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OPTIMIZATION OF THE PREPARATION PARAMETERS OF PCL PARTICLES OBTAINED BY AN EMULSIFICATION/EVAPORATION METHOD

BY

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Abstract. Nanotechnology represents a sector with high potential for the treatment of human diseases. Among different types of drug delivery systems, polymer nanoparticles (NPs) are of main importance in the biomedical field. They are mainly used as vehicles for the delivery of active compounds, thus protecting the drug against enzymatic and chemical degradation and directing it to the various target tissues and cells. Many factors can influence the size of NPs such as stirring speed, polymer concentration, organic phase addition speed or surfactant concentration. The aim of this study was to find the optimum conditions for the preparation of nanoparticles using an emulsification/evaporation method. Using dynamic light scattering technique, it was possible to assess the optimal conditions for the preparation of NPs with size less than 200 nm, such as: 1 wt. % concentration in $CHCl_3$, 1 wt. % concentration of PVA in the aqueous phase and 5 min homogenization. These optimized parameters ensure a stable and monodisperse colloidal suspension suitable for future parenteral administration.

Keywords: poly(ε-caprolactone), drug delivery systems, optimization parameters, dynamic light scattering, colloidal stability.

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1. Introduction

The integration of polymer-based systems for the encapsulation and controlled release of active substances represents a pivotal advancement in modern medicine, particularly for overcoming the physiological limitations of conventional therapies (Altammar, 2023). As highlighted by Chenxi *et al.* (2025), achieving selective delivery to specific organs or cell types remains a primary challenge, especially in oncology, where the protection of therapeutic molecules from enzymatic degradation and systemic metabolism is critical (Bhardwaj and Jangde, 2023). By isolating the active principle within a protective vector, these nanosized systems significantly reduce off-target toxicity and enhance the therapeutic index (Kuperkar *et al*., 2024; Islam *et al*., 2025).

To ensure clinical safety, the polymer matrix must be biocompatible and ideally biodegradable, allowing for total elimination from the body without triggering adverse effects. Among the various materials, poly(ε-caprolactone) (PCL) stands out due to its controlled degradation rate and FDA-approved status for several biomedical applications (Raza *et al*., 2024; Yang *et al*., 2024). These systems can be formulated as nanospheres or nanocapsules, with the choice of morphology being strictly dictated by the intended application and drug release kinetics (Dellali *et al*., 2022; Rata *et al*., 2024; Rata *et al*., 2021).

Due to strict constraints imposed by the healthcare field and health authorities, there is a limited number of polymers that can be used as drug carriers. First, the polymer matrix constituting the nanoparticles must be biocompatible. Ideally biodegradable, it must be able to be eliminated by the body over a more or less short term. Thus, their integration into the body will not trigger local or systemic adverse effects and their degradation will not lead to the formation of toxic compounds.

The method of preparing nanoparticles plays a fundamental role in their physicochemical and biological properties. Indeed, depending on the nature of the active ingredient to be encapsulated and the route of administration, different methods can be used. The methods developed to prepare nanoparticles can be classified into two broad categories depending on whether the formulation requires the polymerization of a monomer or whether it is obtained directly from a macromolecule or a preformed polymer (Bhardwaj and Jangde, 2023).

The emulsion-solvent evaporation technique is one of the very first methods established in the literature for the preparation of polymer nanoparticles from a preformed polymer. The experimental protocol is relatively simple to implement. The basic principle of this technique is based on the preparation of an O/W emulsion which leads to the formation of nanopheres after evaporation of the solvent (Cucoveica *et al*., 2024). On the one hand, the organic phase, or oily phase, comprises the polymer dissolved in a polar organic solvent and the active principle is included by dissolution or dispersion. On the other hand, there is the aqueous phase which contains the surfactant. The two solutions are roughly

emulsified then homogenized at high speed or by ultrasound, which gives rise to an emulsion. In conventional methods, these can be either single (o/w) or double (w/o)/w emulsions. The solvent, which is highly volatile, evaporates by diffusing through the continuous phase of the emulsion and a suspension of nanoparticles is formed. The solid nanoparticles obtained can then be washed with distilled water to remove additives, such as surfactants, and recovered by centrifugation of freeze-drying.

