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Uniform biodegradable microparticle systems for controlled release

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HIGHLIGHTS

- Precision particle fabrication (PPF) provides uniform polymer micrspheres.
- PPF provides microcapsules with precisely controlled shell thickness.
- Particle size controls small molecule and macromolecule release rates.
- PPF microparticles can achieve "zero-order", pulsatile or tandem release of drugs.

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ABSTRACT

Drug delivery methods can impact efficacy as much as the nature of the drug itself. Microparticles made of biodegradable polymers such as poly(D,L-lactide-*co*-glycolide) and poly(lactic acid) (PLA) have been studied extensively for controlled release of diverse drugs. By using a modified solvent extraction/evaporation method called precision particle fabrication (PPF), uniform microparticles such as single-wall microspheres, double-wall microspheres and liquid-core microcapsules have been fabricated with precise control of their geometric structures. By producing particles of uniform size, which has crucial impact on drug release behaviors, PPF-fabricated microparticles provide unique insights about drug release mechanism. Using small-molecule and macromolecule model drugs, our group demonstrated that physicochemical properties of the polymers and drugs and structural properties of the matrix can greatly impact drug distribution within microparticles, particle erosion and drug release rates. By careful selection of particle size and shell thickness, uniform microparticles can achieve "zero-order", pulsatile or tandem release of drugs.

1. Introduction

The IMS Institute for Healthcare Informatics has projected that in 2014 global spending on prescription drugs will top $1 trillion even as growth slows in Europe and North America, and the global pharmaceutical industry may reach $1.2 trillion by the end of 2017 (Rickwood et al., 2013). The method of drug delivery can impact efficacy as much as the nature of the drug itself, and for many years researchers have sought to develop effective systems that can target drugs to specific body sites and/or precisely control drug release rates for prolonged time (Langer, 1998). To produce desired results, the plasma concentration of drug should be maintained within the therapeutic window, which consists of a lower bound, the minimum effective concentration (MEC), and an upper bound, the minimum toxic concentration (MTC). With conventional oral dosing and parenteral injections, peaks and valleys typically appear in the plasma concentration profiles, which can lead to side effects and the need for frequent administration. Controlled release devices, in contrast, may maintain drug concentration within the therapeutic window for a prolonged time with reduced dosage frequency, thus increasing efficacy and patient compliance. Furthermore, multiple drugs can be incorporated into one delivery depot, which may facilitate synergistic therapy strategies.

Biodegradable polymers have been utilized in numerous devices as a means to deliver drugs in a controlled and minimally invasive manner (Park et al., 2005; Varde and Pack, 2004). Compared to non-biodegradable polymers which may pose problems of toxicity and are difficult to remove, biodegradable polymer devices have attracted much attention since the early 1970s (Ha and Gardella, 2005; Sinha and Trehan, 2003). Specifically, spherical biodegradable microparticles

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such as monolithic microspheres (single-wall microspheres), double-wall microspheres with a core and shell composed of two different materials, and microcapsules with liquid cores have been employed for controlled release of various therapeutics (Anderson and Shive, 2012; Singh et al., 2010; Tamber et al., 2005; Wang et al., 2007). Microparticles exhibiting sizes ranging from a few to several hundred microns have received much attention in academia and industry. For example, microparticles approximately 1–5 μm in diameter would be ideal for passive targeting of professional antigen-presenting cells (Evora et al., 1998; Wattendorf et al., 2008). Microparticles 10–20 μm in diameter could be used to target the tortuous capillary bed of tumor tissues by chemo-embolization (Dass and Burton, 1999; Salem et al., 2005). Microparticles 1–5 μm in diameter and highly porous particles 5–20 μm in diameter are effective pulmonary drug delivery vehicles (Langer, 1998). Finally, microparticles 10–100 μm in diameter can serve as intramuscular or subcutaneous depots as they are small enough for syringe injection yet large enough to avoid uptake by phagocytic cells.

Due to the simplicity and versatility of such microparticle devices, many products have been commercialized. For example, Trelstar® injectable microspheres (triptorelin pamoate) and Lupron® depot (leuprolide acetate) for prostate cancer, Sandostatin LAR® depot (octreotide acetate) for acromegaly, Risperdal® Consta® depot (risperidone) for the treatment of schizophrenia as well as for the longer-term treatment of Bipolar I disorder, and Vivitrol® depot (naltrexone) for alcohol dependence are all commercialized implantable or injectable biodegradable microparticle devices (Malik et al., 2007).

