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Investigation of an 11 mm diameter twin screw granulator: Screw element performance and in-line monitoring via image analysis

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ABSTRACT

As twin screw granulation (TSG) provides one with many screw element options, characterization of each screw element is crucial in optimizing the screw configuration in order to obtain desired granule attributes. In this study, the performance of two different screw elements – distributive feed screws and kneading elements – was studied in an 11 mm TSG at different liquid-to-solid (L/S) ratios. The kneading element configuration was found to break large granules more efficiently, leading to narrower granule size distributions. While pharmaceutical industry shifts toward continuous manufacturing, inline monitoring and process control are gaining importance. Granules from an 11 mm TSG were analysed using the Eyecon^{TM}, a real-time high speed direct imaging system, which has been used to capture accurate particle size distribution and particle count. The size parameters and particle count were then assessed in terms of their ability to be a suitable control measure using the Shewhart control charts. d_{10} and particle count were found to be good indicators of the change in L/S ratio. However, d_{50} and d_{90} did not reflect the change, due to their inherent variability even when the process is at steady state.

1. Introduction

Nowadays, there is an imminent necessity for the pharmaceutical industry to deliver pharmaceutical products that comply with the highest quality standards. Regulatory authorities such as the US Food and Drug Administration (FDA) agency and the European Medicines Agency (EMA) are focusing their efforts toward the implementation of the new ICH Q10 “Pharmaceutical Quality System” guidelines that enable industrial manufacturers to put in place better controlled development and manufacturing practices (ICH Q10, 2008). One of the current challenges requires that pharmaceutical industries fully understand the relation between the manufacturing processing parameters or process performance and the critical quality attributes (CQA) of the final product. Therefore, the introduction of process analytical technologies (PAT) for continuous in-line monitoring of manufacturing processes is crucial to assure product quality throughout all the manufacturing stages. In this context, the interest toward the development of continuous manufacturing platforms for the production of pharmaceuticals has increasingly emerged.

One of the main areas that can be applied within a continuous manufacturing environment comprises the initial stages of development and production of pharmaceuticals, where twin-screw granulation (TSG) is being applied as an alternative to traditional batch manufacturing processes. TSG provides flexibility during manufacturing of commercial products as well as time and economic cost reduction that are currently important issues in the pharmaceutical arena. Moreover, the capability offered by TSG processes where it is possible to optimize the processing parameters to achieve high quality attributes of the end product is still being studied and this is where the application of in-line characterisation techniques plays a key role. Recently, Seem et al. (2015) reviewed literature related to twin screw granulation, where they emphasized the need for further process

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understanding and optimization. Screw element configuration is of crucial importance in determining the resulting granule attributes from a twin screw granulator (Djuric and Kleinebudde, 2008; Thompson and Sun, 2009) and its effects on resulting granule properties were extensively studied in literature using conveying elements (CE) (Thompson and Sun, 2009; Dhenge et al., 2013), kneading elements (KE) (Thompson and Sun, 2009; Mu and Thompson, 2012; El Hagrasy and Litster, 2013; Lee et al., 2012; Van Melkebeke et al., 2008; Vercruysse et al., 2012, 2014, 2015; Kumar et al., 2014), distributive mixing elements (DME) (Thompson and Sun, 2009; Sayin et al., 2015; Vercruysse et al., 2015), distributive feed screw (DFS) (Vercruysse et al., 2015), and cutters (Vercruysse et al., 2015). The first attempt to elucidate the effect of screw configuration on granule and tablet properties was made by Djuric and Kleinebudde (2008), using a Leistritz Micro 27GL/28D. In their study, Djuric and Kleinebudde (2008) studied CE, KE, and DFS under the name of combing mixer elements. DFS was found to produce higher yield (granules in the range: 125–1250 μm) when compared to the same pitch CE, as well as less lumps (granules larger than 1250 μm). KE configurations with 30° reverse and 90° (neutral) advance angles gave the least porous granules among the screw configurations studied. Thompson and Sun (2009) studied distributive mixing elements (DME) in addition to CEs and the kneading blocks using an American Leistritz (Model ZSE-27HP) twin screw extruder with no die. They suggest that intermeshing region of KEs is the key region in granule formation and the advance angle is of minor importance. Shah (2005) used 34 and 50 mm twin screw extruders with no die to study CE, KE, and DFS under the name of chopper element. Further studies on the effect of screw configuration include use of a 16 mm Thermo Fisher twin-screw granulator to produce and characterize granule attributes by the inclusion of different screw elements such as conveying elements, kneading elements and distributive mixing elements (El Hagrasy and Litster, 2013; Sayin et al., 2015). Recently, an 11 mm TSG has become available, and there are advantages for early stages of new product development due to the smaller amount of formulation that is required compared to 16 or 24 mm TSGs. However, there are no reported studies on the use of the 11 mm TSG and its performance as a granulator has not been assessed. In particular, the 11 mm TSG offers a new screw element design, the distributive feed screw, whose performance has not been evaluated using a Thermo Fisher twin screw granulator.

