PREPARATION OF POLYMER PARTICLES WITH COTTONSEED OIL AND HERCYNITE BY PRECIPITATION USING AN ATOMIZATION APPARATUS

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ABSTRACT

Atomization is a multifaceted technology that has yet to be consistently used to prepare polymeric particles. The present study evaluated the preparation of polymer carriers by precipitation using an atomization system. Poly(methyl methacrylate) (PMMA) and poly(caprolactone) (PCL) were selected as preformed polymers, while cottonseed oil and nanometric hercynite were used as fillers. Regardless of the polymer type and fillers, the atomization products generally showed a bimodal distribution with nanometric (300-400 nm) and micrometric (4,000-6,000 nm) particles. It was observed that PCL/cottonseed oil particles had an irregular surface due to oil adhesion to the walls, which did not occur for PMMA particles. The formation of polymer/cottonseed oil/hercynite particles was proven via infrared spectroscopy and X-ray diffraction analyses, representing an advance for preparing bioactive carriers with potential therapeutic applications.

KEYWORDS: *PMMA, PCL, solvent shifting, encapsulation, particle size*

I.   INTRODUCTION

The manufacture of polymer materials is the object of constant attention on the part of modern society since there is always a search for the improvement of physicochemical properties or the discovery of new applications [1]. As a result of the union of nanotechnology in the field of polymers, nanocomposites have been consolidated as a fruitful area for research and development. Nanocomposites consist of a solid multiphase material of nanometric dimensions, in which the polymer is usually found in the shell region, and other organic and inorganic materials are arranged as the core [2]. These composites mix the properties of polymers (including optical properties, chemical resistance, and mechanical resistance) with the properties of additives (including bioactivity, catalytic action, specific light absorption, and magnetoresistance). There is a particular interest in generating bioactive carriers in the pharmaceutical field by incorporating ferromagnetic materials and hydrophobic drugs in polymer matrices [3]. Under an external magnetic field, ferromagnetic materials concentrate the composite in the target region to deliver the drug effectively with low toxicity and fewer side effects [4]. Other prominent applications for carrier nanoparticles are magnetic

bioseparation, cell labeling and diagnosis, contrast agents for magnetic resonance imaging, and magnetic hyperthermia for tumor treatment [5]. There are many methods for producing polymer particles, either preformed polymer or polymerization. Each method has particularities and may be more suitable for specific fillers and final applications [6]. The choice of method is a determining factor in reducing contamination and facilitating the treatment of the particles generated. Thus, the production of nanocomposites from preformed polymers has gained prominence for its simplicity and time-saving compared to polymerization methods.

The precipitation method, also called solvent shifting, is widely used in polymers and enables the formation of polymer particles from diffusion between fully or partially miscible solvents. The technique involves adding a prepared preformed polymer solution over an anti-solvent medium, usually a mixture of water or buffer with stabilizers [7]. After stirring, the solvent diffuses into the liquid medium, and the polymer solidifies almost instantly to form nano or microparticles, whether capsules or rigid spheres. The remaining solvent from the dispersion can be evaporated, and the particles generated can be collected via filtration or lyophilization, depending on the polymer and solvent used [6]. The operational conditions of precipitation can be adjusted to modify the nanoparticles' morphology and size. According to Lima et al. [8], the injection technique has crucial importance on the characteristics of the particles obtained by precipitation. The process must be operated in a reactor with a high homogenization capacity and a high antisolvent-organic solution ratio to favor the fraction of particles at the nanometer scale. The use of needles to transfer the organic solution (with preformed polymer) is a common practice in this field, which can be explained by the Gibbs-Marangoni effect. The reduction in the droplet size of the organic solution leads to an increase in the interfacial area, which causes turbulence in the interfacial region and displacement of stabilizers over the interfaces and, consequently, causes the formation of smaller particles [8, 9].

Liquid atomization generates liquid sprays with fine droplets due to the forced passage of liquid streams through a nozzle [10]. This technology increases the specific surface area of the fluid and improves the efficiency of the use of liquids [11]; for this reason, it has been widely incorporated into human devices, from household items to rocket fuel feeding. In addition to knowledge of fluid properties, the key to liquid atomization is the atomization system, as it affects the spray pattern and droplet size. Rotary, pressure, ultrasonic, and two-fluid nozzles are commonly installed in atomization systems. Two-fluid nozzles have a more comprehensive range of applications in chemical processes due to their low installation, operation costs, and easy scaling [12, 13]. Our research group already has experience preparing different polymer particles using atomization systems [13-16]. Particularly, hollow nanoparticles were prepared from the precipitation of preformed polymers poly(methyl methacrylate) (PMMA) and polycaprolactone (PCL) in previous studies, but no filler was added to the organic solution. The presence of the additives affects the rheology of the organic solution and, therefore, can lead to different products from the experiments without fillers. In addition to the proper size distribution and well-established spherical morphology, encapsulation capability is a new aspect to be evaluated.

