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Granulation of increasingly hydrophobic formulations using a twin screw granulator

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ABSTRACT

The application of twin screw granulation in the pharmaceutical industry has generated increasing interest due to its suitability for continuous processing. However, an understanding of the impact of formulation properties such as hydrophobicity on intermediate and finished product quality has not yet been established. Hence, the current work investigated the granulation behaviour of three formulations containing increasing amounts of hydrophobic components using a Consigma™-1 twin screw granulator. Process conditions including powder feed rate, liquid to solid ratio, granulation liquid composition and screw configuration were also evaluated. The size of the wet granules was measured in order to enable exploration of granulation behaviour in isolation without confounding effects from downstream processes such as drying. The experimental observations indicated that the granulation process was not sensitive to the powder feed rate. The hydrophobicity led to heterogeneous liquid distribution and hence a relatively large proportion of un-wetted particles. Increasing numbers of kneading elements led to high shear and prolonged residence time, which acted to enhance the distribution of liquid and feeding materials. The bimodal size distributions considered to be characteristic of twin screw granulation were primarily ascribed to the breakage of relatively large granules by the kneading elements.

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1. Introduction

Wet granulation is a common process used in the secondary manufacture of pharmaceutical products including oral solid dosage forms. Typically, the granulation step precedes formation of the unit dose whereby in-process intermediates of appropriate size, flowability and compressibility are produced, which are suitable for downstream processes such as tabletting and encapsulation (Blair, 2007; Ennis and Litster, 1997). Conventionally, the granulation processes have been conducted in batch mode using established technology such as high shear and fluidised bed granulation (Leuenberger, 2001; Lodaya et al., 2003). However, twin screw granulation (TSG) is generating an increasing level of interest, owing to its great potential for continuous production, rapid technical transfer and improved manufacturing efficiency whilst providing additional cost savings associated with reduced foot print and decreased energy requirements (Cartwright et al., 2013; Keleb et al., 2002; Vervaet and Remon, 2005). The shift from batch mode production to continuous processes is also an aspiration which has received encouragement from leading regulatory authorities (FDA, 2003).

Twin screw extrusion (TSE) was firstly introduced for pharmaceutical applications by Gamlen and Eardley (1986), where they described the production of paracetamol extrudates, in the mid-1980s. In the following two decades, research focused more on the application of the technique and process optimisation (Keleb et al., 2004a,b, 2002; Kleinebudde and Lindner, 1993; Schmidt and Kleinebudde, 1998). The pioneers established the fundamental understanding of twin screw system by comparing the technique with traditional granulation methods (Keleb et al., 2004a; Schmidt and Kleinebudde, 1998) and concluded that twin-screw systems could be used as an ideal alternative to traditional batch wet granulation. In the work by Keleb et al. (2004b), the authors introduced TSG by removing the die block attached to the end of the barrel, which allowed a higher product yield and avoidance of over-compression of the granules.

More recently, studies have been undertaken to explore the influence of process parameters and formulation variables on the

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attributes of granulated materials with the intention of increasing mechanistic understanding of TSG (Dhenge et al., 2013, 2012a,b, 2011; El Hagrasy et al., 2013; El Hagrasy and Litster, 2013; Lee et al., 2012; Thompson and Sun, 2010; Tu et al., 2013). Dhenge et al. (2013, 2012a,b, 2011) reported a series of experimental investigations, covering the effects of feed rate of input blends, viscosity of granulation liquid, granule flow in the conveying system and influence of screw configuration on granulation rate processes. El Hagrasy et al. (2013) granulated placebo formulations containing three different grades of lactose using increasing liquid to solid ratios, and highlighted the importance of liquid distribution. El Hagrasy and Litster (2013) evaluated the influences of kneading elements (*i.e.* angle configurations, number of kneading elements) on the granule attributes and the mechanisms behind. They proposed that the qualities of the TSG produce granules were determined by the rate processes (*i.e.* breakage, shear elongation and layering) which were directly linked to kneading element layout. Lee et al. (2012) employed Positron Emission Particle Tracking (PEPT) as an analytical tool to monitor the barrel filling across a range of conveying and kneading regimes. Tu et al. (2013) examined the performances of three different screw elements, namely conveying, kneading and comb elements. They also studied the effects of the screw elements on the granule attributes (*i.e.* granule size and shape). The outputs from these studies have improved the understanding of the effects of input material properties and processing conditions on twin screw granulation behaviour. These results have the potential to be used in the development of tools to enable the rational design of processes to achieve desirable granule and finished product attributes.

