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A novel formulation for solubility and content uniformity enhancement of poorly water-soluble drugs using highly-porous mannitol

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ABSTRACT

The present study investigates the enhancement of the dissolution rates for poorly-water soluble drugs by a new adsorption method. The results show that the current adsorption method enhanced the dissolution rate of both nifedipine and indomethacin to a significant extent by nano-confinement of drugs into the pore spaces of highly-porous excipients. Porous mannitol particles with a surface area and pore volume of 6.3 ± 0.1 $m^2 g^{-1}$ and 0.036 ± 0.002 ml g^{-1}, respectively, were drug loaded in two different concentrations of indomethacin and nifedipine. The results of drug loading for nifedipine showed an increase from 3.2 ± 0.1% w/w for a 0.08 M drug solution to 9.1 ± 0.3% w/w drug loading for a 0.16 M drug solution, while indomethacin had slightly better performance for the adsorption process, with 4.1 ± 0.2% w/w and 12.6 ± 0.4% w/w for 0.08 M and 0.16 M concentrations of indomethacin, respectively, in the final formulation. This result also indicated highly-uniform blends with a percentage relative standard deviation of less than 4% for drug-loaded mannitol in both nifedipine and indomethacin. This method gave a significant enhancement of the dissolution rate for both drugs due to nano-confinement of drugs into porous excipients and high solubility of porous mannitol, with 80% drug release within the first 15 min for the drug-loaded samples.

1. Introduction

Major challenges facing the design of oral dosage forms are their poor bioavailability and uniformity of drug dosage, especially in low-dose solid-drug products (Garcia and Prescott, 2008; Grigorov et al., 2013; Huang and Sherry Ku, 2010). Bioavailability, as one of the very important quality parameters of drug formulation, refers to the extent and rate at which an active drug reaches systemic circulation. Poor solubility is one of the main causes of low bioavailability (Savjani et al., 2012; Schreiner et al., 2005). More than 40% of newly developed drugs in the pharmaceutical industry are poorly water-soluble, which may cause a range of medication control problems, such as insufficient dosing (Jain et al., 2012; Liu, 2008). Formulation and dosage-form design problems of poorly water-soluble drugs must be addressed to better meet the needs of users and the targeted product requirements, such as clinically-acceptable performance.

There are various solubilization techniques, such as solid dispersion, particle-size reduction, complexation, the use of surfactants and novel excipients, to enhance the solubility of poorly water-soluble drugs (Dhillon et al., 2014; Ojha and Prabhakar, 2013; Savjani et al., 2012). A common strategy to increase the dissolution rate and hence the bioavailability of such drugs includes the reduction of particle size (Leuner and Dressman, 2000) to generate effective surface area. As a particle becomes smaller, the surface area to volume ratio increases and the larger surface area allows greater interaction with the solvent, which causes an increase in solubility (Savjani et al., 2012). Particle-size reduction may also enhance the possibility of API uniformity for solid dosage forms (Huang and Sherry Ku, 2010). Another potential approach to solve the abovementioned challenges for better control of the release characteristics for a drug is loading or nano-confinement of drugs into porous excipients as hosts (Millqvist-Fureby et al., 2014). There are several drug loading methods, such as incipient wetness impregnation (Mellaerts et al., 2008; Van Speybroeck et al., 2009; Verraedt et al., 2010) and the adsorption method, in which carrier particles are immersed in a drug solution and drugs can be dispersed and deposited at the surface and into the pore spaces of porous carriers (Heikkilä et al., 2007; Hillerström et al., 2009; Qu et al., 2006; Xia and Chang, 2006).

Mesoporous silica is of specific interest as excipient for these drug-loading methods due to its high specific area and large pore volume. For instance, the loading and release behavior of five model drugs, such as antipyrine, ibuprofen, griseofulvin, ranitidine, and furosemide into the porous silica were studied through adsorption method by Salonen et al. (2005). Various drug-loading efficiencies between 9% and 45% were obtained using different solvents for loading and the drug loading into the mesoporous silica improved the dissolution rate. Van Speybroeck et al. (2009) used an incipient wetness impregnation method to improve the solubility of ten poorly water-soluble drugs

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including indomethacin and nifedipine by encapsulating the drug molecules in the mesoporous silicates.

Mesoporous silica is fairly expensive and has low solubility (Millqvist-Fureby et al., 2014) in water. Therefore other porous excipients, such as mannitol with its high solubility in water (216 g/l, (Ohrem et al., 2014)), may offer potential carriers for controlled release systems of poorly water-soluble drugs, despite their much lower specific surface area and smaller pore volume compared with those of mesoporous silica. It can be expected that preparing an excipient with higher surface areas and larger pore volumes, such as mesoporous silica, would result in a higher drug loading, since it provides more available pore volume in order to host the drug molecules. However, high drug loadings are not always needed, and in the formulation and manufacture of low-dose drug products, the amount of API in the solid dosage form can be as low as 0.1% w/w (Grigorov et al., 2013; Zheng, 2009). Moreover, major challenges facing the design of the oral dosage form, such as poor bioavailability and uniformity of drug dosage, are more pronounced for low-dose drug products, which may result in undesirable variations in dosage (Cartilier and Moes, 1989; Garcia and Prescott, 2008; Huang and Sherry Ku, 2010; Zheng, 2009). Therefore, providing a porous carrier with enough specific area requirement and reasonable pore volumes for the targeted drug-loadings seems to be a key.

