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Comparison of a continuous ring layer wet granulation process with batch high shear and fluidized bed granulation processes

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ABSTRACT

The traditional batch wet granulation processes encounter several challenges, such as problems in the scale-up step, batch-to-batch variability together with the multivariate and difficult to control nature of the process. A continuous wet granulation technique could be a possible solution for the scale-up problem, offering adjustable production volumes with the same equipment. In this study, a continuous ring layer wet granulation process (factors: shaft speed and binder flow rate) was compared with two batch granulation processes: high shear (factors: impeller speed and chopper speed) and fluidized bed (factors: inlet air temperature during granulation and binder flow rate) with formulations consisting of paracetamol, microcrystalline cellulose and polyvinylpyrrolidone. A quantitative PLS model was formed to assess the effects of the process parameters on the granule properties (the mean granule size and flowability). In the case of the continuous ring layer granulation process, the mean granule size increased linearly with increasing shaft speed and binder flow rate, and the granules resembled morphologically more the granules produced by the high shear granulation than by the fluidized bed granulation. It is notable that the continuous ring layer granulation process was easier to control than the fluidized bed and high shear granulation processes due to the linear responses towards changes in operation conditions. Both types of tablets, compressed either from the granules produced by the continuous ring layer granulation or by the high shear granulation, achieved an immediate drug release. In summary, the continuous ring layer granulation process was demonstrated to represent a promising tool for the production of pharmaceutical granules.

1. Introduction

Wet granulation is a crucial size enlargement process that improves powder flow properties, reduces dustiness and segregation in further processing such as during tableting [1]. Traditionally used batch wet granulation processes, such as high shear and fluidized bed granulation, suffer from the complexity of scale-up and batch-to-batch variability [2,3]. In addition, several process-related factors as well as equipment and material parameters can affect the batch wet granulation processes which means that they are difficult to control [3–5]. The scale-up of a batch process can be costly and complicated. Scale-up strategies of high shear granulation can vary from monitoring of some representative parameter (*e.g.* power consumption) to the usage of experimental design and population balance modeling. Modeling may require performance of many experiments to be carried out with both small scale and larger scale equipment. In the case of the fluidized bed granulation process, the scale-up is rather complicated due to the importance of initial binder distribution together with other input parameters, such as inlet air and binder flow rate [4].

One possible solution to the scale-up issues in wet granulation is to use continuous processing, since here the size of equipment remains constant throughout the manufacturing process development but the manufacturing scale is defined by process throughput and running time [6]. Continuous processes confer advantages, such as decreased expenditure on equipment, premises and operation especially for large volume products [7]. The ability to utilize one-sized equipment minimizes waste during scale-up and the feasibility of testing different process conditions are conducted easily with a continuous process. At present, continuous processes are utilized widely in several industries *e.g.* in the chemical, food, pulp and paper industry [8–10]. There are reports describing continuous pharmaceutical processes; these include continuous mixing [8,9,11–14] and wet granulation. In fact, there are several continuous wet granulation techniques available for pharmaceutical applications, such as extrusion, instant agglomeration, spray drying and fluid bed agglomeration [15].

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Single screw and twin-screw extruders for pharmaceutical granulation were introduced in the late 1980s and have been developed subsequently in recent years [16–20]. In one study, the semi-continuous extrusion wet granulation was compared with the high shear granulation using formulations containing varying lactose grades and an active pharmaceutical ingredient (paracetamol and cimetidine). In that study, extrusion granulation proved to be more efficient than the high shear granulation for the preparation of the paracetamol granules [21]. Nonetheless, rather few studies have compared the batch and continuous wet granulation processes. The aims of this study were to compare the continuous ring layer wet granulation process with the batch high shear and fluidized bed wet granulation processes and assess the effect of the process parameters on the granule properties. The tested formulations consisted of paracetamol as the drug, microcrystalline cellulose as the excipient and aqueous polyvinylpyrrolidone solution as the binder liquid.

2. Materials and methods

2.1. Materials

Paracetamol (d_{50} (geometrical mean size) 15 ± 0.6 μm) was purchased from Xiamen Forever Green Source Biochem Tech. Co., Ltd (Xiamen, China) and microcrystalline cellulose (Avicel PH101, d_{50} 62 ± 0.5 μm), was purchased from IMCD (Malmö, Sweden). Polyvinylpyrrolidone (Kollidon K25) was purchased from BASF (Ludwigshafen, Germany) and was used as a binder in aqueous solution.

2.2. Preparation of granules

A 3^2 full factorial experimental design of experiments was applied to investigate the effects of the wet granulation process parameters on the properties of the granules (Table 1). All the process runs were conducted in a random order.

The required concentration of polyvinylpyrrolidone in the granulation binder solution as well as the levels of the process parameters were determined for each different granulation process in pre-tests before fixing the final formulation (Table 1).

