

# Development of Polycaprolactone/Poly(Vinyl Alcohol)/Clay Microparticles by Spray Drying

Mariana Sato de S. de B. Monteiro<sup>1,2</sup>, Claudia Lopes Rodrigues<sup>1</sup>, Eduardo Miguez<sup>1</sup>,  
Maria Inês B. Tavares<sup>1\*</sup>

<sup>1</sup>Instituto de Macromoléculas Professora Eloisa, Universidade Federal do Rio de Janeiro, Centro de Tecnologia, Bloco J, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, Brazil

<sup>2</sup>Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Bloco L, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, Brazil

Email: \*mibt@ima.ufjf.br

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## Abstract

In this study, nanostructured microparticles was developed with polycaprolactone (PCL), poly(vinyl alcohol) (PVAL) and nanoparticles of the commercial sodium clay NT-25<sup>®</sup> by using the spray drying technique. The systems obtained were characterized by Nuclear Magnetic Resonance (NMR), Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD), Dynamic Laser Light Scattering (DLS) and Differential Scanning Calorimetry (DSC). The NMR <sup>13</sup>C and FTIR techniques showed that both polymers were present in the microparticles and the DSC analysis revealed a small variation in the glass transition temperature of the PCL. The XRD and SEM analyses showed that the microparticles produced were amorphous and had a concave morphology. The NT-25 nanoload reduced the microparticles' size due to the multiple interactions formed in the hybrid nanocomposite material. Therefore, it was possible to develop microparticles by using biodegradable and biocompatible polymers, with different polarities, allowing the incorporation of hydrophilic and hydrophobic materials and enabling the inclusion of otherwise incompatible materials in the same system.

## Keywords

Microparticles, Spray Drying, Polycaprolactone, Poly(Vinyl Alcohol), Sodium Clay NT-25

## 1. Introduction

The microparticles are micrometric systems, ranging from 1  $\mu\text{m}$  to 1000  $\mu\text{m}$ , which have been widely studied and employed in the medical and pharmaceutical areas, par-

ticularly when they are developed with biodegradable polymers, due to its safety and biocompatibility [1]-[5]. Their main advantages are drug protection, mucoadhesion, gastroresistance, and controlled drug release, reducing the dose and frequency of drug administration, obtaining the same therapeutic effect with reduced adverse local and systemic effects and toxicity [6] [7]. Polycaprolactone (PCL) is a biodegradable polymer widely used in the development of microparticles due to its high stability, and permeability, biocompatibility with various drugs, low toxicity and low degradation rate. Its melting temperature varies from 59°C to 64°C, and its glass transition temperature is about -60°C [8]-[11]. Poly(vinyl alcohol) (PVAL) is an amphiphilic semicrystalline polymer, with good interfacial adsorption capacity, and for this reason PVAL has been used in the production of emulsions and microparticles, acting as an emulsifier, to increase the physical stability of microparticles and to encapsulate different drugs. Furthermore, it has low toxicity and it is biodegradable. Its glass transition temperature is around 75°C and its melting temperature is around 150°C [12]-[15].

A good deal of recent research has been devoted to the development of nanostructured materials containing inorganic fillers dispersed in a polymer matrix. However, these new nanostructured materials must be tested for safety and effectiveness. Among nanoparticles, montmorillonite clay is safe for biomedical applications, since this clay is already used in pharmaceutical preparations [16]-[18]. Bentonite is plastic clay consisting mostly of montmorillonite, a natural clay of the smectite group. It is a type 2:1 lamellar silicate (2 silicon tetrahedrons:1 aluminum octahedron) having the general formula  $[M_x (Al_x-4Mg_x) Si_8O_{20} (OH)_4]$ , where M is a monovalent cation and x is the isomorphous substitution degree (0.5 to 1.3). Regarding its microstructure, the lamellae have diameters between approximately 100 - 200 nm and thickness of 1 nm. This clay is used as a functional excipient in tablets due to its ability to form gels at low concentrations by swelling in water, and it is also used as a binder and disintegrant [19] [20]. For these reasons, bentonite is often employed to produce nanostructured microparticles.

There are several studies in literature that describe the development of polymer/clay system, most of them are nanocomposites. Thus, it is relevant to comprise the clay effect in the PCL and PVAL matrix. The clay dispersion in PCL matrix generally decreases the crystallinity and the crystallite size, because of the dispersed silicate layers that represent a physical barrier and hinder PCL crystal growth. A small clay dispersion, less than 5 wt%, in the PCL matrix is able to reduce its water permeability, increase its stiffness and ductility and improve its thermal stability. Moreover, PCL can exhibit a "pseudo solid-like" behavior at silicate loading greater than 3 wt%, suggesting the maintenance of long-range order domains and a clay orientation in some directions [21]. The clay dispersion in the PVAL matrix can increase the mechanical, thermal and gas barrier properties when its content ranges from 3 wt% to 10 wt%. It was also noticed that up to 5 wt% clay loading, clay particles were highly dispersed in PVAL matrix without any agglomeration. However, some agglomerated structures were formed in the polymer matrix above a 7 wt% clay concentration [22] [23].

