle Size

The particle size distribution of the obtained particles was measured by laser granulometry in a CILAS 1064 Liquid equipment. The accessible range of size of this technique is from 0.04 to 500 μm. The nanoparticles fraction of formulation was measured in an aqueous suspension by Zetasizer 1000/3000 (Malvern) and by dynamic laser light scattering (ALV-5000).

Dynamic Light Scattering

The samples solutions were prepared at high dilution of formulation (generally 40 times) in Millipore water. To eliminate dust and other large particles, all samples were further filtered on 0.2 μm cellulose filters prior to measurements.

The scattering measurements were performed at the temperature of $25 \pm 0.1\,^{\circ}C$ using an ALV apparatus equipped with an automatic goniometric table, a digital ratemeter and a temperature controlled sample cell. The scattered light was measured at different angles in the range of 60° at 120° corresponding to $1.96 \times 10^{-3} < q\ (\text{Å}^{-1}) < 3.3 \times 10^{-3}$ where $q = (4\pi n/\lambda_0)\sin(\theta/2)$; θ is the scattering angle, and n is the refractive index of the medium ($n = 1.33$). The full homodyne autocorrelation functions of the scattered intensity were obtained using the ALV-5000 autocorrelator. The intermediate dynamic scattering function $I(q,t)$ is related to the measured homodyne intensity-intensity time correlation function by the Siegert relation:[5]

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

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 Boltzman energy and η is the viscosity of the medium.

Particles Morphology

The shape, morphology and internal structure of microparticles were investigated by scanning electron microscopy (SEM) with a Philips XL 30 Microscopy at an accelerating voltage of 20 kV. The microparticles were fixed on a double stick tape in aluminum stabs and coated with gold.

The shape and the morphology of the nanoparticles fraction were also visualized by transmission electron microscopy (TEM) in a Jeol–JEM–2000FX equipment, 200 kV. The samples were prepared by placing a drop of preparation on a collodion support on cooper grids.[6]

Encapsulation Efficiency

In an attempt to determinate the encapsulation capacity of this systems, four formulations (F10, F11, F12 and F13) were chosen to encapsulate the levofloxacin, an antibacterial drug fluorescent, used as a model in this study. In solid form, levofloxacin is an odorless, white to yellow, crystallized powder with a melting point of 228.6 °C.[7] For encapsulation, the levofloxacin was added in the monomeric phase during the polyurethane particles synthesis.

The yield encapsulation was considered as the difference between the amount added in the formulation and the amount found in the supernatant after ultra centrifugation at 50 000 rpm for 2 h at 20 °C in a

Beckman–Optima™ TLX. The yield of encapsulation (Y) was calculated as follow:

$$Y = 100 - \left(\frac{C_s}{C_t} \times 100\right)$$

where C_s is the levofloxacin concentration found in supernatant after ultracentrifugation and C_t is the levofloxacin concentration added in the formulation.

Spectrofluorimetric Analysis

High-performance liquid chromatography (HPLC) with ultraviolet detection has been used for the analysis of levofloxacin in pharmaceutical applications. However, in this study, we have chosen the spectrofluorimetric detection because it is less complex, faster, organic solvents free and have good accuracy in the detection.[7]

Fluorescence intensity was measured using a Safas Monaco spectrometer. All the measurements took place in a plastic cell with 10 nm bandwidths for the emission and excitation monochromators.

The levofloxacin did not show the linear correlation between concentration and fluorescence intensity for all concentrations and therefore it was very important to determinate the linear range of concentration for the calibration curve.

Stock standard solution of 400 $\mu g \cdot ml^{-1}$ was prepared dissolving levofloxacin in a mixture of high pure water and ethanol (97:3). A sample of 10 $\mu g \cdot ml^{-1}$ was prepared by dilution of stock standard solution with high pure water. The calibration graph of fluorescence intensity *vs* levofloxacin concentration expressed in $\mu g \cdot ml^{-1}$ was found to be linear in the range 0.1–10 $\mu g \cdot ml^{-1}$, at pH = 7 and 25 °C. The fluorescence was measured at 450 nm using an excitation wavelength of 350 nm against a blank solution. The pH was measured on a Metiler Toledo MP120 pH-meter.

