International Journal of Pharmaceutics 524 (2017) 91–100

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Experimental determination of residence time distribution in continuous dry granulation

Haress Mangal, Peter Kleinebudde*

Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Universitaetsstr. 1, 40225 Duesseldorf, Germany

ARTICLE INFO

Article history:
Received 16 November 2016
Received in revised form 29 March 2017
Accepted 30 March 2017
Available online 31 March 2017

Keywords:
Roll compaction
Dry granulation
Residence time
Milling
Continuous manufacturing
Digital image analysis

ABSTRACT

With increasing importance of continuous manufacturing, the interest in integrating dry granulation into a continuous manufacturing line is growing. Residence time distribution measurements are of importance as they provide information about duration of materials within the process. These data enable traceability and are highly beneficial for developing control strategies. A digital image analysis system was used to determine the residence time distribution of two materials with different deformation behavior (brittle, plastic) in the milling unit of dry granulation systems. A colorant was added to the material (20% w/w iron oxide), which did not affect the material properties excessively, so the milling process could be mimicked well. Experimental designs were conducted to figure out which parameters effect the mean residence time strongly. Moreover, two types of dry granulation systems were contrasted. Longer mean residence times were obtained for the oscillating mill (OM) compared to the conical mill (CM). For co-processed microcrystalline cellulose residence times of 19.8–44.4 s (OM) and 11.6–29.1 s (CM) were measured, mainly influenced by the specific compaction force, the mill speed and roll speed. For dibasic calcium phosphate anhydrate residence times from 17.7–46.4 (OM) and 5.4–10.2 s (CM) were measured, while here the specific compaction force, the mill speed and their interactions with the roll speed had an influence on the mean residence time.

1. Introduction

For continuous manufacturing of solid pharmaceuticals, different processes for particle enlargement are shifting more into focus (Vervaet and Remon, 2005). The methods, which are paid attention to, are wet- and dry granulation. These methods are commonly used in traditional batch processes, but some of them are also suitable for continuous processing. In case of wet granulation the focus is twin-screw granulation, whilst for dry granulation, roll compaction is the method of choice (Leuenberger, 2001).

Continuous manufacturing offers multiple advantages, such as a variable production capacity, smaller production equipment, lower production cost etc. (Ierapetritou et al., 2016). Further, there is a higher quality of intermediate and final products due to installed process analytical technology (PAT) tools, which monitor the process. As continuous manufacturing is a relatively new technique and not widely established yet, there are challenges to overcome. Only a few products are produced by continuous manufacturing up to now. The interaction within all process units and especially in the automation part, including assessment of intermediates and the control of process variables is challenging. Other challenges are regulatory ones, as traceability of different materials is required (FDA, 2001), the definition and differentiation of a batch within the continuous process gets more difficult (Engisch and Muzzio, 2016). In the prior batch wise process, each production step led to a defined amount of product, which constitutes a single batch. As the output of the continuous process can be unlimited, definition of batches can be challenging. One idea is to define a batch within a time span, which means that different batches of API and excipients can be mixed in the final product. Other ideas are e.g. to define a final batch linked to the bulk API batch. Furthermore, other definitions are conceivable (Chatterjee, 2012).

In any case, however, it is crucial to understand how long materials stay within individual parts of the production process. To do so, the residence time analysis is used successfully in different unit operations (Gao et al., 2012). Therefore, the residence time analysis seems to be adequate for continuous manufacturing approach.

* Corresponding author.
E-mail address: Kleinebudde@hhu.de (P. Kleinebudde).

http://dx.doi.org/10.1016/j.ijpharm.2017.03.085
0378-5173/

Residence time analysis is often conducted as pulse experiment, where a tracer is added to the process. Depending on which type of tracer is used, the concentration can be determined in different ways at the end of the process. A distribution of residence time can be identified and is expressed in an exit age function. The mean residence time (MRT) is calculated out of the residence time distribution (RTD) and is used as standard value for comparing results.

It is also possible to use computational models for the residence time distribution, but as model based distributions represent idealistic distributions, it is absolutely essential to conduct experimental work.

Different residence time models, as well as experimental work is available for twin-screw granulation (Kumar et al., 2016; Meier et al., 2016). But so far, no estimations and experiments are available for a pharmaceutical dry granulation processes. An additional difficulty is, that machine suppliers equip their machines with different milling systems, which could strongly influence the residence time distribution.

