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Effect of impeller design on homogeneity, size and strength of pharmaceutical granules produced by high-shear wet granulation

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ABSTRACT

Small mixer impeller design is not tailored for granulation because impellers are intended for a wide range of processes. The aim of this research was to evaluate the performances of several impellers to provide guidance on the selection and design for the purposes of granulation. Lactose granules were produced using wet granulation with water as a binder. A Kenwood KM070 mixer was used as a standard apparatus and five impeller designs with different shapes and surface areas were used. The efficacy of granulate formation was measured by adding an optically sensitive tracer to determine variations in active ingredient content across random samples of granules from the same size classes. It was found that impeller design influenced the homogeneity of the granules and therefore can affect final product performance. The variation in active ingredient content across granules of differing size was also investigated. The results show that small granules were more potent than larger granules.

Introduction

Granulation is a size enlargement unit operation in which granular products are produced by agglomerating powdered particles with a binder, normally in a high-shear mixer. It has wide applications in several industries, such as pharmaceuticals, detergents, fine chemicals, and fertilisers. Particle agglomeration through wet granulation improves the bulk properties of the formulation by enhancing its flow properties, reducing dust generation, and improving its compression properties. Several studies have described the effects of granulation parameters applied to the high-shear mixer on product attributes and demonstrated that controlling process parameters is necessary to obtain products with desired attributes (Björn, Jansson, Karlsson, Folestad, & Rasmuson, 2005; Campbell, Clancy, Zhang, Gupta, & Oh, 2011; Johansson & Alderborn, 2001; Mangwandi, Adams, Hounslow, & Salman, 2010, 2012; Mangwandi, Albadarin, Al-Muhtaseb, Allen, & Walker, 2013; Shiraishi, Kondo, Yuasa, & Kanaya, 1994). The final product properties are influenced by the process parameters and formulation attributes. In addition to formulation and process variables, equipment-related variables can influence the properties of the granule. Examples of these variables are the type and shape of the vessel, the presence of a chopper (Chitu, Oulahna, & Hemati, 2011), and the nozzle geometry.

The main source of energy in high-shear granulation is power dissipation by impeller rotation. The main task of the impeller is to agitate the powder particles to ensure they are constantly in motion and to ensure collision between the binder and powder particles. The other purpose of the impeller is to ensure proper mixing of the materials being granulated. Previous work carried out on mixing of fluid systems has shown that the design of the impeller has a significant effect on fluid flow (Jirout & Rieger, 2011; Kacunic, Akrap, & Kuzmanic, 2013; Khare & Niranjan, 2002; Kumaresan & Joshi, 2006).

There are scant papers in the literature discussing the effect of impeller design on the granulation process (Björn et al., 2005; Campbell et al., 2011; Knight, Seville, Wellm, & Instone, 2001; Schaefer, Taagegaard, Thomsen, & Kristensen, 1993; Smith, Liu, & Litster, 2010; Voinovich, Campisi, Moneghini, Vincenzi, & Phan-Tan-Luu, 1999). Schaefer et al. (1993) studied the effect of equipment variables on granulation and found that the impeller blade design affects the shape of the granules formed. Granules were more spherical if an impeller with a curved blade was used,

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Nomenclature

$\bar{c}$	average concentration (ppm)
$\bar{d}$	average granule size (mm)
D	granule diameter (mm)
F	force (N)
m	mass (g)
n	number of samples analysed
V	volume of dissolution medium (mL)
S	standard deviation of the methylene blue concentration (ppm)
x	arithmetic average size of the granules in a size range (mm)

Greek letters

η	homogeneity coefficient
κ	average granule size (mm)
σ	granule strength (N/mm^2 or MPa)
ψ	product yield (%)

Subscripts

bat	batch
bin	binder
exp	experimental value
f	failure
i	sample index
MB	methylene blue
p	powder
pro	product
s	sample
theo	theoretical value

whilst granulating with a flat blade impeller resulted in the formation of irregular-shaped granules.

