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# Preparation of uniform poly-caprolactone Microparticles by membrane emulsification/solvent diffusion process

Alessandra Imbrogno [a,b,*], Emma Piacentini [a], Enrico Drioli [a,b], Lidietta Giorno [a]

[a] Institute on Membrane Technology, National Research Council, ITM-CNR, Via P. Bucci 17/C at University of Calabria, 87036 Rende (CS), Italy
[b] Dipartimento di Ingegneria per l'Ambiente e il Territorio e Ingegneria Chimica, University of Calabria, Via P. Bucci 42/A, 87036 Rende (CS), Italy

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ABSTRACT

Over the last decade, the use of polycaprolactone has attracted much interest in drug delivery compared to biodegradable polyesters derived from lactic and glycolic acids. The methodologies commonly used for the preparation of polycaprolactone microparticles are associated with many problems regarding the control of particle size and size distribution and particles morphology. Membrane emulsification/solvent diffusion processes offer great potentials in manufacturing particles. In this work, polycaprolactone microparticles with mean diameter of 20 μm, spherical shape and smooth surface have been successfully produced using the emulsification/solvent diffusion method. The fluid-dynamic and chemical parameters have been optimized to produce uniform particles with a span value of 0.5. The effect of process parameters controlling the solvent diffusion on the shape and surface morphology has also been investigated. The use of microporous membranes allowed the simultaneous particle size and size distribution control during the emulsification step. Also, the solvent diffusion permitted easy control of the size and morphology of particles during the solidification of polymer within the droplets.



## 1. Introduction

Biodegradable microparticles are widely investigated drug delivery systems for bioactive compounds such as low molecular weight and macromolecular therapeutics. This is because they offer possibilities to produce drug delivery systems where the matrix material can be decomposed into non-toxic and low molecular-weight species with the concomitant release of drug. During the last two decades, among common biodegradable polyesters derived from lactic acid and glycolic acid (poly-lactic acid, poly-glycolic acid, and poly-lactic-co-glycolic acid), there has been an increasing interest in the use of polycaprolactone (PCL) in drug delivery. Reasons for this include its excellent biocompatibility, ability to be fully excreted from the body once bioreabsorbed, relatively inexpensive production routes and superior rheological and visco-elastic properties when compared with other aliphatic polyesters [1].

Owing to its low glass transition temperature ($Tg \sim -60\ ^{\circ}C$), PCL is in a rubbery state at body temperature, giving it a highly flexible structure that permits easier diffusion of drugs than in glassy or crystalline drug carriers. It is thus a good candidate for developing diffusion-controlled drug delivery systems. On the contrary, the glass transition temperature of polyesters derived from lactic acid and glycolic acid, is reported to be above the physiological temperature of 37 °C. As a consequence they are characterized by a predominantly glassy structure with fairly rigid chains resulting in lower permeability to drugs [2–4].

PCL is an advantageous material also for its high permeability to small drug molecules and its negligible tendency to generate an acidic environment during the degradation process as compared to polylactids and polyglicolids, a problem that contributes to the generation of inflammatory reactions. The degradation of PCL is very slow compared to the other polyesters making it more suitable for long-term delivery systems with the advantage of less frequent administrations, increase of patient compliance and reduction of discomfort. Delivery of PCL particles can also be easily modulated with appropriate blending and copolymerization. Functional groups could also be added to design the desired mechanical and chemical properties or degradation kinetics [1].

Microspheres based on the use of PCL have been used to encapsulate many drugs such as antigens [5], antihypertensive [6], contraceptives [7], taxol [8], and were found resistant to simulated gastric fluid allowing the entrapped drugs to pass intact into the intestine [9]. Within the last decades, PCL polymers have been also successfully used to develop controlled delivery systems

* Corresponding author at: Institute on Membrane Technology, National Research Council, ITM-CNR, Via P. Bucci 17/C at University of Calabria, 87036 Rende (CS), Italy. Tel.: +39 0984 492134; fax: +39 0984 402103.
*E-mail address:* a.imbrogno@itm.cnr.it (A. Imbrogno).

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especially for peptides and proteins. Jameela et al. [5] showed that PCL has a good permeability to proteins unlike polylactids and polyglycolids and is a good carrier for vaccine delivery because it does not generate the acidic environment that affects antigenicity of vaccines.

PCL microparticles have been typically prepared by two kinds of processes: spray drying and emulsion solvent evaporation or diffusion. In the spray drying method, particles are formed directly by atomization of the organic solvent containing the polymer and the treatment with hot air to remove the solvent. However, this process is not suitable when highly temperature-sensitive compounds have to be encapsulated and control of particle size is difficult [10]. In the emulsion step of the emulsion/solvent evaporation process, a polymeric solution (obtained by dissolving the preformed polymer in the organic phase) can be emulsified in an aqueous phase to produce a simple O/W emulsion. The polymeric solution can also be used as oil phase for the preparation of simple water-in-oil (W/O) emulsion, which is emulsified again in an aqueous phase to produce a multiple water-in-oil-in-water (W/O/W) emulsion. In the solvent evaporation step, the organic solvent is removed after the emulsification step by evaporation. Solvent evaporation depends mostly on temperature and the concentration of solvent in the air. The process could be accelerated either by increasing the temperature of the continuous phase or by reducing the pressure. However, larger size, decreased drug encapsulation efficiency and coarser morphology have been reported in literature [11].