Results and Discussion

Suspension-Polyaddition Reaction and Particle Characterization

PU aqueous suspension was prepared in two steps by the suspension-polyadditon technique. The polymerization reaction can be briefly described as follows.[8] In the first reaction (1), isocyanate groups (a) react with hydroxyl groups of castor oil or PEG 400 (b) to form the PU chains. In a secondary reaction (2), isocyanate groups can react with water by diisocyanate diffusion to the aqueous phase forming an amino acid group (c), which is unstable and dissociates into a chain with amine end-group and carbon dioxide (d). The carbon dioxide formation in this reaction contributes significantly to the porosity of microspheres.[8]

Polymerization reaction by polyurethane formation (1)

(a) O=C=N-R-N=C=O +

(b) OH-R-OH or

$$\text{CH}_2\text{–R–OH}$$
$$\text{-[|-C(O)N(H)-R-N(H)C(O)O-R-O-]}_n\text{–}$$
$$\text{CH}_2\text{–R–OH}$$
$$|$$
$$\text{CH}_2\text{–R–OH}$$

Secondary Reaction, Isocyanate Groups React with Water (2)

$$-\text{N=C=O} + \text{H}_2\text{O} \rightarrow -\text{NH–COOH (c)}$$
$$\rightarrow -\text{NH}_2 + \text{CO}_2 \text{ (d)}$$

The completion of polyaddition reaction between MDI and polyol or MDI and polyol/PEG400 was confirmed by ATR-FTIR analysis. ATR-FTIR spectra of polyurethane particles are presented in Figure 2. A strong absorption band with peak location at 2 272 cm^{-1}, due to N=C=O stretching vibration of the isocyanate groups, was used to identify MDI. A comparison of IR spectra of the reactants and the resulting products shows the disappearance the isocyanate group after the reaction (peak at 2 272 cm^{-1}). The amide vibration at 3 300 cm^{-1}, the carbonyl vibration at 1 729 cm^{-1} and the C–N vibration at 1 534 cm^{-1} are strong evidence

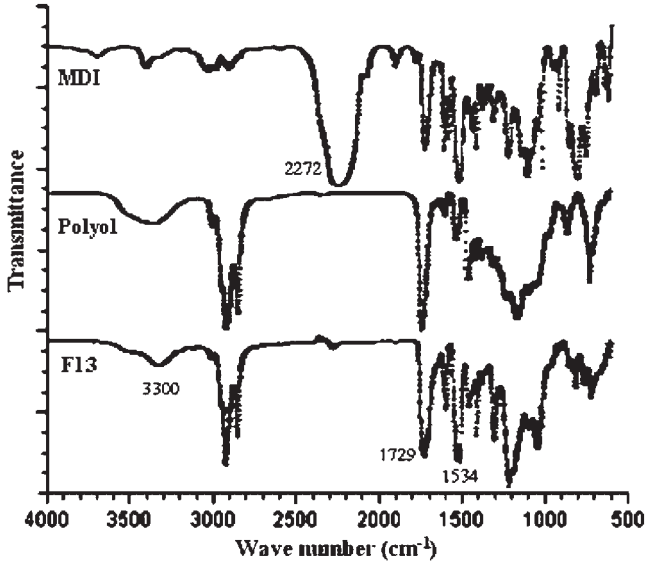

Figure 2.
ATR-FTIR absorption spectra of the MDI, polyol (castor oil) and polyurethane particles (F13) prepared by suspension-polyaddition technique.

for the formation of a polyurethane particles.

Particle Size Distribution

Analysis by Laser Granulometry

The formulations were analyzed by laser granulometry and the results are listed on Table 2.

Formulations F1, F5 and F9, that do not contain PEG, showed particles with size larger than 500 μm, and were not analyzed by this technique.

This table shows that the particles of polyurethane prepared by suspension-polyaddition technique have a large size distribution. There are micro- and nanoparticles in the same formulation.

The average size of the polyurethane particles produced by suspension-polyaddition technique can be controlled by, among other factors, the type and concentration of

Table 2.
Laser granulometry results.