In addition to bioavailability, pharmaceutical formulations contain an active pharmaceutical ingredient (API), and its excipients are required to ensure the consistency of the dosage units. Tablets and capsules currently account for over two-thirds of the total number of medicines produced all over the world (Sahoo, 2012). The homogeneity of the blend, the content uniformity of the finished products, and the poor blending uniformity of finished products, especially for low-dose drug products, are typical problems due to a combination of factors (Cartilier and Moes, 1989; Garcia and Prescott, 2008; Grigorov et al., 2013; Huang and Sherry Ku, 2010; Zheng, 2009). These problems include insufficient blending, segregation, and the large particle size of the drug substance when using blending or mixing unit operations. Control of the particle size for the drug substance may be a solution to ensure the content uniformity of the finished products, but the particle size and size distribution of excipients also have a significant impact on blending homogeneity, powder segregation, and flowability. This situation can result in unacceptable content uniformity of excipients for product quality (Garcia and Prescott, 2008; Huang and Sherry Ku, 2010; Zheng, 2009). Therefore, it is critical that the drug be uniformly distributed in the final product to ensure that the proper dosage of the drug is delivered to the patient (Garcia and Prescott, 2008). According to the Food and Drug Administration (FDA), the relative standard deviation (RSD) for content uniformity of pharmaceutical products must not exceed ±6% at the time of manufacture, while the maximum acceptable deviation in the active substance content of the finished products requires a RSD of less than 5% at the time of manufacture, according to European Pharmacopoeia requirements (Directive, 2003/63/EC; FDA, 2003).

Presenting a suitable drug-loaded particle that consists of dispersing poorly water-soluble drugs in the host pore-space of highly-porous excipients may offer multiple benefits in one formulation step. First, the dissolution rate should improve due to nanconfinement of the drug molecules inside the internal void structures of nanoporous excipients. This situation results in an increase in the solubility with a reduction in the particle size of the drug, and it maximizes the surface area of the compound that comes into contact with the dissolution medium as the carrier dissolves. This outcome often results in significant increases in bioavailability. Second, water-soluble excipients with high porosity can improve the drug release rate by enabling faster release of the drug into the dissolution medium. Moreover, greater porosity of excipients facilities the diffusion of the API components and increases the rate of drug adsorption. Last but not the least, the adsorption method should be independent of the control strategy for both the particle size of the drug and excipients in the finished dosage units, so the particle size of the final formulation should not have any effect on the content uniformity and the delivered dose.

For this purpose, an adsorption technique has been developed by modifying the templating process described in our previous works (Saffari et al., 2015a, 2015b; Ebrahimi et al., 2015a, 2015b, 2015c) to produce highly-porous excipients with high surface areas which, furthermore, have been used for adsorption to investigate drug dissolution. Highly-porous mannitol particles with high surface areas have been successfully produced through the spray drying of mannitol solutions containing sucrose, as a templating agent that is commonly used as excipients in drug delivery for pharmaceutical applications. Then, the sucrose has been removed by ethanol washing of the spray-dried powders to create porous powders. Production of highly-porous frameworks of mannitol having unique properties, such as a significant surface area of 6.3 ± 0.1 $m^2\ g^{-1}$, a total pore volume of 0.036 ± 0.002 ml g^{-1}, and high water solubility makes this material suitable as a carrier for adsorption. The resultant porous mannitol, after ethanol washing, has been transferred to acetone solutions to dissolve and precipitate nifedipine and indomethacin molecules onto the voids of the porous mannitol carrier.

2. Materials and methods

2.1. Sample preparation

In these experiments, the following materials have been used:, indomethacin ($C_{19}H_{16}ClNO_4$, ≥99%) and nifedipine ($C_{17}H_{18}N_2O_6$, ≥99%) from Baoji Guokang Bio-Technology Co., China), D-Mannitol ($C_6H_{14}O_6$), 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), acetone (C_3H_6O), and sodium chloride (NaCl) laboratory-grade reagent from Chem-Supply (Australia) and methanol (CH_4O, ACS spectrophotometric grade, ≥99.9%, Sigma-Aldrich).

2.2. Porous mannitol production and drug loading process

Mannitol (10% w/w)-sucrose (2% w/w) solutions were prepared according to the method explained in our previous work (Saffari et al., 2015a) using a magnetic stirrer to enhance the dissolution rate of mannitol at the room temperature of 25 °C for at least 30 min. The resultant clear solutions were then spray dried using a Buchi mini spray dryer B-290, Switzerland with an inlet air temperature of 150 °C, a main air flow rate of 38 m^3/h (aspirator setting of 100%), the pump rate of 8 ml/min (25% of the maximum rate), and the nozzle air flow rate of 470 L/h (40 on the nozzle rotameter scale).

Freshly spray-dried powder has been collected from a collection vessel at the bottom of a cyclone, and 2 g of powder has been washed with 80 ml of ethanol for 48 h at the room temperature of 25 °C to remove the templating agent (sucrose) and then filtered under vacuum. The resultant pastes were immersed in acetone solutions with two different concentrations of indomethacin and nifedipine (0.08 M and 0.16 M) as model drugs in order to load the drug onto highly-porous mannitol for 12 h at the room temperature of 25 °C. The carrier: drug ratios were 1:2 (w/w) and 1:4 (w/w) for 0.08 M and 0.16 M drug solutions, respectively. The final processed powders were obtained after vacuum filtering and oven drying at 60 °C to the constant weight for the drug-loaded powders in order to remove any residual acetone. The final powder has been used for analytical tests. In this study, for each drug concentration, the experiment has been done three times, and data have been presented as means ± STD (standard deviation). The drug content uniformity of final powder, % RSD, was obtained from one set of independent experiment for each drug and different drug concentrations.