The preparation of particles using polyesters as polymeric material and emulsion solvent diffusion was proposed for the first time by Quintanar-Guerrero [12]. In that work, the emulsification of the partly water soluble solvent containing the polymer in an aqueous phase, is followed by the addition of water to the system. This causes the diffusion of solvent into the external phase, resulting in the solidification of polymer within droplets. This technique presents advantages such as the use of pharmaceutically acceptable organic solvents, high reproducibility and better control of particle size.

Moreover the use of preformed polymers is preferable compared to polymerization processes as the latter is associated with the presence of residual substances and cross reactions with the drug which produce potentially-toxic effects [12,13].

The conventional emulsification processes (homogenization, sonication or stirring) do not offer the possibility to easily control droplet size and size distribution simultaneously. Therefore, a significant quantity of microparticle product would be recycled as off-spec, thus potentially incurring a substantial increase in processing cost. Particle size is an important parameter that influences almost every aspect of particle function including degradation, flow properties, clearance and uptake mechanisms. It can be controlled through physical properties of the materials, such as polymer and surfactant concentration, or through the experimental parameters of the fabrication method [14]. Relatively newer emulsification techniques, such as membrane emulsification, offer great potentials in manufacturing “made-to-measure” emulsions and other solid particulates [15].

Membrane emulsification basically consists in the permeation of the dispersed phase through a porous membrane to form droplets at the opening pore and the subsequent detachment from the membrane surface occurred by the shear stress of the moving continuous phase. A distinguishing feature of membrane emulsification is the possibility to control the resulting droplet size primarily by the choice of the membrane and not by the generation of turbulent droplet break-up which characterizes conventional methods. The technique is highly attractive for its simplicity, potentially lower energy demands, and resulting narrow droplet size distributions. Moreover, membrane systems are particularly suitable for large scale production because they are mainly based on multiplication of small-scale processing units (e.g. membrane modules) rather than the simple enlargement of processing vessel sizes [16].

Membrane emulsification has been applied for the preparation of microspheres and microcapsules using mainly polyesters derived from lactic acid [17–20] and copolymers with glycolic acid [21,22]. In these works, the organic solvent was removed by evaporation or in some cases by extraction with alcohols.

PCL particles have been prepared by combining the use of membrane contactors and nanoprecipitation [23]. In this case, an organic solvent completely soluble in water, containing dissolved PCL, was used as dispersed phase to form solidified particles directly at the opening pore. The solidification of the particles occurs after the droplets are in contact with the aqueous continuous phase. Charcosset and coworkers mainly focused on evaluating the effects of operating parameters (such as membrane pore size, dispersed phase flux and cross-flow velocity of the continuous phase) on particle size. They observed that the particles size was mainly controlled by the nanoprecipitation due to the interfacial deposition of the polymer followed by the displacement of the solvent and the effect of dispersed phase flux, continuous phase cross-flow velocity and membrane pore size was not as significant as expected by the use of the membrane process. To our knowledge, no other work is reported in literature about the preparation of PCL particles using membrane-based processes.

In this work, the preparation of PCL microparticles was carried out in a two-step process: (a) *the pre-emulsification step*, where the membrane was used to prepare an O/W emulsion with an organic solvent partly soluble in water as dispersed phase and (b) *the post-emulsification step*, where the solidification of particles was carried out by the solvent diffusion process. The membrane was used to disperse the droplets of organic phase in the water phase saturated with the organic solvent, without promoting the direct exchange of the solvent and non-solvent at pore level. In this case, the pre-emulsification step is expected to finely control the production of particles in terms of size and size distribution by selecting the appropriate process parameters and membrane pore size. The effect of phase composition (polymer concentration in the dispersed phase and the kind of emulsifier in the continuous phase) and fluid-dynamic parameters (dispersed phase flux and shear stress) on particle size and size distribution have been investigated in the pre-emulsification step. In the post-emulsification step, the effect of the volume of water used to carry out the solvent diffusion on particle size and size distribution, particle shape and surface morphology have also been studied.

## 2. Experimental section

A polymeric solution of polycaprolactone (PCL, Sigma-Aldrich, Mw 14 kDa) in dichloromethane (DCM, Sigma-Aldrich) was used as dispersed phase for the preparation of O/W emulsions and particles. Polycaprolactone is a hydrophobic polyester approved by Food and Drug Administration for human use. Ultrapure water (USF Elsa, model Purelab Classic PL5221) with a resistivity of 18.2 MΩ cm was used as continuous phase for the preparation of the emulsions and as dilution medium for the preparation of particles by the solvent diffusion process. The continuous phase was saturated with solvent in order to avoid its diffusion during the emulsification process. Poly-vinylalcohol (PVA, 1 wt%), sodium dodecyl sulfate (SDS, 2 wt%) and polysorbate (Tween 80, 2 wt%), all purchased from Sigma Aldrich, were tested as emulsifiers.

### 2.1. O/W emulsion preparation: membrane emulsification equipment

The preparation of the emulsions with a Dispersion Cell was carried out with a hydrophilic flat-sheet metallic membrane with