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The effect of dry granulation on flow behaviour of pharmaceutical powders during die filling

Serena Schiano [a], Lan Chen [b,*], Chuan-Yu Wu [a,*]

[a] Deprtment of Chemical & Process Engineering, University of Surrey, Guildford GU2 7XH, UK
[b] School of Medical Instrument and Food Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China

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ABSTRACT

Flowability that quantifies the flow behaviour of powders is an important material attribute for such applications as packing, hopper flow and powder transport. It is also one of the critical material attributes of pharmaceutical formulations for solid dosage forms. It is anticipated that size enlargement via dry/wet granulation will improve the flowability of feed powders, but it is still unclear how significant the flowability can be enhanced. Therefore, in this study, an experimental investigation was performed to explore how dry granulation affects the flowability of pharmaceutical powders, such as microcrystalline cellulose (MCCs), mannitol and lactose. Both as-received powders and binary mixtures were considered. Granules of various sizes were produced using roll compaction followed by ribbon milling, and the flowability of as-received powders and produced granules was characterised using two methods: 1) the critical filling speed measured using a model die filling system and 2) the flow index measured using a Flodex tester. It was shown that the flowability increases as the size of the granules increases for all materials considered. Furthermore, it was found that there is a strong correlation between the critical filling speed and the flow index: the critical filling speed is proportional to the flow index to a power of −5/2.

1. Introduction

In the pharmaceutical industry, it is well recognized that composition variation and the quality of tablets are determined by material properties and process conditions. One of the greatest challenges in pharmaceutical development is to identify i) the causal relationship between material properties, process variables and final product properties, and ii) the critical material attributes dominating the product properties, which is of practical importance to obtain high quality products. Pharmaceutical tablets are generally manufactured by compressing dry powders or granules in a die, i.e., the die compaction, which is the so-called tabletting process. The tabletting process consists of three primary stages: die filling, compaction and ejection [1]. Die filling is a process in which powders are deposited into a die under the effect of gravity or suction. It is a critical process step during tabletting, as the flow behaviour during die filling determines tablet properties (e.g. weight variation, content uniformity), and dictates the segregation tendency of powder blends during the tabletting process [1–3].

During die filling, flow behaviour of powders depends on particle density (i.e. true density) and bulk density. For example, Xie and Puri [4] investigated the die filling process using a pressure deposition tester with alumina powders of different bulk densities. The tester generated real time pressure distributions of powders at the base of the die during die filling. It was shown that materials of low bulk density led to irregular and low reproducible pressure profiles, implying that powders of lower bulk density had a higher tendency to produce non-uniform packing during die filling, which led to non-homogeneous tablet density during tabletting. The influence of particle density during die filling was also examined by Guo et al. [5], who explored segregation behaviour of a binary mixture consisting of particles having the same size but different densities using a coupled discrete element method with computational fluid dynamic (DEM-CFD). It was shown that the difference in densities caused segregation during die filling, in particular, light particles tend to settle on the top of the packed powder bed while dense particles at the bottom. It was also found that this tendency was enhanced in the presence of air.

Particle size also affects die filling behaviour.For instance, Mills and Sinka [6] explored the effect of particle size on gravity and suction filling with different grades of microcrystalline cellulose powders and found that fine particles showed intermittent flow behaviour due to strong cohesion, while smooth mass flow was observed for large particles. Wu et al. [7] investigated powder flow behaviour during die filling using the positron emission particle tracking technique (PEPT) that measured the velocities of individual particles. Two grades of spherical microcrystalline cellulose powders with different particle sizes were examined using a model shoe

* Corresponding authors.
E-mail addresses: lanchen@usst.edu.cn (L. Chen), C.Y.Wu@surrey.ac.uk (C.-Y. Wu).

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system [1]. It was shown that coarse powders resulted in a higher critical filling speed, indicating that they possess a better flowability and a higher die filling efficiency can be achieved, comparing to the fine powder. This was attributed to the presence of air in the die, which can significantly inhibit the flow of small particles. These observations were consistent with the numerical results of Guo et al. [8], who modelled the die filling process in vacuum (i.e. absence of air) and in the presence of air using DEM-CFD. They found that, during die filling in presence of air, the air inhibited the flow of powders of small particles and of low density, as no significant difference was observed for die filling with particles of different sizes and densities in vacuum.

