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Drug release study of large hollow nanoparticulate aggregates carrier particles for pulmonary delivery

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Abstract

The aim of the present work is to examine the viability of using large hollow nanoparticulate aggregates as the therapeutic carrier particles in dry powder inhaler delivery of nanoparticulate drugs. The large hollow carrier particles are manufactured by spray drying of nanoparticulate suspensions of biocompatible acrylic polymer with loaded drugs. The size and concentration of the nanoparticles, as well as the phospholipids inclusion, have been known to influence the resulting morphology (i.e. size and degree of hollowness) of the spray-dried carrier particles. The effects of the resulting morphology of the carrier particles on the drug release rate are therefore investigated by varying the above three variables. The results of the drug release study are presented using aspirin and salbutamol sulfate as the model drugs with a varying degree of water solubility. The results indicate that the drug release rate is governed by the degree of hollowness of the carrier particles, and to a lesser extent by the nanoparticles size, as a result of the variation in the drug loading capacity of nanoparticles of different sizes.

Keywords: Dry powder inhaler; Pulmonary delivery; Hollow particles; Nanoparticulate drugs; Drug release; Formulation

1. Introduction

Dry powder inhaler (DPI) delivery of therapeutic agents has recently become a subject of very active research with the FDA approval of the use of spray-dried insulin dry powder aerosols, Exubera from Pfizer, to treat patients with type 1 and type 2 diabetes. The FDA approval of Exubera provides a major boost for research activities in discovering innovative pharmaceutical technologies to deliver therapeutic agents by inhalation for systemic circulation. In pulmonary drug delivery, the inhaled particles are subjected to the phagocytic clearance mechanism in the lung alveolar region by the scavenging alveolar macrophages. The lung phagocytosis is most significant for particles having geometric diameter (d_g) between 1 and 2 μm, and diminishes for particles having smaller or larger geometric diameters (Ahsan et al., 2002; Makino et al., 2003). Recent studies on pulmonary nanoparticle deposition suggest that inhaled nanoparticles (<100 nm) are the optimal particle size for alveolar deposition, as well as for minimizing the lung phagocytosis (Hoet et al., 2004).

However, the application of nanoparticulate drugs for DPI delivery is not straightforward, as direct inhalation of nanoparticulate drugs is not feasible due to their extremely small size. The nanometer size leads to the nanoparticulate drugs being predominantly exhaled from the lungs, without any deposition taking place. Moreover, a severe aggregation problem arising from the small size makes their physical handling extremely difficult for DPI delivery. To circumvent the above problems, a novel formulation technique to manufacture large hollow carrier particles of nanoparticulate drugs has been developed by Tsapis et al. (2002) using a spray drying technique. The formulation technique has since been subsequently enhanced by Hadinoto et al. (2006).

The large and hollow features of the carrier particles are specifically designed to produce inhaled particles with high aerosolization efficiency and high therapeutic efficacy (Edwards et al., 1997). The large hollow carrier particles, whose shells are composed of nanoparticulate aggregates, exhibit a large geometric diameter ($d_g \approx 10$–15 μm), but with a small aerodynamic diameter ($1 \leq d_a \leq 3$ μm). The small aerodynamic diameter of

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Nomenclature

D.O.F.	the degree of freedom
$n_{1,2}$	the number of independent replicates of samples 1 and 2
$s_{1,2}$	the standard deviation of samples 1 and 2
$x_{1,2}$	the mean of samples 1 and 2

Greek letters

α	the probability of error, alpha parameter, in the *t*-test
$\mu_{1,2}$	the mean of populations 1 and 2

the large hollow particles, which makes them highly suitable for DPI applications, is attributed to the hollow structure. Importantly, the nanoparticulate aggregates have been shown to disassociate into primary nanoparticles once they are exposed to an aqueous environment, such as in the alveolar lung region. Because the large hollow nanoparticulate aggregates re-disperse into nanoparticles having a much smaller size, they do not retain the shortcomings of the original large hollow particles developed by Edwards et al. (1997). Their large hollow particles have been shown to exhibit (1) an extremely slow drug release rate (particularly for water-insoluble drugs), and (2) a slow polymer degradation rate in the case of biodegradable polymers, which are both due to their large geometric size (Dailey et al., 2003).

