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Preparation of biodegradable polymeric nanoparticles for pharmaceutical applications using glass capillary microfluidics

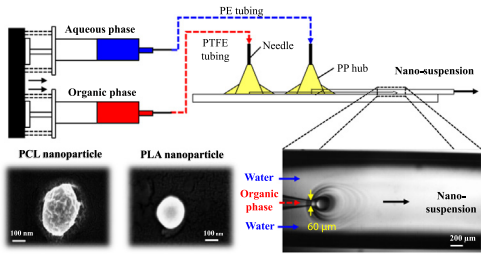
Rahimah Othman [a,c,*], Goran T. Vladisavljević [a,**], Zoltan K. Nagy [a,b]

[a] Department of Chemical Engineering, Loughborough University, Ashby Road, Loughborough, Leicestershire, LE11 3TU, UK
[b] School of Chemical Engineering, Purdue University, West Lafayette, IN 47907-2100, USA
[c] School of Bioprocess Engineering, Universiti Malaysia Perlis, Kompleks Pusat Pengajian Jejawi 3, Arau, 02600 Perlis, Malaysia

HIGHLIGHTS

- Glass capillary devices were used to prepare PLA and PCL NPs with tuneable sizes.
- PLA formed smaller NPs with a smoother surface morphology and more rounded shape.
- Smaller NPs were produced by counter-current flow focusing than co-flow.
- PCL NPs formed in flow focusing device with 200-μm orifice were smaller than 200 nm.
- The higher the aqueous-to-organic flow rate ratio, the smaller the NPs formed.

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of this study was to develop a new microfluidic approach for the preparation of nanoparticles with tuneable sizes based on micromixing/direct nanoprecipitation in a coaxial assembly of tapered-end glass capillaries. The organic phase was 1 wt% poly(ε-caprolactone) (PCL) or poly(dl-lactic acid) (PLA) in tetrahydrofuran and the antisolvent was Milli-Q water. The size of nanoparticles was precisely controlled over a range of 190–650 nm by controlling phase flow rates, orifice size and flow configuration (two-phase co-flow or counter-current flow focusing). Smaller particles were produced in a flow focusing device, because the organic phase stream was significantly narrower than the orifice and remained narrow for a longer distance downstream of the orifice. The mean size of PCL particles produced in a flow focusing device with an orifice size of 200 μm, an organic phase flow rate of 1.7 mL h^{-1} and an aqueous-to-organic flow rate ratio of 10 was below 200 nm. The size of nanoparticles decreased with decreasing the orifice size and increasing the aqueous-to-organic phase flow rate ratio. Due to higher affinity for water and amorphous structure, PLA nanoparticles were smaller and exhibited a smoother surface and more rounded shape than PCL particles.

1. Introduction

Biodegradable polymeric nanoparticles (NPs) have attracted considerable attention of the scientific community in the last several decades due to their high potential for a site-specific

* Corresponding author at: Department of Chemical Engineering, Loughborough University, Ashby Road, Loughborough, Leicestershire, LE11 3TU, UK.
** Corresponding author.
E-mail addresses: R.Othman@lboro.ac.uk (R. Othman), G.Vladisavljevic@lboro.ac.uk (G.T. Vladisavljević).

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(targeted) drug delivery, especially for oral administration of proteins and peptides and gene therapy (Legrand et al., 2007; Douglas et al., 1987). Biodegradable polymeric NPs are solid carriers with a mean size of less than 1 μm, which are capable to dissolve, entrap, encapsulate or attach active ingredients to its nanoparticle matrix (Legrand et al., 2007). Depending upon the method of NPs preparation and formulation, nanospheres or nanocapsules can be obtained. Nanocapsules are carriers in which the drug is confined to a cavity surrounded by a polymeric shell, while nanospheres are matrix systems in which the drug is uniformly dispersed in a polymer matrix (Mohanraj and Chen, 2007; Soppimath et al., 2001).

Polymeric NPs can be prepared from preformed polymers by emulsification-solvent evaporation, salting-out, dialysis, nanoprecipitation, and supercritical fluid technology or directly synthesised by polymerisation of monomers using polymerisation techniques such as micro-emulsion, mini-emulsion, surfactant-free emulsion and interfacial polymerisation (Nagavarma et al., 2012; Rao and Geckeler, 2011; Galindo-Rodriguez et al., 2004). In nanoprecipitation, two mutually miscible liquids are required, a solvent and non-solvent of the polymer, typically a volatile organic solvent and water, respectively. The NPs are formed almost instantly when the polymer solution is mixed with an excess of non-solvent, after which the solvent can be evaporated off. The method does not require high stirring rates, sonication, elevated temperatures or surfactants, and Class 1 solvents can be avoided (Fessi et al., 1989, 1992; Jain, 2000).

Bilati et al. (2005) have investigated the effect of the type of solvent and non-solvent, solvent/non-solvent volume ratio and polymer concentration on the nanoprecipitation of polylactide (PLA) and poly(d,l-lactic-*co*-glycolic acid) (PLGA). The size of NPs was dependent of the type of non-solvent and increased in the following order: methanol < ethanol < propanol. Lince et al. (2008) prepared poly-ε-caprolactone (PCL) nanoparticles in a Confined Impinging Jets Reactor (CIJR) and found a significant effect of mixing on the final particle size. The mixing efficiency increased with increasing the flow rate of the liquid phases entering the CIJR, which favoured nucleation and led to a marked reduction in the particle size.

