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Improving the dissolution rate of hydrophobic drugs through encapsulation in porous lactose as a new biocompatible porous carrier

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ABSTRACT

T he dissolution rates of indomethacin (IMC) and nifedipine (NIF) as poorly water-soluble model drugs have been significantly improved by encapsulating their molecules in the porous structure of engineered-particles of lactose as a new biocompatible porous carrier. The formulation method used in this study utilized a template-based spray-drying technique for *in-situ* production of porous lactose followed by two solvent-based drug-loading methods: (i) adsorption from organic solution, and (ii) incipient wetness impregnation to incorporate the drugs inside the porous lactose. In both cases, the results of DSC and XRD have revealed the deposition of nano-sized crystals of drugs inside the nanopores due to the nanoconfinement phenomenon. Greater extents of drug loadings have been achieved during the indomethacin adsorption due to the hydrogen-bonding interaction with the surface of lactose, as determined by FTIR spectroscopy. The *in vitro* release studies in simulated gastric fluid (SGF) have shown faster release rates for the impregnated particles compared with drug-loaded particles *via* the adsorption method.

1. Introduction

There are many poorly water-soluble drugs, for which their low and irregular dissolution rates cause problems regarding the safety and efficacy of pharmaceutical formulations. Conventional strategies for improving the drug solubility focus mainly on reducing the particle size of the drugs and increasing the surface area available for dissolution using mechanical comminution techniques, such as crushing, grinding, and milling of drug particles (Jinno et al., 2006; Williams et al., 2013). However, these micronization techniques tend to produce cohesive particles with poor flowability (Buckton et al., 1988; Mura et al., 2002).

Crystal engineering research has offered a novel approach to improve the dissolution rate of hydrophobic drugs (Blagden et al., 2007) by modifying their physical or chemical properties through controlled crystallization to form co-crystals, metastable polymorphs, high-energy amorphous forms, and ultrafine particles. For instance, McNamara et al. (2006) reported the effect of co-crystal formation with glutaric acid on improving the oral bioavailability of a model drug with low aqueous solubility. The co-precipitation of drug molecules with carriers, such as polyvinylpyrrolidone (PVP), has also been reported to be effective in inhibiting the crystallization of amorphous drug in a solid-dispersion system for enhanced dissolution rate (Alonzo et al., 2011; Matsumoto and Zografi, 1999; Simonelli et al., 1969). Crystal engineering techniques, such as Rapid Expansion of Supercritical Solutions (RESS) (Foster et al., 2003; Türk and Lietzow, 2004; Yu et al., 2012) and melt sonocrystallization (da Fonseca Antunes et al., 2013; Manish et al., 2005) have also been investigated as novel size-reduction methods to produce ultrafine drug particles for improved dissolution rate.

There has been growing interest in the use of mesoporous materials to increase the bioavailability of hydrophobic drugs by encapsulating the drug molecules inside the confined space of the nanopores (Beiner et al., 2007; Salonen et al., 2005; Song et al., 2005; Van Speybroeck et al., 2009). Incorporation of drug molecules into the pore sizes only a few times larger than the drug molecular size restricts the crystal growth, leading to the formation of nanocrystals of drugs, deposition in the form of amorphous solids, or molecular dispersion (Rengarajan et al., 2008; Santos and Hirvonen, 2012). For this purpose, various

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drug-loading methods have been proposed, such as adsorption from drug solutions (Kinnari et al., 2011; Salonen et al., 2005; Song et al., 2005; Sriamornsak et al., 2010), drug deposition *via* solvent evaporation (Hu et al., 2011; Mellaerts et al., 2008; Williams et al., 2005; Zajc et al., 2005), heating a physical mixture of drug and porous carrier above the drug's melting point or the "*melt method*" (Li et al., 2011; Watanabe et al., 2001), and the "*incipient wetness*" impregnation technique (Charnay et al., 2004; Van Speybroeck et al., 2009; Verraedt et al., 2010).

Adsorption from drug solution by soaking the carrier particles in a solution of the drug and an organic solvent is the most common drug-loading method due to its simplicity (Kinnari et al., 2011; Salonen et al., 2005; Song et al., 2005; Wang et al., 2010). It has been suggested that the loading capacity in this method depends on the chemistry of the active compound and the carrier surface and their interactions with the organic solvent (Hillerström et al., 2009).

Another solvent-based loading method is incipient wetness impregnation, in which a minimum amount of highly concentrated drug solution (just enough to fill the pore volume of the carrier) is added to the carrier particles and drawn into the porous matrix by capillary action (Charnay et al., 2004; Ji et al., 2010; Van Speybroeck et al., 2009; Verraedt et al., 2010). In this method, the internal pore volume of the carrier and the concentration of drug in the organic solution directly affect the extent of drug loading. This method was used by Van Speybroeck et al. (2009) to improve the solubility properties of 10 poorly soluble drugs, including indomethacin and nifedipine, by encapsulating the drug molecules in the mesoporous silicates. In all cases, the loaded drug was found to be amorphous due to the nanoconfinement of drug molecules within the nanoporous host system. *In vitro* release studies showed significant improvements in dissolution rates of these amorphous drugs compared with their crystalline forms.

