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INNOVATIONS IN POLYMERIC NANOPARTICLES FOR PHARMACEUTICALS APPLICATIONS

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INTRODUCTION

Polymer nanoparticles are submicron-sized colloidal systems widely used for delivering an active pharmaceutical ingredient to the tissues/cells of interest.

Depending on the manufacturing process either nanocapsules or nanospheres can be prepared. Nanocapsules are vesicular systems in which a drug is tethered inside a cavity surrounded by a polymeric membrane; nanospheres are systems in which the drug is dispersed throughout the particle. The efficacy of these systems is strongly dependent on their mean size and on the particles size distribution (PSD). Nanoparticles are generally composed by biodegradable homopolymers or copolymers, as well as by non-biodegradable compounds. Poly-ε-caprolactone (PCL), an aliphatic semicrystalline polyester is widely used as it is biocompatible, biodegradable and nontoxic.

Among the various techniques that can be used to prepare polymer nanoparticles the solvent displacement is of great interest due to the fact that it allows controlling the PSD of the nanoparticles modifying the operating parameters, the size of the particles is highly reproducible, and it is possible to use solvents with low toxic potential. At first the polymer is dissolved into a solvent and, then, the solution is mixed with the antisolvent and the nanoparticles are spontaneously formed. Special micro-mixers are used to ensure good mixing conditions as the process of nanoparticle formation is generally very fast and, thus, it is influenced by mixing [1].

The research activity of the PolyNANO research team of the Politecnico di Torino is currently pursuing the development of new methodologies for the synthesis of polymeric nanoparticles in micro-reactors, focusing, in particular, on particles functionalization (in such a way that drug release in the target cells is expected to occur) and on the increase of drug loading (taking into account also the kinetics of drug release). Besides, PolyNANO has also investigated new ways to produce nanocapsules that can either be based on conventional technologies such as the mini-emulsion polymerization or involves more recent technologies such as the aerosol polymerization. A selection of the main results is briefly presented in the following.

1 NANOPARTICLES SYNTHESIS IN MICRO-REACTORS

The synthesis of polymer nanoparticles using the solvent displacement method has been carried out in two different micro-reactors, namely the Confined Impinging Jets Mixer (CIJM), and the Multi Inlet Vortex Mixer (MIVM). In a CIJM two high velocity jets of fluid flow and impinge in a small chamber that induces a very intense turbulent flow, which provides high mixing efficiency. In a MIVM two (MIVM-2) or four (MIVM-4) streams tangentially enter in a cylindrical mixing chamber, where mixing occurs. The test drug has been the ciprofloxacin, a quinolone antibiotic, and chitosan was used for surface functionalization, aiming to obtain a positive surface charge, useful to improve the mucoadhesive characteristics of the particles. Poloxamer 388 was used as surfactant, aiming to control particle size. In all tests PCL was initially dissolved in acetone and, after nanoparticle synthesis, this solvent was removed through evaporation. Then, centrifugation was used to separate the particles from the liquid medium, and dialysis was used to investigate the release of the drug in vitro, considering buffers with different values of the pH, simulating various target tissues of the human body.

Figure 1a shows the mean particle diameter obtained after synthesis in the MIVM and in the CIJM, ad after two other key stages in the manufacturing process, namely evaporation (for solvent removal) and centrifugation (for particle separation). It appears that when using the MIVM the size of the particles is smaller than with the CIJM, but the greater simplicity of the CIJM motivated the further investigation of this device. Besides, it appears that nanoparticles produced are highly stable, and the various processing steps after the synthesis do not affect particle size.

With respect to reactant concentrations, it appears, from Figure 1b, that Poloxamer 388 is needed to stabilize the nanoparticles, thus obtaining a particle diameter compatible with the final application. With respect to ciprofloxacin concentration in the feed, it appears that a non-linear relation exists between the initial drug concentration and the amount of drug encapsulated in the particles, as shown in Figure 2a, where the encapsulation efficiency appears to range between 7 and 20%.

