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Glass capillary microfluidics for production of monodispersed poly (DL-lactic acid) and polycaprolactone microparticles: Experiments and numerical simulations

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ABSTRACT

Hypothesis: Droplet size in microfluidic devices is affected by wettability of the microfluidic channels. Three-dimensional countercurrent flow focusing using assemblies of chemically inert glass capillaries is expected to minimize wetting of the channel walls by the organic solvent.
Experiments: Monodispersed polycaprolactone and poly(lactic acid) particles with a diameter of 18–150 μm were produced by evaporation of solvent (dichloromethane or 1:2 mixture of chloroform and toluene) from oil-in-water or water-in-oil-in-water emulsions produced in three-dimensional flow focusing glass capillary devices. The drop generation behaviour was simulated numerically using the volume of fluid method.
Findings: The numerical results showed good agreement with high-speed video recordings. Monodispersed droplets were produced in the dripping regime when the ratio of the continuous phase flow rate to dispersed phase flow rate was 5–20 and the Weber number of the dispersed phase was less than 0.01. The porosity of polycaprolactone particles increased from 8 to 62% when 30 wt% of the water phase was incorporated in the organic phase prior to emulsification. The inner water phase was loaded with 0.156 wt% lidocaine hydrochloride to achieve a sustained drug release. 26% of lidocaine was released after 1 h and more than 93% of the drug was released after 130 h.

1. Introduction

Porous microparticles made from synthetic biodegradable polymers are increasingly being investigated for use in medical, biotechnological, and pharmaceutical applications in areas such as contrast-enhanced ultrasound imaging [1], controlled drug delivery [2] and cell growth in tissue engineering scaffolds [3]. Ultrasound is among the most popular medical imaging techniques used for visualizing subcutaneous body structures and blood flow [4]. However, with current technology, 20% of echocardiograms are unusable due to low contrast of the images. To address this issue, ultrasound contrast agents (UCA's) are increasingly being used with ultrasound to improve the quality of the images.

UCAs are intravenously administered gas-filled core–shell or matrix type microspheres with a lipid, protein or synthetic biodegradable polymer shell or matrix, which increases the backscattered signal from blood when insonified by low frequency ultrasound waves [1,5]. Targeted UCA's (TUCAs) may also be used for more specific molecular imaging [6], where particles are retained on the endothelium at the site of pathology via adhesion ligands incorporated into their surface [7]. TUCAs can be loaded with drugs to provide targeted non-invasive drug release on application of high frequency ultrasound [5,8].

Commercial UCAs have a relatively broad size distribution. For example, Optison® (GE Healthcare) has a mean particle diameter of 2.0–4.5 μm and a maximum diameter of 32 μm [9] while Definity® (Bristol-Myers Squibb Medical Imaging) has a mean particle diameter of 1.1–3.3 μm and a maximum diameter of 20 μm [9]. The resonant frequency of a capsule is directly related to its diameter. A capsule that is vibrated (using ultrasound) at its resonant frequency responds to ultrasonic excitation much more efficiently than one that is vibrated but not at its resonant frequency. Given that available ultrasound systems have limited frequency bandwidth, it is highly important that capsules have a narrow size distribution. In addition, monodispersed particles distribute more homogeneously in a patient's body, degrade in a more predictable way, and ensure a predictable therapeutic effect. Furthermore, capsules of the same size can supress the Ostwald ripening effect by reducing the Laplace pressure difference [10]. Therefore, there is

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a strong demand for UCAs and drug microcarriers with controllable size and a narrow particle size distribution.

Conventional methods for manufacturing UCAs such as spray drying [11], sonication or mechanical agitation [12] lead to polydisperse particles, due to the random nature of drop generation and breakup in atomization, mixing and cavitation processes. Monodispersed UCAs can be obtained by differential centrifugation of polydispersed particle population [13], ink-jet printing [14], microchannel emulsification [10–15], and co-axial electrohydrodynamic atomization [16], but these processes are either time-consuming and require multi-step processing or complex and relatively expensive. Monodispersed polymer particles can also be prepared using planar flow focusing microfluidic devices fabricated in polydimethylsiloxane (PDMS) by soft lithography [17,18]. In a planar (2D) flow focusing microfluidic device, the dispersed phase jet is forced through a rectangular orifice, where it is broken up into droplets due to high shear and pressure forces from the surrounding continuous phase. In this planar geometry, the dispersed phase contacts the orifice walls at low continuous phase flow rates (Fig. 1). However, surface wettability of PDMS can change after exposure to organic solvents. For example, extensive hydrophobic wetting of PDMS channels was noticed after exposure to dichloromethane [17]. In addition, due to its softness, PDMS channels are highly deformable.

In this work, monodisperse poly(lactic acid) (PLA) and polycaprolactone (PCL) microparticles with water droplets embedded within the polymer matrix were produced using a novel approach based on emulsification in a 3D (axisymmetric) flow focusing glass capillary device [19,20]. These particles can be used as intermediate products in the production of UCAs. The main objective was to investigate the effects of phase flow rates and geometry of the device on the droplet and particle size and droplet formation behaviour. In a 3D flow focusing device, the dispersed phase jet is completely surrounded by the continuous phase flow irrespective of the hydrodynamic conditions, due to circular orifice geometry (Fig. 1). Therefore, the organic phase does not make contact with the orifice and hydrophilic nature of the wall can be preserved [21]. Although glass capillary devices cannot be replicated as those made from mouldable polymers, they are more rigid and chemically stable than PDMS devices, have superior optical properties, low surface roughness and can be fabricated with a wide range of orifice sizes. In combination with the above experiments, we also developed a numerical model so that the drop size can be predicted for the given combination of system geometry, fluid flow rates and physical properties of fluids. The modelling results were used to better understand the mechanisms of drop generation.