Formulation	Diameter at 50%	Diameter at 90%	Average diameter	Size range
	μm	μm	μm	μm
F2	45.4	142.1	64	0.07–400
F3	96.6	228.6	110	0.04–400
F4	83.0	227.8	103.9	0.04–400
F6	77.8	142.1	79.5	0.04–240
F7	45.1	89.2	48.4	0.20–140
F8	22.3	79.2	32.7	0.04–140
F10	16.5	40.0	19.3	0.04–71
F11	2.6	13.7	5.4	0.04–45
F12	3.5	14.4	5.3	0.04–36
F13	27.8	138.5	52.4	0.07–300
F14	51.7	108.3	55.7	0.07–180
F15	26.4	77.6	34.4	0.04–140
F16	12.3	60.0	22.9	0.04–112

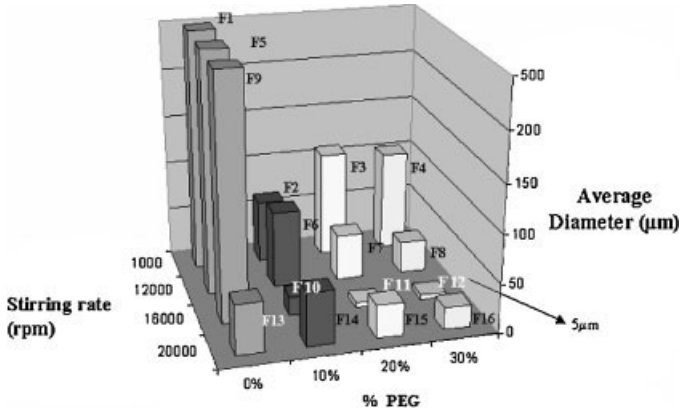

Figure 3.
Effect of stirring rate and addition of poly(ethylene glycol) on the average diameter of polyurethane particles.

stabilizer, volume ratio of the monomer to polymerization medium, and the stirring rate.[4]

In this work, we will show that the particle size can be also modulated by the addition of PEG in the monomer phase. The addition of increasing amounts of PEG reduced significantly the mean diameter of particles from 400 to 5 μm (Figure 3). It is also shown that the increasing of stirring rate contributes to particle size reduction. However, when PEG was not added to the formulations, a stirring rate of 20 000 rpm was needed to obtain particles presenting sizes around 50 μm.

This effect is related to the nature of PEG. The PEG is a hydrophilic polymer and it has a tendency to diffuse in aqueous phase (polymerization medium) breaking the monomer drops and therefore reducing the size of the particles.

The best formulations, those with smaller size particles, were chosen for the next studies.

These formulations are: (i) F10 made with 10% of PEG 400 and 16 000 rpm stirring rate, (ii) F11 made with 20% of PEG and 16 000 rpm, (iii) F12 made with 30% of PEG and (iv) 16 000 rpm and F13 made without addition of PEG and 20 000 rpm.

The stirring rate of 16 000 rpm was the more efficient in the production of nanoparticles. When the PEG was not added in to formulation, a stirring rate equal to 20 000 rpm was needed to reduce the particles size. The stirring rate is as important parameter in the microparticles preparations using several techniques and normally, the size particle is reduced with the increase of stirring rate.[9]

Light Scattering Technique

A sample of F10, F11, F12 and F13 with and without levofloxacin was diluted 40 times and filtered using membrane filters with 0.22 μm of porous. Table 3 shows the mean diameter of nanoparticles and polydisper-

Table 3.
Mean diameter and polydispersity index of particles using Zetasizer.

Formulation	Without levofloxacin		With levofloxacin	
	Average diameter nm	Polydispersity index	Average diameter nm	Polydispersity index
F10 (MDI:P:PEG, 4:5:1)	93.4 ± 2.40	0.430 ± 0.06	106.5 ± 0.7	0.447 ± 0.01
F11 (MDI:P:PEG, 4:4:2)	84.9 ± 0.60	0.441 ± 0.02	110.5 ± 0.20	0.368 ± 0.02
F12 (MDI:P:PEG, 4:3:3)	123.8 ± 1.20	0.258 ± 0.03	115.1 ± 1.00	0.272 ± 0.09
F13 (MDI:P, 4:6)	130.3 ± 0.60	0.278 ± 0.03	109.5 ± 2.10	0.354 ± 0.02

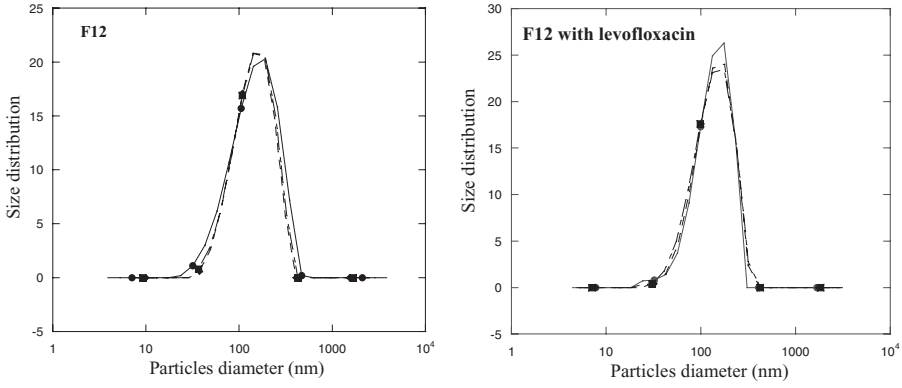

Figure 4.
Particles diameter of F12 nanoparticles with and without levofloxacin.

sity index of the formulations obtained using Zetasizer at 90°.