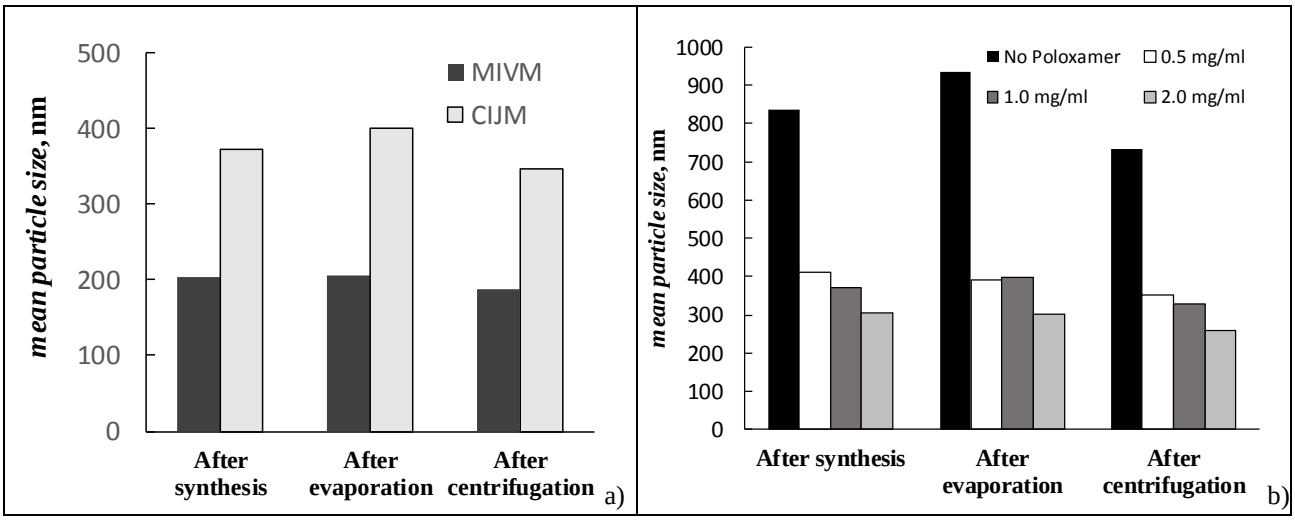

Fig. 1. a) Comparison between the mean particle size obtained in the MIVM and in the CIJM in different stages of the manufacturing process (ciprofloxacin: 2 mg/ml, chitosan: 2.5 mg/ml, Poloxamer: 1 mg/ml, PCL: 5 mg/ml) ; b) Effect of Poloxamer concentration on mean particle size in different stages of the manufacturing process using CIJM (ciprofloxacin: 2 mg/ml, chitosan: 2.5 mg/ml, PCL: 5 mg/ml)