Nevertheless, there are no reports of the development of nanostructured micropar-

ticles containing PCL, PVAL and clay particles. However, Dong & Feng developed nanostructured nanoparticles of Poly(D, L-lactide-co-glycolide)/montmorillonite (PLGA/MMT) by emulsion/solvent evaporation method. It was observed that the MMT played the role of a co-emulsifier and the nanoparticles presented a mean size of around 310 nm [24]. Dyab *et al.* developed core/shell hybrid organic-inorganic polymer microspheres, using polystyrene and laponite nanoparticles. The formed emulsion showed excellent stability against droplet coalescence and against microparticles coagulation. Generally, the number of microparticles increased and their size decreased with the content of laponite particles, ranging from 1% to 4%, used in stabilizing and it was attributed to the formation of a rigid layer of the inorganic nanoparticles around the microparticles, increasing the stability [25].

Several methods can be applied to produce polymeric microparticles, such as: 1) Oil/water emulsion extraction/evaporation method, where a required amount of polymer is dissolved in an organic phase which is emulsified under stirring to form an emulsion and to evaporate the organic phase; 2) Spray dryer technique, where the organic solution with dispersed polymers is sprayed through a nozzle in a spray dryer under different experimental conditions; 3) Solution-enhanced dispersion method, the microparticles were prepared by spraying a solution of polymer in mixture of carbon dioxide and organic solvent into air was termed as rapid exposition of supercritical solutions. As an alternative, the organic polymer solution could be atomized into a vessel containing pressed carbon dioxide; and 4) Hot melt technique, where polymers with low melting point were fabricated into microspheres by hot melt technique [26] [27].

In choosing among them, simplicity, reproducibility and yield should be considered. The emulsification/solvent evaporation technique is widely used in the preparation of microparticles and allows the incorporation of hydrophilic and hydrophobic drugs. However, one of the restrain factors of this technique is the system homogenization, which is typically carried out mildly, for 3 hours at 500 rpm, to form the microparticles by the solvent's evaporation at the interface, causing the polymer to precipitate [4] [6]. In this context, this work initially used oil/water emulsion extraction/evaporation method, and then used a high speed mixing to emulsification, in order to achieve a narrow particle size distribution. The spray drying technique has been used after the emulsification process to promote solvent removal and form microparticles, in a shorter time. This method has many advantages, such as good reproducibility, control of particle size and less dependence on the solubility of the active ingredient in the polymer. However, this technique still has limitations, especially for hydrophobic polymers with low melting point, such as PCL [28]-[31].

The main objective of this study was to produce nanostructured microparticles of PCL/PVAL containing a commercial sodium clay (NT-25<sup>®</sup>) as the nanoparticle, using the emulsification process followed by spray drying. The second objective was to characterize the systems by using nuclear magnetic resonance, scanning electron microscopy, infrared spectroscopy, differential scanning calorimetry, X-ray diffraction and dynamic laser light scattering.

## 2. Experimental

### Materials

The following polymers were used to produce the microparticles:

- 1) polycaprolactone, obtained from Sigma Aldrich, with melt index of  $1.9 \pm 0.3$  g/10 min (ASTM D-1238), density of  $1.14 \text{ g/cm}^3$  and numerical molar mass ( $M_n$ ) of 80,000 g/mol;
- 2) poly(vinyl alcohol), obtained from Vetec, with hydrolysis degree of 88.3% and numerical molar mass ( $M_n$ ) of 4060 g/mol; and
- 3) sodium clay NT-25, obtained from Bentonit União Nordeste. This clay is a natural calcium bentonite, without the presence of organic modifier, with surface area of  $139 \text{ m}^2\cdot\text{g}^{-1}$  and cation exchange capacity (CEC) of 0.8 meq/g. It has inter-layer spacing (d 001) equal to 1.51 nm [32].

The solvent used was chloroform P. A., obtained from Tedia Brasil. The other reagents employed were of analytic grade and were used as received.

### Methods

#### *Preparation of microparticles*

In the first step, in order to make a primary emulsion 5% w/v of PCL was dissolved in chloroform, under magnetic stirring with stir bar of 2.5 cm, at 500 rpm, for 24 hours, at  $25^\circ\text{C}$ , until former a clear solution. In the second step, to be used as outer aqueous phase 5% w/v of PVAL was dissolved in distilled water and stirred with a magnetic stirrer of 2.5 cm, at 500 rpm, at  $60^\circ\text{C}$  until completely dissolved. Then, when the temperature was around  $25^\circ\text{C}$ , the aqueous phase was poured into the organic phase, under magnetic stirring; at 800 rpm, for 30 minutes, in a flask of 500 ml, to form an initial emulsion system. The systems were prepared in triplicate and separated into three fractions. The initial magnetic stirring is still a technique applied for the development of microparticles, in the research field.

