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Influence of fill factor variation in high shear granulation on the post granulation processes: Compression and tablet properties

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ABSTRACT

This paper describes an investigation of the effect of fill factor; on the compaction behaviour of the granules during tabletting and hence mechanical properties of tablets formed. The fill factor; which is the ratio of volume of wet powder material to vessel volume of the granulator, was used as an indicator of batch size. It has been established previously that in high shear granulation the batch size influences the size distribution and granule mechanical properties [1]. The work reported in this paper is an extension to the work presented in [1], hence granules from the same batches were used in production of tablets. The same tabletting conditions were employed during tabletting to allow a comparison of their properties. The compaction properties of the granules are inferred from the data generated during the tabletting process. The tablet strength and dissolution properties of the tablets were also measured. The results obtained show that the granule batch size affects the strength and dissolution of the tablets formed. The tablets produced from large batches were found to be weaker and had a faster dissolution rate. The fill factor was also found to affect the tablet to tablet variation of a non-functional active pharmaceutical ingredient included in the feed powder. Tablets produced from larger batches show greater variation compared to those from smaller batches.

1. Introduction

High shear wet granulation has been used extensively in the pharmaceutical industrial as a size enlargement process for granulating feed powders in order to improve their flow characteristics. Moreover, it has been used in a number of industries for the manufacture of different products, e.g. fertilisers in agro-based industries [2–4], and for the granulation and mixing of metal or powder oxides such as iron, silica and aluminium in the metal processing industry [5,6]. The quality of the granules formed during this process is sensitive to the process conditions as well as the formulation [1,7–11]. Several studies have been undertaken to investigate the importance of process variables on the granule size and size distribution [8,12–15]. Research on scale-up has focused particularly on the influence of the size distribution of the product [7,12, 16–20]. Hassanpour et al. [21] and Rahmanian et al. [22] examined scale-up rules based on constant speed, shear stress and the Froude number to achieve a target granule strength. It was concluded that a constant tip speed was the most effective. However, even when using the same granulator, small variations in the size of the batch can lead to significant differences in the properties of the granules [10,12,20,23–25].

The fill factor is defined as the ratio of the volume of wet powder material to the vessel volume of the granulator. Recent work has shown that not only is the granule size affected by the variations in the fill factor but also the mechanical properties of the granules formed [1]. The total mass of the granulate material was varied (from 2113 to 2875 g corresponding to fill factors of 0.21 to 0.42 respectively) without changing the other variables such as impeller speed, granulation time and liquid to solid ratio. The resulting mechanical properties, such as strength, yield stress and Young's modulus, of the granules were measured. The granule strength, Young's modulus and yield stress of the granules were shown to increase with increasing batch size as represented by the fill factor.

The implications of batch size variation on the downstream processes due to changes in the material properties have not been investigated and this is the objective of the current work. The main aim was to establish the effects of the fill factor on the compression behaviour of the granules and the consequent effect on the tablet properties. The fill factor was varied by changing the total mass of the feed powder and binder liquid without changing other variables (impeller speed, liquid-to-solid ratio and granulation time) as described in previous work by the current authors [1]. It was found out that changing the fill factor of the granulator resulted in changes in the size distribution and mechanical properties of the granules produced.

The behaviour of granular solids under compression depends on the mechanical properties of the granules and this in turn has an effect on

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the mechanical properties of the tablets formed. A number of parameters that characterise the compression behaviour were determined (efficacy coefficient, net compression work and degree of compression), which will be described in the next section. The objective of this paper was to study the effect of fill factor on the mechanical, dissolution, and homogeneity of tablets formed from high shear granules. The effects of the fill factor on the strength and mean dissolution times of tablets formed from the granules were also measured. Although previous studies have considered the compositional uniformity of tablets [26–30], the effect of granulation process variables on tablet homogeneity has not been addressed.