Thus, the present study investigated the potential of the atomization apparatus to manufacture polymer particles with active ingredients via precipitation. The preformed polymers PMMA and PCL were previously solubilized in acetone and were used as shells of the polymer particles. Cottonseed oil and nanometric hercynite, a ferromagnetic material, were used as fillers. Fabrication experiments focused on encapsulating oil and hercynite separately, and then both materials were encapsulated simultaneously.

II.   MATERIALS AND METHODS

2.1. Chemicals

Poly(methyl methyl methacrylate) (PMMA; molecular weight = ~120 KDa) and polycaprolactone (PCL; molecular weight = ~14 KDa) polymers were obtained from Sigma-Aldrich (MO, USA). Acetone, ethyl alcohol, and polyvinyl alcohol (PVA) were purchased by Vetec Química (Brazil). The cottonseed oil was purchased in the local market, and the nanometric hercynite ($FeAl_2O_4$) was

provided by the Laboratory of Synthesis of Ceramic Materials (LabSMaC) of the Federal University of Campina Grande. Hercynite showed 91.2% purity with traces of hematite (α-Fe_2O_3).

2.2. Experimental apparatus

The preparation of the polymer particles was carried out using an atomization apparatus. The two-fluid nozzle was made of stainless steel with an inlet for the polymer solution and another inlet for the nitrogen gas. A 0.45 mm needle injected the polymer solution intermittently, which allowed conical jets inside the reactor. The valve opening pulses were adjusted by a solenoid valve (on/off), and the valve opening time is defined by valve opening time (ms) = 641.01 × (polymer solution flow rate)-0.76 (R^2 = 0.97). The dispersed liquid medium is continuously recirculated in the reactor in all experiments. It passes through a perforated plate that acts as a sprinkler washer, promoting the dragging of the droplets generated in the atomization and increasing the contact between the phases. The reactor is jacketed and manufactured in borosilicate glass, and its temperature is controlled by a TE-184 thermostatic bath (TECNAL, Brazil). A condenser was installed on top of the reactor operating at a temperature of 10 °C to avoid loss of liquid phase and attenuate the reactor pressure.

2.3. Polymer precipitation

All particle manufacturing experiments were conducted in a rigorous sequence of steps, as reported in the previous paper [15]. Initially, 2% (w/v) polymer (PMMA or PCL) was solubilized in 50 mL of acetone: ethanol mixture (3:1, v/v). Then, the materials to be encapsulated, cottonseed oil (0.5 mL) and $FeAl_2O_4$ (0.1 g), were mixed with the polymer solutions. An amount of PVA (0.1 g) was previously dissolved in 300 g of water to improve particle dispersion. The experiments were conducted at 40 °C and a nitrogen gas pressure of 0.25 bar. After 20 min of operation, the resulting dispersions were collected and placed in an air circulation oven at 30 °C to remove the residual solvent. Finally, the dispersions were collected and characterized according to Section 2.4.

2.4. Characterization of polymer particles

The particle size distribution was performed in triplicate using the dynamic light scattering technique using the 90Plus/Bi-MAS ZetaPlus equipment (Brookhaven Inst. Co., USA). An ultrasonic bath was used to improve particle dispersion before each analysis. The encapsulation of cottonseed oil and $FeAl_2O_4$ was confirmed using Fourier Transform infrared spectroscopy in IRTracer-100 equipment (Shimadzu, Japan) in the 400-4,000 cm^{-1} region. X-ray diffraction (XRD) was also used to proven the encapsulation of $FeAl_2O_4$. The analyses were performed by an XRD-7000 diffractometer (Shimadzu, Japan) using CuKα as a radiation source, monochromator, and scanning range from 5 to 120º with a step of 1º/min.

Particle morphology was investigated through transmission electron microscopy (TEM) and scanning electron microscopy (SEM). In the TEM analysis, a JEM 1400 microscope (JEOL, Japan) was operated using a voltage of 120 kV. The polymer dispersion samples were deposited on 400 mesh copper grids coated with carbon/Formvar®. The images were recorded by high-resolution scanning electron microscopy with an electron emission gun using a Zeiss-Auriga (USA) equipment. The samples were placed onto a silicon wafer, dried for 48 h, and fixed on the stubs with carbon tape. Then, a thin gold layer was deposited using a Baltec SCD 050d metallizer using voltage and current intensity of 5 kV and 2.1 µA, respectively.