In order to achieve a controlled drug release to the specific site of action at the therapeutically optimal rate, NPs should be prepared with a controlled size, adhesion properties and degradation rate (Mohanraj and Chen, 2007). The traditional bulk mixers lack precise control over the mixing process due to their relatively large volume, resulting in poor control over the particle size distribution. Microscale mixers/reactors handle very small fluid volumes, offering the possibility to achieve a homogeneous reaction environment, and have a larger surface-to-volume ratio than conventional bulk mixers, which can greatly reduce the mixing time that becomes comparable with the induction time for nucleation (Capretto et al., 2013).

Ali et al. (2009) prepared hydrocortisone NPs in a microfluidic Y junction. The size of the generated NPs was controlled by the flow rates of solvent and anti-solvent, with smaller particles being formed at higher flow rates. Su et al. (2007) prepared $BaSO_4$ and 2,2-dipyridylamine NPs using a microfluidic set-up composed of three T-junctions. Solvent and anti-solvent droplets were formed in two upstream T junctions and then merged together in a downstream T junction. Génot et al. (2010) positioned a glass capillary at the intersection of the two branches of a Y junction to construct a 3D microfluidic mixer that was used to prepare rubrene nanocrystals. Zhang et al. (2008) and Yun et al. (2009) produced solid lipid nanoparticles using flow focusing devices with cross junction geometry. The particle size was controlled by varying the flow rate ratio of the two phases and introducing gas bubbles downstream of the cross junction. Dev et al. (2013, 2012) used a microfluidic continuous flow rotating tube processor to produce NPs of meloxicam and curcumin by reactive crystallisation.

Membrane micromixing is an alternative strategy of controlled mixing at molecular scale that was combined with nanoprecipitation to produce inorganic nanoparticles (Jia and Liu, 2013), liposomes (Laouini et al., 2013a), micelles (Laouini et al., 2013c), and PCL nanoparticles (Khayata et al., 2012). In a membrane-dispersion reactor, one liquid phase is dispersed through a microporous membrane into another liquid under controlled shear conditions and injection rate.

In this work, a novel microfluidic strategy was developed for fabrication of PCL and PLA NPs based on bringing into contact two co-flowing or counter-current flowing streams in coaxial glass capillaries. Both polymers have been approved by FDA for drug delivery (Jain et al., 1998; Södergård and Stolt, 2002; Panyam and Labhasetwar, 2003) and widely used as excipients in nanoprecipitation processes (Jain, 2000; Lu and Chen, 2004). The main objectives of this study were: (i) to make appropriate choice of good and poor solvent of the polymers, (ii) to observe the mixing process in situ using a microscope video system, and (iii) to investigate the effect of operating parameters, system geometry, and surfactants on the final particle size distribution.

2. Materials and methods

2.1. Chemicals

Tetrahydrofuran (THF) (HPLC grade, purity ≥ 99.9%) and poly(ε-caprolactone) (PCL, M_w = 14,000 g mol^{-1} with a glass transition temperature of 60 °C) were purchased from Sigma-Aldrich (Dorset, UK). Poly(dl-lactic acid) (PLA, Ingeo™ 4060D, M_w = 320,000 g mol^{-1}) was supplied by Natureworks LLC (Minetonka, MN, USA). 4060D is an amorphous polymer with an average D-lactide content of 12 wt% and a glass transition temperature of 55–60 °C. Polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), Tween 20, and Tween 80 were obtained from Sigma-Aldrich (Dorset, UK) and used as water soluble surfactants. All chemicals other than THF were of analytical grade. The antisolvent phase was pure water produced by reverse osmosis (Milli-Q®, Millipore) or aqueous surfactant solutions. The role of surfactant was to prevent agglomeration, coalescence and imperfect surface formation, as well as to reduce the size of the NPs. The organic phase was a homogeneous solution containing 1 g L^{-1} (1000 ppm) of the polymer (PCL or PLA) in THF.

2.2. Equipment

The experiments have been carried out using two different types of glass capillary devices shown in Fig. 1(b) and (c). The main body of the device was made up of two coaxial glass capillaries: an inner capillary with a circular cross section (1 mm O.D. and 0.58 mm I.D.) and an outer capillary with a square cross section (1 mm I.D.). A two-component epoxy glue (Five Minute® Epoxy, ITW Devcon, Rushden, UK) was used to fix the square capillary onto a glass microscope slide that was used as a platform for the microfluidic device. One end of the inner capillary was shaped into a tapered orifice with an I.D. of 60, 150, 200, 300 or 400 μm. It was done by heating and pulling the capillary using a Sutter P-97 Flaming/Brown micropipette puller (Linton Instrumentation, Norfolk, UK) to produce a sharp tip with 20 μm orifice. The diameter of the orifice was then enlarged by grazing the tip against abrasive paper until the required size was achieved and the orifice had a smooth edge, which was observed with a Narishige's MF-830 microforge (Linton Instrumentation, Norfolk, UK). The capillary