The colloidal features of the obtained nanoparticles depend on several parameters, such as: homogenization rate and duration, polymer concentration, ratio between the two phases, the speed of addition of the organic phase, etc.

The aim of the present study was to optimize the emulsion-evaporation protocol in order to quantitatively and reproducibly obtain PCL nanoparticles of approximately 100 to 200 nm, a diameter compatible with parenteral administration. Different parameters were varied and the obtained particles were characterized by dynamic light scattering (DLS).

2. Materials and Techniques

2.1. Preparation of PCL nanoparticles

For preparation of nanoparticles, PCL (Mn = 80,000 $g \cdot mol^{-1}$), PVA (Mw = 13,000-23,000 $g \cdot mol^{-1}$, 87-89% of hydrolysis) and chloroform ($CHCl_3$) were purchased from suppliers Sigma Aldrich and Carlo Erba respectively.

The PCL nanoparticles were prepared using the emulsification-solvent evaporation technique. Briefly, 50 mg of PCL were dissolved in 5 mL of chloroform to form the organic phase. This solution was then added to 60 mL of an aqueous PVA solution (with concentrations ranging from 0.8% to 2% w/v) under magnetic stirring to form a primary emulsion.

This emulsion was subsequently homogenized using a Vibra Cell sonicator (Sonics & Materials, Danbury, USA) equipped with a titanium probe (20 kHz frequency, 130 W nominal power). The homogenization was carried out for 5 minutes at various output levels (1 to 6), using an ice-water bath to maintain a constant temperature (measured at $0 \pm 1°C$) and prevent the thermal degradation of the polymer. Following homogenization, the organic solvent was evaporated by maintaining the dispersion under magnetic stirring at 500 rpm for 24 hours at room temperature. Finally, the resulting nanoparticle suspension was diluted (3-5 drops in 5 mL of distilled water) for DLS analysis.

2.2. Characterization of nanoparticles

2.2.1. Dynamic light scattering (DLS)

NPs can differ in physical properties, such as composition and concentration, as well as size. These properties are generally evaluated by several methods, with the aim of completely characterizing the NPs. The size of the NPs is very important for questions of applicability and nanotoxicology. Their size is thus determined by DLS. A Master Sizer then a Zeta Sizer from the Malvern brand were used. DLS is an optical technique which uses the Brownian movement of particles in suspension by measuring their diffusion coefficient D. A linearly polarized laser source illuminates at a wavelength λ (typically 633 nm) the sample containing the nanoparticles; the light scattered by the nanoparticles in Brownian motion is then collected at a known scattering angle θ (typically 90° relative to the incident beam) using a high photon counting detector. The detector converts scattered intensity fluctuations due to the Brownian motion of particles into an electronic signal which is then digitally processed. Inversion algorithms make it possible to precisely extract the size distributions (hydrodynamic diameter) as well as the polydispersity index (PDI) of the particles.

2.2.2. Zeta potential

The zeta potential (ζ) reflects the surface charge of the particles, which is influenced by changes in the interface with the dispersion medium. These changes may be due to the dissociation of non-functional groups on the surface of the particles, to the adsorption of ionic species present in the aqueous dispersion medium or even to the solvation effect. This parameter is determined using Doppler techniques to measure the particle velocity as a function of voltage, thus the zeta potential is calculated from the electrophoretic mobility of particles in a given solvent. A relatively high zeta potential value, considered |±30 mV|, is important for good physicochemical stability of the colloidal suspension because the large repulsive forces tend to prevent aggregation due to occasional collisions with adjacent nanoparticles. It is interesting to know the value of the zeta potential in order to study the associations of drugs with nanoparticles (Raza *et al*., 2024; Yang *et al*., 2024). The zeta potential of NPs can therefore be adapted to a specific application, by introducing surfactants. The Zeta potential was determined using the Malvern brand Zeta Sizer.

2.2.3. Statistical Analysis

All experiments were performed in triplicate (n=3). The results are expressed as mean ± standard deviation. Statistical analysis was performed using (Excel), considering a p-value < 0.05 as statistically significant.

3. Results

3.1. Influence of sonication time

In order to become familiar with the protocol, several tests were carried out with the equipment available in the laboratory. Two techniques based on sonication (ultrasonic bath and ultrasonic probe) and one technique based on mechanical agitation (Ultra-Turrax) were tested in order to select the agitation technique for emulsification. Emulsification is carried out in two successive stages: a first "pre-emulsification" stage for suspending droplets of the dispersed phase, then a "homogenization" stage whose aim is to reduce the size of the particles so to give the emulsion the required properties and to stabilize it.