III. RESULTS AND DISCUSSIONS

### 3.1. Preparation of polymer particles with cottonseed oil

PMMA and PCL particles were successfully prepared in the atomization apparatus, according to Figure 1. In the TEM images, it is possible to observe that the solvent shifting promoted the formation of spherical polymeric structures. These spheres showed a dark color in their nuclei, probably due to the presence of cottonseed oil. According to Yabu [17], the spherical templates are obtained during precipitation due to the interfacial tension between the polymeric phase and the antisolvent. Another important feature is the heterogeneity of PCL particles. In addition to having cottonseed oil inside the polymer particles, the same oil adhered to the surface of some particles. The particle size distribution

for the PCL/cottonseed oil particles showed a bimodal behavior, with peaks at 450 and 5,000 nm in Figure 2. In turn, the PMMA/cottonseed oil particles showed a uniform size of approximately 5,000 nm. The difference between PCL and PMMA microparticles was already expected due to the polymer chain size [18]. The PCL used in the experiments has only 14 kDa, while the PMMA has an average of 120 kDa.

To assess the impact of atomization on the size of polymer particles, it is essential to know the state of the art. The literature already presents a range of data on preparing PMMA and PCL particles, but precipitation studies generally use surfactants instead of water-soluble polymers. For example, Lino et al. [19] prepared PCL nanoparticles (~200 nm) with encapsulated β-carotene using a dripping method in the presence of Pluronic F68. PCL nanoparticles with encapsulated atrazine, a poorly water-soluble herbicide, were prepared by Grillo et al. [20]. The authors prepared the PCL particles in a magnetic stirrer using Span 80 as a surfactant, reaching a particle size of less than 300 nm. In fact, the cited studies obtained an average particle size slightly smaller than the results found in the present study. However, an important disclaimer about the techniques involved must be mentioned. The PVA added in the present study works as a steric stabilizer, preventing the droplets from coalescing by physical adsorption at the interface. Surfactants can protect the interface by steric hindrance or electrostatic interactions and generate micelles that favor the nucleation and controlled growth of polymer nanoparticles. This second stabilization mechanism can ensure the formation of small particles, which is almost independent of the homogenization performance. For this reason, the experiments were purposely performed using PVA as a stabilizer since the focus of the present study was to clarify the effects of atomization on precipitation. The advantages of atomization are more evident when compared to other studies involving water-soluble polymers as stabilizers. Teeka et al. [21] successfully prepared PMMA/Jasmine oil particles after preparing the O/W system with PVA in a magnetic stirrer followed by solvent evaporation. However, the observed average size of the particles was in the order of 10 µm, being 2-fold larger than PMMA/cottonseed oil particles. This fact raises the possibility of reducing the particle size by adopting atomization in polymer precipitation tests, improving process control and reducing energy consumption.
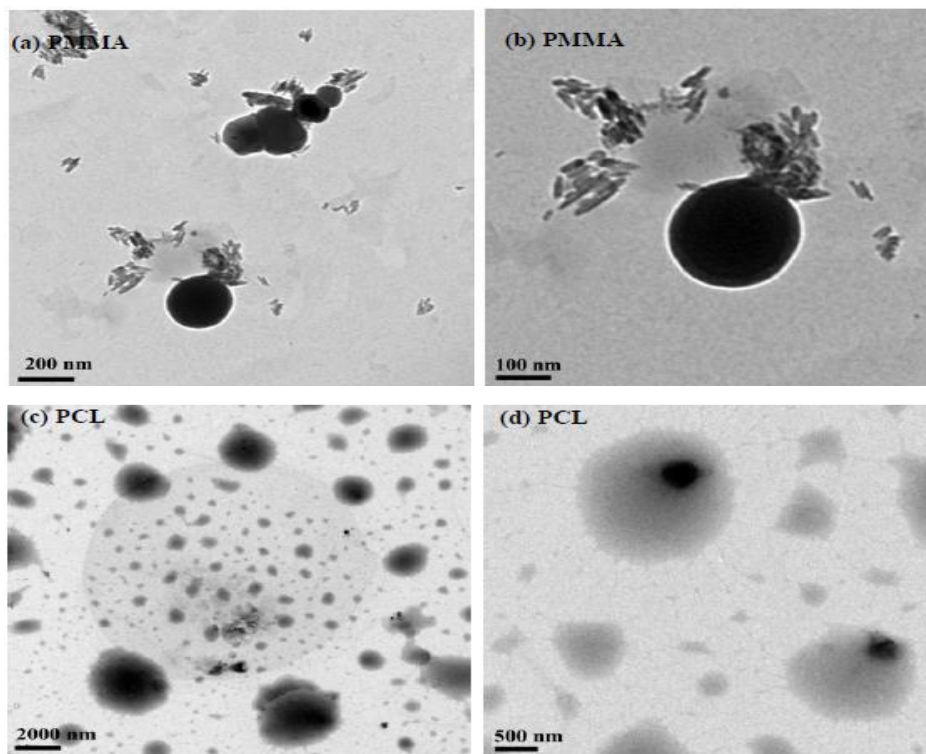