In the present work, large hollow nanoparticulate aggregates of biocompatible PMMA-MeOPEGMa polymer nanoparticles with loaded drug have been manufactured. Salbutamol sulfate is used as the model for freely water-soluble drug (275 mg/mL at 20 °C), and aspirin is used as the model for lowly water-soluble drug (4.6 mg/mL at 20 °C). Salbutamol sulfate and aspirin have been chosen as the model drugs, because they are widely available and cost-effective. PMMA nanoparticulate-system has been chosen as the model nanoparticles due to its biocompatibility (Tao et al., 2003; Tapolsky et al., 2005), its high mechanical strength, and rigid polymeric structure (Stanek et al., 2006). The high structural-strength of the PMMA nanoparticles makes them highly suitable for use in the spray drying formulation, where a high-impact shear force is exerted on the nanoparticles by the atomizing fluid.

The details of the novel formulation technique have been presented in Hadinoto et al. (2006, 2007), and not repeated here. Briefly, nanoparticulate suspension containing the drug is spray-dried at a fast convective drying rate to ensure the formation of spherical nanoparticulate aggregates with large and hollow structures. A minimum threshold value in the concentration of the nanoparticulate suspension must be exceeded to obtain large hollow particles from the spray drying process. The effects of the chemical nature, size, and concentration of the nanoparticles on the resulting morphology of the carrier particles have been thoroughly investigated.

The goal of the present work is to examine the viability of using the large hollow nanoparticulate aggregates, which feature high aerosolization efficiency and high therapeutic efficacy, as the therapeutic carrier particles in inhaled delivery of nanoparticulate drugs. In that regard, an in vitro drug release study of the drug-loaded carrier particles in a phosphate buffer solution has been conducted. The authors are fully aware that, with regard to the aspirin, the nanoparticulate polymer delivery method is not the most suitable method of delivery due to the high dosage requirement of aspirin (~300 mg/day, compared to 400 μg/day for salbutamol sulfate). Therefore, the authors would like to emphasize that the aim of the present work is not to attempt to develop an improved method of delivering the aforementioned drugs, but rather to identify the key facets in the formulation of the large hollow nanoparticulate aggregates, which have significant impacts on the release rate of the therapeutic agents.

Specifically, the objective of the present work is to investigate the effects of (1) the nanoparticles size, and its spray drying concentration and (2) the inclusion of phospholipids (i.e. a major component of pulmonary surfactant) on the drug release rate. Our previous studies (Hadinoto et al., 2006, 2007) have shown the significance of the roles of the above three variables on the resulting morphology (i.e. size and degree of hollowness) of the large hollow nanoparticulate aggregates. Nonetheless, how they subsequently affect the release of drug from the nanoparticulate aggregates is not known. Therefore, the results of our study provide a comprehensive insight into the formulation of the large hollow nanoparticulate aggregates with loaded drug.

2. Materials and methods

2.1. Materials

The monomers for the synthesis of the polyacrylate nanoparticles, i.e. methyl methacrylate (MMa, purity ≥99%), methoxy(polyethylene glycol)methacrylate (MeOPEGMa, MW = 2000), and the initiator 4,4-azobis(4-cyanovaleric acid) (carboxy ADIB, purity ≥75+%) are purchased from Sigma–Aldrich, except for the MeOPEGMa, which is kindly supplied by Cognis Performance Chemicals (UK). Phospholipids S100 (95% phosphatidylcholine from fat free soybean lecithin) is purchased from Lipoid GmbH (Germany). Phosphate buffer solution in water (pH 7.2), TWEEN 20 surfactant, salbutamol sulfate and aspirin are purchased from Sigma–Aldrich. Ultra-pure water, hydrochloric acid, ethanol, ethyl acetate, acetonitrile and tetrahydrofuran analytical grade are used in the experiments.

2.2. Methods

2.2.1. Preparation and characterization of the PMMA-MeOPEGMa nanoparticles

PMMA-MeOPEGMa is prepared by a solution polymerization of MeOPEGMa and MMa in the proportions 15/85 (wt.%) as described in Phanapavudhikul et al. (2002). Ethyl acetate and ethanol are used as the solvents. The polymer is converted into polymer nanoparticles by a solvent replacement (also known as nanoprecipitation) technique. The nanoparticles exhibit steric colloidal stability arising from the MeOPEGMa component. Briefly, 0.15 g carboxy ADIB is dissolved in 15 mL ethanol and