The first fraction was submitted to spray drying in an LM 1.0 MSD (mini spray dryer) (LabMaq do Brasil, São Paulo, Brazil), under the following operating conditions: feed flow of 3.3 ml/min; air flow of 500 l/h; air pressure of  $3 \text{ kgf/cm}^2$ , inlet temperature of  $110 \pm 4^\circ\text{C}$ ; outlet temperature of  $95 \pm 5^\circ\text{C}$ ; atomizer nozzle diameter of 1.0 mm; and vacuum formation rate of  $0.6 \text{ m}^3/\text{min}$ . This first sample was named PCL/PVAL.

The second fraction was homogenized using an Ultra-Turrax® (UT) high-power homogenizer for 2 minutes at 16,000 rpm, at  $25^\circ\text{C}$ , forming a more stable emulsion. Then this emulsion was dried using the same spray dryer, with the conditions described above. This sample was named PCL/PVAL/UT.

For the third fraction, 3% w/w of sodium NT-25 clay was added to the organic phase, followed by 48 hours of stirring, at  $25^\circ\text{C}$ . Then, the aqueous phase was dispersed in the organic phase containing the clay, and this mixture was homogenized in the UT for 2 minutes at 16,000 rpm, forming an emulsion. This emulsion was dried using the mini spray dryer under the conditions described above. This sample was named PCL/PVAL/NT-25/UT. The clay was not sprayed in the system that are used the magnetic agitation, because the system did not form a homogenous emulsion with magnetic stirring.

The concentration of PCL, PVAL, clay and solvents used were chosen according to previous studies in the literature, since the main objective of this work was to verify whether the proposed method was effective in developing nanostructured particles. However, it is recommended to developed stable microparticles, by the emulsion method, using around 2 to 10 wt% of polymer in the organic phase. The variation in PVA concentration will affect the stability of emulsion and the size of the microspheres. More uniform sized and small microspheres are obtained on the concentration of PVA, varying from 2.5 wt % to 5 wt% [33].

Clay is a stabilizing, suspending, adsorbent and viscosity increasing agent and the amount recommended for NT-25 clay acts as a stabilizing agent, ranging from 0.5% to 5% [18]-[20]. Besides, the PCL nanocomposites developed with NT-25 clay, ranging from 1% to 5%, showed that 3 w/w % of NT-25 achieved the best dispersion in the polymer matrix [34].

#### *Characterization of the microparticles*

##### **Nuclear magnetic resonance**

The  $^{13}\text{C}$  NMR analyses were performed at 300 MHz with a Varian Mercury VX 300 spectrometer. The procedures used to obtain the spectra and analytic parameters are described below: For  $^{13}\text{C}$  NMR analysis, the PCL, PVAL and the microparticles were prepared in the following solutions: 100 mg of PCL in 2 ml of deuterated tetrachloroethane (TCE); 100 mg of PVAL in 2 mL of deuterated water ( $\text{D}_2\text{O}$ ); and approximately 100 mg of microparticles in 2 ml of deuterated dimethyl sulfoxide (DMSO). The samples were placed in a NMR tube (10 mm in diameter) and then in a 10 mm probe.

The parameters used in the  $^{13}\text{C}$  analysis were observation frequency of 75 MHz, analysis temperature of  $90^\circ\text{C}$ , 8000 accumulations, pulse width applied ( $90^\circ$ ) equal to 23.4  $\mu\text{s}$ , interval between pulses of 1 second and spectral window of 18,000 Hz. The peak areas in the microparticles'  $^{13}\text{C}$  spectra were integrated, allowing calculation of the proportion of each polymer in the developed system [35] [36].

##### **Infrared spectroscopy**

The FTIR analyses were performed in attenuated total reflection mode (ATR), in order to identify the main functional groups, using a Thermo Scientific Nicolet™ iS™ 10 FTIR spectrometer, in a scanning range of  $4000 - 675 \text{ cm}^{-1}$ , collection time of 25 seconds, with 128 scans and normal resolution spectrum. The reference material (calibration) used in the ATR analysis was a germanium crystal and the samples were placed on both sides of the crystal [37] [38].

##### **X-ray diffraction**

The X-ray diffraction evaluations of the crystalline structure and dispersion of the clay in the nanoparticles were carried out at room temperature with a Rigaku Miniflex X-ray diffractometer, with emission of  $\text{CuK}\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ), 40 KV and 30 mA. The diffraction patterns were collected in a scanning range of  $2^\circ < 2\theta < 30^\circ$ , for 3 seconds at steps of  $0.05^\circ$  [37] [38].

##### **Differential scanning calorimetry**

The miscibility between the PCL and PVAL was evaluated by DSC using a TA In-

struments Q1000 V9.8 Build 296 calorimeter, operating under N<sub>2</sub> flow of 50 mL/min, with a heating rate of 10°C/min, in the range from -70°C to 150°C for PCL, from 25°C to 270°C for PVAL and -70°C to 260°C for the PCL/PVAL microparticles [37].

#### Scanning electron microscopy

The surface texture and shape of the microparticles were observed by SEM with a Jeol JSM-5610 LV scanning microscope. The samples were previously sputtered with gold for 20 seconds (Denton Vacuum Desk II) and the photomicrographs were obtained using voltage of 20 kV and 4000 to 8000 x magnification [11] [12].

