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Enabling direct compression of formulated Danshen powder by surface engineering

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ABSTRACT

The direct compression (DC) technology is increasingly popular in the manufacture of tablets due to its efficiency and economy. However, its use in the production of Traditional Chinese Medicine (TCM) tablets is often limited owing to poor powder flow and compaction properties of TCM powders. In this work, we aimed at improving properties of powders used in Fufang Danshen tablet, a popular TCM for treating angina pectoris, by particle surface engineering. Both the active ingredients (Danshen root, Notoginseng, and Borneol) and formulated Danshen mixture exhibit flowability too poor to be processed directly on a high speed tablet press. By dry coating with 1% silica nanoparticles, the flowability, tabletability, and fillability of these powders were adequately improved to be suitable for DC.

1. Introduction

The direct compression (DC) process for pharmaceutical tablet manufacturing requires fewer unit operations compared with various processes that involve granulation. Since no solvent or water is used in the process, drying is avoided during manufacturing. This is critical for manufacturing tablet of actives that are sensitive to heat or moisture. The manufacturing of DC tablets is inherently free from the over-granulation problem and tablets from a DC process may have faster dissolution than tablets prepared using a wet granulation process. Finally, fewer excipients are generally required in a DC tablet. For example, polymers required for wet granulation are generally not used in DC tablets [1].

Tried and optimized over a period of thousands of years, Traditional Chinese Medicines (TCM) not only play a key role in healthcare of Chinese people but also have gained increasing acceptance in the world-wide healthcare. Although therapeutic benefits of many TCM have been clinically proven, their manufacturing typically involves backward processes that are not efficient for mass production. One major advance in the modernization of TCM was the introduction of tablet dosage forms containing active ingredients of TCM that traditionally had to be extracted by cooking raw herbs in patients' homes.

TCM tablets are manufactured using herb extracts or mixtures of original powder of crude drug and powdered extract, containing proteins, polysaccharides, starch, mucilage, small molecule secondary metabolites, and inorganic salts. These extracts are generally hygroscopic, cohesive, and exhibiting poor flowability [2]. To address the challenges posted by these poor powder properties, granulation processes are typically employed in TCM tablet manufacturing. DC process is feasible only when an unrealistically large amount of excipients is used to mask the undesired powder properties detrimental to tablet manufacture. As a result, a large number of tablets will need to be taken for delivering a therapeutically effective dose of TCM. An attractive strategy for enabling the DC process without using a large amount of excipient is to engineer active TCM powders so that they exhibit powder properties suitable for tablet manufacturing. However, little work has been done in this direction despite of the potentials of powder engineering strategy.

It has been shown that surface coating with nano-sized guest particles can effectively improve flowability of cohesive powders [3–6]. The improved powder flow of coated powder is, in part, because of the reduced powder cohesion by increasing physical separation among adjacent host particles. In addition, the nanoparticles can also behave like ball bearings to reduce inter-particulate friction and interlocking [7]. Nano guests can be of a variety of materials. We recently showed that surface deposition of silica nanoparticles substantially improved the flowability of both pure excipients and a formulated ibuprofen powder [7,8].

Formulated Danshen tablet is commonly used in treating angina pectoris with an estimated annual sale of 300 million US dollars in 2012. The active ingredients are Danshen extract, Notoginseng, and Borneol as detailed in the 2010 Chinese Pharmacopoeia. In this work,

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we coated powders of Danshen extract, Notoginseng, Borneol, and formulated Danshen with 1% nano silica by a continuous dry comilling process. The flowability, tabletability, and fillability of these powders, with and without nanoparticles coating, were characterized. Powder hygroscopicity and particle size distribution were also studied. This work is the first systematic effort in developing a DC manufacturing process for the formulated Danshen tablet. Knowledge derived in this study may be used in the DC production of other TCM tablets, which places this work in an important place in the modernization of TCM tablets.

2. Materials and methods

2.1. Materials

Colloidal silica (M-5, Cab-o-sil; Cabot Corporation, Tuscola, Illinois) was selected as the coating material (guest). Danshen root, Notoginseng, and Borneol were obtained from Wuhan Chukaitang Pharmaceutical Co., Ltd. (Wuhan, China). Microcrystalline cellulose (MCC, Avicel PH102) was obtained from Chengdu Xiya Reagent Co., Ltd. (Chengdu, China). Danshen roots were extracted according to the method described in the Chinese Pharmacopoeia (CP, 2010) and the extract powder was obtained by spray drying (OPD-8 Spray Dryer, Shanghai Dachuanyuan Drying Machinery Co., Ltd., Shanghai, China). Drying inlet air temperature was 175 °C, outlet air temperature was 85 °C, and feed-rate was 30 mL/min. Notoginseng and Borneol were pulverized into fine powders and passed through an 80-mesh sieve (180 μm opening) and a 50-mesh sieve (355 μm opening), respectively. A batch of formulated Danshen powders were prepared by thoroughly mixing Danshen root extract powder (198.4 g), Notoginseng powder (125.4 g), and Borneol powder (7.2 g) using a V-shaped lab scale mixer (VH-5, Zhongcheng Pharmaceutical Machinery Factory, Jishou, China) at 26 rpm for 5 min.