The Ultra-Turrax and the ultrasonic bath gave similar results: large particles of the order of a micrometer in diameter. This is explained by the fact that Ultra-Turrax, based on mechanical agitation, creates strong shear to encourage the breakup of droplets. However, they tend to coalesce with the increase in stirring speed (rpm) and the heat thus released. For the ultrasonic bath, the ultrasonic power is not adjustable. From these results, the ultrasound probe was used for the rest of the study. The results of these first tests are available in Fig. 1.

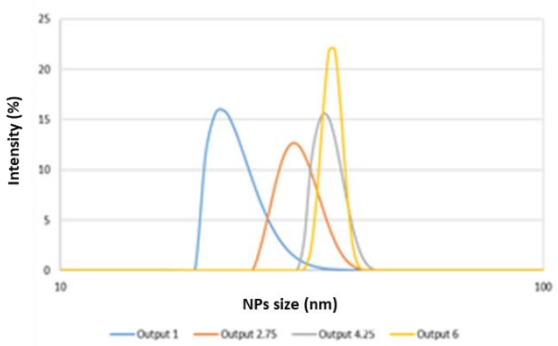

Fig. 1 − Sizes of the nanoparticles obtained according to the power mode of the Ultrasonic probe.

The ultrasound probe used is adjustable to several powers designated by an "output" ranging from 1 to 6. For each test, an emulsion is prepared according to the protocol by varying only the sonication power. Each emulsion is analyzed by DLS to determine particle size and size distribution. The Dx(10), Dx(50) and Dx(90) listed in Table 1 represent the average of five measurements for each speed tested.

To fully characterize the particle size distribution, the cumulative diameters at 10%, 50%, and 90% of the volume (Dv(10), Dv(50), and Dv(90) were recorded. Dv(50), or the median diameter, represents the size below which

50% of the particle volume resides, while the span, calculated as (Dv(90)−Dv(10))/Dv(50), provides an indication of the distribution width.

The data presented in Table 1 demonstrate a direct correlation between the ultrasonic probe output and the resulting particle size. At a low energy setting (Output 1), the nanoparticles achieve a median diameter (Dv 50) of 177 ± 4.5 nm, which is well within the target range for parenteral administration. However, as the power increases to Output 6, a significant growth in particle size is observed, with Dv 50 reaching 993 ± 19.5 nm. This trend suggests that while initial energy is required for droplet breakup, excessive sonication power leads to a substantial increase in the hydrodynamic diameter, likely due to the over-processing effect and localized thermal fluctuations.

Table 1

Influence of sonication power on the cumulative volume diameters of PCL nanoparticles (Mean ± SD, n=3)

Diameter (nm)	Output			
	1	2.75	4.25	6
Dv (10)	126±3.1	323±6.4	645 ± 12.8	750± 14.2
Dv (50)	177±4.5	505±11.2	921± 18.4	993± 19.5
Dv (90)	324±8.2	900±15.6	1470 ± 22.1	1350± 20.8

The unexpected increase in particle size at higher sonication outputs (outputs 4.25 to 6) transcends simple thermal effects. Theoretically, the emulsification process is governed by the Weber number (We), which relates inertial forces to surface tension. While increased sonication typically promotes droplet breakup, excessive power leads to a state of 'over-processing'. At these high-energy levels, the rate of orthokinetic coalescence (driven by high-frequency collisions) surpasses the rate of fragmentation. This is further exacerbated by the depletion of PVA at the rapidly expanding interface, as the surfactant adsorption kinetics cannot keep pace with the generation of new surface area, resulting in larger, poorly stabilized aggregates.

The observed trend transcends simple thermal effects and aligns with the 'over-processing' phenomenon. Theoretically, the emulsification process is governed by the Weber number (We), which relates inertial forces to surface tension. At the high-energy levels generated by output settings 4.25 to 6, the rate of orthokinetic coalescence (driven by high-frequency collisions) surpasses the rate of fragmentation. This is further exacerbated by the rapid expansion of the interface; the PVA adsorption kinetics cannot keep pace with the generation of new surface area, resulting in larger, poorly stabilized aggregates, as illustrated by the distribution shifts in Fig. 2.