Figure 1. TEM images of PMMA/cottonseed oil (a, b) and PCL/cottonseed oil (c, d) particles
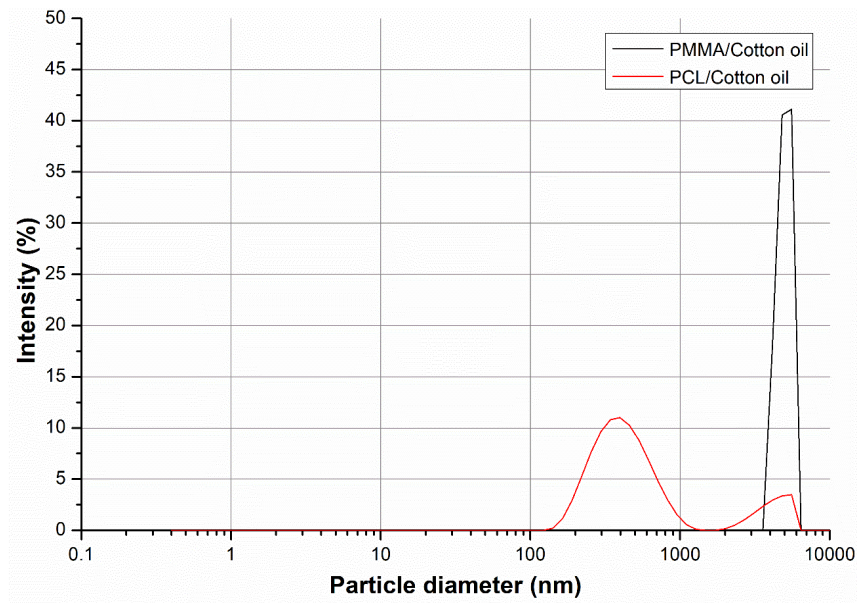
Figure 2. Particle size distribution of PMMA/cottonseed oil and PCL/cottonseed oil particles. The atomization experiments were carried out under the following experimental conditions: 300 g of aqueous phase, 50 mL of acetone: ethanol (3:1, v/v), 1 g of polymer (PMMA or PCL), material to be encapsulated (0.5 mL of cottonseed oil), temperature of 40 ºC, pressure of 0.25 bar and operation time of 20 min.

The encapsulation of cottonseed oil by polymers was confirmed in FTIR analyses, as seen in Figure 3. Notably, spectroscopy in the intermediate infrared region has recognized application in identifying substances. Figure 3A shows the infrared spectra of the isolated materials (PMMA and cottonseed oil) and the PMMA/cottonseed oil particle. Identical peaks are observed in both cottonseed oil and PMMA/cottonseed oil particle spectra at 3,000 cm^{-1}, which may be associated with unsaturated compounds [22]. According to Radcliffe et al. [23], cottonseed oil mainly contains polyunsaturated fatty acids, such as linoleic acid (~53%) and oleic acid (~16%). The characteristic peak of cottonseed oil was also observed in the spectrum of PCL/cottonseed oil particles (see Figure 3B), demonstrating the oil's entrapment in a polymer matrix.
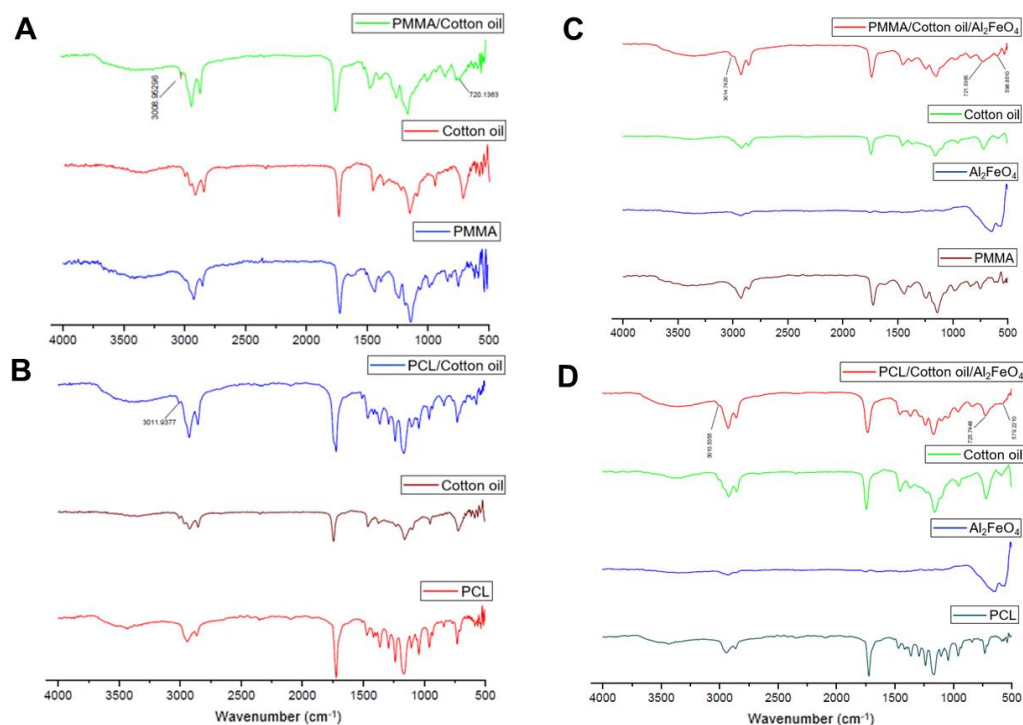
Figure 3. FTIR profiles of PMMA/cottonseed oil (A), PCL/cottonseed oil (B), PMMA/Cottonseed oil/FeAl$_2$O$_4$ (C), and PCL/Cottonseed oil/FeAl$_2$O$_4$ (D) particles.

