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Research paper

Influence of raw material properties upon critical quality attributes of continuously produced granules and tablets

Margot Fonteyne [a,*], Henrika Wikström [a,b], Elisabeth Peeters [c], Jurgen Vercruysse [c], Henrik Ehlers [b], Björn-Hendrik Peters [d], Jean Paul Remon [c], Chris Vervaet [c], Jarkko Ketolainen [d], Niklas Sandler [b], Jukka Rantanen [e], Kaisa Naelapää [e,1], Thomas De Beer [a]

[a] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium
[b] Pharmaceutical Sciences Laboratory, Department of Biosciences, Åbo Akademi University, Turku, Finland
[c] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium
[d] School of Pharmacy, University of Eastern Finland, Kuopio, Finland
[e] Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

Continuous manufacturing gains more and more interest within the pharmaceutical industry. The International Conference of Harmonisation (ICH) states in its Q8 'Pharmaceutical Development' guideline that the manufacturer of pharmaceuticals should have an enhanced knowledge of the product performance over a range of raw material attributes, manufacturing process options and process parameters. This fits further into the Process Analytical Technology (PAT) and Quality by Design (QbD) framework. The present study evaluates the effect of variation in critical raw material properties on the critical quality attributes of granules and tablets, produced by a continuous from-powder-to-tablet wet granulation line. The granulation process parameters were kept constant to examine the differences in the end product quality caused by the variability of the raw materials properties only. Theophylline–Lactose–PVP (30–67.5–2.5%) was used as model formulation. Seven different grades of theophylline were granulated. Afterward, the obtained granules were tableted. Both the characteristics of granules and tablets were determined. The results show that differences in raw material properties both affect their processability and several critical quality attributes of the resulting granules and tablets.

1. Introduction

Currently the interest has arisen in the pharmaceutical industry to shift its manufacturing principles from traditional batch production toward continuous production [1,2]. Continuous manufacturing has several advantages including minimal scale-up issues, reduction in cycle time, less product variability and lower production costs, faster product release, increased flexibility and efficiency, and improvement of product quality. These advantages result for example in a shorter "time-to-market" and lower operating costs. Continuous production allows "just-in-time" production and will minimize the stock, according to LEAN principles. Furthermore, a continuous production line requires less floor space and fewer operators. Hence, once implemented, a continuous manufacturing line will imply a significant cost reduction. Whereas continuous production is well implemented in chemical and food industry, it is still in its infancy when it comes to the pharmaceutical industry. The most common pharmaceutical solid dosage form is the tablet. Tableting often involves a granulation step. Recently, advances in pharmaceutical continuous granulation and tableting have been reported [3–11].

The introduction of continuous manufacturing comes with a major concern: "How to assure a persistent quality of the pharmaceutical products?" The classical off-line quality control analysis

Abbreviations: ICH, International Conference on Harmonisation; PAT, Process Analytical Technology; API, Active Pharmaceutical Ingredient; BET, Brunauer–Emmett–Teller; CQA, critical quality attributes; FDA, food and drug administration; HPMC, hydroxypropylmethylcellulose; MCC, microcrystalline cellulose; PC, Principal Component; PCA, Principal Component Analysis; PLS, partial least squares; PVP, polyvinylpyrrolidone; QbD, Quality by Design; rpm, rotations per minute; SNV, standard normal variate; UV, unit variance; UV–VIS, ultraviolet–visible.

* Corresponding author. Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Harelbekestraat 72, Ghent, Belgium. Tel.: +32 9 264 83 55; fax: +32 9 222 82 36.

E-mail addresses: Margot.Fonteyne@Ugent.be (M. Fonteyne), Thomas.Debeer@-Ugent.be (T.D. Beer).

[1] Current address: Oral Protein Formulation, Novo Nordisk, Måløv, Denmark.

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methods, which are used in traditional batch production, are not directly suitable for continuous production. This situation has been greatly improved after the FDA launched its idea of Process Analytical Technology (PAT). The PAT guidance [12] states that "*quality cannot be tested into products; it should be built-in or should be by design*". This strengthens the need for an enhanced process knowledge, which is a critical element in the ICH Q8 guideline [13]. This guideline on "Pharmaceutical Development" encourages manufacturers to understand systematically and mechanistically the relationship between critical material attributes and drug products' critical quality attributes (CQAs). Unlike for batch production, where a batch which does not meet the specifications can be rejected, this is not the case for continuous production, where all starting materials introduced into the line will be processed. Therefore, it is relevant to understand the characteristics of the raw materials and their influence on the processability and end-product quality.

