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Twin screw granulation: An evaluation of using micronized lactose as a solid binder

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ABSTRACT

In twin screw wet granulation process, the binding excipients could be added in two ways: premixed with powder materials before granulation or dissolved in water as a solution. In this paper, the feasibility of using micronized lactose as a solid binder excipient in twin screw granulation process was examined. Different proportions of micronized lactose were mixed with lactose and microcrystalline cellulose (MCC) powder before granulation, respectively. As a comparison, hydroxypropyl cellulose (HPC) was prepared in solid and liquid phase (i.e. premixed with powder and dissolved as solution respectively). Granulation was carried out to investigate the binding potential by studying the effect of micronized lactose and HPC on the granules properties such as size, shape and surface structure. Due to its small size, micronized lactose was proven to be an ideal alternative as a solid binding excipient to provide strong bonds and produce granules with improved granule size distributions. Furthermore, the binding capacity of micronized lactose was also examined on the compact powder bed where the contact angle, nucleus hardness and surface structure were studied.

1. Introduction

Wet granulation is a particle enlargement process with a use of liquid. Currently, wet granulation has been widely applied in different industries including pharmaceutical, fertilizer, food etc. Twin screw granulator is one of the most commonly used granulators for wet granulation, mainly because of its continuous granule production (Dhenge et al., 2013).

Water, as a low viscosity and high surface tension liquid, has been widely used to form liquid bridges between particles in twin screw wet granulation process. It could spread and distribute easily through the particles. In some cases, the bonds may not be strong enough, resulting in the production of a large amount of fines or weak granules. Therefore, extra binding excipient would be needed to enhance the binding capability of the water. Binding excipient (binder) addition can be divided into two methods. Firstly, the binding excipient could be dissolved in water and used as a binder solution to enhance the strength of liquid bridge between particles increasing the strength of granule effectively. Consequently, the liquid with increased viscosity would be harder to penetrate and distribute in the powder (Ai et al., 2016). In this case, the binder solution and powder may not be mixed evenly, leading to a wider granule size distribution and increase in the proportions of oversized granule and fines (Saleh et al., 2015). In addition, the binding excipient could be premixed with powder in advance (solid form), in order to make sure the binding excipient particles distribute before the water comes in contact with powder material (Saleh et al., 2015; El Hagrasy et al., 2013). In this case, the liquid (water) would be easier to distribute in the powder during granulation. However, the limited amount of water may be insufficient to dissolve the binder particles, especially big-size particles, and thus reduce the efficiency of the binding excipient. Therefore, more binding excipient would be needed to compensate its relatively low efficiency. Recently, the effect of the presence of hydroxypropyl cellulose (HPC) particles in compacted powder bed was studied (Ai et al., 2016). They found that the undissolved HPC delayed the liquid penetration in the powder bed and caused a reduction in nuclei hardness in the powder bed. To tackle the problem that solid binder particles could not dissolve properly in order to enhance the bonding during granulation effectively, assessments for the effect of smaller binder particles was carried out in both high shear mixer or fluidised bed (Alvarez-Lorenzo et al., 2000; Van der Watt, 1987; Nyström and Glazer, 1985; Nyström et al., 1982; Schæfer and Mathiesen, 1996; Li et al., 2011; Kato et al., 2006). It was found that the use of smaller sized binder particle could promote the growth of granule and have positive effects on the strength of the granules due to its outstanding specific surface area. In terms of twin screw granulation, none of the previous works has covered.

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Nomenclature

List of symbols

A	Contact area [m^2]
h	Depth [m]
P	Pressure [kPa]
R	Diameter [m]
α	Friction constant
ε	Natural strain [m]
τ	Average agglomerate strength [kPa]

In this paper, micronized lactose would be introduced as a new type of highly effective binding excipient. In the meantime, HPC in liquid and solid phases were applied as comparators. The binding capability of micronized lactose was first examined and compared on compact powder bed. Then, twin screw granulator was used to examine its binding capability in the wet granulation process. It was found that micronized lactose has an excellent binding and dispersion capability comparing with HPC in liquid and solid phases.