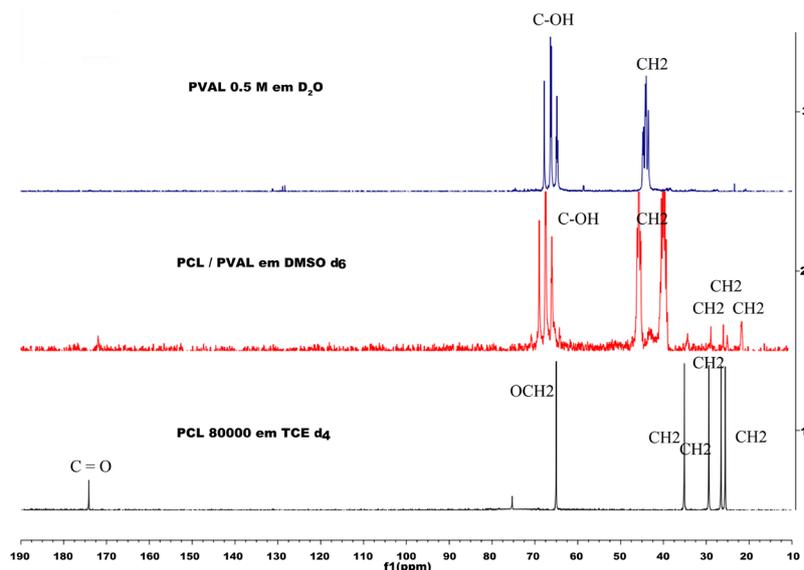
#### Dynamic laser light scattering

The average diameter of the particles was determined after their dispersion in distilled water at a concentration of 1:1000. The diameter was measured in a Brookhaven multi-angle particle sizer, with detection angle of 90°, in a quartz cell with 1 cm optical path, and the data were integrated using the MAS OPTION software [11] [12].

### 3. Results and Discussion

Nuclear magnetic resonance is a spectroscopy that analyzes the nuclear spin movement and behavior in the presence of a strong external magnetic field. From this spectroscopy it is allowed to analyze different nuclei in a sample, employing a specific sequence of pulses. The NMR spectroscopy is widely used to study the chemical assignments and molecular dynamics of various types of materials detected through the intermolecular interaction, dispersion and the distribution of their components [37]-[39]. The solution <sup>13</sup>C NMR spectrum allows identifying the different types of carbon in samples, facilitating study of the microstructure of microparticles [40] [41].

The <sup>13</sup>C NMR solution spectra of PCL, PVAL and microparticles produced are presented in **Figure 1**. Analyzing the <sup>13</sup>C NMR solution spectrum of the PCL, carbonyl



**Figure 1.** NMR spectra of <sup>13</sup>carbon in solution of the polymers PCL, PVAL and PCL/PVAL microparticles.

group presents its chemical shift located at 174 ppm, the OCH<sub>2</sub> group (I) at 65.2 ppm, the CH<sub>2</sub> group (II) at 35.2 ppm, the CH<sub>2</sub> group (III) at 29.5 ppm, the CH<sub>2</sub> group (IV) at 26.7 ppm and the CH<sub>2</sub> group (V) at 25.7 ppm [42]. The spectrum of the PVAL showed two signals in the one referrer to the C-OH group located at 68.4 ppm and the other one due to the CH<sub>2</sub> group at 45.3 ppm [43].

The <sup>13</sup>C NMR solution spectrum of the microparticles presented peaks characteristic of both PCL and PVAL. The peaks with chemical shifts at 174 ppm, 35.2 ppm, 29.5 ppm, 26.7 ppm and 25.7 ppm correspond to the carbonyl, CH<sub>2</sub> group (II), CH<sub>2</sub> group (III), CH<sub>2</sub> group (IV) and CH<sub>2</sub> group (V) of the PCL, respectively. In turn, the peaks with chemical shifts located at 68.4 ppm and 45.3 ppm correspond to the C-OH and CH<sub>2</sub> PVAL groups, respectively. However, the peaks corresponding to the chemical shift of the functional groups of the PCL were less intense than the peaks of the PVAL, due to the lower ratio of PCL in the microparticles.

By integrating the areas under the peaks of the microparticles in the NMR <sup>13</sup>C spectra, it was possible to confirm the proportion of each polymer in the system, as reported in **Table 1**. The proportion of PCL in the system was about 10%, with PVAL making up the other 90%. All the samples produced presented similar results. The proportion of each polymer in the systems can be correlated with its thermal properties and with the processing method used.