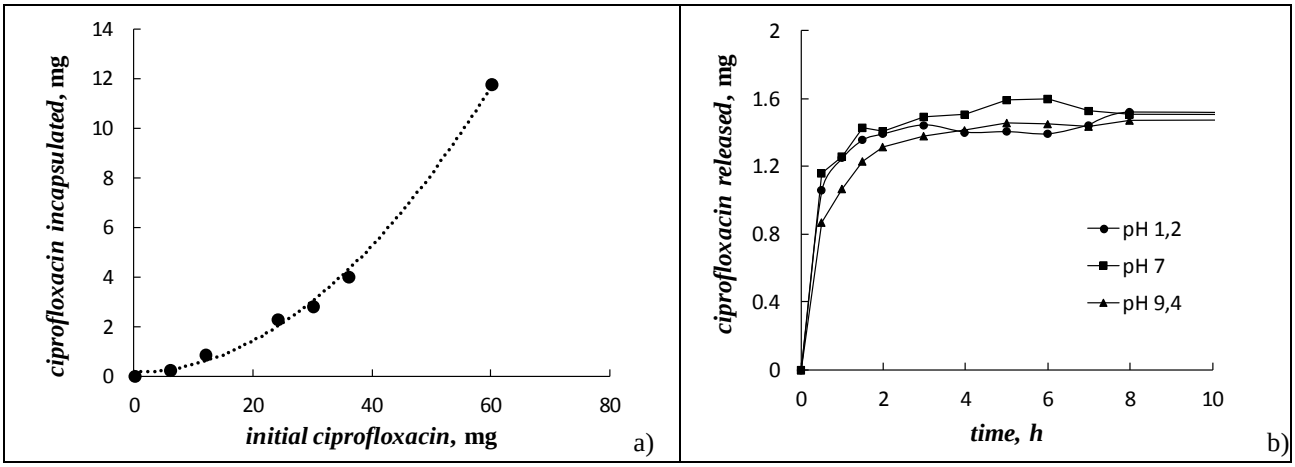

Fig. 2. a) Amount of encapsulated ciprofloxacin as a function of the initial drug concentration (CIJM, chitosan: 2.5 mg/ml, Poloxamer: 1 mg/ml, PCL: 5 mg/ml); b) Amount of ciprofloxacin released in the dialysis tests in different buffers.

Finally, release study (Figure 2b) evidence that about 15% of the drug encapsulated in the particles is released, mainly in the first 6 hours, and that the kinetic release is almost unaffected by the pH of the medium.

2 INTERFACE-EMILSION POLIMERIZATION

As widely discussed above, a common way to produce nanocapsules is by precipitation of a preformed polymer at the interface between the continuous and the dispersed phase of an emulsion. If the starting point is a monomer, the emulsion polymerization can still be used to produce nanoparticles with a core-shell structure; this result is commonly obtained through a double emulsion (e.g., water/oil/water) using a two-stage emulsification and then inducing the polymerization reaction by heating or UV irradiation. However, the production of a double emulsion cannot be controlled precisely and, thus, the size and distribution of the final particles is scarcely reproducible. Because of that, the PolyNANO team worked on the development of a new polymerization method (named interface-emulsion polymerization) that does not involve the creation of a double emulsion [2].

The idea is to dissolve the monomer and the initiator in two separate phases, the monomer in the continuous phase and the initiator in the dispersed one. This configuration allows us to carry out the polymerization reaction at the droplet interface, making the liquid droplet to act as a template on which surface the polymeric shell can grow. The final result is the production of a core-shell polymeric structure. A schematic of the mechanism at the basis of this method is given in Figure 3.

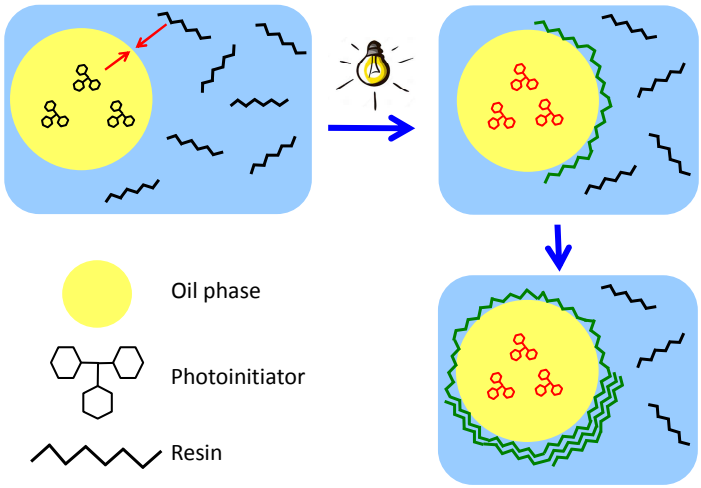

Fig. 3. Schematic of the interface-emulsion polymerization.

The production of a core-shell structure was confirmed by the TEM micrograph shown in Figure 4. This structure can be obtained independently of the starting monomer.

This approach also facilitates the encapsulation of active ingredients, provided that the therapeutic ingredient can be solved into the dispersed phase. The size and the shape of the nanocapsules can be modified by acting on both the manufacturing conditions (namely time of sonication and time of UV irradiation) and the type of monomer.

