Powder Technology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Developing a miniaturized approach for formulation development using twin screw granulation

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ARTICLE INFO

Article history:
Received 27 October 2015
Received in revised form 23 March 2016
Accepted 30 April 2016
Available online xxxx

Keywords:
Nucleation
Compact powder bed
Hardness
Twin screw granulation
Miniaturisation
Lactose
Microcrystalline cellulose

ABSTRACT

The present research is focused on developing a novel, scaled-down approach based on the liquid droplet-powder bed interactions for the estimation of an optimal liquid to solid ratio (L/S) required in the twin screw wet granulation. A single droplet 'powder-bed-nucleation' process using compacted powder beds of α-lactose monohydrate (soluble) and microcrystalline cellulose (insoluble, swells upon water addition) with varying proportions of hydroxypropyl cellulose, was used to produce wet lumps of powder called 'powder bed nuclei'. The knowledge from such nuclei formation, droplet weight and its penetration time into the powder bed and weight and hardness of nuclei was used to develop a novel method allowing the estimation of optimal amount of liquid required to produce granules with desired particle size distribution using twin screw granulator. The estimated and the experimental values for L/S showed an acceptable agreement.

1. Introduction

1.1. Background

Granulation is a size enlargement process where small powder particles are bound together to form larger aggregates called as granules. Compared to powder, granular materials have a number of improved physical properties including controlled dissolution and disintegration rate, higher flowability and compressibility etc. These excellent physical properties are desired in the pharmaceutical, detergent and fertiliser industries.

Twin screw granulation is one of the most popular techniques for the wet granulation nowadays. The twin screw granulator encloses two co-rotating screws with specifically designed configurations to convey and mix powder(s) and liquid to form granules. There is currently a fast growing interest of using twin screw granulation in the pharmaceutical industry with the intention to move from the conventional batch based manufacturing process to a continuous approach. The underlying reason behind the intended move is the enhanced consistency in the quality of granules produced using the twin screw granulator [5]. Previous research on twin screw granulation was focused on understanding the influence of the process and formulation variables on the granules properties ([2,4,5,7–9,16,19,23,24,29]. Some other studies provided more detailed understanding of granule formation in the twin screw granulator ([3,18,19,21,23,29]. These pioneering studies helped developing fundamental knowledge about the twin screw granulation and promoted it as a method of choice for wet granulation. The performance of twin screw wet granulation for the pharmaceutical formulation and process development has also been investigated previously [17,27,30]. However, the existing formulation and process development using twin screw granulation still consumes significant amount of expensive powders. Therefore, there is still a lot of scope to improve the efficiency of the twin screw granulation by developing novel approaches or methods which will only use small amount of powders (miniaturize) to estimate the process performance. This will allow minimising the wastage of expensive powders from trial and error based formulation and process optimisation techniques.

1.2. Development of regime map

In batch granulation, especially high shear granulation, regime map has been regarded an ideal approach to reduce the waste and predict the granule properties in advance. According to Hapgood et al. [12] nucleation, which is the first step of granulation process, has been studied extensively, as it could directly affect the properties of final products. By using lactose with two different size distributions and different liquid binders, Hapgood et al. [12] developed the nucleation regime map to link the nucleation process to the mechanism of granule growth. In their work, nucleation was regarded as the combination of single droplet behaviour and multiple droplets interaction. This nucleation regime map could predict the granule size distribution by the interaction

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http://dx.doi.org/10.1016/j.powtec.2016.04.051

Please cite this article as: Q. Ai, et al., Developing a miniaturized approach for formulation development using twin screw granulation, Powder Technol. (2016), http://dx.doi.org/10.1016/j.powtec.2016.04.051

between liquid and powder during nucleation process. The work and its applicability was accessed and extended by including dry binder in formulation by Kayrak-Talay and Litster [14].

However, the applicability of nucleation regime map for batch (high shear) granulation cannot be directly applied to continuous twin screw granulation, as wetting and nucleation zone in twin screw granulation is physically separated from the consolidation zone [3,9]. Currently, the study on establishing nucleation criteria for twin screw granulation has just started receiving attention [3,10,18,23]. The research has been forced on understanding the roles of various process (screw configuration, powder feed rate etc.) and formulation (liquid to solid ratio (L/S), liquid binder viscosity etc.) on growth (rate processes) and properties (size, shape etc.) of granules.

1.3. Research objective

In this study, the microscopic powder and liquid interactions have been studied to develop a miniaturized approach to estimate the optimal amount of liquid required to produce granules with desired particle size distribution. The powder beds were prepared using range of compression stresses. The nuclei were produced by adding drops of liquid binders on the surface of powder beds while measuring the penetration time and contact angles. Furthermore, an indentation experiment, which was regarded as a method for material hardness testing, was carried out to measure nuclei hardness [26]. The variation of compression stress was also found to have a relationship with the wettability of powder. The mass ratio between liquid and the powder it wets, was found to be quite close to the optimal L/S ratio used in the literature. Therefore, an approach using compact powder bed to predict an L/S ratio that leads to the maximum granule productivity for a chosen size range (180–710 μm) was proposed [11,13]. The predicted L/S was accessed using twin screw granulation experiments and found to have a potential to miniaturize the formulation development.

