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Investigation of influence of process variables on mechanical strength, size and homogeneity of pharmaceutical granules produced by fluidised hot melt granulation

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ABSTRACT

The overall aim of the project was to study the influence of process variables on the distribution of a model active pharmaceutical ingredient (API) during fluidised melt granulation of pharmaceutical granules with a view of optimising product characteristics. Granules were produced using common pharmaceutical excipients; lactose monohydrate using poly ethylene glycol (PEG1500) as a meltable binder. Methylene blue was used as a model API. Empirical models relating the process variables to the granules properties such as granule mean size, product homogeneity and granule strength were developed using the design of experiment approach. Fluidising air velocity and fluidising air temperature were shown to strongly influence the product properties. Optimisation studies showed that strong granules with homogeneous distribution of the active ingredient can be produced at high fluidising air velocity and at high fluidising air temperatures.

1. Introduction

Size enlargement processes have been extensively used in the pharmaceutical industry to reduce the potential difficulties in the manufacture of solid dosage due to poor compactability, compressibility and flowability of many drugs [1]. There are a number of granulation techniques that have been applied such as high shear granulation, twin extrusion and fluidised bed granulation. In an effort to overcome some of the limitations of the conventional process, new granulation techniques are being investigated and developed, among these processes is melt granulation (MG) technique [1].

Melt granulation is a size enlargement process in which powders are agglomerated using low-melting point materials as meltable binders. The meltable binders can be added either as molten liquid or as solid that melts during the process. During the process, heat is continuously applied to maintain molten state of the binder consequently facilitating granule formation. Once the correct size of the granules is achieved the system is cooled to allow solidification of the binder. MG can be performed in a high shear mixer or a fluidised bed unit, with the former being the most common. The process is named in accordance to the type of equipment used, high shear melt granulation (HSMG) or fluidised bed melt granulation (FBMG). There are a number of articles that have been published that look at the effect of process variables in HSMG [2–7]. Similarly several articles can be found in literature that looks at the effect of process variable on the granule growth kinetics in FBMG. In FBMG binder is sprayed onto a bed of agitated powder. The binder droplets wet the powder particles thereby forming liquid bridges which subsequently solidify to form solid bridges upon cooling. The fluidising temperature, binder spray rate, type of binder, droplet size and binder viscosity have been shown to significantly affect the process [1,2,8,9].

Fluidised hot melt granulation (FHMG) is an alternative to FBMG and HSMG; this is a novel process in which granules are produced by mixing low-melting point binders with other excipients and drug directly in fluid bed of hot air. Unlike FBMG and HSMG no spraying system is required. In comparison to other conventional granulation techniques fluidised hot melt granulation offers several advantages [1,10]. For instance there is no need to use solvents hence no solvent recovery issues and associated safety and environmental considerations are eliminated. It is a good alternative to wet granulation when dealing with moisture sensitive materials.

In the literature regarding the effect of process and formulation variables of granule homogeneity in high shear granulation, most of these articles identified impeller speed, amount of binder, primary particle size, chopper speed and hydrophobicity of the components as contributors to product homogeneity/heterogeneity [3,5,6,11–17]. Some of the studies on FHGM have been centred on understanding the granulation mechanism [10,18] and the influence of the process and formulation variables on granule properties like size, growth kinetics and strength

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[1,9,19,20]. The subject of product homogeneity in FHGM has received limited attention.

The aim of this research was to study the influence of process variables on API homogeneity of granules produced via fluidised bed melt granulation with a view of optimising the process for product homogeneity. It is not sufficient to have a granular product that is homogeneous in terms of the composition. The mechanical properties of the product are also very important as they influence the post granulation processes and handling [21]. The influence of fluidising air velocity (FAV), fluidising air temperature (FAT) and granulation time on product homogeneity were investigated.

2. Materials and methods

2.1. Materials

Lactose monohydrate powder, supplied by Sigma Aldrich GmbH, was used as the main excipient. The binder was poly (ethylene glycol) with an average molecular weight of 1500 (81210 Fluka analytical grade), produced and supplied by Sigma Aldrich GmbH, Germany. Methylene Blue (MB)-high purity biological strain, produced and supplied by Sigma Aldrich, was used as a model active ingredient. The lactose powder had mean size (d_{50}) of about 50 μm. The size of the MB powder particles was less than 75 μm.

2.2. Granulation equipment

A Sherwood Scientific (Mark II) Fluidised Bed Drier was used for granulation of lactose monohydrate, MB and PEG mixture. It consists of a 5-L glass container with a fine mesh nylon gauze air distributor, stainless steel support gauze and a filter bag at the top of the unit. The inlet air temperature of the granulator can be controlled accurately to ±1 °C.

