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Nano-confinement of acetaminophen into porous mannitol through adsorption method

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ABSTRACT

A new formulation has been developed successfully, which includes production of highly-porous mannitol particles with high surface areas through the spray drying of mannitol solutions containing ethanol-soluble sugar or food-grade acids as templating agents. The resultant porous particles after ethanol washing have been transferred to ethanol solutions containing the drug component. The results of this study showed that deposition of acetaminophen in the pore-space of highly-porous mannitol resulted in better blending uniformity of drug dosage, as well as a fast drug release rate due to nano-confinement of drugs into porous excipients. Within the first 5 min of the experiment 80% of the drug was released for the drug-loaded samples. Low variability for the drug content was found for the finished products, even for low-dose drug products with around 4% relative standard deviation or less. The drug content of porous mannitol with a surface area and pore volume of 6.1 ± 0.1 m^2 g^{-1} and 0.037 ± 0.003 ml/g, respectively, significantly increased from 0.62 ± 0.03 wt% to 21.7 ± 0.8 wt% when the concentration of acetaminophen was increased from 0.01 M to 0.5 M.

1. Introduction

Solid-dosage form drugs that include tablets and capsules are some of the most popular and commonly-employed methods of drug delivery, which currently account for over two-thirds of the total number of medicines produced in the world [1]. Their final formulation contains an active pharmaceutical ingredient (API), its excipients and also additives, which may be included in the formulations to enhance the physical appearance, improve stability, and aid in disintegration after administration. However, major challenges facing the design of the oral dosage form are poor bioavailability and uniformity of drug dosage, especially in low-dose solid drug products [2,3]. Among other essential qualities of a well-made pharmacopeia, uniformity of drug dosage is very important. The problems associated with the mixing of an active pharmaceutical ingredient (API) with excipients are many and complex, especially for low-dose (˂100 μg) drugs during the manufacturing of solid dosage forms, which may result in undesirable variations in dosage [1,3].

Therefore, it is critical that the drug be uniformly distributed in the final product. The problem associated with the control of dose uniformity needs to be addressed carefully to ensure that the proper dosage of the drug is delivered to the patient. The content-uniformity requirements are regulated throughout the world to ensure that the mixture of the drug and its excipients is adequately uniform in the finished products [2]. The Food and Drug Administration (FDA), in setting standards for the content uniformity of pharmaceutical products, requires that the relative standard deviation (RSD) is less than or equal to 6%, while the maximum acceptable deviation in the active substance content of the finished products must not exceed ±5% at the time of manufacture, according to European Pharmacopoeia requirements [4,5].

Particle size control of the API can enhance the uniformity of solid dosage forms; however, this approach for drugs may not be able to maintain the level of homogeneity throughout processing due to the possibility of blend desegregation, and consequently poor blending uniformity as a result of differences in particle size, shape, or density of the materials being blended [1,2].

In addition to blending uniformity, bioavailability, as one of the very important quality parameters of drug formulations, 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 [6,7]. More than 90% of small molecular-weight drugs are

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delivered to the human body in crystalline form; however, most of crystalline drugs have low solubility in water [8]. Low aqueous solubility is the major problem encountered with formulation development, and poorly soluble drugs often require high doses in order to reach the desired bioavailability after oral administration, which may lead to increased side effects. Formulation and dosage-form design must ensure that solubility requirements are met for manufacturing as well as clinical applications.

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, in which drug molecules can be dispersed in the pore spaces of a porous carrier [9]. The reduction in the particle size of an active pharmaceutical ingredient (API) to the nano-crystal size range may cause a significant increase in the dissolution rate of the API, often resulting in significant increases in bioavailability. There are several drug loading methods, such as incipient wetness impregnation [10,11] 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 [12,13]. For successful drug-loading, highly-porous excipients are needed, with high surface areas being the most important property. Carriers with high porosity can improve the solubility by enabling faster release of the drug as a result of better penetration of the solvent into the drug-excipient matrix. Mesoporous silica is of specific interest as excipient for these drug-loading methods due to its high specific area and large pore volume, however, mesoporous silica is fairly expensive and has low solubility [9] in water. Therefore other porous excipients, such as mannitol with its high solubility in water, 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.

Presenting a suitable drug-loaded particle that consists of dispersing APIs in the host pore-space of highly-porous excipients results in particle size reduction of the drug powders to the size range of nanometers. Nanconfinement breaks up the intermolecular interactions of the API molecules and separates them inside the internal void structures of nanoporous excipients. This situation combines the benefits of an increase in the solubility with a reduction in the particle size of the API and maximizes the surface area of the compound that comes into contact with the dissolution medium as the carrier dissolves.

