International Journal of Pharmaceutics 466 (2014) 21–30

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

In silico modeling of in situ fluidized bed melt granulation

Ivana Aleksić [a,*], Jelena Đuriš [a], Ilija Ilić [b], Svetlana Ibrić [a], Jelena Parojčić [a], Stanko Srčič [b]

[a] Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia
[b] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 23 February 2014
Accepted 28 February 2014
Available online 5 March 2014

Keywords:
In situ melt granulation
Fluid bed
Experimental design
Artificial neural networks
Response surface methodology

ABSTRACT

Fluidized bed melt granulation has recently been recognized as a promising technique with numerous advantages over conventional granulation techniques. The aim of this study was to evaluate the possibility of using response surface methodology and artificial neural networks for optimizing in situ fluidized bed melt granulation and to compare them with regard to modeling ability and predictability. The experiments were organized in line with the Box–Behnken design. The influence of binder content, binder particle size, and granulation time on granule properties was evaluated. In addition to the response surface analysis, a multilayer perceptron neural network was applied for data modeling. It was found that in situ fluidized bed melt granulation can be used for production of spherical granules with good flowability. Binder particle size had the most pronounced influence on granule size and shape, suggesting the importance of this parameter in achieving desired granule properties. It was found that binder content can be a critical factor for the width of granule size distribution and yield when immersion and layering is the dominant agglomeration mechanism. The results obtained indicate that both in silico techniques can be useful tools in defining the design space and optimization of in situ fluidized bed melt granulation.

1. Introduction

Granulation is a common and often necessary process step in the production of solid dosage forms. Fluid bed processors are widely used in the pharmaceutical industry for various unit operations, including wet granulation. Fluidized bed wet granulation can be classified as a single-pot process because different unit operations (mixing, granulation, and drying) are performed in a single piece of equipment (Parikh and Mogavero, 2005). This is one of the main advantages of fluid beds over other granulation methods. Numerous variables (including process parameters, formulation, and equipment-related factors) have been recognized as affecting the agglomeration process in fluidized beds, and consequently the final granule quality (Dixit and Puthli, 2009; Parikh and Mogavero, 2005). Therefore, the use of fluid bed processors in the pharmaceutical industry still relies more on experience than on real knowledge and understanding of the process.

Regulatory guidelines (Food and Drug Administration FDA, 2004; International Conference on Harmonization, 2009; International Conference on Harmonization, 2005) emphasize the importance of product and process understanding; that is, systematic and scientific approaches to pharmaceutical product development and manufacturing processes. It is emphasized that quality should be built into the pharmaceutical product during the development phase (Quality by Design, QbD). This approach requires an enhanced understanding of the relationships among various formulation and process factors in order to achieve consistent product quality. It is suggested that establishment of the relevant design space leads to development of a controllable and robust manufacturing process, as well as flexible regulatory approaches. Design space is defined as "the multidimensional combination and interaction of input factors (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality" (ICH Q8, 2009).

It has been recognized that a consistent and well-controlled granulation process in a fluid bed processor requires a thorough understanding of the complex influence of various factors on critical granule attributes and identification of the design space, as opposed to the traditional reliance on operator experience (Faure et al., 2001; Lipsanen et al., 2007). Design of experiments techniques have been used extensively in order to elucidate the complex influence of numerous formulation factors and process parameters and to optimize the fluidized bed wet granulation process (Ehlers et al., 2009; Lourenço et al., 2012; Otsuka et al., 2011; Rambali et al., 2001a, 2001b; Rantanen et al., 2001; Tomuță et al., 2009). Among the design of experiments techniques, response surface methodology

* Corresponding author. Tel.: +381 11 395 1367; fax: +381 11 397 4349.
E-mail address: ivana.aleksic@pharmacy.bg.ac.rs (I. Aleksić).

http://dx.doi.org/10.1016/j.ijpharm.2014.02.045
0378-5173/

(RSM) is most frequently used for optimization. However, the relationship between formulation factors, process parameters, and critical quality attributes (e.g., granule size, flowability, shape, etc.) is often very complex, and application of advanced non-linear modeling techniques such as artificial neural networks (ANNs) may be required in order to establish the design space. Good results can be achieved by complementing design of experiments techniques with ANNs (Ibrić et al., 2012). Studies have reported the successful application of an ANN for defining the design space and optimization of fluidized bed wet granulation (Behzadi et al., 2005; Đuriš et al., 2012; Petrović et al., 2011).