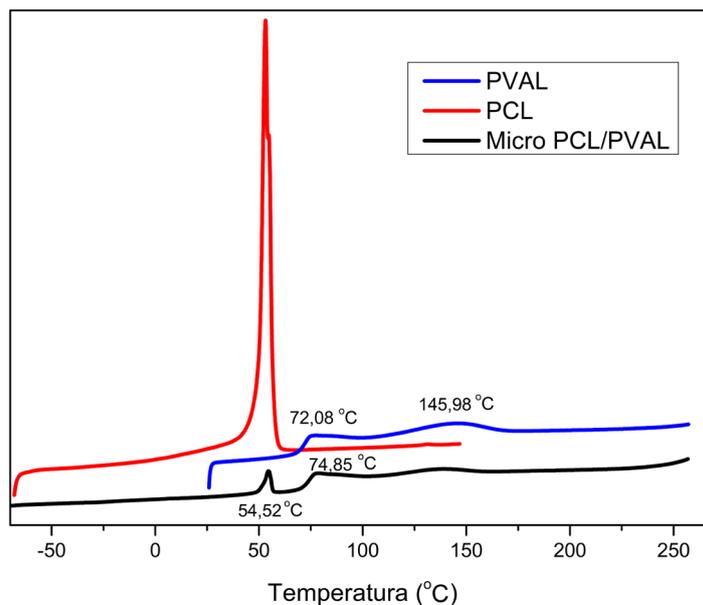
#### DSC Measurements

PCL has a glass transition temperature (T<sub>g</sub>) of around -70 °C and melting temperature (T<sub>m</sub>) of about 55 °C while PVAL has a T<sub>g</sub> near 75 °C and T<sub>m</sub> of about 150 °C, as can be seen from analyzing the DSC spectra in **Figure 2**. In the spray drying process, the incoming air temperature was 110 °C, set at this level to promote proper dehydration of the material. PVAL has a higher melting point than the air temperature used in the drying process, so it was not in the melted state during the drying process, causing it to have lower propensity to stick together or adhere to the surfaces of the drying chamber. In contrast, PCL's melting point is lower than this air temperature, so it was in the melted state during the drying process, causing a greater tendency to stick and form aggregates. This phenomenon explains the higher proportion of PVAL than PCL in the microparticles, as can be seen from the <sup>13</sup>C spectra obtained by NMR [12] [13].

The DSC analysis **Figure 2** was used to determine the miscibility of the polymer system developed. While it was not possible to observe the T<sub>g</sub> of the PCL due to the limitations of the DSC instrument, the T<sub>g</sub> of the pure PVAL was about 72 °C. The micro-

**Table 1.** Chemical shift and area under the peaks of the <sup>13</sup>C spectra of PCL/PVAL microparticles.

<sup>13</sup> C of PCL/PVAL Microparticles	Chemical Shift	Normalized Peak Area	Absolute
CH <sub>2</sub> (PCL)	36.69 - 16.47	8.34	55,429
CH <sub>2</sub> (PVAL)	48.53 - 43.08	41.72	277,114
C-OH (PVAL)	73.77 - 61.26	53.28	353,866
C = O (PCL)	174.34 - 168.63	1.00	6642

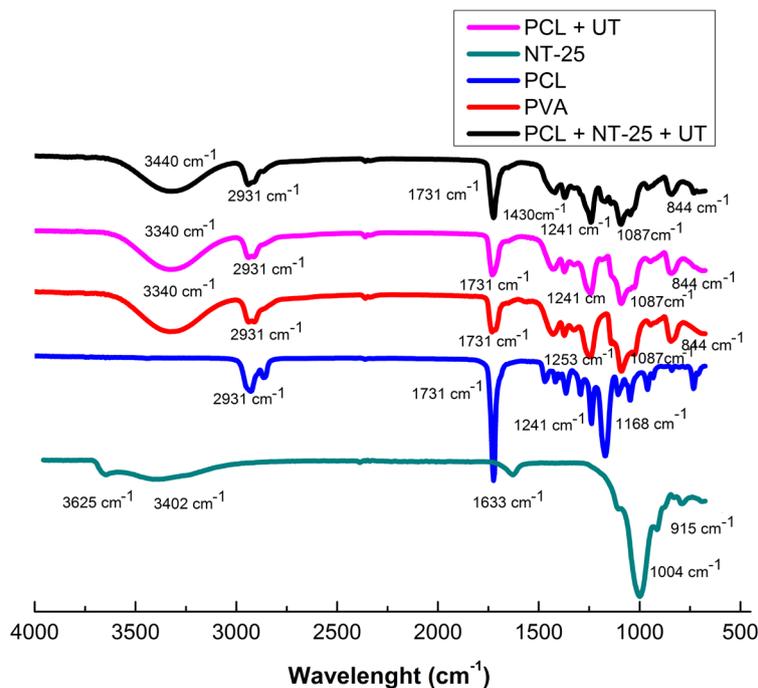


**Figure 2.** DSC curves for PCL, PVAL and PCL/PVAL microparticles.

particles presented a peak related to melting of the PCL crystals at 54.52 °C and a plateau referring to the T<sub>g</sub> of the PVAL at 74.85 °C. Because of this small change of the T<sub>g</sub>, it was not possible to confirm that interaction occurred between the polymers. Systems formed of compatible polymers have T<sub>g</sub> values that are shifted in relation to the values of the pure polymers, with this shift being greater than the stronger specific interactions of each polymer are. Therefore, if an interaction occurred between the polymers, it was not a strong one, since the shift of the T<sub>g</sub> was not significant [44]. Besides this, the T<sub>g</sub> of a miscible mixture depends on the composition of each polymer in the mixture, so a higher PVAL content in the mixture causes the T<sub>g</sub> value of the microparticles to be more shifted toward the T<sub>g</sub> of the pure PVAL.