The influence of raw materials in roller compaction, a continuous dry granulation method, has been investigated by several research groups. The potential impact of starting material properties and processability together with end-product specifications and their respective characterization methods has been listed by Hlinak et al. [14]. Mixtures of microcrystalline cellulose (MCC) and lactose, both with varying particle sizes were blended with magnesium stearate and roller compacted by Kushner et al. The particle size of the excipients had a significant influence on the particle size of the granules: larger starting material particles resulted in larger granules. The granulation parameters were kept constant [15]. Different types of lactose were roller compacted by using different combinations of the roller compactor settings (air pressure, roll speed, vertical screw speed and horizontal screw speed) after which the granule friability was evaluated [16]. Soh et al. [17] also roller compacted three different grades of MCC, three grades of lactose and their blends. They used a multivariate data analysis approach in order to construct a model to predict ribbon and granule characteristics. The model consisted of the roller compacter parameters together with the characteristics of the starting materials. Herting and Kleinebudde used theophylline as a model drug [18]. Binary mixtures of MCC and anhydrous theophylline, which differed in particle size, were roller compacted and compressed into tablets. Three different kinds of MCC and anhydrous theophylline with two different particle sizes were evaluated. The tensile strength of both direct compressed tablets and tablets made after roller compaction increased with lower particle size of the starting powders. Hadzovic et al. [19,20] used the same API (Active Pharmaceutical Ingredient) and excipients. Roller compaction, direct compression and tableting after roller compaction were performed on two different grades of anhydrous theophylline (powder and fine powder) and theophylline monohydrate and their blends with MCC. They focused on tensile strength [19] and compressibility [20]. The compressibility of the two anhydrous theophylline powders was higher than of the granules, and the compressibility of theophylline monohydrate increased after roller compaction. The influence of raw material properties of mannitol and dicalcium phosphate on roller compaction and subsequent tableting was investigated by Souihi et al. [21], who applied a QbD approach. A study on a twin screw granulator has been conducted as well [22]. Mixtures of lactose, MCC, HPMC and croscarmellose sodium were granulated, while the primary particle size of lactose was varied. The granulator performed robust when changing starting materials, however starting material with a smaller particle size resulted in smaller granules. A similar study was performed by the same researchers, using the Eyecon™ camera [23]. Granules with a different porosity were obtained when the grade of lactose was changed. Haware et al. [24] made tablets by means of direct compression, using nine different types of lactose, differing in particle size, in combination with 1% of magnesium stearate. They found differences in powder compression properties and tensile strength of the tablets, but a clear relationship with the particle size of the starting materials could not be determined. They further managed to predict the tensile strength of the tablets successfully by means of partial least squares models (PLS-1) with the type of lactose and two compression parameters as input. Similar work was done by the same research group, comparing five different grades of MCC. The MCCs differed in particle size distribution and brand [25]. For MCC, they did not find an impact on the compression response (value of plastic deformation) but could correlate the tensile strength to the particle size of the raw materials. Smaller starting material led to stronger tablets. To date, limited studies regarding raw material variability on continuous wet granulation have been published.

It is clear that inherent, undetected variability of the raw materials may be manifested in the final product properties. Furthermore, processing difficulties can arise, which can result in a failure of the aimed end-product specifications. Mevik et al. [26] described a process as follows:

$$y = f(x) + \varepsilon$$

where y = vector of one or more response variables; x = vector of model variables; f = vector-valued function, which is unknown and needs to be estimated by means of data and ε = error term.

In the case of continuous granulation and tableting y might for example be the granules' particle size distribution or the tensile strength of the tablets. The model variables x are factors that influence the quality of the end product. Examples for x are process settings, environmental factors and starting materials' quality characteristics. The aim of this study is to evaluate the influence of the model variables upon y in a continuous wet granulation process. Process settings were held constant; hence, the focus was only on the variability of the raw materials. This project aims at examining and understanding the effects of the physical variability (e.g. particle size distribution, density, etc.) of raw material properties on the critical quality attributes of continuously produced granules and tablets. Furthermore the influence of varying raw material properties on processability was investigated.

2. Materials and methods

2.1. Materials

Seven different grades of anhydrous theophylline were compared. One was purchased from Farma-Quimica sur SL (Malaga, Spain). Additionally, theophylline anhydrous powder, fine powder, 200, 200M, 325M and Micronized powder (all donated by BASF, Ludwigshafen, Germany) were used. The 200 grade is referred to as 200_ in order to make a clear distinction with 200M. Thirty percent of theophylline was blended with 67.5% (w/w) of lactose monohydrate 200M (Caldic, Hemiksem, Belgium). Polyvinylpyrrolidone (Kollidon®30, BASF, Ludwigshafen, Germany) was used in a 2.5% (w/w) concentration as a binder. Demineralized water was used as granulation liquid.

2.2. Methods

2.2.1. Production of granules and tablets

All granules were produced using the ConsiGma™-25 unit (GEA Pharma Systems, Collette, Wommelgem, Belgium), which consists of three major parts: a continuous twin screw high shear granulator, a six parallel cell fluid bed dryer and a discharge system. The equipment is extensively described elsewhere [10]. For this study only the granulator with a standard screw configuration was used