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Characterisation of lactose powder and granules for multivariate wet granulation modelling

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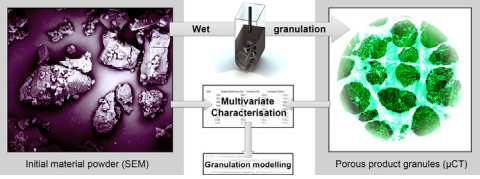
HIGHLIGHTS

- Multivariate data for lactose and its wet granulation product granules are reported.
- Measured properties are granule size, porosity, surface structure and strength.
- The data were used to improve a multivariate population balance granulation model.
- The 5-dimensional model was solved using a Monte Carlo method.

GRAPHICAL ABSTRACT



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ABSTRACT

Granulation and size enlargement of particulate materials is a complex process with broad application in industry. For better understanding of the governing mechanisms, we aim to develop a multivariate population balance model to describe granulation. For meaningful model design we require physical characteristics of real materials undergoing granulation. In this work, α-lactose monohydrate powder was investigated as a representative substance due to its broad use in the pharmaceutical industry for tablets. Powder and granules resulting from a high-shear granulation process are characterized with respect to size, shape, porosity and strength using various analytical methods. Particle size distributions are obtained by static image analysis, laser scattering and sieving. Granule porosities are determined using μCT and mercury intrusion porosimetry. Lactose granules show absolute porosities increasing from 30% to 40% along the size classes. The μCT derived visual information of larger granules shows internal pore structures with denser cores and porous shell parts. AFM, SEM and μCT are used for surface characterisation, yielding a maximum value for model particle roughness up to 0.7 μm. The strength of the product granules measured via uniaxial compression testing follows a logarithmic decrease with size from 1.2 to 0.2 MPa. The multivariate data set was then used for model performance analysis and parameter fitting. The size and porosity prediction performance of the computer model could be improved using the newly available data. The rate of coagulation was found to be the most dominant simulation parameter. Comparison with the experiment revealed limitations, for example in PSD shape predictions.

1. Introduction

In the pharmaceutical industry, the active substance is often delivered to the customer as a tablet, which is usually pressed from agglomerates of a digestible powder like lactose. Since the drug itself represents only a ppm-quantity, the excipient material's

Abbreviations: AFM, atomic force microscopy; BET, Brunauer–Emmett–Teller gas adsorption; DI, de-ionized; LS, laser scattering; μCT, X-ray computed tomography for small objects; MIP, mercury intrusion porosimetry; PSD, particle size distribution; RI, refractive index; SEM, scanning electron microscopy; SIA, static image analysis; SSE, sum of squared errors; TH, threshold

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properties significantly affect the quality of the final product, *e.g.* strength and dissolution behaviour of the tablet (Narayan and Hancock, 2003). Those agglomerates, or granules, are derived from a high-shear wet granulation process and should feature well-defined properties such as size distribution, porosity, surface structure, strength, flow properties (Rhodes, 2001; Crowley et al., 2004; Perry and Green, 2008). Therefore, understanding granulation and its mechanisms is key for optimal drug processing in order to yield high quality products. For example, the control of porosity is a desired ability, as porosity conversely affects disintegration behaviour, which controls drug release, and tensile strength, which controls mechanical stability of the product tablet. In a scenario where quick disintegration of the tablet is favourable, the optimum lactose tablet porosity may lie between 20% and 25% porosity (Keleb et al., 2004; Bi et al., 1999). Thus, the industry requires computer-aided process design and detailed product property prediction, however, universally applicable computer models for this complex process are not yet available. The kinetics and interaction forces between particles during granulation are still poorly understood and models are lacking physical insight. For better understanding of the governing mechanisms and to eventually take granulation computer models from an investigation-based to an industrially applicable level, we aim to develop the multivariate population balance model published by Braumann et al. (Braumann et al., 2007, 2010a, 2010b, 2010c, 2011). It is designed to track the changes of individual particle properties due to the main identified granulation mechanisms, which are explained in a later section.