The addition of levofloxacin appears not to affect the particle sizes. Figure 4 shows the F12 and F12 with levofloxacin obtained using Malvern. All measures were made three times.

To go further in the analysis we have chosen the formulation prepared from 30% of PEG and stirring rate of 16 000 rpm to carry out dynamic light scattering at different scattering angles. The particle suspension was filtered through a 0.22 μm cellulose membrane. Measurements were carried out at angles of 60° and above, to minimize the possible influence of dust particles that may have survived the filtration process.

The filtered suspension showed hydrodynamic radii around 12 and 70 nm, which confirm the presence of a fraction of nanoparticles in the formulation (Figure 5). These results are in very good agreement with these obtained using Zetasizer.

A typical autocorrelation function obtained at scattering angle $\theta = 60°$, 90° and 120° is displayed in Figure 6. The dots

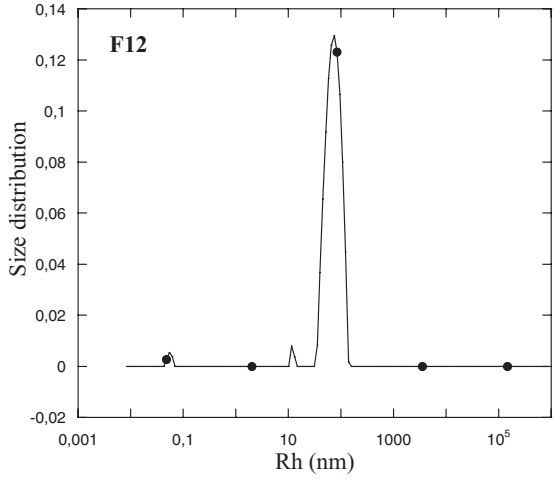

Figure 5.
Hydrodynamic radius (nm) of polyurethane nanoparticles.

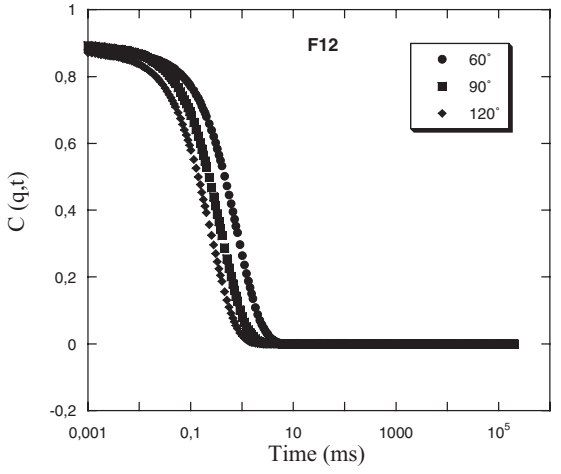

Figure 6.
Typical autocorrelation function measured at 25 °C at $\theta = 60^\circ$, 90° and 120°.

represent the experimental data. This Figure shows that the autocorrelations functions are essentially represented by a single exponential decay.

The angular variation of these frequencies $\Gamma = 1/\tau_s$ measured shows a q^2 behavior indicating a diffusive motion.[10] Figure 7 illustrates this linear behavior where it is plotted Γ vs q^2.

Morphology Analysis

Microparticles Morphology

The shape, morphology and internal structure of PU microspheres were investigated using SEM. The micrographs obtained by SEM from polyurethane microparticles prepared from 0 and 10% of PEG 400 are visualized in Figure 8(a) and (b), respectively. Spherical particles were obtained in both formulations, and the porosity of particles is increased as the PEG is added in the monomer phase. Poly(ethylene glycol) acts as porous former in the polymeric matrix. This has an important effect in controlling the release rate of active agents encapsulated in the particles.[13] The porous formation in PU microparticles can be attributed the CO_2 formation during PU synthesis reaction.[8] However, in our study, the formulation F13, prepared without PEG addition did not show any porosity and this can be a strong evidence that the PEG is responsible for porous particles. In the literature, the formation of carbon dioxide in the PU synthesis by the reaction between isocyanate and water contributes significantly to the porosity of microspheres.[8] In this work, the absence of porosity in PU particles prepared without PEG (F13) did not show any evidence of secondary reaction between isocyanate and water [see Figure 8(a)].