Various PAT techniques for in-line measurement of continuous wet granulation processes have recently been studied. Soppela et al. (2011) compared the application of a 3D-imaging technique (FS3D) and a spatial filtering technique (SFT or also called Parsum) identifying good correlation values in the characterization of granule particle size distribution and flowability properties. Further investigations regarding solid state transformations during continuous twin-screw wet granulation have been studied using Raman and near-infrared (NIR) spectroscopy (Fonteyne et al., 2013). Moreover, Kumar et al., (2014) applied a near infrared chemical imaging system within residence time distribution (RTD) studies in a continuous TSG process, showing that variations in screw speed, material throughput, screw configuration, number and geometry of kneading elements have an impact on granule RTD and axial mixing degree achieved. Similar RTD studies on a TSG were performed by Lee et al., (2012) applying Positron Emission Particle Tracking (PEPT) technique where barrel design modifications were required. Moreover, previous granule characterisation studies performed by El Hagrasy and Litster (2013) showed a relation between the granulation rate processes involved in granule growth such as breakage or layering with granule shape by applying different screw configurations, kneading element advance angles and angle direction. Introduction of a high-speed imaging camera, such as the Eyecon™ particle characterizer was reported (El Hagrasy et al., 2013) as a successful non-contact technique for in-line characterisation of TSG processes. Assessment of granule particle size distribution as well as granule shape enabled evaluation of granule growth based on parameter changes with variations in liquid to solid (L/S) ratios (El Hagrasy et al., 2013).

This study aims at characterizing the distributive feed screw and assessing capability of a high-speed imaging technique for the in-line control of granule size parameters produced by an 11 mm TSG. Particle attributes such as particle size and liquid distributions are presented from offline analyses. The measurement of particle attributes using an in-line method provides a better understanding of real-time product characteristics providing a design of space network for continuous manufacturing applications. The TSG process comprising a distributive feed screw (DFS) as main granulation element is introduced and characterised in a Thermo Fisher twin screw granulator for the first time. In-line characterization of granule size parameters are obtained using a high-speed imaging camera attached to a Thermo Scientific® Process 11 twin-screw granulator. Offline particle size and liquid distributions obtained using DFS are also compared to values achieved using a kneading element (KE) configuration comprised of 7 kneading elements with 90-degree advance angle. Further analytical procedures included data processing and elaboration of Shewhart control charts to evaluate the applicability of particle size parameters such as d_{10}, d_{50}, d_{90} and particle count to monitor the influence of small process variations in L/S ratio values.

2. Materials and methods

2.1. Granulation experiments

In this study, a placebo formulation composed of α-lactose monohydrate (Pharmatose 200 M, 73.5%), microcrystalline cellulose (Avicel PH101, 20%), hydroxypropylmethyl cellulose (Hypromellose, 5%) and croscarmellose sodium (Ac-Di-Sol, 1.5%) was used. These dry ingredients were pre-mixed using a Turbula® T2F mixer (Glen Mills Inc., New Jersey, United States) in batches of 500 g of blend for 20 min. A volumetric feeder (DDSR20, Brabender Technologie GmbH, Duisburg, Germany) was used to feed the

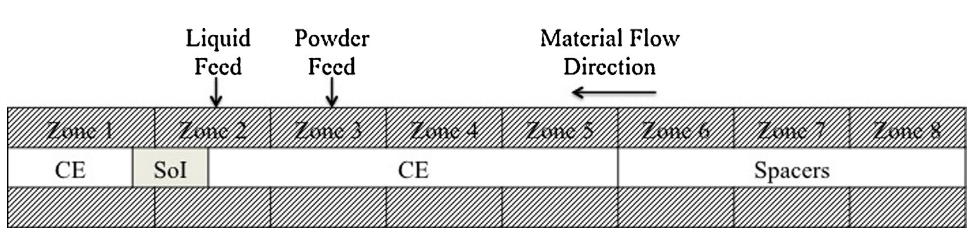

Fig. 1. Schematic of the screw configurations used.