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Printing particles: A high-throughput technique for the production of uniform, bioresorbable polymer microparticles and encapsulation of therapeutic peptides

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HIGHLIGHTS

- An ink-jet droplet generator allows individual polymer microparticles to be "printed".
- Rapid phase-separation produces highly uniform PLGA and PLA/PLGA blend microparticles.
- Peptides can be encapsulated and produce effective sustained release over several months.
- Using ink-jet nozzle arrays, particle production frequency was increased to >1 MHz.

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ABSTRACT

Bioresorbable polymer microparticles are widely used to provide long-lasting drug delivery in several chronic diseases. Having fine control over the physical properties of such microparticles can improve product reproducibility, performance and process efficiency. By using an ink-jet based droplet generator device, a new approach to microparticle manufacture was explored that uses an extremely rapid phase-separation to produce highly uniform, injectable microparticles from PLGA and a PLA/PLGA blend. To demonstrate the possible pharmaceutical applicability of the microparticle printing technique, the approved peptides ciclosporin A and octreotide were formulated, producing low-density microparticles that showed between sustained release over several months. The facile scale-up of the technique was demonstrated by using an array of 256 ink-jet nozzles, allowing over 1 million discrete particles per second to be produced. The new apparatus and methods described herein could be used across a wide range of biomaterials and therapeutic compounds.

1. Introduction

Bioresorbable polymer microparticles are a fundamental component in several blockbuster pharmaceutical products, including Sandostatin LAR™ (Grass et al., 1996), Lupron Depot™ (Okada et al., 1989; Okada, 1997), Bydureon™ (Taylor et al., 2013) and Risperdal Consta™ (Knox and Stimmel, 2004). Typically, their function is to control drug release rate and provide a depot effect, enabling several weeks or months of sustained-release therapy from a single injection (Jain et al., 2016; Lee et al., 2016). The patient-experience and patient-compliance benefits this affords are significant (Gilroy et al., 2016; Lasser et al., 2005; Lancranjan et al., 1995; Hamm et al., 2001; Anselmo and Mitragotri, 2014). Though numerous other techniques are available for the production of bioresorbable microparticles, for example spray-drying or super-critical fluid extraction, historically the most widely-used techniques for preparing biopolymer microparticles involve a surfactant-stabilised single or double emulsion and evaporation of a volatile solvent (Jeffery et al., 1991; Cleek et al., 1997; Sah, 2000). Control over particle size and morphology has numerous advantages relating to yield, release kinetics, injectability, suspension homogeneity and stability and overall efficiency of drug encapsulation (Erden and Celebi, 1996; Wang et al., 2015). In recent years, advanced microparticle processing methods such as templated and membrane emulsification have been developed that afford such improvements, most notably control of particle size and of drug release rate (Wang et al., 2015; Wu et al., 2015; Zhu et al., 2015; Qi et al., 2013). Recently, promising microfluidics-based production methods have been demonstrated, which potentially address the limited particle size-control that is often a disadvantage of bulk emulsion processing (Keohane et al., 2014; Perez et al., 2015;

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Fontana et al., 2016; Palmer et al., 2008). Generally, these use segmented flow arrangements to produce uniformly-sized droplets of a dispersed phase, in which a polymer may be dissolved. In our own exploration of multi-channel microfluidic devices for microparticle production (unpublished results), the high viscosity and low surface tension of concentrated polymer solutions (>10% w/v, defined as mass of polymer dissolved in volume of solvent; Mw range 4–15 kDa, i.v. 0.14–0.22 dL/g) produced flow distribution challenges and unacceptable inter-channel variability at all but the lowest droplet production frequencies.

An alternative approach to the production of monodisperse droplets was considered, involving ink-jet-like piezoelectric actuation. In fact, oil/water emulsions involving PLGA have already been demonstrated using a submerged piezoelectric droplet generator (Fletcher et al., 2008). However, at elevated polymer concentrations, this approach may also be frequency limited by low liquid/liquid interfacial surface tension. To try to move away from an emulsion-based approach, it is necessary to rethink the types of solvents used for polymer and drug solvation, and their properties, including biocompatibility and relative miscibility. In 2003, another dual piezo-actuated flow process was described by Park et al., in which the synthesis of microparticles was accomplished via the phase separation of dissolved polymer within a droplet, which was induced by coalescence with another droplet consisting of a miscible anti-solvent (Yeo, 2003). Similarly, polymers of the PLGA and PLA families are highly soluble in DMSO but insoluble in solvents with high hydrogen-bonding potential such as water and alcohols. It was postulated that solid PLGA particles could be manufactured by manipulating this difference in solubility. As DMSO and water are infinitely miscible, a fixed volume of a concentrated PLGA solution in DMSO should rapidly phase separate when exposed to a larger volume of a miscible anti-solvent (such as water) as solvating DMSO molecules diffuse away.