2. Materials and methods

2.1. Materials

In the experiment, microfine lactose (Lactochem, DMV-Fonterra Excipient GmbH and Co., Goch, Germany) was mixed into α-lactose monohydrate (Pharmatose 200 M, DMV-Fonterra Excipient GmbH and Co., Goch, Germany) and microcrystalline cellulose (MCC, Avicel PH 101, FMC Biopolymer, Cork, Ireland, 57 μm) in different proportions (0, 5, 10, 15% w/w), respectively (Table 1). The primary particle size was obtained using Camsizer XT (Retsch Technology, Germany) and shown in Fig. 1. As for comparisons, hydroxypropyl cellulose (HPC, Klucel-EF Pharm, Aqualon, Wilmington, DE, USA, 66 μm) excipient was added in liquid (4%, w/w) and solid phases (4%, w/w), respectively (Table 1, Type 5, 6, 11 and 12).

The powder components were premixed in a high-shear mixer (Romaco Roto Junior) for 5 min with an impeller speed of 300 rpm. Then, the powder (mixture) were conditioned in an environmental chamber (Camlab, Memmert, UK) with a constant temperature of 25 °C and relative humidity of 40% for 48 h (Ai et al., 2016).

2.2. Preparation of compact powder bed

A Zwick Roell strength tester (Zwick GmbH and Co., Ulm, Germany) was used to produce a series of static compact powder beds. Powder with a mass of 4 g was poured into a steel die with a diameter of 30 mm and a height of 25 mm. Different compression forces of 100, 200, 300 and 450 N were applied to produce the compact powder bed and the corresponding stresses of 142 kPa, 283 kPa, 425 kPa and 637 kPa which were within the stress range exerted in twin screw granulator (Li et al., 2014). Compression speed was set to 1 mm/min, giving the particles more time to rearrange themselves and enhance the reproducibility (Yang et al., 2016).

Table 1 – Formulation composition and binder delivery ways.

Type	Powder (mixture)	Liquid binder
1	Lactose	Water
2	Lactose + 5% micronized lactose	Water
3	Lactose + 10% micronized lactose	Water
4	Lactose + 15% micronized lactose	Water
5	Lactose + 4% HPC	Water
6	Lactose	4% HPC solution
7	MCC	Water
8	MCC + 5% micronized lactose	Water
9	MCC + 10% micronized lactose	Water
10	MCC + 15% micronized lactose	Water
11	MCC + 4% HPC	Water
12	MCC	4% HPC solution

2.3. Measurement of contact angle

An electronic pipette (Eppendorf, multipette stream, Germany) with comb-tip of 0.1 mL was used to generate droplets. The volume of the droplet was set as 15 μL and the tip was 10 mm away from the powder surface. The droplet movements were captured using a high-speed camera (Photron, Fastcam, 100 K, USA) with a frame rate of 200 fps. The camera was placed horizontally to the surface of the compacted powder bed in order to distinguish the end of penetration accurately. The images obtained from the high-speed camera was analysed using FTA 32 contact angle software. The contact angle value could be obtained by plotting out the droplet liquid–air and liquid–solid boundaries. Due to the use of porous powder bed, the apparent maximum contact angle was obtained as the representative of wettability of liquid–powder system (Yuan and Lee, 2013; Charles-Williams et al., 2011).

The powder bed was dried in an environmental chamber with a constant temperature of 25 °C and relative humidity of 40% for more than 48 h.

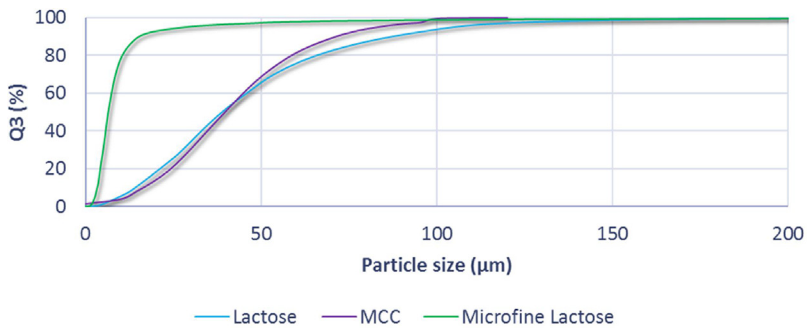

Fig. 1 – Micronized lactose primary particle size distribution: the x-axis represented the primary particle size and y-axis represented the volume based frequency (%).