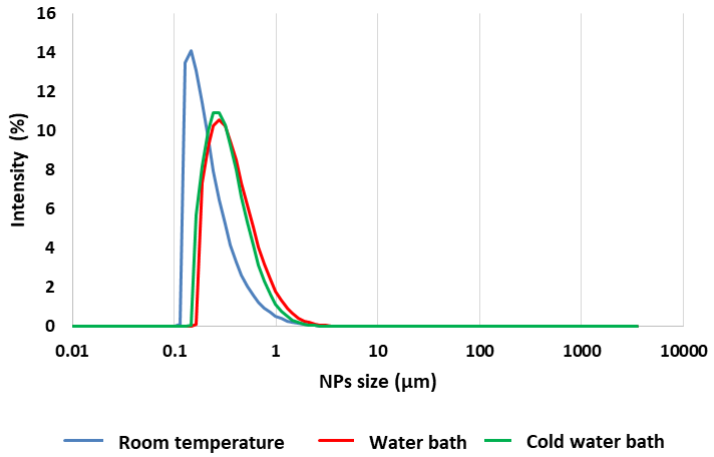

Fig. 2 − Influence of temperature on the size of nanoparticles.

3.2. Influence of surfactant concentration

The influence of surfactant concentration is one of the major parameters making it possible to control particle size and promote the stability of an emulsion. In theory, the higher the surfactant concentration, the better the emulsion particle stabilization. This avoids the phenomenon of coalescence and leads to the formation of smaller NPs. Therefore, tests were carried out for PVA mass percentages of 0.8% to 2% in order to optimize the size of the particles obtained. Above 2% by weight, it is described in the literature that surfactants preferentially combine in the form of micelles instead of aggregating around the particles to stabilize them. For each test, an emulsion is prepared according to the protocol described by varying only the surfactant concentration. The Dx(10), Dx(50) and Dx(90) listed in Table 2 represent the average of five measurements for mass concentration tested.

Table 2

Diameter values as a function of PVA mass concentration (Mean ± SD, n=3)

Diameter (nm)	*% mass in PVA*			
	0.8 %	1 %	1.5 %	2 %
Dv (10)	215±5.2	126±3.1	137 ±3.5	226 ±4.8
Dv (50)	331±7.8	177 ±4.1	228 ±5.6	373±8.1
Dv (90)	718±12.4	324±6.9	496 ±9.2	789 ±13.5

Following these results, a solution of 1% by mass of PVA was used for the remainder of this study.

Our findings regarding the 1% PVA concentration as optimal for PCL stabilization align with previous reports by Raza *et al*. (2024), who noted that

concentrations above 2% often lead to a 'micellar effect' rather than improved surface coating. However, our study deviates from the trends reported for lower molecular weight polyesters, where size reduction is typically linear with energy input. This suggests that the high molecular weight of our PCL (80,000 g·mol $^{-1}$) increases the viscosity of the organic phase, necessitating a narrower window of homogenization parameters to achieve monodispersity.

3.3. Influence of the speed of addition of the organic phase

Other tests were carried out to evaluate the influence of the speed of addition of the organic phase (pre-emulsification time) and the homogenization time of the emulsion thus formed. These tests were carried out by adding the organic phase to the aqueous phase using a syringe. For the pre-emulsification time, the initial protocol provided for an organic phase addition rate of 1 mL/45 sec, i.e. a total time of 225 seconds. It was also chosen to test an emulsion for which the contents of the syringe are poured in a single jet, approximately 30 seconds. The results regarding the influence of the pre-emulsification time on the nanoparticle size and PDI are summarized in Table 3.

Table 3

Nanoparticle sizes and associated PDIs as a function of solution pre-emulsion time (Mean ± SD, n=3)

Parameters	Pre-emulsification time (sec)	
	30	220
Z-average (nm)	168.8±3.4	167.2±3.1
PDI	0.101±0.008	0.106±0.009

The results summarized in Table 3 and Fig. 3 reveal that the pre-emulsification time (30 s vs. 220 s) has a negligible impact on both the Z-average and the polydispersity index (PDI). From a thermodynamic perspective, this suggests that the final particle size is not determined during the initial macro-emulsification stage, but is rather a function of the equilibrium reached during the subsequent high-energy homogenization step.