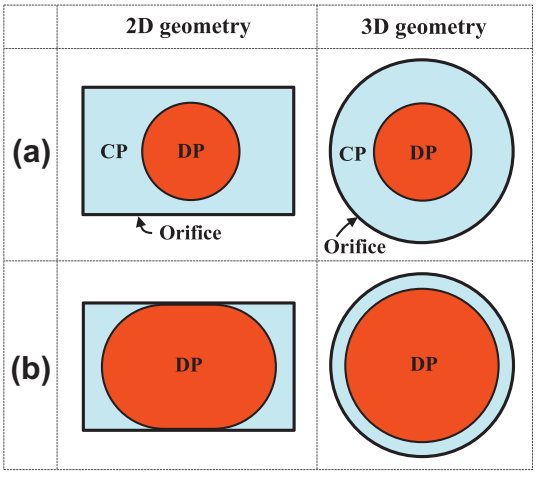

Fig. 1. Cross sectional view of a flow-focusing orifice showing the position of the dispersed phase (DP) in 2D and 3D microfluidic devices at: (a) high flow rate of the continuous phase (CP) and (b) low flow rate of the continuous phase. In the 2D device, the dispersed phase contacts the orifice wall at low continuous phase flow rates and the wall rapidly becomes hydrophobic. In the 3D device, the dispersed phase does not make contact with the orifice at any flow rate conditions and the orifice wall retains its hydrophilic properties.

2. Materials and methods

2.1. Materials for emulsion preparation

The oil phase in oil-in-water (O/W) emulsions was 1 wt% polycaprolactone (PCL, M_w = 14,000 g mol^{-1}, Sigma–Aldrich, UK) dissolved in dichloromethane (DCM, HPLC grade, Fisher Scientific, UK). The oil phase in water-in-oil-in-water (W/O/W) emulsions was a mixture of 1–3 wt% poly(DL-lactic acid) (PLA, M_w = 15,000 - g mol^{-1}, Polysciences, Inc., US) or polycaprolactone (PCL, M_w = 14,000 g mol^{-1}, Sigma–Aldrich, UK) dissolved in dichloromethane (DCM, HPLC grade, Fisher Scientific, UK) or 1:2 mixture of chloroform and toluene. 5–10 wt% polyglycerol polyricinoleate (PGPR, E476, Abitec Ltd., New Milton, UK) was added in the oil phase to prevent coalescence of inner water droplets, and 0.1–2 mM Nile red to help in visual identification of the particles. The inner water phase was Milli-Q water or 0.156 wt% lidocaine hydrochloride monohydrate (Sigma–Aldrich, UK). The continuous phase was 5 wt% aqueous solution of polyvinyl alcohol (PVA, M_w = 13,000–23,000 g mol^{-1}, 87–89% hydrolysed, Sigma–Aldrich, UK), pre-filtered by Whatman® Puradisc 30 syringe filters with 5 μm cellulose nitrate membrane. All chemicals were used as supplied. The physical properties of some of the fluids used in this work are listed in Table 1. The interfacial tension was measured using a Krüss DSA-100 pendant drop tensiometer.

2.2. Fabrication of microfluidic device

Microfluidic device was made up of two borosilicate glass capillary tubes where an inner capillary with a circular cross section (Intracel, Royston, UK, inner diameter 1 mm, outer diameter 580 μm) was inserted in an outer capillary with a square cross section (AIT Glass, Rockaway, US, inner dimension 1.05 mm) (Fig. 2a). One end of the the inner capillary was shaped into a tapering orifice with an inner diameter of 60–300 μm. First, a Flaming/Brown micropipette puller (P-97, Sutter Instrument Co., Linton Instrumentation, Norfolk, UK) was used to produce a sharp tip. The orifice diameter was then increased by sanding the tip against abrasive paper until the orifice with a required size and smooth rim was obtained. A microforge (MF-830, Intracel Ltd., Linton Instrumentation, Norfolk, UK) microscope was used to control the orifice size via a built-in scale (Fig. 2c). The capillary was flushed with water to remove any glass debris and treated with 2-[methoxy(polyethylenoxy)propyl]-trimethoxysilane (MPEOPS) (FluoroChem, Hadfield, UK) to enhance hydrophilicity of the glass surface. Subsequently, the treated round capillary was partly inserted into the square capillary and fixed in position onto a microscopic slide using epoxy resin adhesive (5-Minute Epoxy®, Devcon). Hypodermic needles with polypropylene hub (BD Precisionglide®, Sigma–Aldrich, UK) were glued over both ends of the square capillary to act as tube connectors for the continuous and dispersed phase, while the exposed end of the inner capillary was connected to a sampling vial.

2.3. Microfluidic experiments

Glass capillary device, placed on the stage of an inverted microscope (XDS-3, GX Microscopes, UK) was connected to gas tight SGE syringes via medical tubing (Fig. 2b). The continuous phase was pumped through polyethylene tubing, while the dispersed phase was supplied using polytetrafluoroethylene tubing to prevent