The availability of food-grade porous carriers that are suitable for drug encapsulation is mainly limited to hydrophobic aerogels (Tkalec et al., 2015), hydrogels (Braga et al., 2008; Ji et al., 2010), and mesoporous amorphous silica particles (Charnay et al., 2004; Verraedt et al., 2010). Incorporation of drugs into aerogels and hydrogels usually involves a supercritical technique with a significant drawback of high investment costs for large-scale production due to the high working pressures. In addition, despite the many applications of amorphous silica as drug delivery vehicles, commercialization of porous silica particles has still been limited, slowing down its biomedical applications (Santos and Hirvonen, 2012).

Lactose has particular properties, such as high water solubility, availability, biocompatibility, and low production cost. This material has been widely used as an excipient for oral administration of drugs (Rowe et al., 2009). Its poor solubility in organic solvents, such as ethanol and methanol may make lactose an ideal carrier for solvent-based loading methods. However, its non-porous structure, with a low specific surface area, has been a major drawback (Grigorov et al., 2013). A BET surface area of $2.58 \pm 0.02\ m^2/g$ and $0.34 \pm 0.01\ m^2/g$ have been reported for spray-dried lactose with an 80% amorphous content and for crystalline spray-dried lactose, respectively (Harjunen et al., 2002). In our previous studies (Ebrahimi et al., 2015a; b; Saffari et al., 2015), porous lactose particles with a good stability, due to their highly-crystalline structure, were produced using a template-assisted spray-drying technique. In the proposed method, spray-dried mixtures of lactose (core material) and food-grade template were treated with ethanol for template removal and for crystallization of lactose. In our recent work (Ebrahimi et al., 2016), these porous particles were used as porous carriers in a new formulation method involving adsorption from ethanolic solution of acetaminophen as a model drug. It was found that incorporating the drug molecules inside the carrier particles, instead of physically distributing among them, improves the blend uniformity of solid dosage forms.

The main objective of this work is to introduce a porous structure using lactose as a new food-grade and water-soluble porous carrier for the dissolution rate improvement of hydrophobic drugs. The formulation method used in this study includes the *in-situ* production of porous lactose during the templating step and the incorporation of the drug molecules into the nanopores of porous lactose using two solvent-based drug-loading methods: 1) adsorption from organic solutions and 2) incipient-wetness impregnation process.

2. Materials and methods

2.1. Materials

Indomethacin ($C_{19}H_{16}ClNO_4$, ≥ 99%) and nifedipine ($C_{17}H_{18}N_2O_6$, ≥ 99%) were purchased from Baoji Guokang (Bio-Technology Co., China). Pure α-lactose monohydrate crystals ($C_{12}H_{22}O_{11}\cdot H_2O$; analytical reagent), sucrose ($C_{12}H_{22}O_{11}$,), sodium lauryl sulfate (SLS) ($CH_3(CH_2)_{11}(OCH_2CH_2)_nOSO_3Na$), pepsin, hydrochloric acid (32%, HCl), absolute ethanol 100% denatured (C_2H_5OH), and sodium chloride (NaCl) laboratory-grade reagent from Chem-Supply (Australia) and methanol (CH_4O, ACS spectrophotometric grade, ≥99.9%, Sigma-Aldrich) were used in this study.

2.2. Experimental procedures

2.2.1. Template-based spray drying process for porous lactose preparation

Porous lactose was prepared according to the procedure described in our previous work (Ebrahimi et al., 2015b). In this study, an aqueous solution containing 10% and 1% (w/w, solution basis) of lactose (core material) and sucrose (templating agent) respectively, was prepared and magnetically stirred at room temperature (25 °C) until a clear solution was reached. A Buchi-B290 Mini Spray Dryer with an inlet gas temperature of 150 °C, a main air flow rate of 38 m^3/h (aspirator setting of 100%), a pump rate of 8 ml/min (25% of the maximum rate), and a nozzle air flow rate of 470 l/h (40 on the nozzle rotameter scale) was used to spray dry the lactose/template solution. The ethanol-soluble template was then removed from the lactose structure by washing the spray-dried powder with ethanol. Two grams of spray-dried mixture were immersed into 60 ml of ethanol and stirred for 24 h at room temperature, followed by vacuum filtration to recover the template-free lactose particles. The ethanol washing was performed twice. In case of adsorption loading, the lactose particles were transferred into the drug solution after vacuum filtration while they were still wet with the organic solvent. By contrast, for the incipient wetness impregnation method, the filtrate was oven-dried at 60 °C for one hour, crushed, and ground to be used for drug-loading experiments. A portion of this dried porous lactose was used for nitrogen physisorption tests to measure the pore volume and specific surface area of the lactose carrier before drug loading.

2.2.2. Drug loading procedures

2.2.2.1. Adsorption from drug solution. The ethanol-washed lactose particles were immersed into the drug solutions while they were still wet with the organic solvent. Different amounts of IMC and NIF were dissolved in 60 ml of ethanol at 30 °C to reach a clear solution with different drug concentrations. Due to the higher solubility of indomethacin in ethanol, a broader range of drug