European Journal of Pharmaceutical Sciences 115 (2018) 223–232

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Breakage and drying behaviour of granules in a continuous fluid bed dryer: Influence of process parameters and wet granule transfer

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ARTICLE INFO

Keywords:
Continuous manufacturing
Fluid bed drying
Critical quality attributes
Twin screw granulation
Process understanding
Particle size distribution
Moisture content

ABSTRACT

Although twin screw granulation has already been widely studied in recent years, only few studies addressed the subsequent continuous drying which is required after wet granulation and still suffers from a lack of detailed understanding. The latter is important for optimisation and control and, hence, a cost-effective practical implementation. Therefore, the aim of the current study is to increase understanding of the drying kinetics and the breakage and attrition phenomena during fluid bed drying after continuous twin screw granulation. Experiments were performed on a continuous manufacturing line consisting of a twin-screw granulator, a six-segmented fluid bed dryer, a mill, a lubricant blender and a tablet press. Granulation parameters were fixed in order to only examine the effect of drying parameters (filling time, drying time, air flow, drying air temperature) on the size distribution and moisture content of granules (both of the entire granulate and of size fractions). The wet granules were transferred either gravimetrically or pneumatically from the granulator exit to the fluid bed dryer. After a certain drying time, the moisture content reached an equilibrium. This drying time was found to depend on the applied airflow, drying air temperature and filling time. The moisture content of the granules decreased with an increasing drying time, airflow and drying temperature. Although smaller granules dried faster, the multimodal particle size distribution of the granules did not compromise uniform drying of the granules when the target moisture content was achieved. Extensive breakage of granules was observed during drying. Especially wet granules were prone to breakage and attrition during pneumatic transport, either in the wet transfer line or in the dry transfer line. Breakage and attrition of granules during transport and drying should be anticipated early on during process and formulation development by performing integrated experiments on the granulator, dryer and mill.

1. Introduction

Traditionally, batch processes are used to produce pharmaceutical products. However, the pharma industry is willing to invest in continuous processes since many benefits are associated with continuous manufacturing (e.g. flexibility, smaller equipment, cost, time-to-market reduction and improved product quality) (FDA, 2004; Plumb, 2005; Teżyk et al., 2015; Vercruysse et al., 2013; Vervaet and Remon, 2005). However, it is essential to gain fundamental knowledge about the mechanisms occurring during continuous processes to allow process optimisation and control for reliable real-time release of produced products.

Tablets are the most commonly used solid dosage forms in the pharmaceutical industry (Gohel and Jogani, 2005). Direct compression is the preferred continuous manufacturing method for production of tablets, but often an intermediate agglomeration step is required to improve the flowability, homogeneity and compressibility (Armstrong,

Abbreviations: L/S, liquid-to-solid; LOD, loss-on-drying; PBM, Population Balance Model; V_0, bulk volume; V_{500}, tapped volume after 500 taps; ρ_b, bulk density; ρ_t, tapped density after 500 taps

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https://doi.org/10.1016/j.ejps.2018.01.037
Received 28 September 2017; Received in revised form 12 December 2017; Accepted 20 January 2018

Fig. 1. Horizontal ConsiGma™-25 system (left) and vertical ConsiGma™-25 system (right) with 1. loss-in-weight feeder, 2. twin screw granulator, 3. wet transfer line (only in horizontal set-up), 4. six-segmented fluid bed dryer, 5. dry transfer line and 6. product control unit with option for milling.

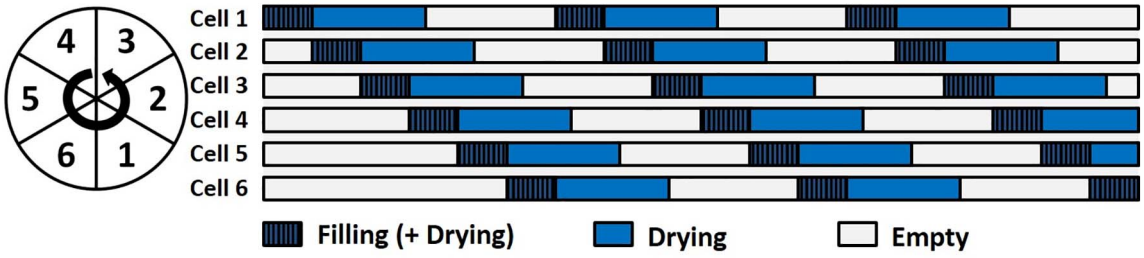

Fig. 2. Visual presentation of the filling cycle in the six-segmented fluid bed dryer of a ConsiGma™-25 line.

