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Preparation of core-shell microspheres of lactose with flower-like morphology and tailored porosity

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ABSTRACT

Flower-like lactose microparticles with tailored porosity on the core and the shell have been synthesized using sugars, such as sucrose, glucose and fructose as templating agents. The proposed mechanism for tailoring the porosity is based on the difference in the diffusion coefficients of templating sugars compared with that of lactose as the core material, resulting in the migration of template molecules to the core or the shell of spray-dried particles during the spray-drying process. Focused ion beam (FIB) and scanning electron microscopy (SEM) techniques have been used to investigate the internal structure of the porous lactose particles. It has been found that using sucrose, with a lower diffusion coefficient compared with lactose, resulted in a porous shell upon template removal by ethanol washing, since lactose molecules with higher diffusivity tend to migrate to the core. By contrast, glucose and fructose, with higher diffusion coefficients, led to a porous core due to their tendency to accumulate in the core of the spray-dried particles. Nitrogen physisorption tests showed that the flower-like lactose microspheres have a large surface area of 26–31 m^2/g and a high pore volume of 0.57–0.78 cm^3/g with a pore size distribution predominantly in the micro- and mesoporous range (1.6, 3.8 and 30 nm). The pore size distributions of these flower-like lactose microparticles show that fructose, with the lowest glass-transition temperature (T_g) and consequently the highest crystallization rate during spray drying gave in larger pores, while the sucrose with the highest T_g led to smaller pores.

1. Introduction

Over the past decades, inorganic and organic porous materials have been widely used for catalysis, separation, ion exchange, adsorbents, and other chemical applications [1,2]. The control of the structures for these porous materials is based on different function-led designs, and their functionality largely relies on the pore structures. Thus, tailoring porosity in solid materials has been an emerging topic for the design of functional materials, such as silica nanoparticles (for drug delivery) [3], manganese oxide particles (for catalytic oxidation) [4], carbon xerogels (for lithium-ion battery electrodes) [5], block copolymer particles (for pH-controlled release) [6], collagen-hydroxyapatite scaffolds [7] (for bone tissue engineering).

Regarding biocompatibility, many reported works have preferred carbohydrates for encapsulation and delivery of active ingredients in food and pharmaceutical engineering [8,9]. In order to achieve high porosity for enhanced encapsulation and delivery, a template-assisted spray drying technique has been recently employed for producing biocompatible porous particles of lactose [10] and mannitol [11] using food-grade templating agents, such as citric acid [12], ascorbic acid, boric acid and lactic acid [13], maltose, sucrose, fructose and glucose [14]. The mechanism of this templating technique is to produce porous structures by removing the templating agents from the spray-dried mixtures, in which the components are initially mixed.

Like other inorganic and organic porous materials, the properties of porous carbohydrate materials rely on their shapes and pore structures [15]. For example, fabricating particles with uniform shapes and size distribution is of paramount importance in the drug-delivery performance of Pickering emulsions [16] and food-grade hydrogels [17]. The extent and efficiency of drug or nutrient loading largely rely on the pore structures of food-grade materials, due to the physiochemical adsorption. Saffari et al. [18] developed a formulation using highly-porous mannitol for nano-confinement, solubility and content uniformity enhancement of poorly water-soluble drugs. Ebrahimi et al. [19] improved the dissolution rate of hydrophobic drugs through encapsulation in porous lactose as a biocompatible porous carrier. Wang et al. reported a porous material made of corn starch for the adsorption of grape seed proanthocyanidins [20]. Thus, the synthesis of porous carbohydrate materials with uniform shapes and tailored porosity would be beneficial in encapsulation and delivery of ingredients in food and pharmaceutical engineering.

In this work, the fabrication of lactose core-shell microparticles with flower-like morphology and tailored porosity has been developed using

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the templating technique in spray drying. The core-shell pore structure within the microparticles of porous lactose has been investigated using FIB (focused ion beam) etching-assisted SEM (scanning electron microscopy). The mechanism for the formation of tailored core-shell pore structure has been discussed based on the difference between the molecular diffusion of different templates and the lactose during droplet drying stage. In fact, such a difference in diffusivity during spray drying has been used to control the position of pores in the shell or in the core of the particles. Controlling the distribution of pores by positioning them in the shell or in the core of porous particles has implications in modifying the release profiles of active compounds loaded inside the porous structure. Since no studies have been carried out for tailoring the porosity of lactose microparticles as new biocompatible carriers, this work has explored a way to fabricate food-grade carriers with novel porous structures.

2. Material and methods

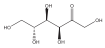
2.1. Chemicals

Lactose, sucrose, glucose, fructose and ethanol were used in this work and were analytical reagents (AR) purchased from Chem-Supply (Australia). The main characteristics of these chemicals are shown in Table 1, with information about their structures, molecular weights, diffusion coefficients and glass transition temperatures.