For this purpose, we have developed a method to produce highly-porous excipients with high surface areas [14,15] which, furthermore, has been used for adsorption to investigate drug dissolution. This work has been done by applying a adsorption technique and modifying our current templating process. The non-hygroscopic nature of mannitol, and consequently its low moisture content, make it a desirable additive and excipient for moisture sensitive ingredients and, recently, the use of mannitol as an alternative to lactose in food products and pharmaceutical formulations has significantly increased [16–18]. Highly-porous mannitol particles with high surface areas have been successfully produced through the spray drying of mannitol solutions containing ethanol-soluble food-grade acids, such as citric acid as a templating agent, and then removing the citric acid 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 $9.1 \pm 0.9\ m^2\ g^{-1}$, and a total pore volume of $0.11 \pm 0.03\ ml\ g^{-1}$, which can be tuned by varying the concentrations of citric acid and WPI, makes this material suitable as a carrier for adsorption method. However, in the current work, the possibility of using carbohydrate sugars, such as sucrose, as non-acidic templates that are commonly used as excipients in drug delivery for pharmaceutical applications, has also been investigated. The resulted porous particles after ethanol washing have been transferred to ethanol solutions to dissolve and carry acetaminophen as a sample drug into the pores of porous mannitol.

2. Materials and methods

2.1. Sample preparation

In these experiments, the following materials have been used: D-Mannitol ($C_6H_{14}O_6$, laboratory-grade reagent), acetaminophen (BioXtra, ≥99.0%, Sigma–Aldrich), sucrose ($C_{12}H_{22}O_{11}$, laboratory-grade reagent), citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$, analytical reagent), whey protein isolate (WPI) (Balance, Vitaco Health Ltd, Auckland, New Zealand, consisting of 92 g protein, 0.4 g fat (total) including 0.2 g saturated fat, 0.5 g carbohydrate, and sodium 0.6 g per 100 g), potassium phosphate monobasic (KH_2PO_4, ACS reagent), sodium hydroxide (NaOH, ACS reagent), absolute ethanol 100% denatured (C_2H_5OH, laboratory reagent), and methanol (CH_4O, ACS spectrophotometric grade, ≥99.9%).

Mannitol solutions with citric acid (2% w/w) and WPI (0.5% w/w) were prepared, with the aim being to produce the highest possible surface area of the ethanol-washed mannitol particles, as developed in our previous work [15]. In order to investigate the effects of sucrose concentrations as a templating sugar on the BET surface areas of ethanol-washed mannitol, experiments were carried out by varying the composition of the solutions with different amounts of sucrose. In order to increase the yield of the spray-drying process, 0.5% (w/w) whey protein isolate has been added to 10% (w/w) mannitol with different concentrations of sucrose. For all experiments, the mannitol concentrations were kept constant at 10% (w/w), and each solution was made up to a total weight of 100 g. A magnetic stirrer was used to enhance the dissolution rate of mannitol at the room temperature of 25 °C for at least 30 min, so that clear solutions were obtained without any visible crystals being present. The clear solutions were then spray dried.

2.2. Porous mannitol production and drug loading process

A Buchi mini spray dryer B-290, Switzerland has been used in the experiments. The inlet air temperature has been 150 °C, the main air flow rate through the dryer has been 38 m^3/h (aspirator setting of 100%), the pump rate has been 8 ml/min (25% of the maximum rate), and the nozzle air flow rate has been 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 has been washed with ethanol for 48 h at the room temperature of 25 °C to remove the templating agents (citric acid or sucrose) and then filtered under vacuum. The resultant pastes have been immersed in the ethanol solutions with four different concentrations of acetaminophen (0.01 M, 0.05 M, 0.2 M, and 0.5 M) as a model drug in order to load the drug onto highly-porous mannitol for 12 h at the room temperature of 25 °C. The final-processed powder has been obtained after vacuum filtering and oven drying at 60 °C for 1 h to remove any residual ethanol. . Since there was no change in the weight for the drug-loaded powders after 1 h of oven drying, suggesting that no solvent residues were left in the final material. Sieving has then been carried out on the portion of dried filtrate with a set of sieve sizes ranging between 63 μm and 300 μm, and the final powder has been used for analytical tests. Fig. 1 illustrates the overall process. In order to investigate the effect of excipient porosity on the efficiency of the adsorption approach, porous mannitol with a range of porosities has been produced through the templating process by varying the concentrations of templating agents and WPI. This material has been used for the