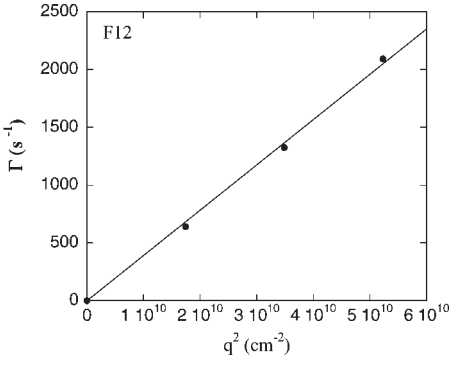

Figure 7.
Γ vs q^2 for F12 formulation.

Figure 9 shows the F12 formulation, prepared with 30% PEG 400, stirring rate

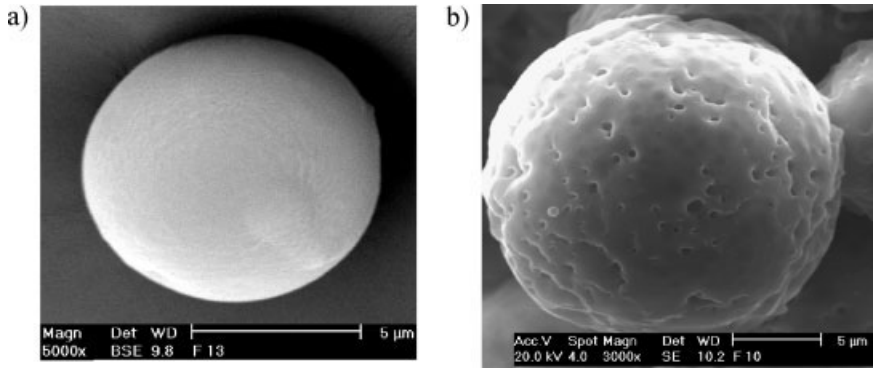

Figure 8.
Scanning electronic micrographs of polyurethane microparticles obtained with (a) 0% PEG and stirring rate of 20 000 rpm and (b) 10% PEG and stirring rate of 16 000 rpm.

16 000 rpm and levofloxacin. The microparticles were transversally sectioned and the internal structure reveals the levofloxacin crystals encapsulated into the particles.

Nanoparticles Morphology

The supernatant of formulations was diluted and analyzed by transmission electron microscopy (TEM). The samples were prepared as described in 3.3.3. Figure 10 shows the TEM micrograph of the F12 formulation.

The TEM micrographs reveal that nanoparticles fraction of F12 formulation is also constituted by spherical particles (a). Figure 10(b) shows that polidispersity. This observation is in agreement in the size with laser granulometry results that showed that the formulations of polyurethane prepared by suspension-polyadditon technique have a large size distribution.

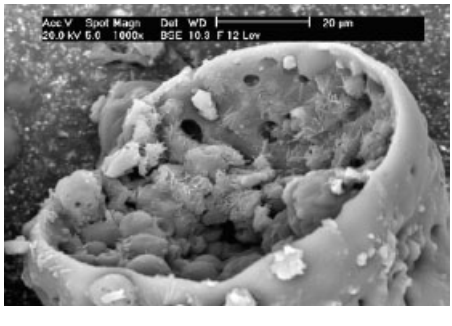

Figure 9.
SEM micrograph of a microsphere prepared with 30% PEG 400, stirring rate of 16 000 rpm (F12) containing levofloxacin. Magnification of 1 000×.

Encapsulation Efficiency

The better formulations F10, F11, F12 and F13 were also chosen to encapsulate levofloxacin. The levofloxacin was added in the monomer phase during the synthesis procedure.

The evaluation of drug loading in the particles needed to examine particles with and without levofloxacin. The separation technique most widely used by researchers is ultracentrifugation.[11,12] The formulations containing levofloxacin was ultracentrifuged and the levofloxacin non-encapsulated into the particles was studied by fluorescence spectroscopy as described in 3.3.4 and 3.3.5.