Many attempts were also made to understand the correlation between powder flowability and die filling behaviour. For example, Xie and Puri [4] argued that fine particles had poor flowability due to the small size and the increased surface area, which led to an increase of cohesive forces. Consequently, lower die filling efficiency and poorer content uniformity were obtained. However, other studies showed that there was not a strong correlation between powder flowability and filling behaviour. For example, Felton et al. [9] investigated capsule filling with mixtures composed of MCC and silicified microcrystalline cellulose (SMCC) using a tamping-tape encapsulation machine, aiming to understand the influence of powder flowability on the encapsulation filling. They showed that the fill weight was higher and more reproducible with SMCC that has better flowability. However, similar results were obtained for the MCC powder even though their flowability was poorer. They hence suggested that powder flowability might not be a critical parameter for encapsulation filling. Wu et al. [10] evaluated the correlation between flow behaviours of powders during die filling and flow properties characterised using various methods, include the shear cell tester, flowmeter, angle of repose, Hausner index and Carr index, and found that the flowability testing methods mimicking the powder flow in an actual application gave the better indication of the ability of powder to flow in that specific application than other powder flowability tests.

Although die filling has attracted increasing attention in the past two decades, previous studies primarily focused on feed powders but the influence of the granule properties on die filling behaviour was not investigated. Hence, in this study, the flow behaviour of granules produced using dry granulation with roll compaction was investigated. The influence of granule size was examined and the correlation between flow behaviour of granules and flowability measurements using the Flodex tester was explored.

2. Materials and methods

Three commonly used pharmaceutical excipients, microcrystalline cellulose (MCC) of three different grades: Avicel PH 101, Avicel PH 102 and DG (FMC, Biopolymer, USA), lactose monohydrate (Granulac 140, Meggle GmbH, Germany) and mannitol (Pearlitol 200 SD, Roquette, UK) were considered. All the powders are of pure component apart from MCC DG that is a formulated microcrystalline-based excipient composed of 75% of MCC and 25% of anhydrous calcium phosphate [11]. Three binary mixtures (see Table 1) of MCC Avicel PH 102 and lactose were also considered. These samples were produced by mixing the powders in a mixer (TURBULA T2F, Wab, UK) for 15 min at a constant speed of 34 min^{-1} and named as mixture 1, 2 and 3 based on their compositions.

Table 1
Mixtures composition.

Mixture	Lactose (%)	MCC Avicel PH102 (%)
1	25	75
2	50	50
3	75	25

The same custom-made gravity fed roll compactor as reported in Wu et al. [12] was used to produce ribbons with a roll gap of 1.2 mm at a roll speed of 1 rpm. The ribbons were then milled into granules using a cutting mill (SM 100, Retsch, Germany) equipped with a 4 mm mesh size screen at a constant speed of 1500 rpm. The produced granules were then sieved into different granule size cuts (1–90, 90–250, 250–500, 500–1000, 1000–1400, 1400–2360 μm).

The flowability of the granules, as-received powders and powder mixtures was characterised using a Flodex tester (Flodex™, Gradco, UK) that assesses the ability of powder to flow freely through an orifice in a funnel. The diameter of the smallest orifice through which the sample can pass three times was considered as the flow index. For each test, around 50 g of sample were poured in the funnel, and the lever device was triggered to open the orifice quickly to initiate the powder flow. All tests reported here were repeated three times. From the Flodex tests, the higher the flow index (the larger the orifice diameter through which the sample can flow), the poorer the powder flowability.

Die filling experiments were then performed with the produced granules, the as-received powders, and powder mixtures, using a model die filling system (see also [1]), which consists of a shoe driven by a pneumatic driving unit, a positioning controller unit and a displacement transducer. Shoe speeds in the range of 10 to 400 mm/s were employed. In each test, the mass deposited in the die was weighed and the fill ratio was calculated by

$$\delta = \frac{m_x}{m_T} \tag{1}$$

where m_x is the mass deposited into the die at a certain shoe speed, and m_T is the mass in a completely filled die that can be directly measured or calculated using the bulk density of a powder and the volume of the die. In this study, m_T was directly measured when the die is full of a powder.

From the definition of the fill ratio adopted by Wu and Cock [13], the critical filling speed V_c and the index, n, were determined using

$$\delta = \left(\frac{V_c}{V_s}\right)^n \tag{2}$$

where V_c is the critical filling speed, V_s is the shoe speed and n is a parameter having a value of 0.8–1.6 for most powders [2,13].

3. Results

3.1. Flowability of granules made of pure powders

The flow indices (ψ) measured using the Flodex tester for granules made of pure powders are presented in Fig. 1, in which the flow indices of the as-received powders are also superimposed. The flow index is

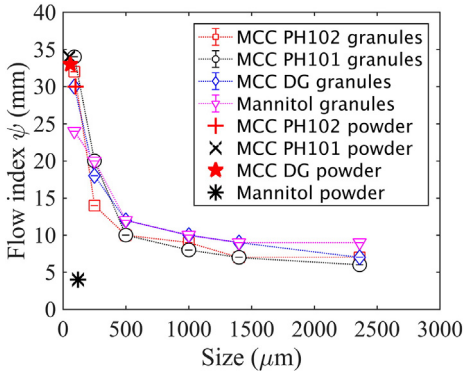

Fig. 1. Flow index (ψ) as a function of granule size for granules made of four different materials.

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