2.3. Granule production

Preliminary experiments were done to find the feasible range of process variables over which it was possible to produce decent granules in the fluidised bed unit. The results showed that granulation time in the range 10–20 min, blower speed settings between 4 and 6 and bed temperature of between 50 and 60 °C would be suitable for granule production. The PEG1500 flakes were mashed through a 0.5 and 1.0 mm sieves. Trial experiments on the suitable binder to solid ratio showed that a ratio of 0.1 was suitable. Each batch was composed of 200 g of lactose powder, 20 g of the PEG1500 particles and 200 mg of MB powder.

Two-level factorial design with five repetitions in the central point was used to investigate the influence of the process variables of the granules properties and variability in API concentrations in the granules and tablets. Design of experiment (DOE) software, Design Expert Version 8 (Stat Easy Inc., USA), was used to produce a list of experiments and to analyse the results. A three level factorial design was used to study the influence of fluidising air velocity, granulation time and bed temperature on the product characteristics. Table 1 shows the process variables that were investigated.

Table 1
Summary of process variables and their range of values.

Variable	Level		
	Low (−1)	Medium (0)	High (+1)
Blower speed setting	4	5	6
Fluidising air velocity (m/s)	2.04	2.25	2.45
Fluidising air temperature (°C)	50	55	60
Granulation time (min)	10	15	20

2.4. Characterisation of the granules

2.4.1. Size analysis

The granules were then sieved using Retsch sieves on an orbital sample shaker (Stuart Orbital Shaker, Cole-Parmer, UK) for 5 min at speed of 180 rpm. Previous work done by our research group with similar type of granules, showed that at this setting the amount of granule breakage was insignificant [22]. The aperture sizes of the sieves used in the analysis were in the range of 500 to 4000 μm.

The mass mean diameter ($\bar{d}_m$) of the granules was calculated according to

$$\bar{d}_m = \frac{\sum_{i=1}^{n} m_i \bar{x}}{\sum_{i=1}^{n} m_i}. \quad (1)$$

In Eq. (1) m_i is mass of granules in the interval x_i to x_{i+1} and $\bar{x}$ is average size of the size class given by $\bar{x} = \frac{(x_i + x_{i+1})}{2}$.

2.4.2. Granule strength analysis

The strength of granules in the size range 1.4–1.7 mm was determined from compression of a bed of granules in a confined cylindrical die using a method previously described in Ref. [23]. The choice of this size range for all the analysis of the granules was based on the availability of the sufficient granules from this class across all batches that were produced. The punch used in the test had a diameter of 9.95 mm and the dimensions of the die were as follows; internal diameter of 10 mm; external diameter of 22 mm and height of 10 mm. Work done earlier on similar granules had shown that the granules were strain rate-independent for compression speed ranging from 0.1 to 50 mm/min [24]. The beds of granules were compressed to a maximum compression force of 500 N using a compression test speed of 10 mm/min. The setting of 10 mm/min was chosen which allowed compression tests to be performed within a reasonable time whilst also provide sufficient data points for the analysis. The force-displacement data obtained during the compression of bed or granules were analysed using a method described previously [12,25,26] to obtain the single granule strength. Eq. (2) was fitted to the plot of lnP versus natural strain to obtain the granule strength parameter.

$$\ln P = \ln\left(\frac{\tau}{\alpha}\right) + \alpha\varepsilon + \ln\left(1 - e^{-\alpha\varepsilon}\right). \quad (2)$$

In Eq. (2) α is a pressure coefficient, τ the Adam's parameter, P is the applied pressure and ε is the natural strain.

2.4.3. Determination of API concentration calibration

Solutions of different concentrations of the pseudo API ranging from 1 to 20 ppm were produced by dissolving the MB in deionised waster. The absorbance of the resultant solutions at a wavelength of 664 nm was measured with a spectrophotometer (HACH DR2800, HACH Inc., USA). The calibration equation for conversion of absorbance to concentration was obtained from the linear plot and the concentration was correlated to absorbance according to:

$$c_{MB} = 5.1666\, A_{664} + 0.0358. \quad (3)$$

In Eq. (3) c_{MB} is the concentration of the MB solution and A_{664} is the absorbance of the solution at a wavelength of 664 nm. The correlation coefficient, R^2, of the plot of c_{MB} versus A_{664} was 0.9991.

2.4.4. Composition analysis of granules

The distribution of the API across different size of the granules was measured by dissolving a known mass of granules in a known volume