International Journal of Pharmaceutics 529 (2017) 678–693

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

In-depth experimental analysis of pharmaceutical twin-screw wet granulation in view of detailed process understanding

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ARTICLE INFO

Article history:
Received 24 May 2017
Received in revised form 12 July 2017
Accepted 14 July 2017
Available online 15 July 2017

Keyword:
Twin-screw wet granulation

ABSTRACT

Twin-screw wet granulation is gaining increasing interest within the pharmaceutical industry for the continuous manufacturing of solid oral dosage forms. However, limited prior fundamental physical understanding has been generated relating to the granule formation mechanisms and kinetics along the internal compartmental length of a twin-screw granulator barrel, and about how process settings, barrel screw configuration and formulation properties such as particle size, density and surface properties influence these mechanisms. One of the main reasons for this limited understanding is that experimental data is generally only collected at the exit of the twin-screw granulator barrel although the granule formation occurs spatially along the internal length of the barrel. The purpose of this study is to analyze the twin-screw wet granulation process using both hydrophilic and hydrophobic formulations, manufactured under different process settings such as liquid-to-solid ratio, mass throughput and screw speed, in such a way that the mechanisms occurring in the individual granulator barrel compartments (i.e., the wetting and different conveying and kneading compartments) and their impact upon granule formation are understood. To achieve this, a unique experimental setup was developed allowing granule characteristic data-collection such as size, shape, liquid and porosity distribution at the different compartments along the length of the granulator barrel. Moreover, granule characteristic information per granule size class was determined. The experimental results indicated that liquid-to-solid ratio is the most important factor dictating the formation of the granules and their corresponding properties, by regulating the degree of aggregation and breakage in the different compartments along the internal length of the twin-screw granulator barrel. Collecting appropriate and detailed experimental data about granule formation along the internal length of the granulator barrel is thus crucial for gaining fundamental physical understanding of the twin-screw wet granulation process.

1. Introduction

Traditional pharmaceutical solid oral dosage manufacturing exists as a series of batch unit operations which are rather inefficient and expensive. Today, efficiency, cost, lean manufacturing and regulatory-driven efforts have shifted processing from batch to continuous. Twin-screw granulation is an effective wet granulation technique for continuous solid-dosage manufacturing, since it offers the flexibility to deal with varying batch sizes (i.e. small clinical supply batches and large production batches), which allows industry to develop a continuum of knowledge throughout development and can avoid tedious and costly scale-up procedures (Srai et al., 2015). This enables manufacturers to reduce their investment and running costs while drastically reducing the footprint requirements (Vervaet and Remon, 2005; Leuenberger, 2001; ConsiGma™ Continuous Tableting Line, 2016).

Nevertheless, only limited fundamental physical understanding has been gained about the granule formation mechanisms and

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http://dx.doi.org/10.1016/j.ijpharm.2017.07.045
0378-5173/

kinetics along the internal length of a twin-screw granulator (TSG) barrel and about how process settings, barrel screw configuration and formulation properties influence these mechanisms and the resulting granule critical quality attributes (CQAs).

Previous studies have mainly focused on the cause-effect relationships between factors (process settings (Vercruysse et al., 2012; Fonteyne et al., 2013) and formulation properties (Dhenge et al., 2013)) and granule properties (responses) at the outlet of the TSG. Although these studies provide relevant information, limited knowledge is gathered about the effect of these factors on the mechanisms of granule formation in the TSG, leaving it as a "black box". Thus, the contribution to fundamental twin-screw granulation understanding is rather limited. A few studies (Vercruysse et al., 2015; Djuric and Peter, 2008; Thompon and Sun, 2010) made a first step towards describing the underlying granulation physics by investigating the impact of the different screw elements on the twin-screw granulation process and the resulting granule properties.

Dhenge et al. (Dhenge et al., 2011) and El Hagrasy et al. (El Hagrasy et al., 2013) further attempted to understand and describe the steps involved in granule formation in the TSG by varying process settings and formulation properties. However, experimental data was only collected at the TSG barrel outlet. For a more mechanistic understanding of the TSG process, local information should be gathered, since the individual physical phenomena occur spatially along the internal length axis of the TSG barrel, where the individual granulator barrel compartments (i.e., the wetting and different conveying and kneading compartments) have individual distinct contributions to the granule formation and resulting granule properties. One approach was introduced by Kai et al. (Lee et al., 2012) where flow and mixing of single particles throughout the different compartments within the TSG barrel was tracked using radioactive particle tracking (PEPT). Since only a single tracer particle was monitored during the twin-screw granulation process, local quantitative information is still lacking which can provide in-depth knowledge about the underlying granulation mechanisms occurring in the different compartments along the length of the granulator.