### Infrared Spectroscopy

The FTIR ATR analysis supplies important information, such as the chemical composition, configuration and conformational structure [37]. Therefore, we used this technique to evaluate the chemical groups of the polymers. **Figure 3** presents the FTIR spectrum of the PCL, showing the main absorption bands: in the 500 - 900 cm<sup>-1</sup> range, referring to the CH<sub>2</sub> deformation; 900 - 1000 cm<sup>-1</sup> range, due to the C-O-C symmetric deformation; 1000 - 1100 cm<sup>-1</sup> range, attributed to the C-C deformation; 1100 - 1150 cm<sup>-1</sup> range, referring to the C-O deformation; at 1168 cm<sup>-1</sup>, associated with the symmetric O-C-O vibration; at 1241 cm<sup>-1</sup>, related to the asymmetric C-O-C vibration; at 1724 cm<sup>-1</sup>, referring to the carbonyl vibration; and at 2931 cm<sup>-1</sup>, attributed to the asymmetric CH<sub>2</sub> vibration [43] [45]. In turn, the FTIR spectrum of the PVAL has bands at 3440 cm<sup>-1</sup>, referring to the stretching of the OH group; 2927 cm<sup>-1</sup>, referring to the vibration of the -CH<sub>3</sub> group; 1731 cm<sup>-1</sup>, referring to the -O = C-OR vibration; 1087 cm<sup>-1</sup>, due to the -C-O-C vibrations; and 844 cm<sup>-1</sup>, referring to the -CH vibration [46]. The FTIR spectrum of the NT-25 exhibits bands at 3625 cm<sup>-1</sup> and 3402 cm<sup>-1</sup>, referring



**Figure 3.** Overlapping infrared spectra of PCL, PVAL, NT-25 clay and microparticles of PCL/PVAL/UT and PCL/PVAL/NT-25/UT.

to the axial stretching vibrations of the -OH groups of adsorbed water between lamellae, since untreated clays swell more in water, resulting in broadening of the peaks in question,  $1633\text{ cm}^{-1}$ , referring to the angular deformation of hydration water,  $1004\text{ cm}^{-1}$ , referring to the Si-O-Si bonds and  $915\text{ cm}^{-1}$ , referring to the octahedral layer of aluminosilicate [47].

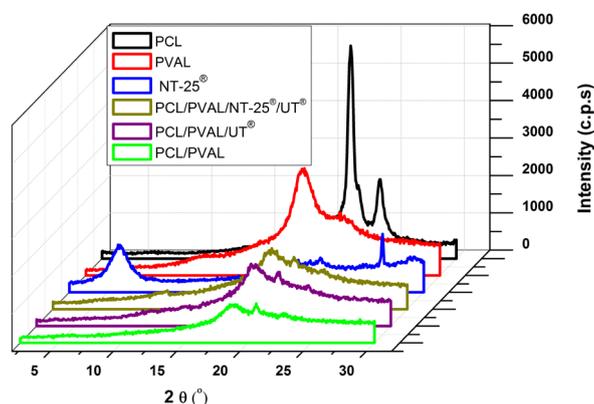
The microparticles produced presented characteristic bands of both PCL and PVAL, as follows: at  $844\text{ cm}^{-1}$ , referring to the -CH vibration of PVAL; at  $1087\text{ cm}^{-1}$ , due to the -C-O-C vibration of PVAL, at  $1731\text{ cm}^{-1}$ , referring to the -O = C-OR vibration of PVAL; at  $3440\text{ cm}^{-1}$ , referring to the stretching of the OH group of PVAL, at  $1241\text{ cm}^{-1}$ , related to the asymmetric C-O-C vibration of PCL; and at  $2931\text{ cm}^{-1}$ , attributed to the asymmetric  $\text{CH}_2$  vibration of PCL. It was not possible to see any peaks characteristic of the clay in the PCL/PVAL/NT-25/UT sample, because the clay's peaks were superimposed on those attributed to the vibrations of the PCL and PVAL.

The NMR  $^{13}\text{C}$  and FTIR techniques showed that the two polymers were present in the microparticles, because the main functional groups of both were detected in the samples. The DSC analysis showed only a small variation of the  $T_g$ , so it was not possible to confirm an interaction between the PCL and PVAL. However, Kesel and collaborators developed polymer blends of PCL/PVAL, in the form of films, by the solvent evaporation method. The measurement of spin-lattice relaxation time of the  $^1\text{H}$  nucleus, using solid-state cross-polarization NMR, demonstrated the occurrence of some physical interactions between the PCL and PVAL and showed that the polymers were finally dispersed in the sample and were compatible at a scale of 60 - 90 nm [13].