For granulation model development, we require highly detailed data sets with characterisations of the various granulation material properties mentioned above in order to validate model parameter estimations as well as to compare and fit experimental results. Among others, Takano et al. (2002), Narayan and Hancock (2003), Adi et al. (2007), Mangwandi et al. (2010) and Wikberg and Alderborn (1991) investigated lactose powders and the granules from different granulation processes with respect to varying properties such as size, strength, porosity and surface structure. Rahmanian et al. (2011) used calcium carbonate powder and polyethylene glycol binder in a high-shear granulator. Mechanical strength of different granules was investigated by several authors (Hiramatsu and Oka, 1966; Mangwandi et al., 2010; Cheong et al., 2005; Rahmanian et al., 2011; Ryu and Saito, 1991; Antonyuk et al., 2010, 2006). A survey through the literature on lactose granulation shows that numerous studies have been undertaken to characterise lactose granulation materials and the influencing process parameters. However, the formulations of the initial material and the granulation setup vary, which makes comparability of experimental granulation results difficult. Further, detailed quantitative information are rarely reported. Therefore, we aimed to establish a carefully analysed multivariate data set of the powder (raw material) and the granules (product) derived from an exemplary high-shear granulation process as a basis for our model development and understanding the challenges of granulation processes. α-lactose monohydrate powder was the substance of choice due to its broad use in the pharmaceutical industry for tablet production.

In the course of this paper, the experimental and modelling aspects are explained, followed by a discussion of the results derived from experimental analysis of the granulation materials and the model outputs. An evaluation of the performance of the current model and an optimised version using the newly available data is presented.

2. Materials and methods

2.1. Wet granulation setup

In the following we study a high-shear wet granulation of Granulac 230 α-lactose monohydrate powder from Meggle, Germany, with de-ionised water as the binder liquid. The core piece of the experimental setup is a 5 L horizontal ploughshare mixer which was described in Kastner et al. (2013), Jones and Bridgwater (1998) and is presented schematically in Fig. 1. The radial mixing behaviour is illustrated using 1.8 mm ballotini in Fig. 2.

The mixing chamber is 22.5 cm long, the bowl radius (approximately equal to each plough's length) is 7.5 cm and the headboard height above the main shaft is 15 cm. One centimetre above that is the outlet of a single fluid spray nozzle (d=0.5 mm, 60° spray angle, Düsen-Schlick, Germany) including drip cup, all mounted to a transparent plastic box on the granulator. A study to examine different available nozzles for granulation, their spray radius and their atomization efficiency was performed prior to this work and concluded in our current granulation setup. A controlled flowrate of binder is added by nozzle atomization. The nozzle specification has a 70 um mean droplet size under the experimental conditions used. Liquid addition, mixer speed and process times scheduling are controlled via a LabVIEW program. After granulation, the granulation product was collected from the granulator with brushes. The material was spread over aluminium trays and dried in an oven at 60 °C before sieving. The process parameters are

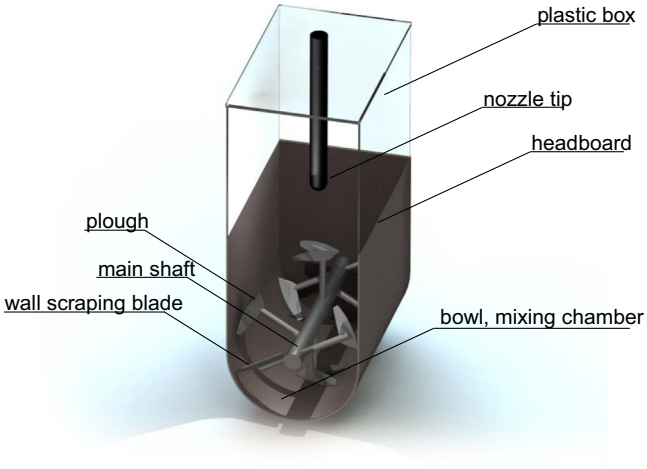

Fig. 1. CAD representation of the 5 L horizontal ploughshare granulation mixer, wall excluded.

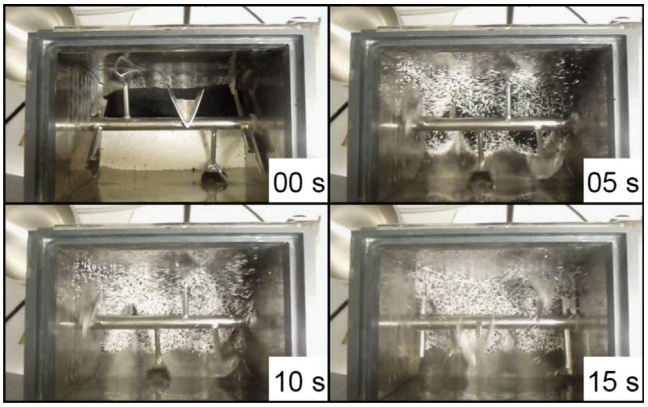

Fig. 2. Radial granulator mixing behaviour illustrated with 1.8 mm ballotini. The finer lactose powder was observed to be more dusty and airborne.