Fabrication methods of biodegradable microparticles include solvent extraction/evaporation (Bindschaedler et al., 1988), polymer extrusion (Poncelet et al., 1994), spray drying (Pavanetto et al., 1993), coacervation or precipitation (Kawashima et al., 1989), electrospray (Almería et al., 2010), particle replication in non-wetting templates (PRINT) technology (Gratton et al., 2007) and microfluidic flow-focusing (Xu et al., 2009). Common features of these methods include (i) the biodegradable polymer should be dissolved in a suitable solvent such as dichloromethane or ethyl acetate; (ii) therapeutics are co-dissolved with polymer, suspended as solid particulate or dissolved in an immiscible solvent (*e.g.*, aqueous) and emulsified with polymer solution; and (iii) the drug–polymer solution, suspension or emulsion is disrupted to produce droplets from which the solvent is removed to form the hardened particles. A key limitation of these biodegradable microparticle production methods, however, is the difficulty of controlling particle sizes. Since outer diameter, shell thickness, and size distributions have great influence on drug release rate and localizing behaviors, uniform or monodisperse microparticle systems are often preferred.

Several techniques to produce uniform microparticles have been reported. Sugiura et al. fabricated uniform solid lipid microspheres using a temperature-controlled microchannel emulsification process (Sugiura et al., 2000). Radulescu et al. developed a technology for fabricating uniform polymer microspheres by dispensing polymeric material from an orifice of a drop-on-demand ink jet printhead while the orifice was immersed in a solvent extraction media (Radulescu and Wawro, 2003). Desimone et al. pioneered a technique known as particle replication in non-wetting templates (PRINT) based on the exploitation of the low surface energy of novel fluoropolymeric molds. The molds are derived from liquid perfluoropolyether (PFPE) precursors, which can be photochemically cross-linked at room temperature. The resulting elastomeric solids enable high-resolution imprint lithography and fabrication of uniform organic particles of varying shapes (Gratton et al., 2007; Rolland et al., 2004). Although PRINT is highly versatile in terms of particle size and shape, fabrication requires clean-room facilities for creation of molds, and scale-up appears to be more complicated. Bohmer et al. adopted ink-jet printing technology and fabricated uniform polymer microspheres as well as hollow-core microcapsules (Böhmer et al., 2006). Microfluidic methods have also been proven effective in fabricating uniform microparticles. Taking advantage of the periodic and predictable breakup of immiscible fluids, discrete and monodisperse droplets can be formed in T-junction or flow-focusing channels (Hung et al., 2010; Shum et al., 2008; Teh et al., 2008; Xu et al., 2009; Zhang et al., 2009). This paper presents a review of uniform microparticle systems fabricated by a unique technique called precision particle fabrication and the study of drug release behaviors from these vehicles.

2. Precision particle fabrication

Precision particle fabrication (PPF) is a technology developed to produce uniform particles of a variety of materials (Foster et al., 1977; Gilliard et al., 1981; Kim et al., 1991, 1989) and adapted for fabrication of controlled-release microparticle systems comprising biodegradable polymers. The main apparatus of PPF (Fig. 1(A),(B)) is based on passing a fluid containing the sphere-forming material (s) and any drug to be encapsulated through a small (10–100 μm) orifice to form a smooth, cylindrical stream. To break the stream into uniform droplets, the nozzle is acoustically excited by a piezoelectric transducer driven by a wave generator at a defined frequency. By employing an annular flow of a non-solvent phase, called the carrier stream, surrounding the polymer–drug jet to provide additional "drag" force, microparticle size and shape can be further controlled; particles even smaller than the nozzle openings can be generated. The particle size (r_d) can be controlled by jet radius (r_j), solution flow rate (v_j) and acoustic wave frequency (f). By changing the flow rates of the polymer and carrier streams and the acoustic wave frequency droplet sizes vary as predicted in Eq. (1) (Rayleigh, 1879, 1882). Thus, we can control the particle size to within one micron (Berkland, 2003).

$$r_d = (3r_j^2 v_j/4f)^{1/3} \quad (1)$$

The nozzle system is the key part of PPF. To produce single-wall microspheres (SWMS), a hypodermic needle was used as the innermost nozzle carrying the drug–polymer solution, which was surrounded by a second glass nozzle for forming the non-solvent carrier stream. For fabrication of double-wall microspheres (DWMS) and liquid-core microcapsules (MC), a triple nozzle system was employed comprising the double-nozzle system surrounded by a larger glass nozzle. The core phase (polymer, aqueous or oil stream) passes through the inner metal nozzle, the shell-phase polymer stream passes through the inner glass nozzle, and the outer glass nozzle was for the non-solvent carrier stream (Fig. 1(C),(D)).

3. Uniform microparticle systems for controlled release of small-molecule drugs

Compared to conventional dosage forms, biodegradable polymeric matrices provide enhanced delivery for small-molecule drugs, yet an important limitation of these matrices has been the difficulty of designing systems exhibiting precisely controlled release rates. Because microparticle size is a primary determinant of small-molecule drug release rate, uniform microparticle systems are preferred to better control drug release rates as well as study other factors which might contribute to release rates.

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