The primary aim of this work was to explore a new, scale-able technique for the production of injectable, sub-50 μm diameter microparticles. Inkjet printing technology has been specifically developed for the facile, highly controllable production of uniform picolitre droplets; and as printing applications have evolved, devices have become compatible with non-conventional 'inks' with solvent content and indeed, pharmaceutical payloads (Liu et al., 2017; Kim et al., 2017; Daly et al., 2015; Cheow et al., 2015). It was therefore postulated that a piezoelectric droplet generator could be used to create a semi-continuous stream of DMSO droplets in air. Further, without a liquid/liquid interfacial surface tension limit, significantly higher polymer concentrations could be processed. Herein, a first small-scale apparatus for printing microparticles was developed that utilises a commercially available single-nozzle piezoelectric device to generate a continuous vertical stream of uniform droplets of a DMSO polymer solution; and a transverse anti-solvent jet to capture and separate these droplets before solvent extraction.

Each of the sustained release therapeutics mentioned above comprises an injectable mass of polydisperse polymer microparticles, in which a biologically-active small molecule or peptide is encapsulated. The efficiency of drug encapsulation and drug loading level are key parameters (Iqbal et al., 2015). Both affecting the viability, injectability and cost of a product. To assess the utility of the microsphere production method developed here, the encapsulation of two peptide-based pharmaceuticals was performed. Octreotide acetate, a cyclic 8 amino acid peptide that is indicated in acromegaly and carcinoid syndrome, has been widely studied and is available as a polymer depot formulation (Sandostatin LAR, Novartis). The latter is an once-monthly injection, comprising non-linear PLGA microparticles with a nominal octreotide loading of 4.65% w/w, defined as mass of drug/mass of solid (Mertens et al., 2010).

The cyclic peptide ciclosporin A is widely used as an immunosuppressant. It is administered orally, with 40% bioavailability. In several studies, ciclosporin A has been successfully encapsulated within bioresorbable polymer microparticles (Keohane et al., 2014; Sanchez et al., 1993; Urata et al., 1999). The drug has potential use in the ocular auto-immune disease non-infective uveitis, particularly in patients with posterior segment involvement where very long-acting anti-inflammatory therapeutics are required, and front-of-eye therapeutics are ineffective (Lallemand et al., 2003; Vitale et al., 1996).

The industrial relevance of the microparticle production technique described here is only realised upon achieving a certain throughput level. Modern inkjet printing technology has developed around linear arrays of 256 or 512 piezo-actuated nozzles. These are routinely used to accurately deposit nanolitre and picolitre volumes of various "inks" onto a range of solid substrates (Wijshoff, 2010; Thesen et al., 2014). It was hypothesised that similar devices could be adapted to allow the printing of picolitre volumes of a polymer solution onto a liquid anti-solvent substrate, to enable microparticle production at increased frequency and thus increased product mass/time.

2. Materials and methods

2.1. Chemicals

Poly(D,L)lactide (RG202H, Mw range 10–18 kDa, i.v. 0.16–0.24 dL/g) and Polyl(D,L)lactide-co-glycolide (RG752H Mw range 4–15 kDa, i.v. 0.14–0.22 dL/g) were purchased from Evonik, Germany. Ciclosporin A, dimethyl sulfoxide, phosphate-buffered saline and tert-butanol were purchased from VWR, UK. Sterile water was obtained from an Elga Purelab Option-Q (DV25) (electrical resistivity 18.2 MΩ). Octreotide acetate was obtained from PolyPeptide Laboratories Inc, USA.

2.2. Single-nozzle piezoelectric droplet generation

PLGA (RG752H, 400 mg) was allowed to dissolve in anhydrous DMSO (1 mL) at 37 °C over a period of 12 h. The resulting solution was filtered (PTFE 13 mm syringe filter, 0.45 μm) into a clean, dry glass vial. An MD-K-140 piezoelectric dispenser head (MicroDrop Technologies GmbH, Germany) with internal capillary diameter 70 μm was connected to a MD-K-140 digital pulse-generator. The device fluid feed-tube was submerged in the polymer solution and the vial was screw sealed. Using voltages in the range of 65–90 V, pulse-lengths between 8 and 15 μs and ejection frequencies between 2 and 4 kHz, stable ejection of discrete, satellite-free 180 pL droplets of feed solutions was achieved.

2.3. Anti-solvent fluid jet

To generate a horizontal anti-solvent jet, comprising either water or 15% v/v tert-butanol solution, a MZR 7255 pulseless micro-gear pump (HNP Mikrosysteme GmbH) was connected by HPLC tubing to a stainless-steel nozzle with a circular orifice of internal diameter 500 μm. At a pumping rate of 300 rpm (14.4 mL/min) the fluid jet had exit velocity 1.2 m/s and diameter of approximately 500 μm. The nozzle was located in transverse alignment with the vertical droplet stream, such that the anti-solvent jet coincides and captures the falling droplets. The jet travel distance was 13 mm, before meeting an elbow-shaped stainless-steel collecting tube. For experiments involving the 256 nozzle array, a higher velocity jet was required to prevent droplet coalescence, hence flow rate was increased to 125 mL/min. Here, the jet travel distance was 72 mm. Surface tensions of anti-