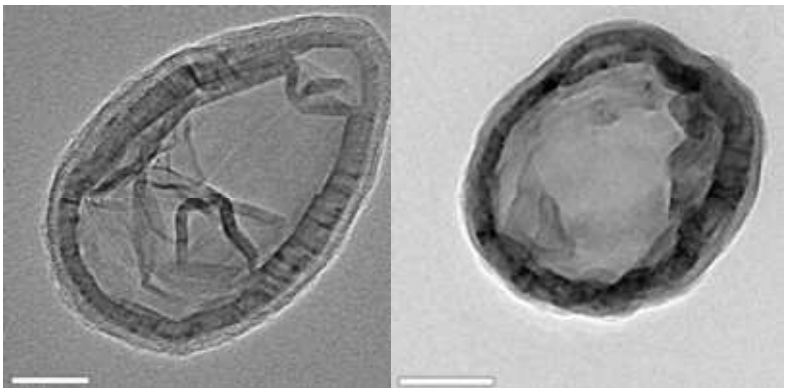

Fig. 4. TEM pictures of the nanocapsules prepared from (left graph) poly(ethylene glycol) diacrylate and (right graph) poly(ethylene glycol) methyl ether methacrylate. Bar scale is 50 nm.

As an example, Figure 5 shows the dependence of the average size of the nanocapsules upon the ratio between two resins: (A) poly(ethylene glycol) diacrylate and (B) poly(ethylene glycol) methyl ether methacrylate.

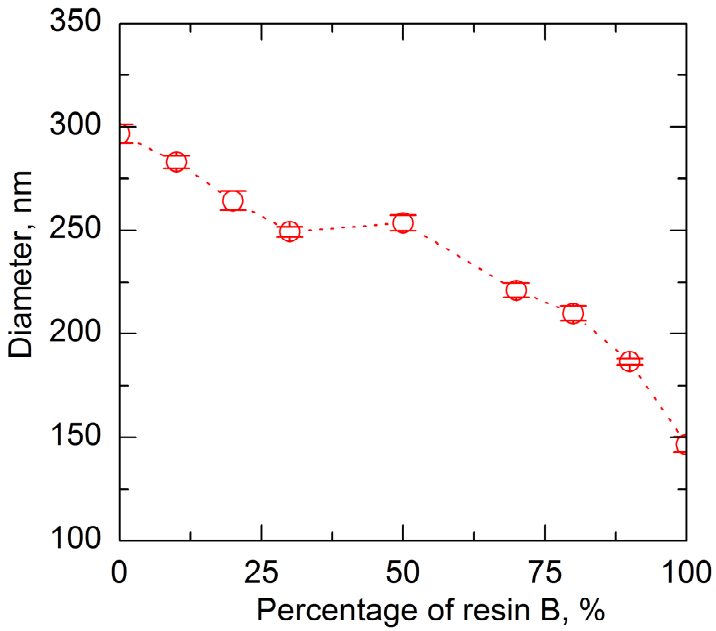

Fig. 5. . Effect of the ratio between resin B and resin A on the average size of the nanocapsules. Samples produced using a lipophilic photo-initiator, bis(2,4,6-trimethylbenzoyl)-phenylphosphineoxide, 15 min as sonication time and 10 min as UV-irradiation time.

The average size of the nanocapsules linearly decreased with the ratio between resins B and A, because the number of the available crosslinked sites decreased promoting the formation of a more open structure that can be swelled. It follows that the average size of the nanocapsules can precisely be controlled varying the composition of the initial photocurable mixture. A similar result can be obtained by adjusting the manufacturing conditions as widely described in Bazzano *et al*. [2]. Overall, the manipulation of the manufacturing factors allows a precise control of the nanocapsules structure (average pore size and thickness of the polymeric shell), which is essential for the regulation of the release rate of a therapeutic agent as shown in [2].

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[2] Bazzano M., Pisano R., Brelstaff J., Spillantini M.G., Sidoryk-Wegrzynowicz M., Rizza G., Sangermano M., *In press*. Synthesis of polymeric nanocapsules by radical UV-activated interface-emulsion polymerization. *Journal of Polymer Science Part A: Polymer Chemistry*.