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Effect of spray-drying temperature on the formation of flower-like lactose for griseofulvin loading

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ABSTRACT

The effect of spray-drying temperature has been studied for the first time on the formation of flower-like lactose for drug loading in this work. The synthesis of the flower-like lactose involves two steps, namely spray drying and ethanol washing. Four inlet temperatures (140 °C, 150 °C, 160 °C and 200 °C) have been used in the spray-drying step. The effect of the spray-drying temperature was significant on the formation of flower-like lactose, in terms of crystallinity, porosity and drug loading capacity. Higher inlet temperatures are more likely to produce lactose in the β form. The engineered flower-like lactose is highly porous, with pores of 1.4, 3.4 and 29.3 nm (diameter). Compared with other inlet temperatures, the flower-like lactose dried at 150 °C has the lowest degree of crystallinity, the largest pore surface area (38 ± 4 m^2/g) and pore volume (0.65 ± 0.09 cm^3/g), and the highest griseofulvin loading capacity (16.2 ± 0.3%, w/w). A griseofulvin dissolution test has suggested that the flower-like lactose can be used as a drug carrier to enhance drug solubility.

1. Introduction

Griseofulvin can inhibit fungal mitosis and has been clinically used for tinea capitis, severe tinea corporis, tibia ringworm, hand, foot and ringworm (Blumer, 1999). However, griseofulvin is a poorly water-soluble drug, which requires drug carriers to enhance its dispersibility and solubility in water for an effective absorption by humans. There have been many drug carriers used for loading griseofulvin in literature, such as saccharides (Saito et al., 2002), cyclodextrins (Rasheed and VVNS, 2008), niosomes (Jadon et al., 2009), liposomes (Ong et al., 2016), and silica aerogels (Smirnova et al., 2005).

Lactose is a typical drug carrier which has been used for many years (Healy et al., 2014; Ibrahim et al., 2015). The most commonly used lactose carriers are spherical or block-like solid-particles (Fu et al., 2012), on which the drug can only be loaded on the surface. In order to increase the drug loading capacity, porous lactose has been fabricated by Ebrahimi et al. using a spray-drying assisted templating technology (Ebrahimi et al., 2016). The synthesized porous lactose was shown to load acetaminophen with a mass fraction of 0.65–39%. With control of the crystallization process in ethanol, flower-like lactose with a highly porous structure has been engineered, using spray-drying assisted templating technology (Tan et al., 2017). The flower-like lactose microparticles have the potential to be used as drug carriers in dry powder inhalation (DPI), since lactose is a U.S. FDA-authorized DPI carrier due to its low toxicity (Iskandar et al., 2003; Wu et al., 2014). Lactose also has been used as fine excipient particles, which can enter the lung, to enhance DPI performance (Gilani et al., 2004; Jones and Price, 2006). Moreover, lactose has been used directly in respirable drug particles by spray drying with salbutamol sulphate (Corrigan et al., 2006) and lipid/polycation/pDNA vectors (Li et al., 2005).

The synthesis process of the flower-like lactose involves two steps, namely spray drying and ethanol washing. Since the ethanol washing mainly removes the templating agent, the choices of the parameters for spray drying have the highest impacts on the synthesis process, especially for good mixing and low crystallinity (Vehring, 2008). For spray drying, the drying temperature affects the crystallinity of spray-dried powders (Chiou et al., 2008a,b), which may also affect the post-crystallization process in this work. Here, the effect of the spray-drying temperature on the drug (griseofulvin) loading capacity of flower-like lactose has been studied for the first time. The crystallinity and porosity of flower-like lactose have been measured and discussed along with the griseofulvin loading capacity. This work has explored a novel technique for drug loading using porous, flower-like lactose microparticles.

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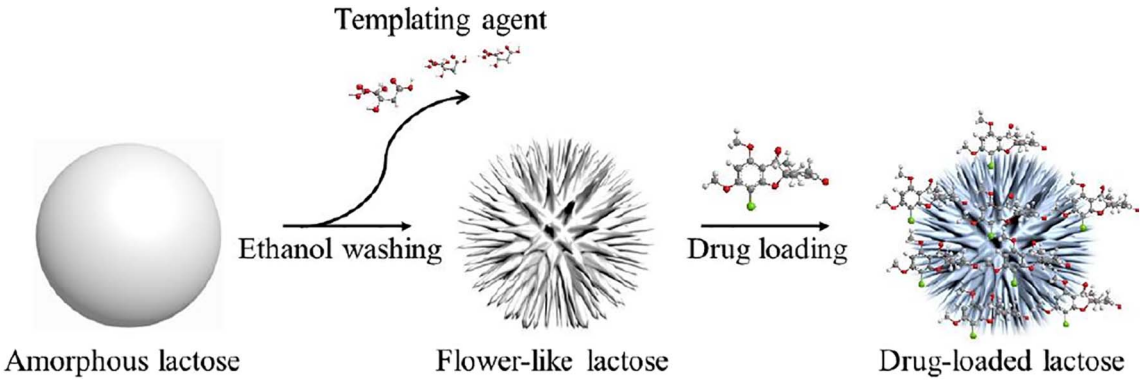

Fig. 1. Mechanism diagram for the formation and drug loading of the flower-like lactose.