2. Materials and methods

2.1. Production of the granules and tablets

Granules were produced in a 10 L high shear granulator (RomatoRoto Junior) from a mixture of lactose monohydrate powder (Granulac 230, MolkerelMeggelGmBH, German) and potato starch (Solani, Pharma, Quality Avebe) using an aqueous solution of hydroxypropyl cellulose (HPC) as the binder. Sodium chloride was added to the powder mixture (1% w/w) as non-functional active ingredient. In all the experiments, the feed powder was pre-mixed at an impeller speed of 250 rpm for 2 min. The subsequent inclusion of the binder involved pouring for a period of about 1 min with an additional granulation period of 6 min [1]. The granules were dried in a fluidised bed at a temperature of 50 °C to a moisture content of approximately 4% w/w, which required a drying time of about 25 min. The fill factor was calculated from the following expression [1]:

$$\psi = \frac{m_w}{\rho_w \pi R_B^2 H} \tag{1}$$

where m_w and ρ_w are the mass and bulk density of the wet powder, and R_B and H are the radius and height of the cylindrical granulator vessel. The bulk densities of the dried granules, ρ_b, in the size range 0.5 to 0.6 mm, from the different batches, were determined by measuring the mass, m, of a known volume of granules, V:

$$\rho_b = \frac{m}{V}. \tag{2}$$

2.1.1. Production of tablets

100 mg tablets were also produced from the granules in the size range 0.5–0.6 mm at a maximum compression force of 5 kN using a universal material tester (Instron model 3555); the loading and unloading data were stored in a computer. The loading and unloading speeds were both 10 mm/min and the internal diameter of the die was 6.35 mm. The tablets were stored in sealed plastic bags before their strength and dissolution characteristics were measured. The force–displacement data was recorded during compression of bed of granules into tablet and was used to determine the strength of the granules as described in Section 2.1.2.

2.1.2. Determination of granule strength

During compression of a bed of granules to form tablets, the force and corresponding displacement data were recorded. They were analysed using a method described previously [31] to obtain the single granule strength:

$$\ln P = \ln\left(\frac{\tau}{\alpha}\right) + \alpha\varepsilon_n + \ln\left(1 - e^{(-\alpha\varepsilon_n)}\right) \tag{3}$$

where P is the applied pressure, ε_n is the natural strain, α is a pressure coefficient and τ is the strength parameter which is a measure of the single granule strength. The values of τ and α were obtained by fitting Eq. (3) to the measured values of $\ln P$ as a function of ε_n using non-linear regression.

2.1.3. Analysis of the granule compaction data

The stored elastic energy per unit mass of granules during compression of granules into tablets, W_e, was calculated from the integral of the unloading force data:

$$W_e = \frac{1}{m_b} \int_{\Delta_m}^{\Delta_0} F_{unl}(\Delta)\, d\Delta \tag{4}$$

where $F_{unl}(\Delta)$ is the force during unloading, m_b is the mass of the bed of granules in the die; Δ_0 and Δ_m correspond to the displacement at zero and maximum loading respectively. The net compaction work, W_{net}, which represents the energy dissipated, corresponds to the difference between the integrals of the loading and unloading curves:

$$W_{net} = \frac{1}{m_b}\left(\int_0^{\Delta_{max}} F_l(\Delta)\, d\Delta - W_e\right) \tag{5}$$

where $F_l(\Delta)$ is the force during loading.

The degree of compression was determined from the initial bed height, h_0, and bed height at maximum compression pressure, h_{max} using [32]:

$$C_p = \left(\frac{h_0 - h_{max}}{h_0}\right) \times 100\%. \tag{6}$$

This parameter corresponds to the maximum percent engineering compressive strain.

2.1.4. Tablet tensile strength

The tablets were compressed diametrically at a speed of 2 mm/min, until fracture occurred and the force–displacement data were automatically logged. A minimum of 10 tablets were measured for each experimental condition and compact type. The strength of the tablets, σ_t, was calculated from the maximum load, F_{max} and the dimensions of the tablet, i.e. the tablet diameter D_t and thickness, x [33,34]:

$$\sigma_t = 2\frac{F_{max}}{\pi x D_t}. \tag{7}$$

The specific fracture energy required to fracture the tablets, W_t, was determined from the integral of the force–displacement curve:

$$W_t = \frac{1}{m_t} \int_0^{\delta_{max}} F(\delta)\, d\delta \tag{8}$$

where $F(\delta)$ is the current compressive force, δ is the current displacement, δ_{max} is the displacement corresponding to fracture of the tablet, and m_t is the mass of the tablet. The fracture energy was normalised by the mass.

2.1.5. Efficacy of compression coefficient

The efficacy of compression coefficient, C_{eff}, which expresses the ability of the granules to convert the net compression energy into cohesion energy, was determined [35,36]. The cohesion energy is that required to form bonds between the granules during compression:

$$C_{eff} = \frac{W_t}{W_{net}} \times 100\%. \tag{9}$$

Values > 0.1% are characteristic of an effective conversion of net compression work into cohesion [36–39]. The strength of the tablets formed