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Microfluidic-assisted nanoprecipitation of (PEGylated) poly (D,L-lactic acid-*co*-caprolactone): Effect of macromolecular and microfluidic parameters on particle size and paclitaxel encapsulation

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ABSTRACT

In this work we evaluate the effect of polymer composition and architecture of (PEGylated) polyesters on particle size and paclitaxel (PTX) loading for particles manufactured via microfluidic-assisted, continuous-flow nanoprecipitation using two microfluidic chips with different geometries and mixing principles.

We have prepared poly (D,L-lactic acid-*co*-caprolactone) (PLCL) from ring-opening polymerization (ROP) of LA and CL mixtures and different (macro) initiators (namely, 1-dodecanol, a MeO-PEG-OH, and a 4-armed star PEG-OH), rendering polyesters that vary in monomer composition (i.e. LA/CL ratios) and architecture (i.e. linear vs 4-armed star). Continuous-flow nanoprecipitation was assayed using two microfluidic chips: a cross-flow chip with a X-shaped mixing junction (2D laminar flow focusing) and a micromixer featuring a Y-shaped mixing junction and a split and recombine path (2D laminar flow focusing convinced with stream lamination for faster mixing). Nanoparticle formulations were produced with Z-average sizes in the range of 30–160 nm, although size selectivity could be seen for different polymer/chip combinations; for instance, smaller particles were obtained with Y-shaped micromixer (30–120 nm), specially for the PEGylated polyesters (30–50 nm), whereas the cross-flow chip systematically produced larger particles (80–160 nm). Loading of the anti-cancer drug paclitaxel (PTX) was also heavily influenced not only by the nature of the polyester, but also by the geometry of the microfluidic chip; higher drug loadings were obtained with the cross-flow reactor and the star block copolymers. Finally, decreasing the LA/CL ratio generally had a positive effect on drug loading.

1. Introduction

Nanoprecipitation has gained attention as one of the most simplistic preparative methods for the manufacturing of nanoparticles with the view to designing delivery systems with good drug loadings, controlled drug release, long circulation times, and hence, the ability to increase the therapeutic index of drugs (D'Addio and Prud'homme, 2011; Schubert et al., 2011). In this preparative process, a solution of a hydrophobic polymer dissolved in a water-miscible organic solvent is streamed into an aqueous solution (non solvent) and, as the solubility of the polymer in the mixture decreases, polymer aggregates form (nucleation) that increase in size via both deposition of further chains and coalescence (growth). Particle growth is halted by the gradual adsorption of a surfactant onto the particle, making it unsuitable for further polymer association; the surfactant is generally present in the water phase, or as an alternative, the polymer itself can have surfactant (amphiphilic) properties resulting in a preferential localisation of the hydrophilic block in the particle surface. Particle properties such as size can be controlled by acting on the polymer's macromolecular parameters (i.e. composition and architecture) and/or on the nanoprecipitation conditions (i.e. solvent/water ratio, solvent/surfactant type, flow rates in flow processes, agitation speed in batch ones). In addition, by

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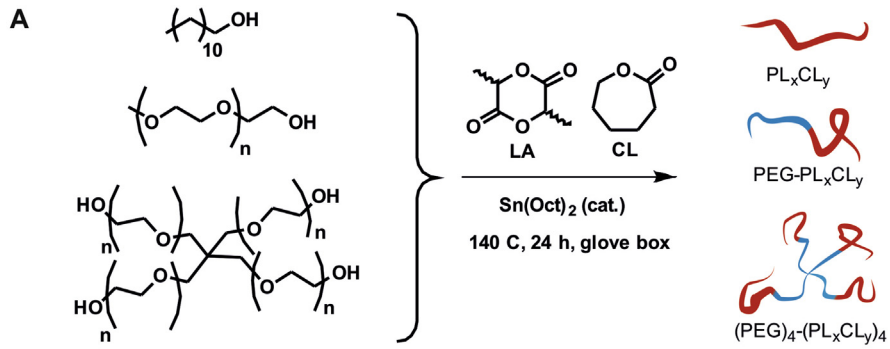