The calibration graph of fluorescence intensity (Y) vs levofloxacin concentration (X) expressed in $\mu g \cdot ml^{-1}$ is shown in Figure 11.

Table 4 shows the encapsulation efficiency of PU particles synthesized by suspension-polyaddition.

Table 4 shows the interesting effect of the encapsulation efficiency reduction as a function of poly(ethylene glycol) addition. The formulation F13 constituted by MDI and polyol (castor oil) showed yield of encapsulation near 70%. When the PEG

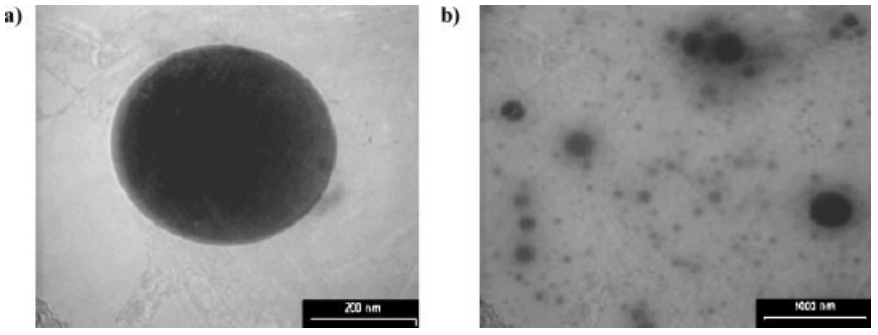

Figure 10.
TEM micrographs of F12 formulation. (a) scale corresponds to 200 nm, (b) scale corresponds to 1000 nm.

400 was added as second polyol in the formulation F10, F11 and F12, the yield of encapsulation was reduced to 20%.

This phenomena was observed in our other study[13] and can be explained by the fact that poly(ethylene glycol) can act as co-solvent that increases the solubility of levofloxacin and contributes for its partition in aqueous phase (polymerization medium) and consequently reducing the encapsulation efficiency.

Table 4.
Encapsulation efficiency of polyurethane particles.

Formulation	Levofloxacin in supernatant	Encapsulation efficiency
	%	%
F13 (MDI:P, 4:6)	31.16	68.84
F10 (MDI:P:PEG, 4:5:1)	80.56	19.44
F11 (MDI:P:PEG, 4:4:2)	78.64	21.36
F12 (MDI:P:PEG, 4:3:3)	79.36	20.64

Conclusion

Micro- and nanoparticles of polyurethane based on natural polyol, castor oil, were synthesized by suspension polyadditon technique, using poly(ethylene glycol) as second polyol, Tween 80 and Span 80 as surfactants and water as polymerization medium. The advantage of this method was the not-use of organic solvents and the use of castor oil as polyol.

The nanoparticles formation was confirmed by ATR-FTIR analysis. The absence of isocyanate absorption band at 2 300 cm^{-1} confirms that isocyanate groups reacted. Microscopy analysis shows spherical and porous microparticles (SEM) also observed by TEM and quantified in solution using dynamic light scattering.

Important effects were associated with PEG addition. We observed that poly-(ethylene glycol) reduces the particles size and increases the porosity of the particles. This effect is related with its hydrophilic nature and tendency to migrate to aqueous phase. However, the PEG addition is responsible also for the reduction in the particles encapsulation efficiency. PEG acts as co-solvent for the levofloxacin, contributing for its partition in aqueous phase (polymerization medium) and consequently reducing the encapsulation efficiency of the particles.

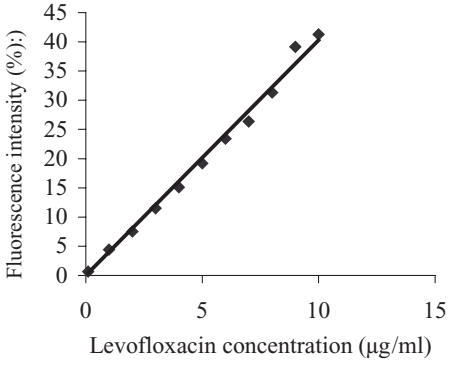

Figure 11.
Calibration graph of levofloxacin.

Studies of enzymatic degradation of these formulations are in progress and the potentiality for degradation will be described in a forthcoming paper.

Acknowledgements: This work was supported by the Alban Program, the European Union Program of High Level Scholarships for Latin America, n. E04D044566B, CAPES/Brasil and Rede Nanobiotec/CNPq/Brasil.

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