2.2. Preparation of the flower-like lactose microparticles

The mechanism for the formation of the flower-like lactose microparticles with tailored porosity is illustrated in Fig. 1. The fabrication of flower-like lactose microparticles was performed by the template-directed spray-drying technique developed in our research group [21]. In a typical synthesis, 10% (w/w) lactose (as the core material, insoluble in ethanol [22]) and 1% (w/w) sugar templates (sucrose, glucose or fructose, soluble in ethanol [23]), 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 orifice diameter of 2 mm, an inlet air temperature of 150 °C, an outlet air temperature of 73 ± 1 °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 536 L/h (45 on the rotameter scale). The yield from spray drying was 62 ± 2% for the operating conditions used in this work. The spray-dried particles thus obtained were immediately transferred into a desiccator for storage. In the ethanol-washing process, 1 g of the spray-dried particles was washed by 40 mL ethanol for 15 min on a vortex mixer at 600 rpm to remove the templating agents, at room temperature of 25 °C. After another 15 min of resting for stabilization, the specimen was centrifuged at 600 rpm for half a minute to separate insoluble lactose from the ethanol solution. The above process of ethanol washing was then repeated for further removal of the remaining templating-agents from the lactose sediment. After ethanol washing, inert nitrogen gas was blown gently over the specimen for 10 min, removing some of the remaining ethanol. The flower-like lactose microparticles with tailored porosity (from different templating agents) were obtained after removing all the solvent, by vacuum drying at 50 °C to a constant weight.

Table 1
The relative characteristics of lactose, sucrose, glucose and fructose for spray drying.

	Lactose	Sucrose	Glucose	Fructose
Structure				
Molecular weight	342	342	180	180
Diffusion coefficients (10^{-9} m^2/s) [37]	0.565	0.521	0.677	0.684
T_g (°C) [42]	101	62	31	5

2.3. Drug loading and dissolution

In drug loading, 1 g acetaminophen was dissolved in 40 mL ethanol to obtain the drug solution with an acetaminophen concentration of 0.17 M. For drug loading, 10 mL acetaminophen solution was mixed with 0.25 g flower-like lactose (from each type of templating agent) for 15 min. After centrifugation at 600 rpm for 1 min, the acetaminophen-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 iced water) was maintained at 0 °C with ice in the solution. Drug (acetaminophen) release was compared using each type of flower-like lactose fabricated with different templating agents. The concentration of acetaminophen was analysed by a Cary 60 UV–Vis spectrophotometer at 240 nm to obtain the absorbance wavelength of acetaminophen. In a typical dissolution test, 50 mg acetaminophen-loaded lactose powder was added to the release media. The percentage of dissolved acetaminophen was measured by comparison with the final concentration of acetaminophen representing the 100% dissolution level when the sample was completely dissolved in water after 30 min.

2.4. Instrumental analysis

2.4.1. Scanning electron microscopy (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 2 min at 15 mA by a Quorum-SC7620 Mini Sputter Coater (Quorum Technologies, UK), the morphologies of spray-dried microparticles and flower-like lactose microparticles were observed using a Phenom-Prox SEM (Phenom-World, Netherlands) in the detector mode for secondary electrons with an operating voltage of 15 kV and an operating pressure of 1 Pa. In order to study the interior structure of the flower-like lactose microparticles for tailored-porosity analysis, a Zeiss Auriga FIB-SEM (Zeiss, Germany) was used to cut the particles by FIB etching (course-line) with an operating voltage of 30 kV and a current of 1 nA, followed by FIB polishing (fine-line) with an operating voltage of 30 kV and a current of 100 pA. Prior to the FIB etching process, a platinum coating process (30 kV, 250 pA) was performed for 60 s in the FIB instrument to protect the sample from electrical damage, leading to the change in the surface morphology (less spiky). Images were taken in SEM mode with the same SEM operating conditions after FIB processing.

2.4.2. Fourier transform infrared (FTIR) spectroscopy

FTIR spectroscopy was used to investigate the components of spray-dried microparticles and flower-like lactose particles, showing the removal of the templating agent. For FTIR, the specimen was placed on the detector of a single bounce diamond ATR (Universal ATR) in a Nicolet 6700 FTIR spectrometer (Thermo Fisher Scientific, Australia) controlled using the software OMNIC 8.2.387. The FTIR spectra used a resolution of 2 cm^{-1} with 64 scans, and the scans were baseline corrected using the software OMNIC 8.2.387.

2.4.3. Raman spectroscopy

Since the sucrose, glucose and fructose (sugar templates) have similar functional groups to the lactose (core material), Raman spectra for the spray-dried microparticles and flower-like lactose particles were collected to support the results from FTIR analysis. The Raman analysis was performed using a Raman Station 400 F (PerkinElmer, USA) with a laser source of 785 nm. The specimen (dry powder) was placed on glass slide in the Raman instrument. The exposure time was 5 s for each scan (out of 64 scans per sample with a