2. Materials and methods

2.1. Powder bed nuclei hardness measurement

2.1.1. Experimental materials

Compact powder beds were used in the experiments to explore the relationship between the compression stress and powder bed nuclei hardness, which could enhance the understandings of influence of system stress on granulation process in the twin screw granulator. During experiments, solid binder (hydroxypropyl cellulose) could directly be mixed with powder to study the effect of solid binder on the properties of powder bed nuclei. Therefore, different amounts of solid binder were mixed with lactose and MCC, separately.

α-Lactose monohydrate (Pharmatose 200M, DMV-Fonterra Excipient GmbH and Co., Goch, Germany, 55 μm) and microcrystalline cellulose (Avicel PH 101, FMC Biopolymer, Cork, Ireland, 57 μm) were used as the experimental materials. Each of these materials was mixed with solid hydroxypropyl cellulose (Klucel-EF Pharm, Aqualon, Wilmington, DE, USA, median size 66 μm) at varying compositions shown in Table 1. All powders used were pre-conditioned in an environment chamber (Camlab, Memmert, UK) with a temperature of 25 °C and relative humidity of 20% for 24 h before experiment.

Table 1
Powder sample preparation.

Formulation no.	Powder (w/w)	Solid binder (w/w)
1	100% α-lactose	0
2	100% MCC	0
3	98% α-lactose	2% HPC
4	98% MCC	2% HPC
5	96% α-lactose	4% HPC
6	96% MCC	4% HPC

In this experiment, in order to track the distribution of liquid, a red dye (Erythrosine B; Acid red 51, Sigma-Aldrich Company Ltd., Dorset, UK) was dissolved in distilled water with a dry weight based concentration of 0.1% (w/w). Furthermore, aqueous solutions of HPC (2% & 4% w/w) were also used to compare and explain the mechanism of liquid penetration in the powder bed with premixed solid HPC powder.

2.1.2. Preparation of compact powder beds

A static compact powder bed was produced by using a Zwick Roell strength tester (Zwick GmbH and Co., Ulm, Germany). 4 g of powder was poured in a die with an inner diameter of 30 mm and height of 25 mm. Different compression forces (100, 200, 300, 450 N) were applied using a punch to produce the powder bed. To simulate the different stresses in a twin screw granulator, corresponding stresses (142 kPa, 283 kPa, 425 kPa, 637 kPa) from the punch were obtained. The compression stresses used in the study were close to the stresses exerted in twin screw granulator [21]. At each compression stress, 10 beds were made. The compression speed was set as slow as 1 mm/min, aiming to give particles in the powder bed sufficient time to arrange themselves so that reproducibility of the powder beds produced can be ensured.

2.1.3. Observation of HPC particle dissolution

A microscope camera (AM 4000 series, ANOM Electronica Corporation, Taiwan) with a magnification of 40× was used to observe the changes of solid binder before and 1 min after the water was introduced. Solid HPC particles (median size - 66 μm) were stuck onto a glass layer by waterproof glue with a thickness no more than 0.5 mm. Water was added using an electronic pipette (Eppendorf, multipette stream, Germany) that could produce a fixed volume of 15 μL.

2.1.4. Measurement of penetration time and advancing contact angle

The powder bed was placed on a substrate with an electronic pipette 10 mm away from the surface of the powder bed. The volume of the droplet was set as 15 μL. The speed of droplet formation was produced was set as 1 mL/min to reduce the influence of pressure on droplet size. The penetration process was captured using a high speed camera (Photron, Fastcam, 100 K, USA) using a frame rate of 2000 fps. The liquid shined due light refection as it penetrated into the powder bed. The end point of penetration was marked by the disappearance of the light reflection. By using a high speed camera, the dynamic motion of droplet penetration and spreading was closely observed and the penetration time was accurately obtained. After the observation of penetration process, powder bed nuclei formed on a bed of powder were taken to the Zwick Roell strength tester for indentation experiment (see Section 2.1.5). Powder beds compressed at a stress of 637 kPa were used to measure the contact angle using FTA32 contact angle software.

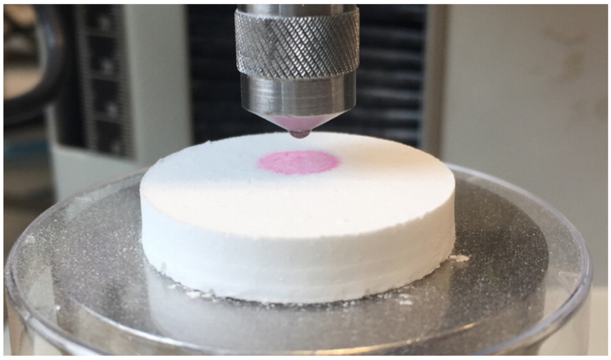

Fig. 1. Indentation experimental set up.

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