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An investigation into the usefulness of different empirical modeling techniques for better control of spray-on fluidized bed melt granulation

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ABSTRACT

Melt granulation in fluid bed processors is an emerging technique, but literature data regarding the modeling of this granulation method are lacking. In the present study different techniques (response surface analysis, multilayer perceptron neural network, and partial least squares method) were applied for modeling of spray-on fluidized bed melt granulation. Experiments were organized in line with central composite design. The effect of binder content and spray air pressure on granule properties was evaluated. The results obtained indicate that binder content can be identified as a critical factor controlling the granule size and size distribution. It was found that agglomeration mechanism involved, i.e., granule shape, can be greatly influenced by binder properties. The spray air pressure was identified as critical process parameter affecting granule flowability. The results presented indicate that application of in silico tools enables enhanced understanding and better control of novel pharmaceutical processes, such as melt granulation in fluidized bed. The artificial neural networks and partial least squares method were found to be superior to response surface methodology in prediction of granule properties. According to the results obtained, application of more advanced empirical modeling techniques complementary to design of experiments can be a suitable approach in defining the design space and optimization of spray-on fluidized bed melt granulation.

1. Introduction

Melt granulation is based on the use of materials with low melting point (50–80 °C) that act as molten binding liquids (Heng and Wong, 2006). It can be performed in fluid bed granulator, and there are two binder addition methods: melted binder can be sprayed onto the fluidized powder particles (spray-on procedure) or discrete binder particles can be fluidized with other powder particles, and melt with increase in air temperature (in situ procedure). More intensive research regarding melt granulation in fluid bed processors has begun in recent years (Walker et al., 2009; Zhai et al., 2014; Prado et al., 2014). Most of the reported studies on fluidized bed melt granulation (FBMG) are related to the in situ procedure, and there are very limited results regarding spray-on melt granulation in conventional fluid bed processor (Abberger, 2001; Abberger et al., 2002; Seo et al., 2002), including those obtained by using ballotini (glass) beads as model particles (Tan et al., 2005, 2006a, 2006b). Agglomerate growth is considered to be less controllable when spray-on FBMG is applied (Vilhelmsen and Schæfer, 2005). Because of the continuous spraying of the molten binder and wetting of the particle/agglomerate surface, coalescence is more likely to occur, which can lead to rapid agglomerate growth. Therefore, thorough understanding of the influence of process parameters and formulation variables, as well as their interactions, is needed to achieve good control of granule characteristics.

Fluid bed processors are widely used in pharmaceutical industry, but their application is still guided mostly by the experience of the operator. Because of the complex interplay of various factors affecting the product quality (including process parameters, formulation, and equipment-related factors), the optimization and/or scale-up of the process is often demanding and time consuming (Dixit and Puthli, 2009; Summers and Aulton, 2007). A systematic approach is, therefore, required in order to achieve enhanced understanding of the influence of these variables. ICH Q8 (R2) guideline (ICH, 2009) states that linking of material attributes and process parameters to drug product critical quality attributes can be performed through design of experiments and various mathematical models, which can be derived from first principles reflecting physical laws or from

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experimental data. It is considered that each of these approaches can contribute to higher level of process understanding and can be used to predict the system behavior under a set of conditions.

Wet granulation in fluid bed processors has been studied extensively over the last decade by using empirical modeling techniques, such as design of experiments and other more advanced non-linear modeling techniques. However, there are few studies concerning the application of design of experiments for better understanding of the influence of various factors on characteristics of the granules obtained by spray-on melt granulation in conventional fluid bed processor (Andrade et al., 2015), and there are no reports on the application of other empirical modeling techniques.

In our previous study (Aleksić et al., 2014) response surface methodology and artificial neural networks were successfully applied for modeling of in situ FBMG. The aim of the present study was to evaluate the possibility of using different non-linear empirical modeling techniques for better understanding of spray-on melt granulation process. The effect of binder content and spray air pressure on granule size and size distribution, granule shape, flowability and yield has been analyzed. The response surface methodology (RSM), artificial neural networks (ANN), and partial least squares method (PLS) were applied for data modeling and the ability of these techniques to simultaneously analyze the influence of process parameters and formulation factors on critical quality attributes of the granulates has been evaluated.