2.2. Silica surface deposition by comilling

Coating with 1% silica nanoparticles was carried out using an under-driven Comil (Model U5, Quadro Engineering Corporation, Waterloo, Ontario, Canada). Before the comilling operation, approximately equal volumes of actives and silica were manually mixed in a plastic weighing pan before passing through a standard 50-mesh sieve with 355 μm opening. The sieved powder was then mixed with remaining uncoated powder following a geometrical dilution process. A batch size of 140 g powder was used throughout this study. The sieved powder was blended in V-shaped powder mixer for 5 min at 26 rpm and then placed in the powder-receiving chamber of the Comil fitted with a stainless screen (round hole, 0.018 inch diameter, part number 7L018R01530). The impeller (150 grit round impeller with square arms) was run at the lowest available speed of 1100 rpm. A total of 10 comilling cycles were used for coating all powders in this work.

2.3. Measurement of flowability and fillability

A Powder Tester (Type E, Hosokawa, Osaka, Japan) was used to measure the flowability and fillability of powders following the recommended methods by the manufacturer [9]. The bulk density, tape density, angle of repose, angle of spatula, and cohesiveness were determined to calculate the flowability index (FI), which ranges from 1 to 100. A higher FI indicates better powder flow property. All measurements were performed at 23.5 ± 0.5 °C and 55 ± 5% relative humidity.

The angle of repose was obtained by measuring the angle formed between the horizontal flat base and the slope of a powder pile formed by freely falling onto the base through a glass funnel. Three experiments were performed for calculating average and standard deviation of the measurements.

The angle of spatula was measured by covering a spatula with a certain thickness of powder on a base plate. The spatula was held still while the plate was slowly lowered to expose the spatula. The angle of the powder remaining on the spatula was carefully measured first. The spatula was then tapped gently to disturb the powder sitting on the spatula. The angle of the remaining powder was measured again. The average of two measurements was taken as the spatula angle. Average and standard deviations of the angle of spatula were calculated based on three measurements for each powder.

To measure bulk density, ρ_{bulk}, powders were slowly poured into a 100 cm^3 graduated glass cylinder via a funnel up to the 100 cm^3 mark. ρ_{bulk} was calculated as the ratio between the weight of the sample in the cylinder and the volume occupied (100 cm^3). The graduated cylinder was then attached with an extension cup and additional powder was filled. The assembly was placed on the base of a vibrating platform and tapped for 180 times. The extension cup and excess powder were removed after the tapping. Tap density, ρ_{tap}, was defined as the ratio between weight of the tapped powder and powder volume, which was 100 cm^3.

Compressibility (C) was calculated using Eq. (1).

$$C\% = 100\% \times \left(\rho_{tap} - \rho_{bulk}\right)/\rho_{tap} \quad (1)$$

To assess powder cohesion, a set of standard sieves (100-mesh, 65-mesh, and 50-mesh) were stacked in the order of increasing opening size and placed on a vibration table. A total of 2 g of powder was poured into the 50-mesh sieve and the stack of sieves was vibrated for a certain time T (in seconds), which was predetermined based on Eq. (2).

$$T = 20 + (1.6 - W)/0.016 \quad (2)$$

Where W, termed dynamic bulk density, is calculated using Eq. (3).

$$W = \left(\rho_{tap} - \rho_{bulk}\right)C/100 + \rho_{bulk} \quad (3)$$

After vibration treatment, the powder remaining on each sieve was weighed and adhesiveness was calculated using Eq. (4).

$$Adhesiveness = \left(W_{50mesh} + 0.6W_{65mesh} + 0.2W_{100mesh}\right)/2 \times 100\% \quad (4)$$

FI was the sum of index of angle of repose, index of angle of spatula, compressibility index, and adhesiveness index, which were obtained by comparing respective results to a standard table provided by the powder tester manufacturer [9]. We note that many instruments are available for characterizing powder flowability. Each of these instruments has its own unique set of advantages and disadvantages. In this work, the Hosokawa Powder Tester is considered adequate for monitoring the relative change in flow properties after powder coating.

2.4. Scanning electron microscopy

A thermally activated field-emission gun-type scanning electron microscope (SEM) (JSM-6390LV, NTC, Japan) was used to observe particles under high vacuum (10^{-4}–10^{-5} Pa). Before scanning electron microscopy analysis, samples were sputter-coated with a thin layer of platinum (thickness ~50 Å) using an ion-beam sputter.

2.5. Particle size distribution

Particle size distribution of each powder was measured in triplicates with a dry laser diffraction particle size analyzer (Mastersizer