3.2. Preparation of polymer particles with FeAl$_2$O$_4$

According to Figure 4A, both PMMA and PCL particles showed a bimodal size distribution. For PMMA/FeAl$_2$O$_4$ particles, the first population presented sizes between 220 and 712 nm, while the second population (with lower intensity) presented sizes between 1,718 and 5,560 nm. Likewise, the most significant fraction of PCL/FeAl$_2$O$_4$ particles had sizes between 164 and 712 nm, and the other population had a size close to 5,000 nm. The bimodal size distribution of PMMA/FeAl$_2$O$_4$ particles differs from the monomodal behavior shown in section 3.1 and the previous study [15]. The morphologies of polymer particles with FeAl$_2$O$_4$ were investigated by SEM analysis. For the PMMA/FeAl$_2$O$_4$ particles or the PCL/FeAl$_2$O$_4$ particles, spherical structures were observed with dimensions similar to the results obtained in the DLS analysis, as shown in Figures 4B and 4C. The EDS results confirmed the presence of FeAl$_2$O$_4$ in both samples due to the intensity of peaks relative to iron, as seen in Figure 5. It is important to note that the sharp peak of gold in these dispersions is due to the metallization treatment of the samples before analysis.
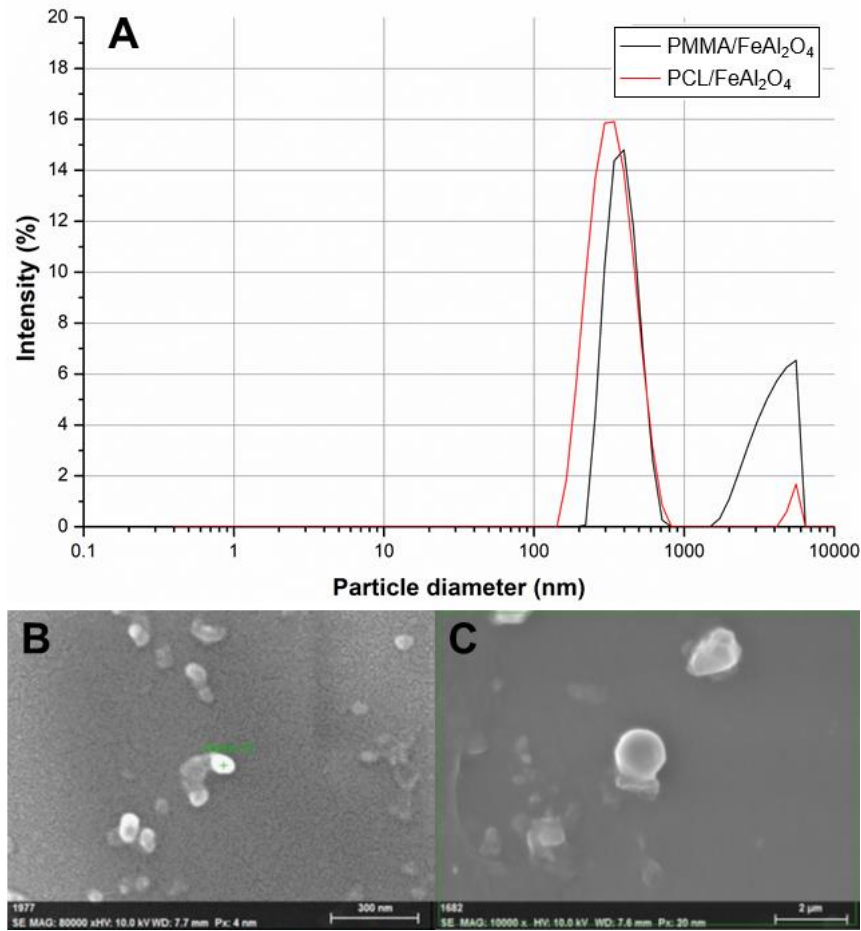
Figure 4. Particle size distribution of PMMA/FeAl$_2$O$_4$ and PCL/FeAl$_2$O$_4$ (A) particles. SEM images of PMMA/FeAl$_2$O$_4$ (B) and PCL/FeAl$_2$O$_4$ (C) particles. The atomization experiments were carried out under the following experimental conditions: 300 g of aqueous phase, 50 mL of acetone: ethanol (3:1, v/v), 1 g of polymer (PMMA or PCL), material to be encapsulated (0.1 g of FeAl$_2$O$_4$), temperature of 40 °C, pressure of 0.25 bar and operation time of 20 min.
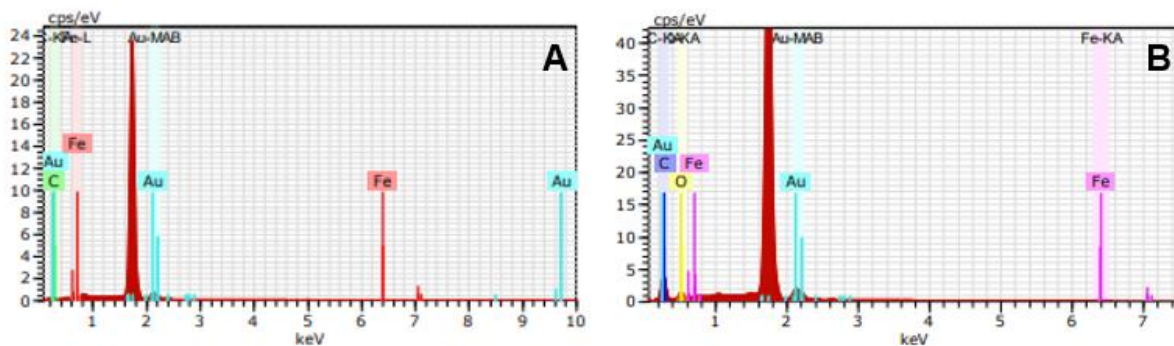
Figure 5. EDS results for PMMA/FeAl$_2$O$_4$ (A) and PCL/FeAl$_2$O$_4$ (B) particles.