2. Materials and methods

2.1. Materials

Lactose monohydrate (Carlo Erba Reagents, Milan, Italy) was chosen as commonly used diluent for solid dosage forms, and Gelucire® 44/14, lauroyl macrogol-32 glycerides (Gattefosse, Saint-Priest Cedex, France) was used as meltable binder.

2.2. Methods

2.2.1. Characterization of primary materials

The melting range and the melting onset temperature of Gelucire® 44/14 was determined by a differential scanning calorimeter DSC 1 (Mettler-Toledo GmbH, Gießen, Germany) equipped with STARe Software (Mettler-Toledo GmbH, Gießen, Germany). Samples of about 10 mg were non-hermetically sealed in a 40 μl aluminum pan, and scanned between 25 and 250 °C at a heating rate of 10 °C/min under nitrogen atmosphere (50 ml/min).

Molten binder viscosity was estimated in the temperature range of 45–90 °C using the Anton Paar MCR 301 rotational rheometer (Anton Paar GmbH, Graz, Austria) coupled with the concentric cylinder measuring device CC27. The heating rate was 2 °C/min and the shear rate was 50 s^{-1}.

The contact angle was measured using Krüss DSA100 (Krüss GmbH, Hamburg, Germany). The molten binder was preheated to 46 °C and then dropped onto the lactose compact. Lactose compacts (200 mg) for contact angle determination were prepared using a round stainless steel punch and die assembly (d = 13 mm) in a Specac hydraulic press (Specac Ltd., Kent, England) with a 30 s dwell time at a force of approximately 49 kN. The contact angle was measured using circle method on at least five samples.

2.2.2. Granule preparation

Granulation was performed in Mycrolab fluid bed processor (OYSTAR Hüttlin, Schopfheim, Germany) connected to a personal computer allowing the process parameters to be monitored and recorded. In order to avoid premature binder congealing and nozzle clogging, certain modifications on the equipment have been introduced (for more detailed information refer to Mašić et al., 2014). The batch size was 200 g.

Lactose was filled into the fluid bed chamber, fluidized and preheated to product temperature of 42 °C. The tube that delivers molten binder to the nozzle was heated to 60 °C using the electric coil, and compressed air (spray air and microclimate) was heated to 70 °C using the tube heat exchangers. Molten binder was added through a three-component nozzle in a bottom-spray position, with an orifice of 0.8 mm. The addition of melted binder (preheated to 46 °C) was started when the powder temperature reached 42 °C. The binder feed rate was 6 g/min. The inlet air flow rate was 20 m^3/h. After the binder addition, heating was switched off and the inlet air flow rate increased to 25 m^3/h. When the product temperature decreased below 25 °C, the fluid bed processor was stopped and the product was collected.

2.2.3. Experimental design

The investigated variables were: binder content (X_1) and spray air pressure (X_2). The experiments were performed in the randomized order according to the central composite design, giving a total of 11 granulates designated as G1–G11. Real and coded values of the investigated variables are given in Table 1. Analysis of variance (at the 0.05 level of significance) was performed to determine the significance of each factor. The response variables were median particle diameter (d_{50}), span (S_{75-25}), Carr index (CI), aspect ratio (AR), projection sphericity (PS), circularity (C), and yield (Y).

2.2.4. Granule size analysis

The size distribution of granules was evaluated by sieves analysis, using the vibratory sieve shaker (Retsch GmbH, Haan, Germany) and a set of standard sieves in the range 125–2000 μm. Sieve analyses were performed on 100 g samples and the sieving time was 10 min.

Median granule diameter (d_{50}) was calculated by linear interpolation of the cumulative percentage frequency curve (fraction of particles < 125 μm, was considered to be ungranulated material and was excluded from calculation). The span was determined as a quotient of difference between the particle sizes corresponding to the quartile points at 75% and 25% and mass median diameter (estimated from the entire particle size distribution).

The yield (%) was calculated as the mass relative ratio of the 125–1250 μm sieve granule fraction, which was defined as the "useful" fraction.

Table 1
Real and coded values of the evaluated factors.

Independent variable		Coded and real values					Test formulations		
		$(-2^{1/2})$	(-1)	0	$(+1)$	$(+2^{1/2})$	T_1	T_2	T_3
Binder content (%)	X_1	12.9	15	20	25	27.1	16	19	17
Spray air pressure (bar)	X_2	0.48	0.6	0.9	1.2	1.32	1	0.7	0.6