Table 1
Overview of the granulation parameters.

Screw speed (rpm)	900
Barrel temperature (°C)	25
Throughput (kg/h)	20
L/S ratio	0.15

2007; Gohel and Jogani, 2005; Vervaet and Remon, 2005).

Several equipment manufacturers currently offer integrated from-powder-to-tablet lines for continuous production of tablets via continuous twin screw granulation (e.g. QbCon® by L.B. Böhle, Granuformer® by Freund Vector, ConsiGma™ by GEA Pharma Systems, MODCOS system by Glatt). Whereas in the Granuformer® line (Freund Vector) a spiral dryer is implemented, the other continuous lines pneumatically transfer the wet granules from the granulator to a segmented fluid bed dryer (Kleinebudde, 2017; Byrn et al., 2014). However, on the ConsiGma™ system (GEA Pharma systems) gravimetric instead of pneumatic granule transfer is also possible. Therefore two different set-ups can be distinguished: (1) a horizontal set-up (granulator is positioned next to the dryer) with pneumatic granule transfer via a wet transfer line, (2) a vertical set-up (granulator is positioned above the dryer) with gravimetric transfer of wet granules to the dryer (Fig. 1).

Segmented fluid bed dryers are currently most often implemented in continuous manufacturing lines. Although other designs of continuous fluid bed dryers are available such as horizontal fluid bed dryers (e.g. GF series by Glatt, Niro Contipharm granulator, Heinen drying technologies) or the AGT fluid bed dryer by Glatt, these systems are typically not applicable in the pharmaceutical industry due to the long material residence time and lack of plug-flow (Gotthardt et al., 1999; Vervaet and Remon, 2009; Tężyk et al., 2015). Short and controllable residence times are of utmost importance during granulation of pharmaceutical products for traceability and to avoid product degradation.

While twin screw granulation was widely studied in recent years, only few studies addressed subsequent drying on a segmented fluid bed dryer which is required after wet granulation. Fonteyne et al. and Chablani et al. reported on the implementation of Raman and NIR probes in the six-segmented fluid bed dryer unit of the ConsiGma™-25 for monitoring of moisture content and polymorphism while Vercruysse et al. evaluated the stability and repeatability of the granulation and drying units during long runs with constant process parameters (Chablani et al., 2011; Fonteyne et al., 2014a; Vercruysse et al., 2013). However, these studies did not focus on the influence of dryer parameters on critical quality attributes of granules and did not aim to explore and understand breakage and attrition phenomena taking place during drying.

Although batch-wise fluid bed drying has been intensively studied and the influence of most parameters (air flow, drying air temperature and drying time) on the granule quality is expected to be similar during continuous fluid bed drying, the set-up of a batch fluid bed dryer (with a single drying cell) is fundamentally different in comparison to a segmented fluid bed dryer (with multiple drying cells). Whereas an entire batch of wet granules is introduced at the same moment into a batch fluid bed dryer, granules are continuously transferred to a specific cell of the segmented fluid bed dryer for a set time (filling time) after which the next cell of the segmented fluid bed dryer is filled. Therefore, the filling time of a dryer cell is an additional variable inherent to drying in a segmented fluid bed dryer after continuous granulation. However, the effect of the filling time has not yet been investigated. Therefore, the effect of filling time, in addition to other drying parameters (air flow, drying air temperature, drying time), was evaluated in the current study.

The impact of the transfer of wet granules after continuous granulation was also neglected up to now. Using an in-line particle imaging tool, Kumar et al. observed that tray dried granules showed wider granule size distributions in comparison to fluid bed dried granules which was attributed to breakage and attrition in the segmented fluid