Despite productive research in the TSG field over the last decade, the understanding of the process is not as well developed as for batch granulation which has been a major platform used in pharmaceutical production over the last century. Notable, limitations in the mechanistic understanding of twin screw granulation currently exist, particularly with regard to achieving homogeneous granule properties such as size and porosity, whilst the effects of formulation properties (*e.g.* hydrophobicity), and their interplay with process parameters have not yet been investigated in sufficient detail to enable effective formulation development and adequate process control. In this work, a systematic comparison of TSG behaviour for three formulations with increasingly hydrophobic compositions was conducted experimentally. Wet granule size was analysed in order to avoid confounding with effects occurring during drying. Correlations between process conditions and the heterogeneity of granule size were also studied.

2. Materials and methods

2.1. Materials

The input formulations comprised placebo blends consisting of lactose (Pharmatose 200M, DMV-Fonterra Excipients GmbH&Co., Germany), di-calcium phosphate anhydrite (DCPA, Calipharm A, Univar, Netherlands), microcrystalline cellulose (MCC, Avicel PH 101, FMC BioPolymer, Ireland) and croscarmellose sodium (Ac-di-Sol FMC BioPolymer, Ireland). No binding agent was employed, to ensure that any possible variation of the granules was caused by differences in formulation hydrophobicity rather than the performance of the polymeric binder. The commonly used excipient, lactose was chosen as the hydrophilic sample material, while the anhydrite form of di-calcium phosphate was selected as the hydrophobic substrate, owing to its physical stability and resistance to hydration (Miyazaki et al., 2009). The hydrophobicity of the formulations was tuned by controlling the relative amounts of lactose and DCPA as shown in Table 1. Formulations F1, F2 and F3 contain increasing amounts of the hydrophobic material (*i.e.* 8.9 %, 26.7 %, and 44.5 % w/w). Dry blends of each composition (5 kg) were premixed using a mobile drum blender (FTMF 200 MG 10, Müller, Germany) at a rotating speed of 15 rpm for 30 min, to improve the distribution of the components prior to granulation.

Table 1
Compositions of the formulations comprising different ratios of hydrophilic and hydrophobic substrates.

	Lactose (% w/w)	DCPA (% w/w)	MCC (% w/w)	Croscarmellose sodium (% w/w)
Formulation 1 (F1)	80.1	8.9	10	1
Formulation 2 (F2)	62.3	26.7	10	1
Formulation 3 (F3)	44.5	44.5	10	1

The properties of the excipients and formulation blends are shown in Table 2. The particle size distribution was measured following the same methodology as that for the wet granules, using image analysis, to compare the attributes of materials before and after the TSG process. Corresponding drying temperature was set to 100 °C so as not to exceed the melting point or decomposition temperature of the formulation constituents, ensuring that no chemical or physical changes such as chemical reactions, melting or ignition took place.

2.2. Granulation

The granulation experiments were carried out using the twin screw granulator (Consigma™-1, GEA Pharma Systems, Belgium) with a screw diameter (*D*) of 25 mm and barrel length of 20 *D*. During the process, the dry blends were dispensed into the granulator via a loss-in-weight feeder. Two peristaltic pumps enabling the sufficient flow of viscous liquid binder (*i.e.* 4 % HPC solution) were employed to drive the flow of the granulation liquids. The pumps were interfaced with a flow meter to achieve the precise control of the mass flow rate. In order to improve the liquid distribution, granulation liquids were fed into the system through two 0.8 mm nozzles above the centre of each screw, located at a distance of 7.25 *D* from the end of the barrel.

The design of the experiments was replicated for all three formulations, as shown in Fig. 1. The kneading blocks were composed of kneading elements with thickness of 0.25 *D*, whilst the pitch of the conveying elements (*i.e.* the distance between the contiguous pushing flights) was 0.5 *D*. In all the experiments, the angle between the kneading elements, barrel temperature and screw speed was kept constant at 60° forward flow, 25 °C and 750 rpm, respectively. Other process parameters such as the powder feed rate (FR), liquid to solid ratio (L/S) and number of kneading elements (NK) were varied to investigate the effects of

Table 2
Properties of the excipients used.

	Melting point /decomposition temperature (°C)(Rowe et al., 2009)	Particle size measured using image analysis (Qicpic)		
		d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
Lactose	201–202	55.38 ± 1.63	106.89 ± 3.78	186.80 ± 6.94
DCPA	425	26.85 ± 0.12	57.31 ± 2.33	102.30 ± 0.86
MCC	260–270	53.78 ± 0.45	99.04 ± 0.42	164.96 ± 0.44
Croscarmellose sodium	252	38.69 ± 0.31	70.23 ± 0.43	115.38 ± 0.86
F1	N/A	47.86 ± 0.15	93.37 ± 0.79	161.64 ± 0.90
F2	N/A	39.12 ± 0.27	86.53 ± 0.94	160.17 ± 0.97
F3	N/A	35.84 ± 0.16	80.08 ± 0.53	155.40 ± 1.19

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