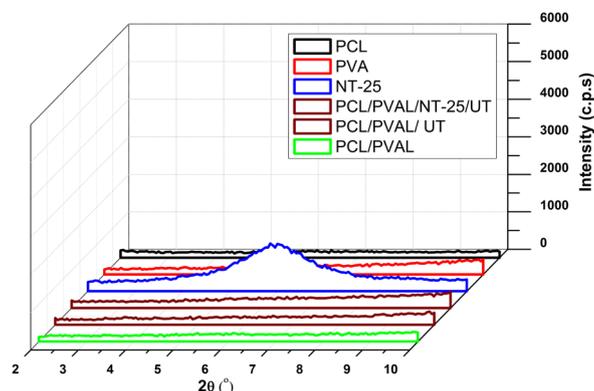
### X-Ray Diffraction

XRD is one of the leading methods to characterize polymers, because it can supply information on the crystalline or amorphous state of the material and its structure by means of the position, shape and intensity of the peaks attributed to the atomic vibrations [37] [38]. Crystals contain ordered arrangements of molecules and atoms, maintained in contact by non-covalent interactions, while an amorphous solid is characterized by the disorderly or random state of its molecules [48].

**Figure 4** shows the X-ray diffraction pattern, for  $2\theta$  ranging from 2 to  $30^\circ$ , of the PCL, PVAL, NT-25 and microparticles. The PCL has a pattern with two reflection peaks, at  $2\theta = 21.4^\circ$  and  $23.8^\circ$ , with basal spacing of 0.412 and 0.325 nm, corresponding to the (110) and (220) of the crystal growth planes, in orthorhombic form [49]. The PVAL **Figure 3** presents an intense reflection peak at  $2\theta = 19.4^\circ$ , which corresponds to a basal spacing of 0.457 nm [50]. The diffractograms of the NT-25 clay are presented in **Figure 4** and **Figure 5**, with interlayer spacing ( $d_{001}$ ) equal to 1.51 nm [32].



**Figure 4.** X-ray diffraction patterns of PCL, PVAL, NT-25 clay, and microparticles of PCL/PVAL, PCL/PVAL/UT and PCL/PVAL/NT-25/UT.



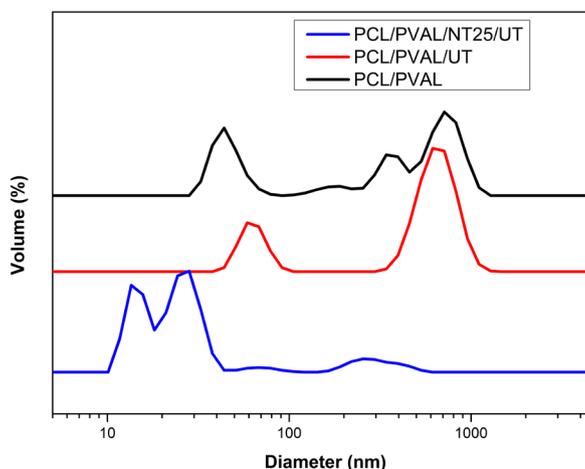
**Figure 5.** X-ray diffraction patterns, expanded in the region of  $2\theta = 0$  to  $10^\circ$ , of PCL, PVAL, NT-25 clay and microparticles of PCL/PVAL, PCL/PVAL/UT and PCL/PVAL/NT-25/UT.

The microparticles produced did not present crystallographic planes corresponding to PCL or PVAL, indicating a loss of crystallinity and the formation of amorphous microparticles, as can be seen in **Figure 4**. In the microparticles composed of PCL/PVAL/NT-25/UT, it was not possible to observe the characteristic peak of clay in the region of  $2\theta = 7.5$  (**Figure 5**), indicating a good dispersion of this nanoload in the polymer matrix. Besides that, in our previous study it was confirmed that the PCL/NT-25 nanocomposite achieved a predominantly intercalated/exfoliated morphology and the thermogravimetric analysis was used to determine the percentage of NT-25 nanoload incorporated in the PCL matrix and the following weight fraction were found: 3.27% w/w [34]. The loss of crystallinity can be attributed to the spray drying process, producing an amorphous material and this behavior has been observed by various authors in studies of the use of polymers and their nebulization by spray drying [51]-[53].

As previously mentioned, the clay addition in the polymeric systems, such as nanoparticles, can influence its morphology, crystallinity, and their thermal and rheological properties. In addition, some studies have reported that the incorporation of high amount of clay decreased the drug encapsulation efficiency [54]. Others studies demonstrated that polymer molecular motions is hindered, since sodium clay swells to about 12 times its original volume in water, increasing the viscosity, by the presence of clay nanoparticles and this behavior is more pronounced at 10 w/w% of clay [55]. The system viscosity is very relevant when the spay dryer is used; since a large amount of clay can interfere the system spraying and a low concentration of clay may not be enough to stabilize the particles.

#### Dynamic laser light scattering

Dynamic laser light scattering (DLS) analysis supplies information on the diameter of the particles in suspension, by measurement of the hydrodynamic diameter (Z) versus volume mean diameter [56]. **Figure 6** shows the distribution of the particles' diameters. It can be seen that the microparticles that were not processed in the UT apparatus (PCL/PVAL) have three main populations: the first with mean diameter of 57.6



**Figure 6.** Particle size distribution by DLS: microparticles of PCL/PVAL, PCL/PVAL/UT and PCL/PVAL/NT-25/UT.

nm, the second with mean diameter of 185.7 nm and the third with mean diameter of 700.3 nm. However, this third population has greater intensity, indicating it represents the main part of the sample. The microparticles submitted to UT processing (PCL/PVAL/UT) have two populations, the first with mean diameter of 66.9 nm and the second with mean diameter of 578.2 nm, which accounted for the largest portion of the sample. Finally, the PCL/PVAL microparticles with NT-25 nanoload and processed in the UT present two populations, the first with mean diameter of 75.8 nm and the second, which made up the largest part of the sample, with mean diameter of 350.8 nm.

