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In vitro release profiles of PLGA core-shell composite particles loaded with theophylline and budesonide

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ABSTRACT

We investigated the effects of drug loading location, matrix material and shell thickness on the *in vitro* release of combinational drugs from core-shell PLGA (*i.e.*, poly(lactic-co-glycolic acid)) particles. Budesonide and Theophylline were selected as highly hydrophobic and hydrophilic model drugs, respectively. The dual-capillary electrospray (ES) technique, operated at the cone-jet mode, was used to produce samples of drug-loaded core-shell composite particles with selected overall sizes, polymer materials, and shell thicknesses. Theophylline and Budesonide were loaded at different locations in a PLGA composite particle. This study illustrated how the aforementioned factors affect the release rates of Budesonide and Theophylline loaded in core-shell PLGA composites. We further identified that core-shell composite particles with both model drugs loaded in the core and with matrix PLGA polymers of low molecular weights and low LA/GA ratios are the best formulation for the sustained release of highly hydrophilic and hydrophobic active pharmaceutical ingredients from PLGA composite particles. The formulation strategy obtained in this study can be in principle generalized for biopharmaceutical applications in fixed-dose combination therapy.

1. Introduction

Recent scientific advances have unveiled pathogenic processes underlying many diseases. The in-depth understanding of disease mechanisms has fueled novel approaches *via* the combination drug therapy, *i.e.*, by applying two or more medicines to the patients, for improving the therapeutic outcome and minimizing the drug toxicity. The fixed-dose combination (FDC) offers an alternative to the patients requiring multiple therapies to manage their diseases by facilitating the medication concordance. Other benefits of FDC, *e.g.*, simplified medication regimen and better patient compliance with the treatment, have made it important as a therapy in many disease categories, including cancers, respiratory diseases, cardiovascular diseases and nervous system diseases (Bell, 2013; Bangalore et al., 2007; Hao et al., 2015).

Similar to the conventional monotherapy, effective drug concentrations at the site of action for a sufficient duration are crucial in the fixed-dose combination drug therapy in order to provide superior therapeutic effectiveness. Frequent drug administration in low doses is certainly an approach to achieve the above goal but with less convenience in drug administration and a higher chance of resultant systemic side effects due to the dose accumulation. The aforementioned challenges can be overcome by sustained (or extended) release formulations of fixed-dose combination therapy designed for reduced dosing frequency and prolonged duration (with the blood level of drugs in the therapeutic window).

Poly(lactic-co-glycolic acid) (PLGA) polymers are well-known synthetic biomaterials approved by U.S. Food and Drug Administration (U.S. FDA) and European Medicine Agency (EMA) for their biodegradability, biocompatibility and easy property manipulation. They have been proposed as the materials of carriers for drug delivery (Nair and Laurencin, 2006; Wischke and Schwendeman, 2008; Kerimoğlu and Alarçin, 2012; Anselmo and Mitragotri, 2014; Danhier et al., 2012). Emulsification-solvent evaporation and nanoprecipitation are the two methods used to fabricate PLGA particles with either the matrix or core-shell structures (Nair and Laurencin, 2006; Danhier et al., 2012; Nagavarma et al., 2012; Yang and Pierstorff, 2012; Ansary et al., 2014). The concerns raised in using these preparation methods are 1) the presence of residual solvent from the processes on produced particles and 2) the incapability of producing uniform-sized core-shell particles with

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high drug encapsulation efficiency (especially for hydrophilic drug compounds) (Sah and Sah, 2015; Hao et al., 2014; O'Donnell and McGinity, 1997; Schubert et al., 2011; Sosnik and Seremeta, 2015). Electrospray-dry (ES) method, on the other hand, is a one-step process to overcome above concerns. It is capable of fabricating monodisperse matrix-type/core-shell PLGA particles with high drug encapsulation efficiency for both hydrophilic and hydrophobic active ingredients (Bock et al., 2012; Hao et al., 2014; Lee et al., 2010; Cao et al., 2014). The content of residual solvents in as-produced particles is generally under the limit of safety standards. It is because very volatile organic solvents are typically used in the ES processes compared to those used in liquid-phase precipitation methods. More, subsequent drying steps could be employed in the processes to further reduce the content of residual solvent to a minimal level (Bai and Yang, 2013; Bock et al., 2012).

To increase the mass throughput of ES, multiple-capillary systems were proposed to produce particles in general and PLGA particles for drug delivery (Deng et al., 2009; Almería et al., 2010). Spacers for isolating individual nozzles are however required in multiple-capillary ES systems to minimize the interference of spray jets and the distortion of the electric field applied for the operation, resulting in the design complication and high manufacture cost. To overcome the above issue, multi-notched ES nozzles were evaluated for particle generation (Duby et al., 2006; Lee et al., 2011a,b). The maximal liquid feeding rate of the prototype nozzle with 12 notches was up to 180 times that of a single capillary nozzle (Lee et al., 2011a,b). It is expected that the mass throughout of a multi-notched ES nozzle could be further increased as the number of notches at the nozzle exit increases.