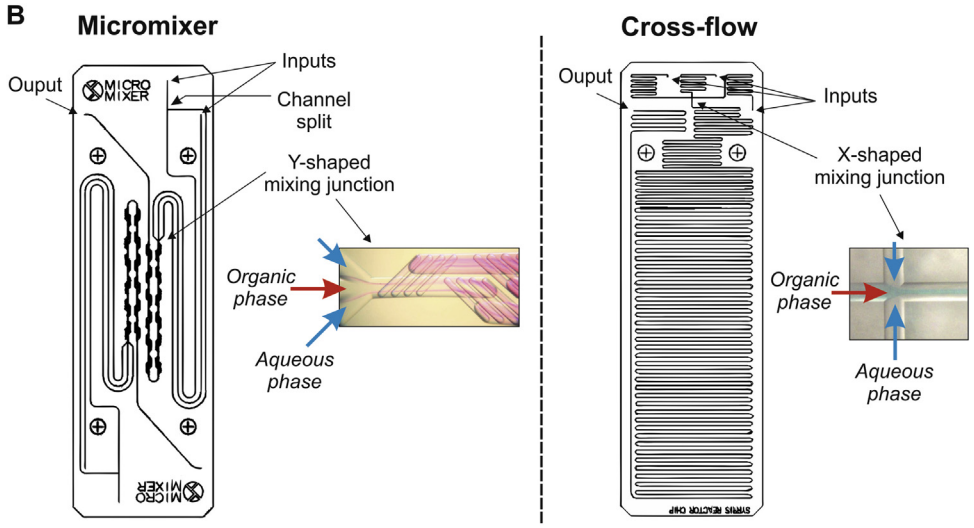

C

Specification	Micromixer	Cross-flow
Number of inputs	2	3
Number of outputs	1	1
Total reaction volume (µL)	26	1000
Internal cross section dimension (depth x width; µm)	50 x 125 (mixing channel) 125 x 350 (reaction channel)	1240 x 161 (mixing channel) 1240 x 391 (reaction channel)
Mixing junction geometry	Y-shaped	X-shaped

Scheme 1. A $Sn(Oct)_2$-catalysed ring-opening (co)polymerisation (ROP) of lactide (LA) and ε-caprolactone (CL) used to provide all macromolecular structures: a) 1-dodecanol was employed to yield linear, hydrophobic PLxCLy (top structure), b) hydroxyl-terminated PEG to yield linear, amphiphilic PEG-PLxCLy) (middle structure), c) a 4-armer PEG to yield 4-armed star, amphiphilic $(PEG)_4$-$(PLxCLy)_4$ (bottom structure). In the drawing of the right, the polyester and PEG blocks are respectively graphically represented in blue and red. B Schematic representation of the micromixer and cross-flow chips used in this study. Inlet pictures represent a magnification of the mixing junction of each chip. Reproduced with permission from Syrris Ltd. C Main specifications of the micromixer and cross-flow chips. Please note that the number of inlets refers to the number of tubing connections of the chip, not to the number of inlet channels at the mixing junction (which is three in both mixers; blue and red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

using emulsifiers (e.g. Pluronics ®) or amphiphilic polymers (e.g. PEGylation) nanoprecipitation also provides a straight forward method to modulate the composition and density of the hydrophilic surface layer of the particles, which is of key importance to avoid their early opsonisation and uptake by the mononuclear phagocytic system (Gustafson et al., 2015; Owens and Peppas, 2006).

The pharmaceutical industry has traditionally relied on batch processes (reactor + agitator) for the production of different types of particles (Martínez Rivas et al., 2017; Paliwal et al., 2014). However, despite being a cost-saving and rather simple manufacturing strategy, batch processes are often affected by fluidodynamic issues (e.g. variable flow rate and Reynolds' number within the vessel), which can give rise to large heterogeneities in the nanoparticles produced in the same batch and to severe practical limitations in terms of process reproducibility and scalability (Ciofalo et al., 1996; Kumaresan and Joshi, 2006).

Currently, attention is gradually being shifted away from batch towards continuous (flow) manufacturing approaches (Lee et al., 2015). In the case of nanoprecipitation this is particularly advantageous for both heat and mass transfer, and offers an unparalleled stability of the mixing fluidodynamics (geometry and rate of mixing of the two phases), and therefore of the parameters defining the kinetics of phase separation, particle nucleation and growth (Liu et al., 2017b). Importantly, in microfluidic-assisted nanoprecipitation the mixing performance of the microfluidic chip is heavily influenced by its geometry (mixing junction and mixing channel) and the stream flow rate, as recently studied by Reckamp et al. (2017) on a series of commercially available microreactors operating under different mixing principles (simple contacting, flow obstacles, split and recombine, and multilamination). Hence, although continuous-flow nanoprecipitation has potential to offer superior manufacturing capabilities in scale-up of formulations (Lim et al., 2014), careful selection of microfluidic chip geometry and flow conditions is key for optimal nanoparticle design.

Since the pioneering work by the group of Benita (Fessi et al., 1989) on the nanoprecipitation of poly(lactic-*co*-glycolic acid) (PLGA) nanocapsules, efforts were initially devoted to develop microfluidic approaches for the preparation of various types of microsystems (Martín-Banderas et al., 2005; Nisisako et al., 2004; Seo et al., 2005; Xu et al., 2005). The first example of this kind for the preparation of self-assembled poly(ethylene glycol)-*bl*-poly(lactic-*co*-glycolic acid) (PEG-PLGA) organic nanoparticles was later published by the group of Farokhzad (Karnik et al., 2008). Since these first examples, many authors have explored continuous-flow approaches for the manufacturing of

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