Here, confirmation of the encapsulation of FeAl$_2$O$_4$ by the polymers was observed in the XRD analyses. Peak positions and relative intensities in the spectra allow the identification of FeAl$_2$O$_4$ in the PMMA (see Figure 6A) and PCL (see Figure 6B) particles. The amorphous behavior of PMMA made it challenging to recognize peaks characteristic of FeAl$_2$O$_4$ in the XRD spectra of the PMMA/FeAl$_2$O$_4$ particle, being observed only at 36.2º. The PMMA sample was possibly contaminated, which may explain the presence of unusual peaks at 44º, 64º and 78º. In turn, it was

possible to identify characteristic crystalline planes of $FeAl_2O_4$ in the $PCL/FeAl_2O_4$ samples at 44º and 64º.
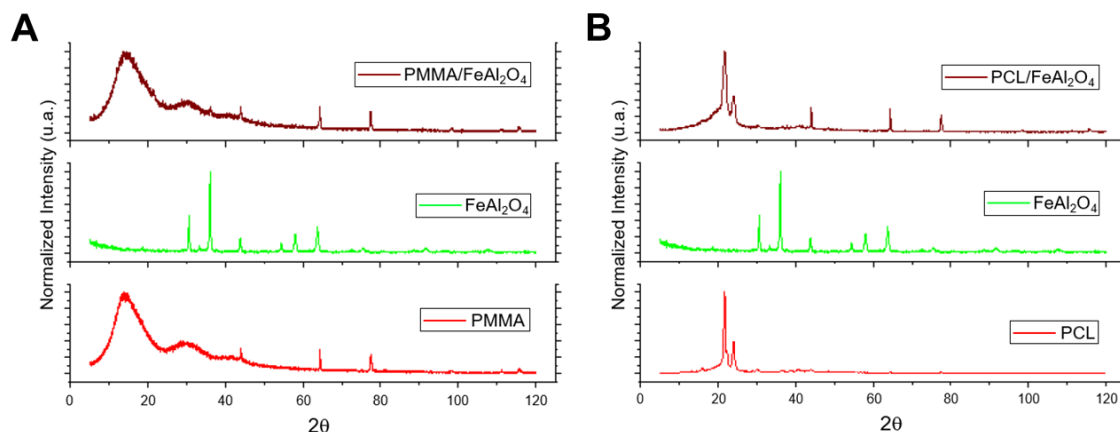
**Figure 6.** X-ray diffractogram profile of $PMMA/FeAl_2O_4$ (A) and $PCL/FeAl_2O_4$ (B) particles.

