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Distributive mixing elements: Towards improved granule attributes from a twin screw granulation process

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HIGHLIGHTS

- Twin screw wet granulation experiments using distributive mixing elements (DME).
- Different configurations (forward, reverse, adjacent, and spaced) of DME were used.
- Granule attributes, residence time and flow visualization were characterized.
- Reverse configurations gave mono-modal size distribution, better liquid distribution.
- Breakage and layering were dominant granulation rate processes in the DME section.

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ABSTRACT

Granulation rate processes were studied in the distributive mixing elements (DME[1]) of a twin screw granulator through characterization of resulting granule attributes. The screw configuration was varied by changing the orientation (forward *versus* reverse) and the placement of the elements (adjacent *versus* spaced). A model placebo formulation composed of α-lactose monohydrate, microcrystalline cellulose, hydroxypropylmethyl cellulose and croscarmellose sodium, and an aqueous granulating liquid were used in the study. Regardless of the screw configuration, DME generated granules through breakage of large wet agglomerates from the conveying section and layering of un-granulated fines. The reverse orientation produced superior granule size distribution with improved liquid distribution attributes compared to the forward orientation. The residence time distribution and flow visualization measured by a high speed imaging camera provided the mechanistic rationale for the superior behavior of the reverse over the forward DME configurations and showed the dominant granulation rate processes therein. The asymmetrical orientation of DME on the rotating shafts significantly improved the breakage capability of the reverse-placed elements, allowing a more homogeneous flow pattern of incoming granular material, with efficient layering and liquid exchange between the lumps and un-granulated fines. The results of this study demonstrate the benefit of using DME in a twin-screw wet granulation process to optimize granule attributes for downstream processing.

1. Introduction

Traditionally, high shear granulation and fluidized beds are used for wet granulation in the pharmaceutical industry but operated in batch mode. However, a twin-screw granulator (TSG) is the preferred equipment for continuous wet granulation in the pharmaceutical industry owing to its flexible design, optimum throughput, robustness toward variation in raw material attributes, process stability, and consistent product quality throughout the production time (El Hagrasy et al., 2012; Vercruysse et al., 2013). The twin screw granulator produces higher porosity granules than a high shear mixer and has a much shorter residence

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[1] DME: Distributive mixing elements CE: Conveying elements DMEAF: Distributive mixing elements, adjacent forward configuration DMESF: Distributive mixing elements, spaced forward configuration DMEAR: Distributive mixing elements, adjacent reverse configuration DMESR: Distributive mixing elements, spaced reverse configuration GSD: Granule size distribution KE: Kneading elements LD: Liquid distribution L/S ratio: Liquid to solid ratio RTD: Residence time distribution VAR: Vertical aspect ratio TSG: Twin screw granulator.

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time than a fluid bed granulator. A TSG has multiple operational variables such as those related to powder and liquid feeding into the equipment. The flexible equipment design introduces additional manipulated variables, including screw configuration, screw speed, and shaft length. Earlier research work has demonstrated that screw configuration has a strong impact on granule attributes (Dhenge et al., 2012; Djuric and Kleinebudde, 2008, 2010; El Hagrasy and Litster, 2013; Thompson and Sun, 2010).

The default screw configuration in most published work in the area of twin screw granulation consists of conveying and kneading elements (El Hagrasy et al., 2012; Vercruysse et al., 2013; Djuric and Kleinebudde, 2008, 2010; Dhenge et al., 2010; Djuric et al., 2009; Keleb et al., 2004; Melkebeke et al., 2008). The underlying premise of using these particular elements is adopted from extrusion technology (Thiele, 2003). The conveying elements are characterized by their excellent axial displacement properties that assist in transporting the fed powder and liquid material into the kneading section. The kneading elements provide a shear-intensive zone that allows granule formation by intimate mixing of liquid and powder. However, the granules obtained are characterized by a broad bimodal size distribution, with the presence of lumps and un-granulated fines (El Hagrasy et al., 2012; Djuric and Kleinebudde, 2008, 2010; El Hagrasy and Litster, 2013; Dhenge et al., 2010, 2012; Djuric et al., 2009; Melkebeke et al., 2008). A broad size distribution is undesirable in a wet granulation process due to potential issues with drying uniformity and powder segregation. Hence, a more quantitative understanding of the mechanisms occurring in each screw element type is necessary to improve the efficiency and control of granulation processes and develop a systematic design approach (El Hagrasy and Litster, 2013; Thompson and Sun, 2010; Faure et al., 2001).

