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Innovative pMDI formulations of spray-dried nanoparticles for efficient pulmonary drug delivery

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ABSTRACT

For drug delivery to the lungs, the aerodynamic size of drug particles plays a predominant role in determining the sites of deposition in the airway, and the particles with the size less than 2 μm are highly expected as they will be preferably delivered to the ideal site of alveolar regions. In this paper, a novel platform technology has been developed, where the water (containing pharmaceutically active agents)-in-oil (w/o) microemulsions were spray-dried to generate nanosized drug particles that were able to be homogeneously dispersed in the propellant to form an exceptionally stable suspensions with no precipitates or flocculates during a long time storage. High fine particle (< 5.8 μm) fraction (~ 70% w/w) was achieved, irrespectively of drug molecular size and storage time. This platform technology works pretty well on chemical drugs (i.e. salbutamol sulphate) and biotherapeutics (i.e. insulin) for the generation of nanoparticles, and the nanoparticle pMDI formulations were homogeneous, stable and of high delivery efficiency to the lungs, representing an ideal way for pulmonary delivery.

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1. Introduction

Pulmonary drug delivery attracts rapidly increasing attentions as a route for the administration of pharmaceutically active agents for the treatment of local and systemic diseases (Patton and Byron, 2007). The drug delivery to the lungs offers a number of great advantages including rapid effective treatment at low dose, avoidance of first pass metabolism, miniature side effects, ease of administration and exceptional patient compliance. Three major systems have been developed for drug delivery to the lungs, classified as pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulizers (Grossman, 1994; Clark, 1995; Rogliani et al., 2017). Nebulizers are claimed as one of the oldest devices for inhalation, and they suffer from the bulky size, relative inconvenience of use, low overall delivery efficiency and long nebulization time for treatment, which terrifically limit their applications in clinic. DPIs usually need adequately high air flow generated by the patients to aerosolize drug particles, which may be very difficult for those patients who grieve from the severe asthma and/or COPD and would therefore reduce the lung delivery efficiency and treatment effects. Additionally, moisture sensitivity is a big concern for most DPIs, and they are not appropriate for emergency conditions. As a promising alternative, pMDIs use the propellant as the vehicle that can provide the energy to aid the dispersion of nanoparticles and further enhance their aesosolisation performance for the lung deposition (Newhouse, 1991). As a revolutionary invention, pMDIs offer great advantages consisting of portability, multi-doses, reasonably efficient delivery, resistance to bacterial contamination and humidity, ease of use and cost effectiveness, and they keep being the utmost prevalent device for inhalation therapy over half a century.

For the pulmonary drug delivery, the size of drug particles has a predominant effect on the sites of respiratory tract. Generally, following inhalation, the particles with the size of larger than 7 μm will be impacted in the oral and pharynx regions, of 2–7 μm will have a sedimentation in the central airway, of 0.5–2 μm can be inhaled into alveolar region that is an ideal site for lung delivery (Colthorpe et al., 1992; Dolovich, 2000). The traditional approach for inhalable particle engineering is jet milling, which produces the particles inefficiently with broad size distribution and severe aggregation (Chow et al., 2007; Thi et al., 2008), unavoidably resulting into the central and oropharyngeal deposition, and this method is inappropriate for micronizing biomacromolecules due to high shear force. Another approach that is well established and widely employed to prepare inhalable particles is spray drying. Spray-drying is a quick one-step process to prepare dry powders, where the solutions or suspensions are forced through a high pressure nozzle to generate millions of droplets into a hot

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environment where the liquids are quickly evaporated and the dry particles are subsequently produced. Spray-drying can be operated continuously and quickly, and the minimum exposure time plus the evaporative cooling create a moderate process, which makes it a suitable way for drying the heat-sensitive biomacromolecules (Yang et al., 2007). Spray-drying has become a powerful tool for the preparation of inhalable dry powders from the solutions or suspensions for pulmonary delivery of chemicals and biotherapeutics (Seville et al., 2007; Shoyele, 2008). However, due to the strong cohesion and adhesion among spray-dried particles, it is not unusual to observe severe aggregates of spray-dried particles, which subsequently causes the mean size larger than 10 μm, and still in the range of 3–6 μm even after being modified through employing various methods to enhance their dispersibility (Li et al., 2005; Seville et al., 2007). Undoubtedly, these microparticles would have a major deposition in the central airway, and not suitable for the delivery to the alveolar regions.

Recently, nanotechnologies have been developed to manufacture nanoparticles for pulmonary delivery, with the aim to increase the aerosolisation performance of drug particles and their delivery efficiency to peripheral regions of lungs (Jacobs and Muller, 2002; Rabinow, 2004). The rudimentary techniques for nanoparticle manufacturing are the milling (Mochalin et al., 2009), precipitation (Rasenack and M&ller, 2002; Rasenack et al., 2003), high pressure homogenization (Keck and Müller, 2006) and the combination of these techniques [Merisko-Liversidge et al., 2004]. However, these methods have severe disadvantages including the poor control over the particle size and morphology, possibly severe agglomerates caused by high energetic surface, inefficiency in manufacturing and unsuitability for biotherapeutics.