Research has studied the *in vitro* drug release profiles of hydrophilic/hydrophobic active agents from loaded PLGA particles produced by a multiplexed single capillary ES technique. Great release rate of hydrophilic compounds and serious initial-burst release due to the surface or near-surface loading of the compounds were reported (Almería et al., 2011). To overcome the issue of initial burst release of drugs, the dual capillary ES was proposed to encapsulate a single drug in core-shell PLGA composite particles. Low initial drug release rate was observed *in vitro* when the drug was loaded in the core of PLGA composites (Bai and Yang, 2013). The effects of polymer concentration, feeding flowrate and electrical conductivity of spray liquids were investigated to encapsulate a single hydrophobic drug in the core of PLGA particles with the overall sizes ranging from 0.12 to 2.5 μm. The encapsulation efficiency of resultant drug-loaded PLGA particles was up to 90% (Enayati et al., 2009; Lee et al., 2010). The dual capillary ES technique was also applied to encapsulate two hydrophobic drugs separately in core and shell of PLGA particles. The encapsulation efficiency of both hydrophobic drugs was up to 90%. As-produced particles were capable of slowly releasing both drugs for 3 days (Cao et al., 2014). *Via* the dual capillary ES, hydrophilic drugs had also been loaded in the core of PLGA submicron composites, enabling their continuous releases for 7 days (Guan et al., 2016). Although the sustained release of small molecule drugs has been demonstrated in core-shell composite particles, our knowledge regarding the sustained release of combined hydrophilic and hydrophobic pharmaceutical agents from core-shell PLGA composites remains limited. A systematic investigation is thus required on the effects of core-shell dimension, filling PLGA polymer and drug loading position on the *in vitro* drug release profiles of core-shell PLGA composite particles loaded with both highly hydrophilic and hydrophobic drugs.

Budesonide is an inhaled corticosteroid for airway inflammation control and asthma attack prevention. Theophylline, on the other hand, is a bronchodilator for symptom minimization of asthma (Shendge and Sayyad, 2013; Sundaran et al., 2013). Greater therapeutic effectiveness of Theophylline as an add-on therapy on corticosteroids for the treatment of asthma has been reported. The immunosuppression caused by corticosteroids deposited in upper airways may be alleviated by formulating both active ingredients (*i.e.*, Budesonide and Theophylline) into sustained release formulations (Barnes, 2002). However, sustained release of Theophylline is a challenge due to its extreme hydrophilicity and small molecular weight. In previous works (Sullad et al., 2010; Rokhade et al., 2007), interpenetrating polymer network (IPN) particles of poly(vinyl alcohol) and methylcellulose or chitosan and methylcellulose in super-micrometer sizes were prepared by the emulsion-crosslinking method to control the *in vitro* release of Theophylline for 32 h. Limited work has been reported for the sustained release of Theophylline from PLGA composite particles with diameters less than 1.0 μm.

2. Objective and scope of this study

The objective of this work is to explore the feasibility of achieving the sustained release of both hydrophobic and hydriplilic drugs when both are loaded in core-shell PLGA particles with the sizes less than 1.0 μm. As an exploratory study, we selected Budesonide and Theophylline as the model hydrophobic and hydrophilic small-molecule drug compounds, respectively. PLGA polymers were used as the filling material. The dual capillary ES technique was used to produce monodisperse, drug-loaded core-shell PLGA composite particles. The capability of using dual capillary ES to produce core-shell composites and the distribution of drugs within the composites had been demonstrated in the works of Lee et al. (2010); and Lee et al. (2011a,b). By tuning the operational variables in the ES process, core-shell particles with various drug-loaded positions, shell thicknesses and overall particle sizes were produced. The *in vitro* drug release profiles of Budesonide and Theophylline from as-produced composite particle samples were characterized to identify key factors influencing the sustained release of PLGA composite particles loaded with both hydrophilic and hydrophobic model drugs.

In vitro release testing was performed in release media with pH 7.4 for all studied formulations. The effect of pH on the drug release profiles of all studied formulations was not considered in this exploratory study. A bacteriostatic agent was added in release media to minimize the concern of biological stability of drugs while releasing from particles.

3. Material and methods

3.1. Materials

Budesonide (Sigma-Aldrich) and Theophylline (Sigma-Aldrich) were the hydrophobic and hydrophilic model drugs used in this study, respectively. Three ester-terminated Poly(lactic-co-glycolic acid)s (PLGAs) with various molecular weights and lactic-to-glycolic (LA/GA) ratios (*i.e.*, Mw: 7000–17,000 g/mol, LA/GA: 50/50; Mw: 24,000–38,000 g/mol, LA/GA: 50/50; Mw: 50,000–75,000 g/mol, LA/GA: 85/15), purchased from Sigma-Aldrich (St. Louis, MO), were used as the filling materials for the core and shell of prepared composite particles. Mixtures of Acetonitrile (ACS reagent, ≧ 99.5%, Sigma-Aldrich) and dimethyl sulfoxide (meets USP and EP testing specifications, Sigma-Aldrich) were selected as the solvents. The electrical conductivity of prepared solutions was adjusted by adding a trace amount of nitric acid (ACS reagent, 70%, Sigma-Aldrich). 0.02 M phosphate buffered saline (PBS), as the release media for the drug release comparison in different formulations, was prepared by dissolving adequate amount of sodium phosphate monobasic (ReagentPlus®, ≥99.0%, Sigma-Aldrich), sodium phosphate dibasic (tested according to Ph. Eur,