There is increased interest and investment in the development of alternative granulation techniques, such as melt granulation. Melt granulation is based on the use of binders that have relatively low melting points (between 50 and 80 °C) and act as molten binding liquids (Heng and Wong, 2006). Melt granulation can be performed in the equipment commonly used for wet granulation, such as high shear mixers and fluid bed granulators. The possibility of using fluid bed granulators for melt granulation has been recognized more recently. Considering that certain advantages have been revealed in comparison with high-shear mixers (particularly in terms of better temperature control and thus simplified and better controlled granulation processes), more intensive research regarding fluidized bed melt granulation (FBMG) has begun in recent years (Walker et al., 2006, 2007a, 2007b, 2007c, 2009; Zhai et al., 2009, 2010; Passerini et al., 2010). However, understanding of the influence of various formulation variables, process parameters, and their interactions on the agglomeration mechanism and characteristics of the granules obtained by FBMG is still insufficient. It has been emphasized that information regarding the predictability and modeling of the FBMG is lacking (Andrews, 2007). There have been several studies concerning the application of design of experiments techniques for analyzing the influence of various factors on the characteristics of granules obtained by FBMG (Pauli-Bruns et al., 2010; Kukec et al., 2012), including our previous papers (Mašić et al., 2012, 2014). The use of an ANN for modeling and optimization of FBMG has still not been reported in the literature.

FBMG can be performed either by adding the binder as discrete particles that melt with increases in air temperature (an in situ procedure) or by spraying the melted binder onto the fluidized powder particles (a spray-on procedure). In our previous study (Mašić et al., 2012) concerning the in situ procedure, the binder particle size, binder content, and granulation time were found to significantly influence granule characteristics. However, the influence of these factors and their interactions on critical granule characteristics has to be clarified and quantified in order to establish the design space and achieve process optimization.

In situ FBMG was employed in the present study, and the effect of binder content, binder particle size, and granulation time on granule size, size distribution, flowability, shape, and yield was analyzed. Response surface methodology and artificial neural networks were applied and compared with regard to their modeling ability and predictability.

2. Materials and methods

2.1. Materials

Paracetamol (Acros Organics, Geel, Belgium) was used as the model drug. Lactose monohydrate (Carlo Erba Reagents, Milan, Italy) was used as a diluent, and Gelucire® 50/13, stearoyl macrogol-32 glycerides (Gattefosse, Saint-Priest Cedex, France) was used as a meltable binder.

2.2. Methods

2.2.1. Characterization of primary materials

Lactose and paracetamol particle size was determined in triplicate by laser diffraction (Mastersizer S, Malvern Instruments Ltd., Worcestershire, UK) using a 300RF lens and a small volume dispersion unit (1500 rpm). Ethanol was used as a dispersion media for lactose, and cyclohexane as a dispersion media for paracetamol.

The melting range and the melting onset temperature of the meltable binder 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 ml aluminum pan and scanned between 25 and 250 °C at a heating rate of 10 °C/min under a nitrogen atmosphere (50 ml/min).

2.2.2. Spray congealing of binder

Small binder particles (a mass mean particle size of ≈94 μm) were prepared using the spray congealing technique (Büchi Mini Spray Dryer B-290, Hessigkofen, Switzerland). Molten binder was added through a dual-fluid nozzle, with a 0.7 mm nozzle tip and a 1.5 mm nozzle cap, into the cooling chamber. A continuous flow of cooled air with temperatures ranging between 0 and 5 °C was used for solidification of particles in the process chamber. Processing air was cooled with a B-296 dehumidifier (Büchi, Hessigkofen, Switzerland) coupled to the spray dryer at the air inlet. The nozzle was thermostated with water to 60 °C using the nozzle's inner loop to prevent solidification in the nozzle. The atomizing air was heated by use of a capillary sunk in the water bath at 60 °C. The molten binder feed rate was 6 ml/min. The tube that delivers the melted binder was heated to 65 °C by a temperature controller (Digi-Sense, Cole Parmer, Vernon Hills, IL, USA). The atomizing air pressure was set at 1.2 bar.

2.2.3. Granule preparation

Granulation was performed in a Mycrolab fluid bed processor (OYSTAR Hüttlin, Schopfheim, Germany) connected to a personal computer allowing the process parameters to be monitored and recorded. Granulates were prepared with a 20% drug load, and the batch size was 200 g. Three different binder particle size fractions were used for granulation. The binder was ground using a mortar and pestle to give a mass mean particle size of ≈374.5 μm (355–400 μm sieve fraction) or a mass mean particle size of ≈655 μm (600–710 μm sieve fraction). Smaller binder particles of mass mean particle size ≈94 μm (63–125 μm sieve fraction) were prepared by the spray congealing technique as described previously. All of the ingredients, paracetamol, binder, and lactose, were loaded into the fluid bed chamber, fluidized, and preheated to a product temperature of 55 °C. The start of granulation time was defined as the point when the product temperature reached 55 °C. The inlet air flow rate was 35 m^3/h. After a specified time (3, 6.5, or 10 min), the inlet air heating was switched off. When the product temperature dropped below 30 °C, the fluid bed processor was stopped and the product was collected.

2.2.4. Experimental design

The investigated variables were: binder content (X_1), binder particle size (X_2), and granulation time (X_3). The experiments were performed in a randomized order according to the Box–Behnken design, giving a total of 17 experiments. 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).