Microemulsion is a thermodynamically stable dispersion, which consists of two immiscible liquids stabilized by surfactants to produce an optically transparent and isotropic system. Because the uncontinueous phase is monodispersed in the immiscible liquid at the size less than 100 nm, microemulsions are therefore considered as an effectual nanotechnology for the preparation of nanosized particles (Eastoe, 2005; Eastoe et al., 2006). Previously, it has been reported that the water-in-oil (w/o) microemulsion, where the water phase containing the drug molecules was dispersed into the hydrocarbon with the stabilizer of lecithin, was utilized as a template to prepare the drug nanoparticles for inhalation. This microemulsion was snapped frozen by liquid nitrogen, and subsequently freeze-dried to produce nanoparticles of small chemicals that were dispersed in propellant to form pMDI formulations for inhalation (Dickinson et al., 2001). This method was further employed to make the nanoparticles of proteins and peptides (i.e. lysozyme, insulin and thymopentin) (Nyambura et al., 2009a, 2009b; Tan et al., 2011, 2012) However, it is dreadfully difficult to keep this kind of microemulsions maintaining their frozen state through the whole long-time freeze–drying process, as the organic phase with low melting points will be liquefied during the freeze–drying process and evaporated more quickly than aqueous phase, which thereafter cause the microemulsions demolished and a large amount of bulky particles are subsequently produced. Moreover, freeze–drying is a batch and time-consuming process, and the succession time for each batch is usually not less than overnight or even much longer, which is therefore limited to such applications as drying high-value and low volume products.

In order to solve the problems associated with freeze-drying w/o microemulsions for the generation of nanoparticles, a novel alternative approach has been developed in this study, which employed the spray-drying technology to desiccate w/o microemulsions. This unique joint nanotechnology of spray-drying microemulsions can steadily and quickly manufacturer nanosized particles of both chemical drugs and biotherapeutics. These nanoparticles were subsequently suspended in environmental-friendly hydrofluoroalkane propellant to prepare pMDI formulations for efficient pulmonary delivery. The therapeutically active agents (i.e. salbutamol sulphate and insulin) will be dissolved in water to form the aqueous phase that will be subsequently dispersed into the isooctane to generate the w/o microemulsions stabilized by lecithin and cosolvent isopropanol, which were subsequently spray-dried to generate the nanosized drug particles. These nanoparticles were consequently suspended in the propellant to produce the pMDI formulations for drug delivery to the lungs. The physicochemical properties of the nanoparticles, the aerosolisation performance and the storage life of the pMDI formulations are investigated.

2. Methods and materials

2.1. Materials

All chemical agents were at analytical, pharmaceutical or HPLC grade based on the experiment requirements, and used as received. Salbutamol sulphate, egg lecithin and heptane sulfonic acid were bought from Sigma-Aldrich (Poole, UK). Insulin, isopropanol, isooctane, methanol, and acetic acid were obtained from Fisher Scientific UK Ltd (Loughborough, UK). 1,1,1,2,-tetrafluoroethane (HFA 134a) at pharmaceutical grade was bought from Solvay Fluor (Hannover, Germany).

2.2. Construction of phase graph

The surfactant system was prepared by fully dissolving egg lecithin into isopropanol with the mass ratio of 1:3 w/w. This surfactant solution (density at 20 °C: 0.7943 g/mL) was subsequently filtered for further use in the preparation of microemulsion.

Water-in-oil (w/o) microemulsion was prepared in a capped tube, where the oil phase of isooctane and the surfactant system of lecithin:isopropanol (1:3 w/w) was mixed and subsequently vortex for 30 s, and a certain amount of 15% (w/v) of salbutamol sulphate solution (density at 20 °C: 1.0731 g/mL) was subsequently dropped in repeatedly and vortexed to determine the phase boundary between the crystal clear micelle phase to opaque multiphase of the system. For constructing the phase diagram, nineteen binary systems were selected where the mass ratios of iso-octane to surfactant system (lecithin:isopropanol = 1:3 w/w) was increased from 5% w/w to 95% w/w with an increment of 5% w/w, and the total mass was 500 mg. A small amount (25 μL) of water phase of drug solution was then added into each binary system and vortexed to get the microemulsion, and then calculated the mass percentage for the water, oil and surfactant. Repeated this process to get a series of microemulsions till the obscuration was observed or to the equal volume line, and a series of microemulsions were obtained, and the mass percentages for oil, water and surfactant in each system were calculated and used for constructing the phase diagram by DeltaGraph.

2.3. Preparation of spray-dried nanoparticles

Spray-dried salbutamol sulphate nanoparticles: the microemulsion system where oil: surfactant: water phase (15% w/v salbutamol sulphate solution) was 30:45:25 w/w/w was selected for spray-drying, as this microemulsion system has larger drug content. The standard operation parameters for the spray-drier (Büchi-290 mini spray-drier, Büchi Labortechnik, Switzerland) were inlet temperature 160 °C, aspirator 100%, flow rate 600 L/h and the feeding speed adjusted to make the outlet temperature at 70 °C. The spray-dried nanoparticles were embedded into the

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