2.2.1. Fluidized bed granulation

In the fluidized bed granulation process (Lödige LFP8, Gebrüder Lödige Maschinenbau GmbH, Paderborn, Germany), the granulation chamber was pre-heated to reach the inlet air temperature of 55, 60 or 65 °C according to the experimental design (Table 1). After preheating, paracetamol and microcrystalline cellulose (total batch size 500 g) were poured into the granulation chamber and the fluidization of air began with an inlet air quantity of 50 m^3/h. The inlet air flow was kept constant for the whole process from mixing to drying. Powders were mixed in fluidized bed for 5 min prior to the addition of the binder solution. The binder solution (12.5% (w/w) polyvinylpyrrolidone in purified water) was added with a peristaltic pump (Watson-Marlow Bredel, UK) through a 1.2 mm nozzle at the rate of 18, 22 or 27 g/min (Table 1). The granulation phase lasted for 23–35 min depending on the run. Liquid to solid ratios in fluidized bed granulation process were 1.22 (18 g/min binder flow rate), 1.21 (22 g/min binder flow rate) and 1.24 (27 g/min binder flow rate), respectively. After the granulation, the granules were dried with the same equipment at a constant inlet air temperature of 60 °C. The drying phase continued until the moisture difference between the inlet and outlet air was under 1.5 g/kg, *i.e.* 25–71 min depending on the run and the conditions of the ambient room temperature and moisture. The end point moisture varied from 0.9 to 1.4 g/kg, corresponding to the theoretical end point moisture contents of 0.6–0.9% (w/w).

2.2.2. High shear granulation

The weighed powder mass was poured into the granulation chamber (volume 5 l) and mixed in the high shear mixer (Lödige MGTL 5/15, Gebrüder Lödige Maschinenbau GmbH, Paderborn, Germany) for 3 min with an impeller speed of either 400, 500 or 600 rpm corresponding the peripheral speeds of 4.5, 5.7 or 6.8 m/s, respectively (Table 1). Chopper speed was chosen for another factor, with levels of 0, 1500 or 3000 rpm. After mixing, the binder solution (7.5% (w/w) polyvinylpyrrolidone in purified water) was added with a peristaltic pump at a rate of 35 g/min. The granulation phase lasted for 10.5 min in each run. Liquid to solid ratio in high shear granulation process was constant 0.74. After granulation, the granules were transferred to pre-heated fluidized bed dryer with the help of a vacuum. The granules were dried with the fluidized bed apparatus (Lödige LFP8, Gebrüder Lödige Maschinenbau GmbH, Paderborn, Germany) at the constant inlet air temperature of 60 °C until the moisture difference between inlet and outlet air was under 1.5 g/kg, *i.e.* 35–70 min. The end point moisture varied from 0.5 to 0.9 g/kg, corresponding to the theoretical end point moisture contents of 0.4–0.8% (w/w). The three best granulation conditions were chosen according to the values of mean granule size (d_{50}, mean granule sizes around 500 μm being the most desirable) and granule flowability (evaluated by Carr's index) and total of three repetition batches for further characterization were made using each of those three best granulation conditions (total of 9 repetition batches from which the granule content uniformity of 6 batches was analyzed).

2.2.3. Continuous ring layer granulation

The continuous ring layer granulator (Lödige CoriMix CM5, Gebrüder Lödige Maschinenbau GmbH, Paderborn, Germany) used here had a high peripheral speed (max. 40 m/s depending on the size of the machine) creating a centrifugal force that caused the granulated material to form a layer on the wall of the granulator, *i.e.* there is a ring layer and mixing occurs with the high intensity [22]. Equipment properties, such as geometry, fill level and tooling of the rotating blade, affect the residence time of material inside the granulator. The throughput of the granulator can vary from 10 to 80 kg/h making this

Table 1
Wet granulation process conditions, based on 3^2 full factorial design.

Parameter	Fluidized bed	High shear	Continuous ring layer
Formulation (% (w/w))			
Paracetamol	26.0	28.4	29.0
Microcrystalline cellulose	60.8	66.3	67.4–67.8
Polyvinylpyrrolidone	13.2	5.3	3.2–3.6
Factor 1	Granulation inlet Air temperature (55, 60, 65 °C)	Impeller speed (400, 500, 600 rpm)	Shaft speed (1000, 1250, 1500 rpm)
Factor 2	Binder flow rate (18, 22, 27 g/min)	Chopper speed (0, 1500, 3000 rpm)	Binder flow rate (7.4, 8.1, 8.8 kg/h)
Constant parameters	Batch size: 500 g Drying by fluidized bed 60 °C (25–71 min)	Batch size: 500 g Drying by fluidized bed 60 °C (35–70 min)	Powder feed rate: 11.2 kg/h Drying by fluidized bed 60 °C (19–27 min)