Recently, granulation rate processes occurring in the conveying and kneading sections of the TSG have been investigated by El Hagrasy and Litster (2013). The researchers characterized the size distribution, liquid distribution, and shape of granules obtained from a series of experiments, in which the length of the kneading section, the advance angle and the angle direction were varied. Two main rate processes were observed: (1) breakage and layering, (2) shear elongation and layering. The multi-dimensional quantitative granule characterization data demonstrated that the poor liquid distribution obtained from dripping the granulating liquid into the conveying section dominated the granule attributes and produced a bimodal broad granule size distribution (GSD) even after passing the kneading section. Improved liquid distribution was only seen with the 30° angle in the reverse direction, albeit at the expense of other critical granule attributes such as shape and porosity. Alternative screw element designs, with improved granulation efficiency, would enhance the potential of integrating this equipment in a continuous pharmaceutical manufacturing line.

Distributive mixing elements (DME), also known as comb-mixing elements, have been previously studied, although their use is less common than kneading elements (Djuric and Kleinebudde, 2008, 2010; Thompson and Sun, 2010; Thiele, 2003). In contrast to dispersive mixing characteristic of kneading elements, DME rely on distributive mixing through cutting and recombination to allow collision between in-flowing granular material. In addition, DME do not exhibit the self-wiping feature displayed by kneading and conveying elements. However, there is little fundamental understanding about granulation mechanisms taking place in this type of screw elements. The purpose of this work is to characterize the distributive mixing elements by investigating the effect of orientation (forward *versus* reverse) and placement (adjacent *versus* spaced) of DME on granule attributes using a similar approach to that adopted with conveying and kneading elements (El Hagrasy and Litster, 2013). The results of granule size, shape, porosity, and liquid distribution characterization from the different DME configurations are presented. The unique attributes of granules obtained from distributive mixing elements in comparison with the kneading elements are highlighted. The mechanistic approach undertaken in this work provides insight into future optimization of the twin screw granulation process.

2. Methodology

2.1. Granulation experiments

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%) is used in this study. All dry ingredients were premixed in a 10 L batch high shear mixer for 5 min. The pre-mixed formulation is then fed into a EuroLab 16 mm TSG, 25:1 L:D (Thermo Fisher Scientific, Karlsruhe, Germany) at a screw speed of 400 rpm and feed rate of 4 kg/h using a gravimetric feeder (Brabender Flexwall® Feeder, Brabender-Technologie, Germany). The granulating liquid is composed of 0.1% (w/w) aqueous solution of nigrosin. A Masterflex® peristaltic pump is used for feeding the granulating liquid at different rates to achieve liquid to solid (L/S) ratios in the range 0.15 to 0.35 at 0.05 increments.

2.2. DME screw configurations

Fig. 1 depicts the design of the distributive mixing screw element characterized in this work. Each element consists of angularly-cut blades that are perpendicular to an annulus portion as seen in Fig. 1A. The annulus portion extends beyond the blades as shown in the side view in Fig. 1B. Thus, the DME are nearly symmetrical from the front view but exhibit asymmetry from the side view because of the spacer extension seen in Fig. 1B. As a result, distributive mixing elements can be mounted on the rotating shafts in a twin screw granulator either with the spacer portion facing the upstream screw elements or the downstream screw elements. In this work, the forward (F) configuration is used to indicate the spacer on the leading screw in the top shaft facing upstream of the DME, while the reverse (R) configuration indicates the spacer on the leading screw facing downstream as seen in Fig. 2. The distributive mixing elements can also be placed adjacent (A) to each other or spaced (S), with conveying elements in between.

In this study, three pairs of distributive mixing elements are used in four different configurations as shown in Fig. 2A–D. The DME are mounted in an adjacent (A) or spaced (S) configuration in the forward (F) or the reverse (R) direction. In the (S) configuration,

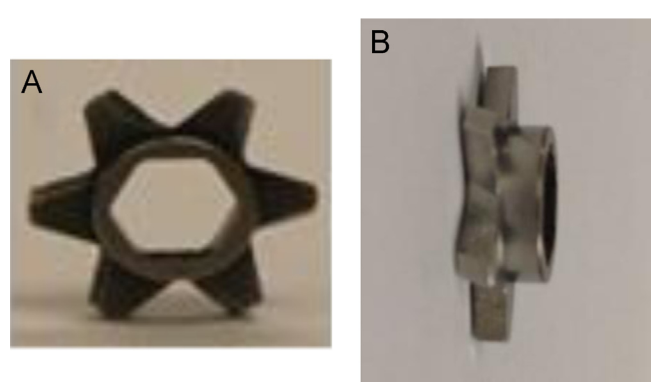

Fig. 1. Front view (A) and side view (B) of a distributive mixing element.