Here, the application of mechanistic population balance models (PBM) can help in filling knowledge gaps by thoroughly investigating gathered detailed experimental data and unravelling the underlying mechanisms involved. However, in order to successfully model the complete TSG system at meso- or macro-scale, the underlying granulation physics at micro- or particle level occurring within the different compartments of the TSG barrel should be well-understood (Kumar et al., 2013). This implies that in-process measurements providing local quantitative information are crucial to capture the modular structure of the TSG process in the PBM. However, in the current state-of-the-art modelling approach, TSG models are generally accomplished under default or best guess parameter values using no (Barrasso et al., 2013) or limited experimental data, exclusively collected at the outlet of the TSG (Barrasso et al., 2015; Paavola et al., 2013).

This is mainly due to the difficulty collecting local data at the intermediate compartments of the TSG barrel needed to develop and calibrate the TSG model, leading to a minimal understanding of the behavior of the processed material along the internal length axis of the TSG. This results in improperly developed, calibrated and validated models, unable to accurately predict the effect of any change in process conditions on resultant granule properties. In other words, these models have a very limited predictive power, severely limiting their applicability for decision making.

The purpose of this study was to analyze twin-screw wet granulation for both hydrophilic and hydrophobic formulations, manufactured under different process settings such as liquid-to-solid ratio, mass throughput and screw speed, in such a way that the impact of the individual granulator barrel compartments (i.e., the wetting and different conveying and kneading compartments) upon granule formation can be linked and understood. Therefore, a unique experimental setup was developed allowing granule property data-collection such as size, shape, liquid and porosity distribution at the different compartments along the internal length of the granulator barrel.

2. Materials and methods

2.1. Materials

Both a hydrophobic model drug and hydrophilic placebo formulation were investigated. For the hydrophobic formulation, a poorly water soluble API (60% w/w), i.e. hydrochlorothiazide (UTAG, Almere, Netherlands) was blended using a 20 L Inversina tumbling mixer blender (Bioengineering AG, Wald, Switzerland), with 16% (w/w) lactose monohydrate (Lactochem® Regular, DFE Pharma, Goch, Germany), 16% (w/w) microcrystalline cellulose (Avicel® PH 101, FMC, Philadelphia, USA), 3% (w/w) hydroxypropylcellulose (Klucel® EXF, Ashland, Covington, Kentucky, USA) and 5% (w/w) crosscarmellose sodium (Ac-Di-Sol®, FMC, Philadelphia, USA).

The hydrophilic model formulation consisted of 97.5% (w/w) lactose monohydrate (Lactochem® Regular, DFE Pharma, Goch, Germany) and 2.5% (w/w) polyvinylpyrrolidone (Kollidon®30, BASF, Ludwigshafen, Germany) in a dry premix. All formulations were processed using demineralized water containing 0.5% (w/w) Congo Red (Sigma-Aldrich, Darmstadt, Germany) as a granulation liquid. It should be noted that Congo Red does not have surface active properties and will not affect the granulation mechanisms.

2.2. Methods

2.2.1. Twin screw wet granulation

Granules were produced using the high shear twin-screw wet granulation module of the ConsiGma™-25 system (GEA Pharma systems, Collette, Wommelgem, Belgium). This continuous granulator consists of two 25 mm diameter co-rotating screws with a length-to-diameter ratio of 20:1. The powder premix enters the granulator barrel using a gravimetric twin-screw loss-in-weight feeder (KT20, K-Tron Soder, Niederlenz, Switzerland). In a next step, the powder premix is moved forward using conveying elements. In this conveying compartment, prior to the first kneading compartment, granulation liquid is gravimetrically dosed into the screw chamber using two peristaltic pumps (Watson Marlow, Cornwall, UK) out of phase and silicon tubing (internal and external diameter of 1.6 and 4.8 mm, respectively) connected to 1.6 mm nozzles. The addition of granulation liquid takes place by injecting the liquid through two liquid feed ports,

Table 1
Overview of granulation process settings for the two studied formulations.

Formulation	Mass flow rate (Kg/h)	Screw speed (rpm)	L/S ratio
Hydrophilic formulation	15–20–25	450–675–900	0.040–0.068–0.096
Hydrophobic formulation	5–12.5–25		0.300–0.450–0.600