3.3. Preparation of polymer particles with cottonseed oil and $FeAl_2O_4$

After the results obtained from the encapsulation of cottonseed oil and $FeAl_2O_4$ separately, other tests were carried out to investigate the simultaneous encapsulation of both materials. As in the previous tests, the generated particles were analyzed by DLS, MET, FTIR, and XRD. According to Figure 7, the PMMA and PCL particles showed a bimodal size distribution with 400 and 5,000 nm peaks, similar to the behavior observed in the $FeAl_2O_4$ encapsulation. In the TEM analysis (see Figure 8), the particles presented spherical shapes, but each polymer particle showed different characteristics. Oil and $FeAl_2O_4$ merged in the core of the PMMA particles since it was impossible to distinguish the encapsulated materials in the TEM images. On the other hand, the PCL particles showed a light color on the outside and a dark color on the inside due to the presence of the oil. In addition, it is possible to observe the presence of $FeAl_2O_4$ on the surface of PCL particles. Therefore, it is necessary to state that the atomization apparatus can manufacture magnetized carrier particles with potential pharmaceutical applications.
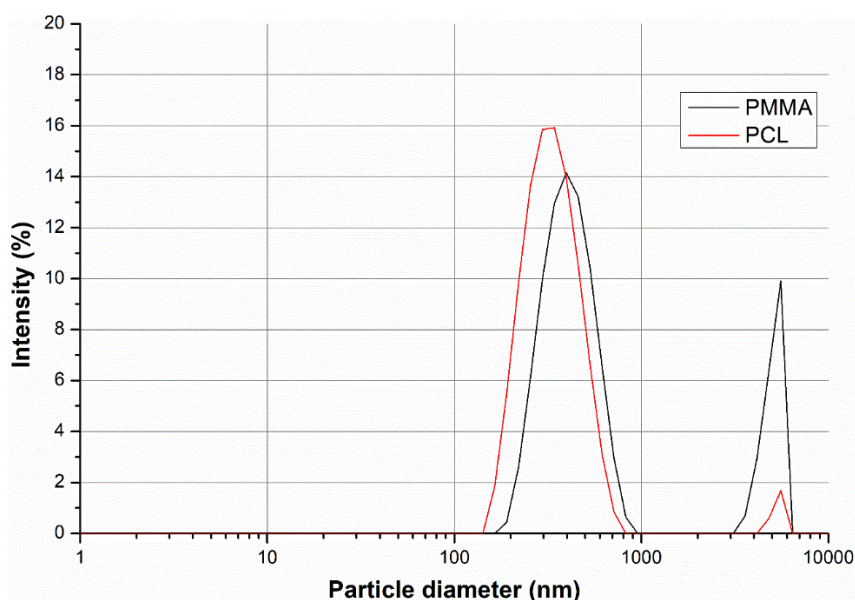

Figure 7. Particle size distribution of $PMMA/$cottonseed oil$/FeAl_2O_4$ and $PCL/$cottonseed oil$/FeAl_2O_4$ particles. The atomization experiments were carried out under the following experimental conditions: 300 g of aqueous phase, 50 mL of acetone: ethanol (3:1, v/v), 1 g of polymer (PMMA or PCL), material to be encapsulated (0.5 mL of cottonseed oil and 0.1 g of $FeAl_2O_4$), temperature of 40 ºC, pressure of 0.25 bar and operation time of 20 min.
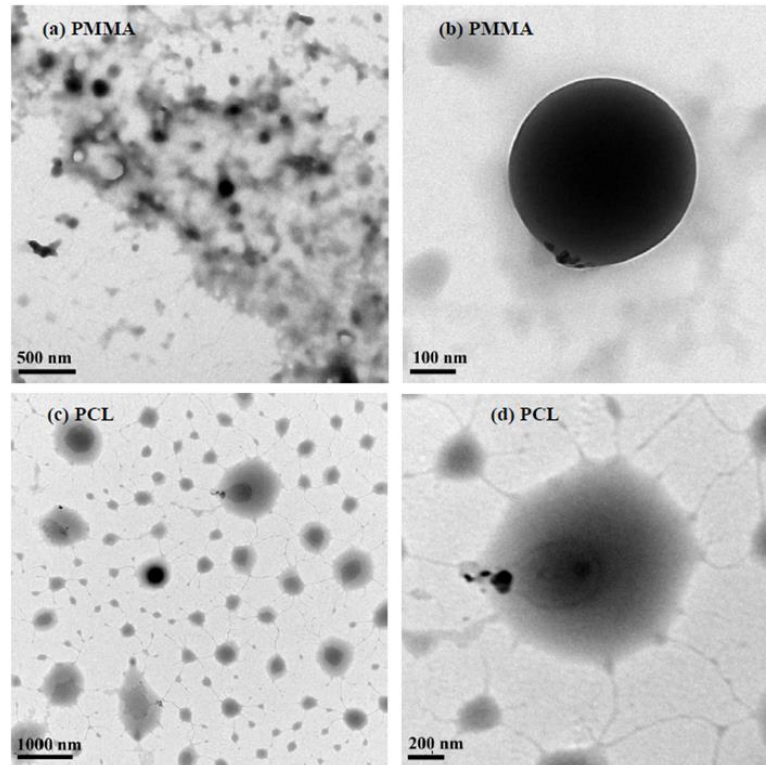
Figure 8. TEM images of PMMA/Cottonseed oil/FeAl$_2$O$_4$ (a,b) and PCL/Cottonseed oil/FeAl$_2$O$_4$ particles (c,d).

