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Hollow flower-like lactose particles as potential drug carriers: Effect of particle size and feed concentration

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ABSTRACT

This work presents a novel structure for lactose particles with hollow interiors and flower-like shapes. The main methods used in this material fabrication technique have been spray drying and templating, where the effect of particle size (5–15 μm) and feed concentration (5–20% *w*/*w*) has been studied. After focused ion beam (FIB) etching, the interior structures of the spray-dried particles and the flower-like lactose particles have been observed using a scanning electron microscope (SEM); the small particles (~5 μm) are solid; the medium-sized particles (~10 μm) are hollow; the large particles (~15 μm) are shell-like. In a drug-loading assay, acetaminophen of 2.7 ± 0.4% (*w*/*w*) concentration has been loaded in the flower-like lactose particles, which have a high surface area of 30 ± 7 m^2/g and peaks in the pore size distribution at 3.4, 5.6 and 12.4 nm (diameter). Confocal Raman microscopy (CRM) mapping shows that the position of acetaminophen molecules in lactose particles depends on the interior structure.

1. Introduction

A drug carrier is intended to load a drug properly in a particular form for enhanced bioavailability. In recent years, significant research has been carried out to develop new formulations and structures of carriers in drug delivery, by interfacing materials science and biology [1,2]. Typically, sugars, such as mannitol, fructose, dextrose and maltose, have been widely used as solid dispersion carriers to improve the solubility and dissolution of drugs [3]. Biodegradable polysaccharide particles have been developed for controlled drug release [4]. Due to their amphiphilicity, some copolymers have been used to create interesting micelle structures for drug loading, using micellization and crosslinking methods [5]. Apart from organic materials, Horcajada et al. have fabricated a porous metal-organic-framework material for drug delivery and imaging [6]. Mesoporous silica nanoparticles also have been synthesized as drug carriers, especially for cancer/tumour therapy [7,8].

Conventional drug-carrier structures, such as solid particles [9], liposomes [10] and emulsions [11], have been studied for their physical, chemical and biological properties to improve drug efficacy and safety, as well as patient compliance and convenience. The roles of carrier size, shape and surface chemistry have significant influences on drug delivery, as reported by Mitragotri's group [12]. Using a rapid microwave-assisted hydrothermal method, Wang et al. [13] have fabricated hollow flower-like hydroxyapatite carriers with the properties of large surface area, high capacity, good biocompatibility and biodegradability, in an anticancer-drug delivery. Apart from their report, few works have used hollow flower-like structures to deliver drugs. Instead, many inorganic hollow flower-like structures have been studied in catalysis, due to their advantages of low density, large surface area, high porosity and good surface permeability [14–17]. However, these hollow flower-like structures cannot be used in drug delivery, since they are toxic and not biocompatible with humans.

Spray drying is a typical technique to fabricate non-toxic microparticles using sugars in pharmaceutical particle engineering for drug delivery [18]. For different applications, many works have been carried out to fabricate spray-dried particles with different structures. In a review by Nandiyanto and Okuyama [19], spray-dried particles have been discussed in terms of their particular properties, when possessing spherical, dense, porous, hollow, doughnut, raspberry-like, and encapsulated components—mixed or hairy structures. Since lactose is an authorized drug carrier for use in DPI (dry powder inhalation) by the U.S. FDA (Food and Drug Administration), many studies have focused on the fabrication of lactose structures [20,21]. The size and density of spray-dried lactose particles, with solid or hollow interiors, are controllable by changing the droplet size during atomization, the concentration of the feed solution, the crystallization propensity and the solubility of the solute [22,23]. Recently, a highly-porous spray-dried lactose material has been reported by Ebrahimi et al. to give enhanced properties of drug loading, using a templating technique [24]. Based on the above works, hollow flower-like lactose particles have been fabricated in this work with the purpose of enhanced functionality for drug loading, using spray drying and a templating technique. Since many food-grade materials (like other sugars) can replace lactose in the fabrication,

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more hollow flower-like particles might be developed in the future as potential carriers for drug loading as described in this work.

2. Materials and methods

2.1. Chemicals

α-Lactose monohydrate, citric acid monohydrate and ethanol were analytical reagents (AR) and purchased from Chem-Supply, Australia. Acetaminophen (BioXtra, ≥99.0%), used in the study of drug loading, was purchased from Sigma-Aldrich, Australia.

2.2. Fabrication of hollow flower-like lactose particles

The fabrication of hollow flower-like lactose particles was performed by a spray drying and an ethanol washing process. In a typical fabrication, 10% (*w*/*w*) lactose and 1% (*w*/*w*) citric acid were dissolved in water at 25 °C for 30 min to obtain a clear solution. The solution was spray dried using a Büchi-290 laboratory-scale dryer (Büchi, Switzerland) with a nozzle opening size of 0.7 mm, an inlet air temperature of 150 °C, an outlet air temperature of 74 °C, a main air flow rate of 38 m^3/h (aspirator setting of 100%), a pump rate of 8 mL/min (pump setting of 25%) and a nozzle airflow rate of 470 L/h (40 on the rotameter scale). The obtained spray-dried particles were immediately transferred into a desiccator for storage. In the process of ethanol washing, 1 g of the spray-dried particles was washed by 40 mL of ethanol for 15 min on a vortex mixer at 600 rpm to remove the citric acid (templating agent), at room temperature of 25 °C. After another 15 min of resting for stabilization, the specimen was centrifuged at 600 rpm for 1 min to separate insoluble lactose from the ethanol solution. Inert nitrogen gas was used to gently blow over the specimen, removing some of the remaining ethanol. The flower-like lactose particles were obtained after removing all the ethanol, by oven drying at 50 °C to a constant weight.

