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Improvement of the dispersibility of spray-dried budesonide powders using leucine in an ethanol–water cosolvent system

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ABSTRACT

A new approach for enhancing the dispersibility of respirable powders containing poorly soluble pharmaceutical actives is demonstrated. Budesonide was spray-dried with leucine from an ethanol–water cosolvent feedstock. For near-azeotropic cosolvent ratios, leucine was enriched on the surface of the particles relative to the bulk composition, and the particles showed a low-density morphology. Partial encapsulation of budesonide was accomplished. The dispersibility and manufacturability of the powder were greatly improved relative to powders made from budesonide alone. Fine particle fractions from a passive dry powder inhaler exceeded 80%. The particle size was in a suitable range for respiratory drug delivery (mass mean aerodynamic diameter between 2 and 3 μm). These results demonstrate that leucine can be used in ethanol–water cosolvent systems to design respirable particles with high dispersibility and good manufacturability.

1. Introduction

Spray-drying of pharmaceuticals for respiratory drug delivery has become a powder manufacturing technique of choice because it allows rational design of particle properties such as particle density, particle size, surface properties, and internal structure of the particles [1–3]. However, particle engineering has been largely restricted to aqueous systems for which suitable excipients have been identified and put into pharmaceutical development, such as leucine and trileucine, which are used to enhance powder dispersibility [4–8].

Spray-drying from an aqueous solution limits the type of drug molecule and excipient that can be processed, as it requires a minimum aqueous solubility. To economically prepare spray-dried powders for inhalation, it is advantageous to use atomizers that produce droplets with a median diameter of less than 10 μm. It follows from a simple mass balance that, for such atomizers, a solid content in the feedstock on the order of 10 mg/mL is required to produce spray-dried particles in the respirable particle size range [9].

Many efficacious pharmaceutical actives of significant commercial interest have much lower aqueous solubility; for instance, inhaled corticosteroids for the treatment of chronic obstructive pulmonary disease or asthma (such as budesonide, fluticasone propionate, beclomethasone dipropionate, and mometasone furoate) are practically insoluble in water [10–13]. Spray-drying has also been used specifically for low-solubility actives to improve their oral bioavailability [14]. Spray drying low-solubility actives from aqueous solution also places a constraint on the minimum size of the spray dryer body. Such actives are formulated at a low feedstock concentration and therefore require a larger droplet size to achieve a particle size within the respirable particle size range. In turn, because drying time is proportional to the square of the initial droplet diameter [9], spray-drying such actives from a low-concentration aqueous solution requires an increase in the size of the dryer chamber. Furthermore, spray-drying of hydrophobic drugs from non-aqueous solvents typically produces powders comprised of spherical, cohesive particles, which are not particularly suited for efficient delivery to the lung.

In this study, we have selected budesonide as a model low aqueous-solubility pharmaceutical active. Budesonide is an anti-inflammatory corticosteroid compound, one of many active pharmaceutical ingredients used to treat asthma or chronic obstructive pulmonary disease by respiratory drug delivery [15]. Budesonide is practically insoluble in water; its aqueous solubility is 28 μg/mL at 298 K [16], as shown in Fig. 1. We have formulated budesonide with leucine, a well-known water-soluble dispersibility enhancing excipient, to explore its potential use for particle design in ethanol–water cosolvent systems. In contrast to budesonide, leucine is sparingly soluble in ethanol, which is a solvent that has been demonstrated to be safe for inhalation. For example, the commercial metered dose inhaler asthma formulation QVAR® contains approximately 10–15% w/w ethanol for the production of ultra-fine inhalable droplets that contain beclomethasone dipropionate [17]. Because of its poor solubility in

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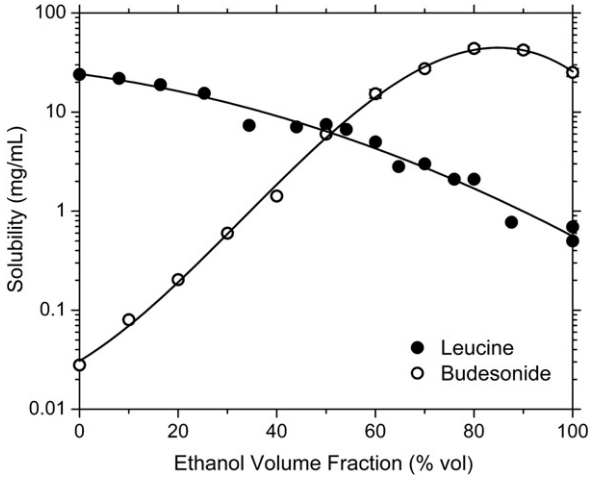

Fig. 1. Solubility of budesonide and leucine in ethanol–water mixtures at 25 °C, as a function of ethanol volume fraction. Data for budesonide solubility in 0 to 40% ethanol are from Ali et al. [16]. Error bars of the budesonide data are smaller than the symbol size.

water, budesonide is usually spray-dried from ethanol or ethanol–water solutions [15,18]. However, budesonide powder spray-dried from 100% ethanol is highly cohesive and difficult to handle [15]. Pharmaceutical powders manufactured for inhalation have to be efficiently delivered from an inhalation device to the lung. This entails the entrainment of powder into the inhalational air flow, and dispersion of the powder into small agglomerates and individual particles. The extent of a powder's dispersibility is a good indication of its ability to target the intended locations in the lung [9].