All available roll compactors follow the main principle, albeit they can be different in their setup, in their way of working and in their equipment. Powder is fed between two counter rotating rolls and is densified (Kleinebudde, 2004). The resulting intermediate product, called ribbon, is milled subsequently to granules. The feeding system, the arrangement of the rolls, the surface of the rolls, the sealing system of the rolls and the granulation system can be different, therefore the material flow pattern can be divergent. During roll compaction numerous parameters can be set, such as the specific compaction force, the speed of dosing and tamper screw, the distance between the rolls, the roll speed, and the configuration of the mill (mill speed, type of sieve, mesh size). Different mill types were evaluated with regard to granule quality attributes (Hancock and Vendola, 2008), but no estimation of the residence of materials was done. The same applies to the other mentioned process variables. Some of them could have a major impact on residence time distribution, therefore it is valuable to investigate the effects of some process parameters and mill types.

This study focuses on the usage of a digital image analysis system for residence time determination to understand how residence time distribution in dry granulation can vary. Special attention was paid to certain process parameters, type of granulation system and material properties. These information are useful for process modelling with regard to traceability and process control. For a future target of monitoring and controlling the particle size by adopting process parameters of upstream processes, RTD measurements could lead to important insights, since PID control systems for such a control can be tuned in a smarter way.

2. Experimental

2.1. Materials

A co-processed microcrystalline cellulose MCCDG (Avicel DG, FMC Biopolymer, USA) and a coarse quality of dibasic calcium phosphate anhydrate DCPA (Di-Cafos A150, Budenheim, Germany) served as model excipients to determine residence time distributions of materials with different deformation behavior.

Two types of red iron oxide were used as tracer. Sicovit Red 30 E172 (BASF, Germany) was used in the experiments with the BRC25. For the experiments with the Mini-Pactor Oxidrot (Kremer Pigmente, Germany) was in use.

2.2. Roll compaction/dry granulation

Dry granulation was performed with two different roll compactors with integrated milling equipment. The BRC 25 (BRC, L.B. Bohle, Germany) was equipped with a 1 mm conical rasp (Fig. 1a) sieve with a rotating, in work direction bended two blade-impeller, while the Mini-Pactor (MP, Gerteis, Switzerland) was installed with a star shaped, oscillating granulator (Fig. 1b) and a 1 mm mesh screen. The star shaped granulator was operated with same speeds in both directions (clockwise, counterclockwise) and a change of direction each 3 rotations.

Both roll compactors were operated with smooth rolls, a rim roll sealing and an automatic gap control (2 mm width) by adjusting feeding and tamper auger screw speeds.

2.3. Production of tracer ribbons

Before performing the residence time distribution measurements, tracer ribbons were produced. The tracer ribbons consisted of 20% red iron oxide and 80% excipient (MCCDG or DCPA). The physical mixture was bl ended for 20 min in a turbula mixer (Willy Bachofen, Switzerland) or in a container mixer (L.B. Bohle, Germany) and fed into the compactor. Except of the milling step, ribbons were produced under the same process conditions as the subsequent process settings. The ribbons were collected below the rolls.

2.4. Residence time distribution measurement

An in-line, non-invasive digital image analysis system was used to perform residence time distribution measurements. The ExtruVis3-system (ExtruVis, Germany) consist out of a high resolution camera (USB-CAM-052H, Phytec, Germany) a LED ring light (Phytec, Germany), and the ExtruVis3 software. To realize RTD measurements for dry granulation, impulse experiments were

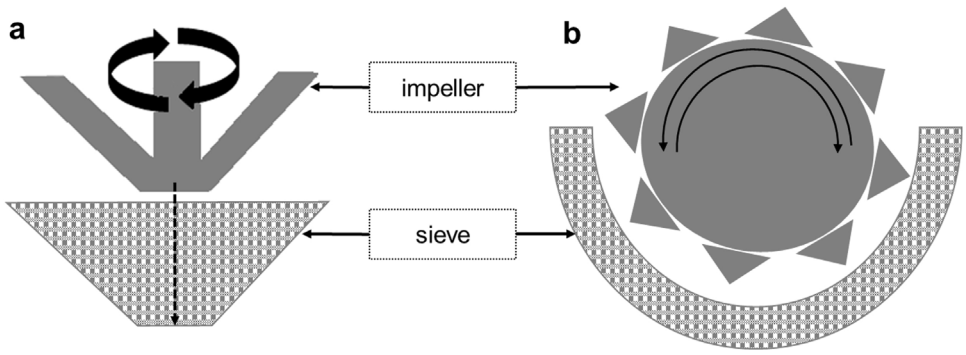

Fig. 1. Different granulation systems: (a) cone mill (b) oscillating mill.