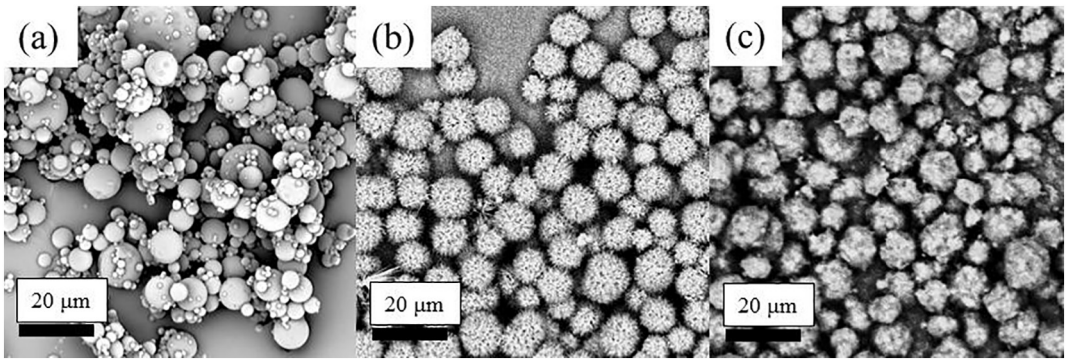

Fig. 2. SEM images of spray-dried lactose (a), flower-like lactose (b) and drug-loaded lactose (c). Loading does not change the morphology much between (b) and (c).

2. Material and methods

2.1. Chemicals

α-Lactose monohydrate ($C_{12}H_{22}O_{11}{\cdot}H_2O$, AR), citric acid monohydrate ($C_6H_8O_7{\cdot}H_2O$, AR), absolute ethanol (C_2H_5OH, LR) and Griseofulvin ($C_{17}H_{17}ClO_6$, ≥ 97%) were purchased from Chem-Supply, Australia. Acetone (C_3H_6O, LR) was purchased from Ajax Finechem, Australia.

2.2. Synthesis of flower-like lactose

The production of the flower-like lactose includes two steps: spray drying and ethanol washing. 10% (w/w) α-lactose monohydrate (core materials, ethanol-insoluble) and 1% (w/w) citric acid (templating agent, ethanol-soluble) were dissolved in water. A magnetic stirrer was applied to improve the dissolution rate of the solution at room temperature (25 °C). After 30 min, a clear feed solution was obtained. The feed solution was pumped into the Büchi B-290 spray dryer (Büchi, Switzerland) to produce amorphous particles of the mixture of lactose and citric acid. The inlet air temperatures were 140 °C, 150 °C, 160 °C and 200 °C for studying the griseofulvin loading capacity, giving outlet air temperatures of 64 °C, 72 °C, 77 °C and 98 °C, respectively. The pumping rate was 8 mL/min (25% of the maximum rate) and the nozzle air flow rate was 470 L/h (40 on the nozzle rotameter). After spray drying, the obtained citric acid-mixed lactose powder was immediately transferred into a desiccator for storage. Afterwards, the moisture content of the spray-dried samples was measured by weighing the samples after oven drying at 85 °C for 24 h.

In ethanol washing, 1 g citric acid-mixed lactose powder was treated with 40 mL ethanol to remove the templating agent (citric acid) for 15 min at a room temperature of 25 °C. A centrifuge was used to separate the template-free (flower-like) lactose from the ethanol solution at 600 rpm for 5 min. The flower-like lactose was pre-dried by inert nitrogen gas and then oven-dried at 50 °C to a constant weight.

2.3. Drug loading and dissolution experiments

In drug loading, 1.76 g griseofulvin was dissolved in 50 mL acetone to obtain the drug solution with a griseofulvin concentration of 0.1 M. For drug loading, 3 mL griseofulvin solution was mixed with 0.25 g flower-like lactose for 15 min, 30 min, 1 h, 2 h and 3 h. After centrifugation at 600 rpm for 5 min, the griseofulvin-loaded lactose was pre-dried by inert nitrogen gas and oven-dried at 50 °C to a constant weight.

In drug release, the temperature of the release media (100 mL water) was maintained at 37 ± 1 °C by a water bath. The saturated solution of griseofulvin was prepared and analyzed by a UV–Vis spectrophotometer at 295 nm to obtain the absorbance wavelength representing the 100% dissolution level of griseofulvin. Drug release from the griseofulvin-loaded lactose was compared with that of their corresponding physical mixture of non-porous lactose and griseofulvin powder. In a typical dissolution test, 0.12 g griseofulvin-loaded lactose powder was added to the release media, while the physical mixture of 0.1006 g non-porous lactose and 0.0194 g griseofulvin powder was added to another release media. The percentage of dissolved griseofulvin was expressed with respect to a saturated solution of griseofulvin.

2.4. Instrumental analysis

2.4.1. Scanning electron microscopy (SEM)

The samples were prepared by placing a sample onto a carbon tape on an aluminium sample stab. After Au-coating for 1 min at 25 mA by a Quorum-SC7620 Mini Sputter Coater (Quorum Technologies, UK), the surface morphologies of the spray-dried particles, the flower-like lactose particles and the drug-loaded lactose particles were observed using a Phenom-Prox SEM (Phenom-World, Netherlands) in the detector mode for secondary electrons with an operating voltage of 10 kV and an