Various approaches to improve the dispersibility of spray-dried powders have been developed. One technique that is compatible with ethanol–water cosolvent systems is the use of volatile salts as pore-forming agents [19]. Typically, the salt is removed from the dried particle by sublimation, which creates voids and leads to a particle morphology that is favorable for improved dispersibility. For example, Nolan et al. achieved significant improvements in powder aerosolization properties and a reduction in particle density by spray-drying budesonide from methanol–water or ethanol–water solutions with ammonium carbonate as a pore forming agent [20].

A second approach is the use of amino acids or small peptides for encapsulation and production of hollow-shell-type morphologies [5]. Leucine is one of the most widely used excipients for dispersibility enhancement [9,21] and is a good candidate for spray-drying of pharmaceutical actives due to its demonstrated safety in rat and canine subjects [4]. However, leucine is of limited use in ethanol spray-drying because it has insufficient solubility in pure ethanol (Fig. 1). This motivates a study into the use of leucine in ethanol–water cosolvent systems, in which both the active and leucine have sufficient solubility if a suitable cosolvent ratio is chosen.

The effectiveness of leucine as a dispersibility enhancer for spray-dried particles relies upon its early precipitation at the surface of the evaporating droplet [22], resulting in the formation of a crystalline leucine shell around the active pharmaceutical ingredient [21]. Early precipitation of leucine in an atomized droplet can be achieved by carefully tuning the formulation composition and the spray-drying parameters. Through formulation and process design, leucine is the first component to reach saturation at the receding surface of the droplet during evaporation. In this way, leucine is the first component to solidify and hence likely becomes the main shell former. The resulting hydrophobic, crystalline shell reduces cohesive forces [5], which improves powder dispersion [9,21]. However, the selection of the optimal leucine concentration and composition of the cosolvent to achieve this goal is not trivial.

A theoretical particle engineering framework that allows estimation of characteristic times for precipitation and crystallization during droplet drying in a spray-dryer has been described [9,22]. The time to achieve leucine supersaturation at the surface of an evaporating droplet is the key parameter to understand the formation of leucine-containing particles [21]. The surface concentration increases during the drying process because of two different, but related mechanisms. The removal of solvent due to evaporation leads to an increase of the average concentration, $c_{m,i}$, of component, i, in the droplet according to:

$$c_{m,i}(t) = \frac{c_{0,i} d_0^3}{\left(d_0^2 - \int_0^t \kappa(\tau)\mathrm{d}\tau\right)^{\frac{3}{2}}} \tag{1}$$

where d_0 is the initial diameter of the droplet, $c_{0,i}$ is the initial concentration of component i in the droplet, and κ is the drying rate, which changes over time for non-azeotropic mixtures. Compared to water, ethanol has a higher vapor pressure and evaporation rate. Consequently, during the evaporation process, the ethanol fraction decreases with an accompanying increase in water mass fraction. In contrast, in an azeotropic mixture, which corresponds to approximately 96% ethanol content in ethanol–water mixtures [23], the equilibrium vapor phase composition is identical to the liquid phase composition and evaporation progresses at a constant rate.

The second mechanism is the enrichment of the droplet's surface with a component due to the relative diffusion rates of the solutes in the shrinking droplet. An approximate expression for the resulting surface enrichment is given by [9],

$$E_i(t) = \frac{c_{s,i}}{c_{m,i}} \approx 1 + \frac{Pe_i(t)}{5} + \frac{Pe_i^2(t)}{100} - \frac{Pe_i^3(t)}{4000} \tag{2}$$

The extent of enrichment depends on the component's Peclet number, Pe_i, which is a function of evaporation rate and the diffusion coefficient of the given solute in the mixture [24]. In general, the Peclet numbers in an evaporating cosolvent system will continuously change as a function of time, because both diffusion coefficient and evaporation rate change during evaporation.

At the time $\tau_{sat,i}$, when the concentration of a component on the surface reaches its equilibrium solubility, $c_{sol,i}$, nucleation and crystallization of this component can commence, and shell formation can be initiated. This time can be derived from the following equation [9]:

$$\int_0^{\tau_{sat,i}} \frac{\kappa(\tau)}{d_0^2}\mathrm{d}\tau = 1 - \left(\frac{c_{0,i}}{c_{sol,i}} E_i\left(\tau_{sat,i}\right)\right)^{\frac{2}{3}} \tag{3}$$

if the evaporation rate as a function of time is known. For near-azeotropic mixtures where a constant evaporation rate is a good approximation of the early stages of the evaporation process, this equation simplifies to the previously reported [9] relationship:

$$\tau_{sat,i} = \frac{d_0^2}{\kappa}\left[1 - \left(\frac{c_{0,i} E_i}{c_{sol,i}}\right)^{2/3}\right] \tag{4}$$

It can be seen from Eq. (4) that the key factors affecting this characteristic time are the initial concentration of leucine in the feedstock and the solubility of leucine [25–27], which is a function of the chosen cosolvent ratio, as can be observed in Fig. 1.

When the ethanol fraction in the cosolvent system is high, the solubility of leucine is low, which is expected to promote its early