2.3. Drug loading

Drug solution was prepared by dissolving 151 mg of acetaminophen in 10 mL of ethanol to obtain a concentration of 0.1 mol/L. 250 mg of flower-like lactose particles (dry) was mixed with 10 mL of drug solution on a vortex mixer for 30 s. The solution was then put on the desk for 15 min without shaking for drug loading. The drug-loaded lactose was centrifuged and dried at 50 °C for 2 h. The mass fractions of drug loaded in flower-like particles were measured using spectrometry (details are given in the supporting information—S5) according to the method reported by Ebrahimi et al. [24].

2.4. Instrumental analysis

2.4.1. Scanning electron microscope (SEM) and focused ion beam (FIB) instrument

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 spray-dried particles, flower-like lactose particles and 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 operating pressure of 1 Pa. In order to study the interior structure of spray-dried particles and flower-like lactose particles, a Zeiss Auriga FIB-SEM (Zeiss, Germany) was used to cut the particles by FIB etching with an operating voltage of 30 kV and a current of 250 pA. Prior to the FIB etching process, a platinum coating (30 kV, 250 pA) was performed for 60 s in the FIB instrument to protect the sample from electrical damage. Images were taken in SEM mode with the same SEM operating conditions after FIB processing.

2.4.2. N_2 sorption analysis

The Quantachrome Autosorb-1 (Quantachrome Instruments, USA) was used to measure N_2 adsorption and desorption isotherms of the samples with a low temperature of 77 K (liquid N_2). The pore surface area was calculated using the Brunauer-Emmet-Teller (BET) equation, while the pore volume and pore size distribution were calculated using the Barrett-Joyner-Halenda (BJH) model. Prior to the measurements, outgassing of the lactose sample was carried out at 80 °C for 720 min.

2.4.3. Confocal Raman microscopy (CRM)

CRM was used to investigate the molecular distribution of lactose and acetaminophen in the flower-like lactose particles after drug loading. A Renishaw Raman inVia Reflex system (Renishaw plc, UK) was used in this study. The lasers and optics were operated via computer controlled software Renishaw WiRE 4.1 (Windows-based). The collection optical system was based on a Leica DMLM microscope. Samples were placed underneath a microscope objective (×5, ×20 and ×50) and were excited by a 785 nm laser. Raman spectra of lactose, acetaminophen and the drug-loaded lactose particles were measured using the point-scanning mode. 3D Raman information of the specimen from the points, lines and planes was measured via the streamline 3D-scanning mode. For every scan, intervals of x, y and z axes were set at 1 μm, laser power was set at 10% and the exposure time was set at 10 s. CRM images were generated after mapping the integrated intensity at 1086 cm^{-1} for lactose and 1608 cm^{-1} for acetaminophen, showing the molecular distributions of lactose and acetaminophen in the drug-loaded flower-like lactose particles.

3. Results and discussions

3.1. Formation mechanism of hollow flower-like particles

The formation of hollow interiors in spray-dried lactose particles has been observed by Elversson's group [22,23]. They have found that the droplet size during atomization depends on the opening size of the nozzle, but not the feed concentration (for feed concentrations around 5–20%, *w*/*w*). When the feed concentration was around 5–20% (*w*/*w*), the diameters of the spray-dried particles here have been observed to be approximately half the diameters of the droplets, and the diameters did not vary by changing the feed concentration as well. Therefore, as illustrated in Fig. 1, the size distributions (small, medium-sized, large) of the droplets and the spray-dried particles are similar for different feed concentrations of 5%, 10% and 20% (*w*/*w*). Hollow particles are more likely to be produced, due to the expansion of air in the liquid feed [25] and the air incorporation during atomization [26]. Since air bubbles may escape more easily from smaller droplets, the spray-dried particles with a larger size can trap more air inside their structure, resulting in hollow interiors. For spray-dried particles with the same sizes, particles from a high feed concentration (20% *w*/*w*) are much denser (double) than those from lower feed concentrations (10% and 5% *w*/*w*), and therefore many of the spray-dried particles from the lower feed concentrations have hollow interiors. Besides, Elversson and Millqvist-Fureby [22] have observed that a high crystallization propensity and a low solubility of the solute are relevant to the synthesis of hollow spray-dried particles. Following from this observation, since citric acid was used as a templating agent here, causing an increase in the degree of lactose crystallinity for the spray-dried particles [27], more hollow spray-dried particles were produced for the following reason. The high crystallinity reduced the permeability of spray-dried particles, where more air bubbles cannot escape from the particles. Besides, a simple method to control the particle size has been completed using a larger nozzle opening with the diameter of 2 mm, resulting in producing larger spray-dried particles (Fig. S1).

The shapes of the spray-dried particles were spherical (Fig. 2a). During ethanol washing, the citric acid component dissolved while the