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Research paper

Use of a continuous twin screw granulation and drying system during formulation development and process optimization

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ABSTRACT

Since small scale is key for successful introduction of continuous techniques in the pharmaceutical industry to allow its use during formulation development and process optimization, it is essential to determine whether the product quality is similar when small quantities of materials are processed compared to the continuous processing of larger quantities. Therefore, the aim of this study was to investigate whether material processed in a single cell of the six-segmented fluid bed dryer of the ConsiGma™-25 system (a continuous twin screw granulation and drying system introduced by GEA Pharma Systems, Collette™, Wommelgem, Belgium) is predictive of granule and tablet quality during full-scale manufacturing when all drying cells are filled. Furthermore, the performance of the ConsiGma™-1 system (a mobile laboratory unit) was evaluated and compared to the ConsiGma™-25 system.

A premix of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate was granulated with distilled water. After drying and milling (1000 μm, 800 rpm), granules were blended with magnesium stearate and compressed using a Modul™ P tablet press (tablet weight: 430 mg, main compression force: 12 kN). Single cell experiments using the ConsiGma™-25 system and ConsiGma™-1 system were performed in triplicate. Additionally, a 1 h continuous run using the ConsiGma™-25 system was executed. Process outcomes (torque, barrel wall temperature, product temperature during drying) and granule (residual moisture content, particle size distribution, bulk and tapped density, hausner ratio, friability) as well as tablet (hardness, friability, disintegration time and dissolution) quality attributes were evaluated.

By performing a 1 h continuous run, it was detected that a stabilization period was needed for torque and barrel wall temperature due to initial layering of the screws and the screw chamber walls with material. Consequently, slightly deviating granule and tablet quality attributes were obtained during the start-up phase of the 1 h run. For the single cell runs, granule and tablet properties were comparable with results obtained during the second part of the 1 h run (after start-up). Although deviating granule quality (particle size distribution and Hausner ratio) was observed due to the divergent design of the ConsiGma™-1 unit and the ConsiGma™-25 system (horizontal set-up) used in this study, tablet quality produced from granules processed with the ConsiGma™-1 system was predictive for tablet quality obtained during continuous production using the ConsiGma™-25 system.

1. Introduction

Continuous processing is well established in several industries (e.g., oil refining, food, chemicals). However, the production of pharmaceutical granules is still based on the batch concept. This is mainly related to the large profit margins within the pharmaceutical industry that allowed to accommodate inefficiencies of the drug manufacturing process, as manufacturing contributed for only a small part to the overall cost of a drug product. During the last decade, small drug pipelines, increased competition from generic companies, and shrinking health budgets have induced a mentality change that all pharmaceutical processes (including

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manufacturing) should run as efficient and cost-effective as possible [1].

It is generally known that scale-up of batch processes leads to high costs. Scale-up of a batch granulation process from lab-scale to production scale requires a whole range of granulators. This demands a large investment in hardware, but the main problem of this approach is that the formulation and the process are optimized using, in general, small scale equipment [2]. Subsequently, the formulation is 'frozen', as during the clinical studies it is no longer possible to change the process and/or the formulation. For this reason, the formulation needs to be robust and has to result in the same quality of the product using small and large-scale equipment. However, during scale-up, the quality attributes of granules may change (e.g., particle size distribution, moisture content, friability, compressibility, compactibility) which may strongly influence the properties of the final tablet including dissolution rate of active substances. Scale-up problems are nowadays carefully analyzed by the registration authorities and in case of doubts about the quality of the production batch, expensive bioequivalence studies between small-scale and large-scale batches manufactured with the small and large size equipment have to be performed [3].

In contrast to the scale-up of a batch process where the dimensions of the equipment x, y, z are enlarged (with a development, optimization, and validation phase at each scale), an extension of process time on the same equipment using the same process settings can be performed for a continuous process [4,5]. This provides enormous flexibility as production time, and not the size of the equipment, determines the total material output. Hence, according to the specific needs, a "Just-in-Time Production" of the desired amount of material can be performed [6]. Furthermore, as the early clinical batches are produced on exactly the same equipment as the large production batches, no bioequivalence test between early clinical batches and later production batches is needed [7]. Therefore, it is believed that the shift to continuous manufacturing will result in significant cost savings and reduce the 'time to market' as process transfers from development to launch will be accelerated.