The stability of the PDI (approx. 0.10) regardless of the addition rate indicates that the PVA surfactant is present in sufficient concentration (1% w/v) to rapidly stabilize the newly formed interface, preventing immediate coalescence even when the organic phase is added in a single jet. Consequently, for process optimization and time efficiency, the rapid addition method was selected, as it does not compromise the monodispersity of the PCL suspension.

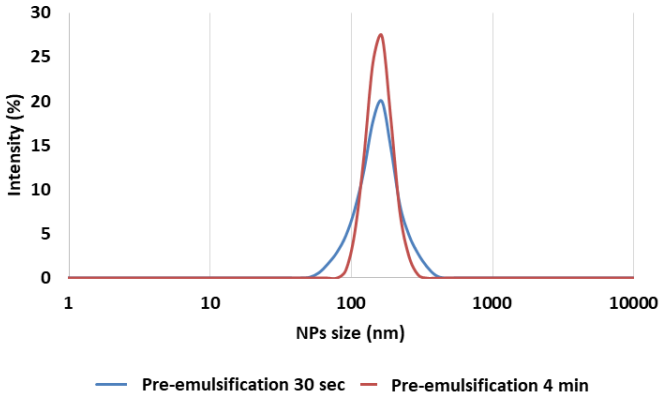

Fig. 3 − Distribution of the size of the nanoparticles according to the pre-emulsification time of the solution.

For reasons of simplicity of implementation, it was chosen to modify the protocol and opt for adding the organic phase all at once.

Furthermore, the influence of the homogenization time (the second stage of emulsification) was evaluated. While the pre-emulsification involves the initial mixing, the homogenization time is critical for achieving the final submicron size. Three different durations (3, 5, and 10 minutes) were tested, keeping all other parameters constant. The results, including the Z-average and Polydispersity Index (PDI), are presented in Table 4.

Table 4

Evolution of Z-average and Polydispersity Index (PDI) as a function of homogenization duration (Mean ± SD, n=3)

Parameters	Homogenization time (min)		
	3	5	10
Z-average (nm)	183.5±4.2	169.9±3.8	165.4±3.5
PDI	0.123±0.011	0.129±0.012	0.144±0.014

The influence of the homogenization duration (3 to 10 minutes) on the colloidal properties is presented in Table 4 and Fig. 4. A slight reduction in the Z-average (from 183.5 nm to 165.4 nm) was observed as the processing time increased. This trend is consistent with the kinetics of emulsification, where prolonged exposure to ultrasonic cavitation facilitates the further fragmentation of larger droplets.

However, a critical observation is the slight increase in PDI (from 0.123 to 0.144) at the 10-minute mark. This phenomenon can be attributed to the heat accumulation at the probe tip during extended sonication intervals. Even with the use of an ice bath, localized micro-heating can alter the viscosity of the PCL-

chloroform droplets and interfere with the surfactant's adsorption-desorption equilibrium at the interface. Therefore, a homogenization time of 5 minutes was identified as the optimal balance, yielding a Z-average of 169.9±3.8 nm with a narrow size distribution, which is ideal for ensuring consistent pharmacokinetic behavior in parenteral applications.

The influence of the homogenization time on the particle size distribution is further illustrated in Fig. 4. It can be observed that while increasing the time from 3 to 10 minutes leads to a slight decrease in the Z-average, the polydispersity remains within a very narrow and stable range. Following these results, it was chosen not to modify the protocol and to maintain a homogenization time of 5 minutes.