A Kenwood food processer (KM070, Kenwood, UK), which has been used as a lab-scale high-shear mixer in previous studies (Mangwandi, Albadarin, et al., 2013; Mangwandi, Liu, Albadarin, Allen, & Walker, 2013b, 2013c), comes supplied with a variety of impellers because it is designed for mixing a range of different materials. Images of the different impeller designs are shown in Fig. 1. In the studies cited above, only one type of impeller was used, the high temperature flexible beater (HTFB-14). The aim of this paper was to evaluate the performance of the other impellers during high-shear wet granulation in terms of extent of mixing, strength of the granules formed, and their size distributions. The extent of mixing was evaluated using the method described previously (Mangwandi, Adams, Hounslow, & Salman, 2011, 2014; Mangwandi et al., 2013c).

Materials and method

Materials

Lactose monohydrate powder, supplied by Sigma Aldrich GmbH (Germany), was used as the main excipient. The binder was polyethylene glycol (PEG) with an average molecular weight of 1500 Da (81210 Fluka, analytical grade), produced and supplied by Sigma Aldrich GmbH. Methylene blue (MB) high-purity biological strain, produced and supplied by Sigma Aldrich, was used as a model active ingredient.

Binder preparation and granulation

All granulation experiments were performed in the Kenwood mixer. Six granulation experiments were carried out in triplicate. The granulation conditions used in all the experiments are summarised in Table 1. The purpose of experiments 1 and 2 was to check whether adding MB to the granulation liquid affected granulation properties. A single type of impeller was used in these experiments. Experiments 2–6 were used to investigate the effect of impeller type on batch homogeneity, granule mechanical strength, and shape. The binder used in these experiments was MB solution, at a concentration of 20 ppm, made by dissolving MB powder in distilled water.

Material characterisation

Data from the powdered samples were collected by X-ray diffraction (XRD) using a Philips Xpert Pro-Pan-Analytical (Netherlands) diffractometer. The instrument used a monochromated Cu-Kα lamp radiating at a lambda value of 1.5406 Å. The samples were housed in a flat plate sample holder and analysed through a 2θ range of 5–40°, using 0.16713° steps over a period of 12 min. XRD patterns for alpha-lactose powder, lactose granulated with water and lactose granulated with water-MB are shown in Fig. 2. As can be seen, no structural differences between the two samples were evident and therefore MB was used as an inert tracer to monitor lactose granulation in water.

Granule drying and size analysis

After granulation, each batch of granules was spread evenly onto flat aluminium trays with dimensions 236 mm × 297 mm × 59 mm. The granule trays were then transferred to an oven (Binder FD249, Binder GmbH, Germany) that was pre-set to a temperature of 60 °C and dried for 12 h. After drying, the granules were allowed to cool to room temperature, then stored in sealed bags until required.

Retsch sieves (Retsch GmbH, Germany) were used for size analysis, with aperture sizes of 350, 500, 600, 710, 1000, 1180, 1400, 1700, 2000, 2360, 3350, and 4000 μm. The stack of sieves with the granules was placed on an orbital sample shaker (Stuart Orbital Shaker, Cole-Palmer, UK). The speed of the shaker was set to 180 rpm and the sieving duration to 5 min.

The targeted range of granule size in the experiments was 0.2–4 mm, which is the typical size range of pharmaceutical granules (Summers & Aulton, 1988). The percentage of granules in this size range was referred to as the *product yield* (Ψ) and was calculated by the following equation:

$$\Psi = \left(\frac{m_{pro}}{m_{bat}}\right) \times 100\%, \quad (1)$$

Table 1
Summary of process and granulation parameters.

Experiment no.	Impeller type	Impeller speed (rpm)	Granulation time (min)	Mass of lactose powder	Binder	Liquid to solid ratio
1	HTFB-14	160	4	200	Water	0.2
2	HTFB-14	160	4	200	Water + MB	0.2
3	SSKB-13	160	4	200	Water + MB	0.2
4	SSPW-15	160	4	200	Water + MB	0.2
5	SDH-16	160	4	200	Water + MB	0.2
6	ST-17	160	4	200	Water + MB	0.2