Our research group recently published a study on the stability and repeatability of three consecutive 5 h production runs performed with a continuous 'from powder to tablet' manufacturing line, the ConsiGma™-25 system introduced by GEA Pharma Systems (Collette™, Wommelgem, Belgium). This system consists of a twin screw granulation unit directly coupled to a six-segmented fluid bed dryer (see Section 2). It was concluded that, after start-up, granule and tablet quality attributes were constant in function of process time [8]. However, as during the early development phase, only a limited amount of drug substance is available and material costs are very high, small scale is key for successful introduction of continuous techniques in the pharmaceutical industry to allow its use during formulation development and process optimization. Therefore, it is essential to determine if the product quality is similar when small quantities of materials are processed compared to the continuous processing of larger quantities.

The aim of the current study was to investigate if processing of the formulation used in Ref. [8] in a single cell of the six-segmented dryer is predictive of full-scale manufacturing when all drying cells are filled. In the current study, the granulation, drying, milling and tableting settings from the production runs described in [8] were used. Process outcomes (torque, barrel wall temperature, product temperature during drying) and granule (residual moisture content, particle size distribution, bulk and tapped density, Hausner ratio, friability) as well as tablet (hardness, friability, disintegration time and dissolution) quality attributes obtained during single cell runs and a 1 h continuous run were compared. Additionally, the same formulation was granulated and dried using the ConsiGma™-1 system (a mobile unit designed for R&D environment, see Section 2) in order to evaluate the predictability of processing with the laboratory system for full-scale manufacturing with the ConsiGma™-25 system.

2. Materials and methods

2.1. Materials

The formulation consisted of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate. A high-dosed slightly soluble API was combined with a low-dosed freely soluble API. The d_{50} values of both APIs were lower than 100 μm. Distilled water was used as granulation liquid. Magnesium stearate was applied as lubricant during tableting. All materials were delivered by Johnson&Johnson, Janssen-Cilag, Italy.

2.2. Preparation of granules and tablets

Granulation and drying experiments were performed using the ConsiGma™-25 unit (C25) and the ConsiGma™-1 (C1) system (GEA Pharma Systems, Collette™, Wommelgem, Belgium). The former consists of three modules, as already extensively described by Chablani et al. [9] and Fonteyne et al. [10]: a high-shear wet granulation module, a six-segmented fluid bed dryer module and a granule conditioning module.

The granulation module consists of a high-shear co-rotating twin screw granulator without die plate. The length-to-diameter ratio of the granulation unit is 20:1. The barrel of the continuous granulator can be divided into two segments: a feed segment, where powder enters the barrel and consisting of conveying elements to transport the material through the barrel; and a work segment, where the powder is intensively mixed with the granulation liquid by kneading elements [10,11]. To evaluate the granulation process, the torque on the screws and the temperature of the barrel wall at the work segment of the granulator were recorded (1 s interval). These parameters give an indication of the shear and compaction forces experienced by the materials inside the barrel. The equipment had an in-built torque gauge (Sensor Technology, Banbury, UK). At the work segment, the temperature of the barrel wall was monitored by a Pt100 temperature sensor (Jumo, Fulda, Germany). The jacket temperature was set at 25 °C for the full length of the barrel. The screw speed was set at 900 rpm. The screw configuration was composed of 2 kneading zones each consisting of 4 kneading elements ($L = D/4$ for each kneading element) at an angle of 60° [8]. Both kneading zones were separated by a conveying element ($L = 1.5D$). An extra conveying element ($L = 1.5D$) was implemented after the second kneading block together with 2 narrow kneading elements ($L = D/6$ for each kneading element) in order to reduce the amount of oversized agglomerates, as reported by Van Melkebeke et al. [12]. During processing, a powder premix of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate was gravimetrically dosed at a feed rate of 20 kg/h by a twin screw feeder (KT20, K-Tron Soder, Niederlenz, Switzerland). Distilled water as granulation liquid was pumped into the screw chamber using two peristaltic pumps (Watson Marlow, Cornwall, UK) and silicon tubings (internal and external diameter of 1.6 and 6.4 mm, respectively) connected to 1.6 mm nozzles. Liquid was introduced in the barrel in front of the first kneading element. The water concentration of the formulation during granulation was 13% (w/w), calculated on wet mass.

In the C25 system, the granulation unit is directly connected to a six-segmented fluid bed dryer. A bottom view of the segmented dryer is presented in Fig. 1. The filling time per cell was 180 s,