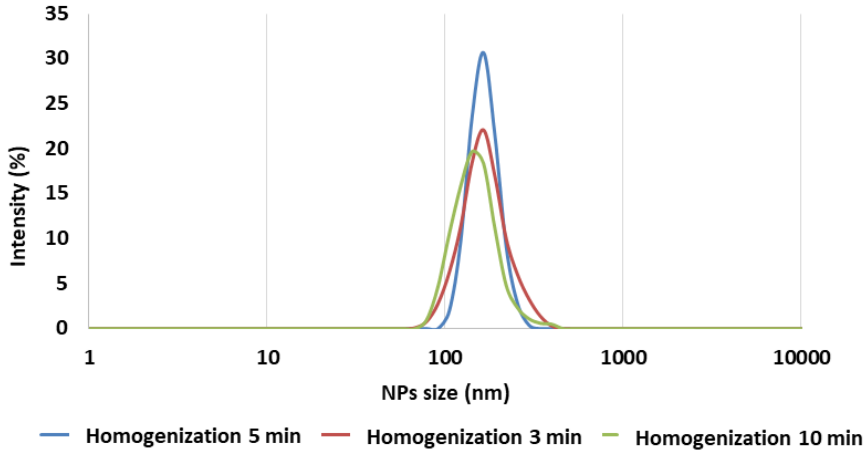

Fig. 4 − Distribution of the size of the nanoparticles according to the homogenization time of the emulsion.

3.4. Zeta potential

The surface charge of the PCL nanoparticles was evaluated to assess their physical stability. The measured Zeta potential values ranged from -1.0 ± 0.2 mV to 2 ± 0.5 mV, which is expected when non-ionic surfactants are used. These values indicate that the physical stability of the suspension is effectively maintained through a steric mechanism provided by the PVA chains. The adsorption of PVA at the PCL surface creates a protective layer that prevents droplet coalescence, as evidenced by the stable PDI values obtained in the optimization study (Table 3, Table 4). These results are consistent with findings by Raza *et al.* (2024) regarding polyester-based systems stabilized by non-ionic surfactants.

4. Conclusions

The obtained results show, firstly, that all the NPs produced by the emulsion-solvent evaporation method have a diameter less than 200 nm, the limiting diameter for parenteral injection. Maintaining the particle size below this 200 nm threshold is crucial for the biological performance of the delivery system. From a physiological standpoint, nanoparticles in the 100-200 nm range are optimal for avoiding rapid clearance by the mononuclear phagocyte system (MPS), particularly in the liver and spleen. This size range also facilitates the potential accumulation of NPs in target tissues through the Enhanced Permeability and Retention (EPR) effect, which is vital for long-circulating injectable formulations. By ensuring a monodisperse distribution (low PDI), the unpredictable behavior of larger aggregates in the bloodstream is minimized, reducing the risk of capillary blockage or acute immune responses.

In addition, the very low PDI values indicate a controlled and monodisperse particle size distribution. Moreover, it appeared that the optimal conditions for the preparation of PCL nanoparticles are: (i) preparation of 5 mL solution at 1 wt. % concentration in $CHCl_3$; (ii) addition of the organic solution into 60 mL of aqueous PVA solution at a concentration of 1 wt. %; (iii) homogenization during 5 min. The emulsion thus obtained is left under magnetic stirring at 500 rpm for 24 h at room temperature for the evaporation of the organic solvent.

In perspective, this work proposes to carry out complementary studies on the biological evaluations of these NPs such as encapsulation efficiency, in vitro release kinetics, hemocompatibility, cytotoxicity and protein absorption.

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OPTIMIZAREA PARAMETRILOR DE PREPARARE A PARTICULELOR PCL OBȚINUTE PRINTR-O METODĂ DE EMULSIONARE/EVAPORARE

(Rezumat)

Nanotehnologia reprezintă un sector cu potențial ridicat pentru tratamentul bolilor umane. Printre diferitele tipuri de sisteme de administrare a medicamentelor, nanoparticulele polimerice (NP) sunt de o importanță majoră în domeniul biomedical. Acestea sunt utilizate în principal ca vehicule pentru administrarea compușilor activi, protejând astfel medicamentul împotriva degradării enzimatice și chimice și direcționându-l către diverse țesuturi și celule țintă. Mulți factori pot influența dimensiunea NP-urilor, cum ar fi viteza de agitare, concentrația polimerului, viteza de adăugare a fazei organice sau concentrația de surfactant. Scopul acestui studiu a fost de a găsi condițiile optime pentru prepararea nanoparticulelor de poli(ε-caprolactonă) folosind o metodă de emulsificare/evaporare. Folosind tehnica de difuzie dinamică a luminii, a fost posibilă evaluarea condițiilor optime pentru prepararea NP-urilor cu dimensiuni mai mici de 200 nm, cum ar fi: o concentrație masică de 1% în $CHCl_3$, o concentrație masică de 1% de PVA în faza apoasă, omogenizare de 5 minute.