The diffractograms of the PMMA and PCL particles confirmed the presence of FeAl$_2$O$_4$ despite the overlap of some characteristic peaks, as seen in Figure 9. The peaks in the regions of 30.75º, 36.23º, 44.05º, and 64.05º correspond to the planes (220), (311), (400), and (440) of FeAl$_2$O$_4$, respectively [25]. In the FTIR analyses, the presence of FeAl$_2$O$_4$ is confirmed by a broad and weak band around 580 cm^{-1}, as seen in Figures 3C and 3D. Based on Wang et al. [4], this band is characteristic of the Fe-O vibration referring to Fe$_2$O$_4$ or Al-O dispersed in the polymer particle. As in section 3.1, absorption bands of C=C groups are observed in the region above 3,000 cm^{-1}, which indicates that the sample has double bonds likely from the oil molecules. In this way, inserting cottonseed oil and FeAl$_2$O$_4$ in the polymer particles was proved possible.
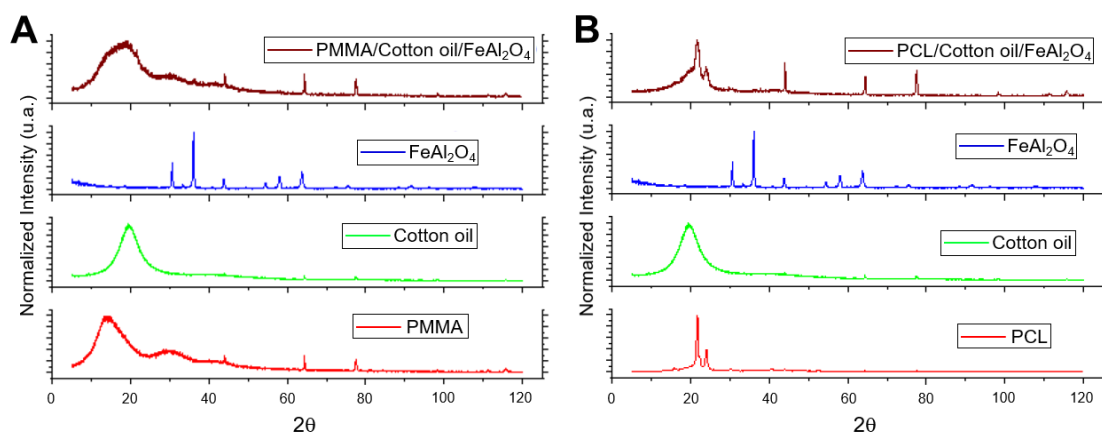
Figure 9. X-ray diffractogram profile of PMMA/Cottonseed oil/FeAl$_2$O$_4$ (A) and PCL/Cottonseed oil/FeAl$_2$O$_4$ (B) particles.

IV. CONCLUSIONS

The versatility of the atomization apparatus was put to the test again in the preparation of polymer particles. The results showed that the atomization apparatus effectively generates filled polymer particles from precipitation. Although most of the tests showed products with a bimodal distribution (nanometric + micrometric), the nanosized particles could be separated by simple filtration. The formed particles generally presented a spherical shape with cotton oil and $FeAl_2O_4$ entrapment, mainly in PMMA tests. In tests with PCL as a preformed polymer, part of the cottonseed oil remains adsorbed on the surface of the particles after the precipitation process (regardless of the presence of $FeAl_2O_4$), which indicates a low encapsulation efficiency. Due to its low molecular weight, the affinity between PCL and cottonseed oil likely made it difficult for polymer molecules to compact, which would explain the irregularity of the particle morphology. Despite this, it is valid to state that the proposed technique is a simple and direct way to encapsulate hydrophobic liquid and ferromagnetic material. Future studies will be carried out by replacing cottonseed oil with other hydrophobic bioactives, in which the encapsulation efficiency and controlled release behavior will be more rigorously observed.

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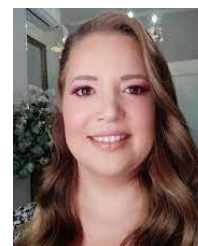
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