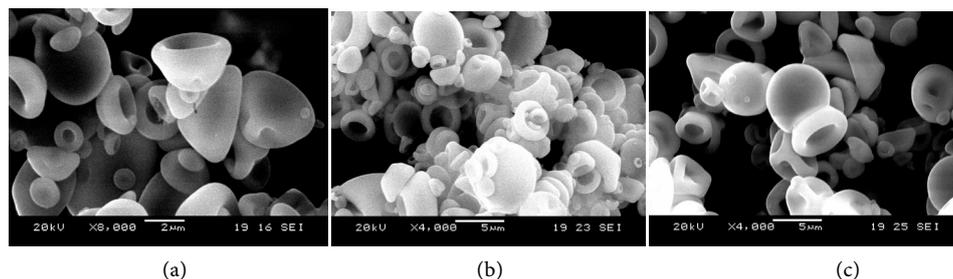
This result was expected and may be related to the use of Ultra-Turrax®, since UT is a high-performance dispersing machine, which increases the system homogeneity and causes a greater shearing of emulsions and suspensions, reducing the particle size. In addition, the PCL/PVAL/NT-25 microparticles showed smaller diameter, indicating that the NT-25 nanoload might have contributed to this phenomenon, once the NT-25 have an average diameter of 211 nm [57]. This result can be related to the fact that montmorillonite clays act as co-emulsifiers, helping the process of forming microparticles by reducing the interfacial tension and keeping the droplets more dispersed [58]-[61]. Besides this, NT-25 also likely acted as an adjuvant during the spray drying process, by reducing the tendency of the polymer suspension to adhere to the interior surfaces of the dryer [62]. The inclusion of clay in this system might have made the suspension more stable and homogeneous, favoring the emulsion's passage through the spray dryer and producing microparticles with smaller diameters.

Although the characteristic peaks of NT-25 clay become superimposed in the FTIR of PCL/PVAL/NT-25 microparticles, the particle size study by DLS can be a strong indication of the clay presence in the system. Since in the PCL/PVAL/NT-25 microparticles there was a strong reduction in the size of particles, while all other parameters remained constants, such as polymers and clay concentration, temperature, solvent, and production method.

Besides, it may consider that the PCL concentrations, PVAL and clay were suitable for the microparticles development. However, it is not interesting works with a less PCL concentration since using the ratio of 50:50 of PCL/PVAL, the percentage of PCL/PVAL in the system was 10:90. The 3% of clay amount was appropriate, once the formulation was sprayed by spray dryer, reduced the size of microparticles, acting as a stabilizing agent. The complete removal of the solvents was confirmed by FTIR, once the spectrum did not show any characteristics bands of solvent.

#### **Scanning electron micrography**

The SEM analyses **Figure 7** indicated the formation of non-spherical microparticles containing concavities and invaginations. The microparticles' surfaces were smooth, without roughness or porosity. This morphology can be attributed to the spray drying conditions, because this technique relies on high temperature and rapid drying kinetics, causing high vapor pressure in the droplets. The fact that the drying temperature of the droplets is higher than the solvent's boiling point keeps the droplets inflated, generating particles with hollow and spherical morphology [51]. Besides this, the indication of the



**Figure 7.** Photomicrographs by SEM of PCL/PVAL/NT-25/UT (a) PCL/PVAL; (b) and PCL/PVAL/ UT; (c) respectively.

encapsulating capacity of a polymer is given by the degree of integrity and porosity of the particles formed. Although the particles produced here had some surface depressions or irregularities, we did not find the occurrence of microfissures and cracks on their surface, suggesting good capacity to encapsulate active ingredients [63].

#### 4. Conclusion

In this study, we obtained innovative microparticles of PCL/PVAL and PCL/PVAL/NT-25, using emulsification techniques followed by spray drying. The DSC analysis showed a small variation in the  $T_g$ , but it was not possible to confirm the occurrence of interaction between the polymers. Besides this, the XRD study showed that amorphous systems were formed, which was interesting from a technological standpoint, because this could increase the bioavailability of the drug molecules included in the system. The nanoparticle, the commercial clay NT-25, helped to reduce the size of the microparticles formed by acting as a co-emulsifier. The SEM images revealed microparticles with concave morphology, without surface depressions and irregularities. These systems have the advantage of being formed by biocompatible and biodegradable polymers, PCL and PVAL, which have distinct polarities, facilitating the inclusion of both hydrophilic and hydrophobic active ingredients. Furthermore, it is possible to disperse the sodium montmorillonite clay, promoting the reduction of the particles size.

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