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Conceptual framework for model-based analysis of residence time distribution in twin-screw granulation

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ABSTRACT

Twin-screw granulation is a promising continuous alternative for traditional batchwise wet granulation processes. The twin-screw granulator (TSG) screws consist of transport and kneading element modules. Therefore, the granulation to a large extent is governed by the residence time distribution within each module where different granulation rate processes dominate over others. Currently, experimental data is used to determine the residence time distributions. In this study, a conceptual model based on classical chemical engineering methods is proposed to better understand and simulate the residence time distribution in a TSG. The experimental data were compared with the proposed most suitable conceptual model to estimate the parameters of the model and to analyse and predict the effects of changes in number of kneading discs and their stagger angle, screw speed and powder feed rate on residence time. The study established that the kneading block in the screw configuration acts as a plug-flow zone inside the granulator. Furthermore, it was found that a balance between the throughput force and conveying rate is required to obtain a good axial mixing inside the twin-screw granulator. Although the granulation behaviour is different for other excipients, the experimental data collection and modelling methods applied in this study are generic and can be adapted to other excipients.

1. Introduction

Traditionally, granulation is performed in batch mode. However, a supportive regulatory environment and process economics are driving the switch towards continuous manufacturing. In this context, twin-screw granulation is emerging as a potential continuous granulation technique. In a twin-screw granulator (TSG) featuring short residence times, mixing of powder and liquid phase and particle enlargement is achieved by the modular/interchangeable configuration of the screw design. The granule size distribution (GSD) is governed by the complex relationship between principal rate processes such as wetting, nucleation, agglomeration, breakage and consolidation (Dhenge et al., 2012; Kumar et al., 2014a), each of which can dominate over others based on the local environment within each module such as degree of mixing and free surface liquid for further granulation. Mixing in these modules of the TSG results from kinematic processes described in terms of displacement (caused by incoming flow) and drag (direct parameters from vectorised fields) flows. The ratio of these flows is related to the screw configuration and the operating conditions of the TSG resulting into different filling degrees and residence time distributions (RTDs).

Changes in screw geometry and operating parameters influence both the mean residence time ($\bar{t}$) and the width of the RTD given by the mean centered variance ($\sigma^2_{t_m}$) (Kumar et al., 2014b). While the radial mixing by the kneading blocks inside the TSG is related to

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Nomenclature

γ	collinearity index	R^2	coefficient of determination
σ^2_{tm}	variance	RSS	residual sum of the square
d	dead flow fraction	TIS	tanks-in-series
e(θ)	normalised residence time	RTD	residence time distribution
n	number of well mixed tank	TSG	twin-screw granulation
p	plug-flow fraction	$\bar{S}$	normalised sensitivity matrix
$\bar{t}$	mean residence time		
t_{min}	minimum residence time		

the ($\bar{t}$), the longitudinal or axial mixing performance is determined by the ($\sigma^2_{t_m}$). Narrow RTDs lead to a uniform product and are generally considered to be favourable. However, axial mixing in addition to the radial mixing is equally required in the TSG to avoid the effect of any inhomogeneities (such as the ones caused by non-optimal performance of the pre-blender and periodicity of the feeders and pumps) at the inlet on the produced granules (Kumar et al., 2014b).

Due to the difficulties to visualise the material flow in the barrel, little efforts have been made thus far towards understanding the RTD and mixing of material inside the TSG barrel. Dhenge et al. (2010) measured the RTD using the impulse-response technique under different processing conditions and showed that the variation in the RTD depends on formulation and process parameters. El Hagrasy et al. (2013) applied the same RTD measurement approach to estimate the response to changes in formulation properties such as raw material attributes as well as granulation liquid properties on granule properties. In a recent attempt, Lee et al. (2012) obtained the RTD using positron emission particle tracking (PEPT) and concluded that the extent of axial mixing was the same for different screw geometries. Although PEPT is a very powerful measurement technique, such a conclusion can also arise due to the inability of the circulated PEPT tracers to provide information on the total flow behaviour as some material paths occur rarely, and are hence not followed by the finite number of tracer paths through the equipment. Therefore, only distributions of passage time rather than a true RTD can be measured using PEPT (Bakalis et al., 2004). Kumar et al. (2014b) applied near infrared chemical imaging (NIR-CI) to measure the RTD to conclude that the extent of axial mixing is significantly influenced by the screw configuration and barrel filling degree. The adequateness of the NIR-CI as an analytical tool for the visualization of the process in a TSG requiring fast measurements was established in an earlier study by Vercruysse et al. (2013). In this study on granulation liquid mixing and distribution along with the residence time analysis in TSG it was concluded that the liquid distribution improved only by increasing the granulation liquid content at the granulator inlet.

As for experimental process visualisation, the efforts toward predictive modelling of the RTD in TSG are sparse compared to other fields employing extrusion based systems, such as the food and polymer industries (Gao et al., 2012). This is mainly due to the difficulties in defining the intrinsic physico-chemical properties of the formulation mixture in the opaque and high-shear process environment of the TSG (Kumar et al., 2013a). Therefore, local mass balances are complex to be solved, hence requiring drastically simplified hypotheses. Kumar et al. (2013b) presented a one-dimensional transport model based on screw geometry and material characteristics. However, conceptual flow modelling is another approach, in which the transport process is modelled as a combination of ideal reactors, the plug-flow reactor (PFR) having no axial mixing and the constantly stirred tank reactors (n) having perfect axial mixing. Originally derived for chemical reactors, different types of single and multi-stage models and their applications have been widely discussed in the literature (Levenspiel, 1999; Puaux et al., 2000; Fogler, 2006; Kumar et al., 2008). For a non-ideal flow system like the TSG, the conceptual model used for RTD modelling generally consists of combinations of plug-flow volume fraction (p), a finite number of n with stagnant pockets or dead zones (d) to closely represent the flow pattern. This approach was also adopted by Lee (2013) to explain the experimental RTDs obtained from PEPT measurements in a continuous TSG.

However, to our best knowledge, a systematic evaluation of the performances of different conceptual models for their ability to describe flow and transport in a TSG for a broad spectrum of process conditions is still not available. Therefore, the objective of this study was to compare some of the existing conceptual models based on goodness-of-fit between the calibrated model and the experimental data, in order to identify the most suitable model configuration for describing the RTD in a TSG. Furthermore, the effect of input variables, screw configuration (number and stagger angle of kneading discs) and fill ratio (governed by screw speed and powder feed rate), was analysed by simulating the calibrated model.

2. System analysis and model formulation

2.1. Continuous wet-granulation using TSG

The TSG consists of a barrel enclosing two co-rotating self-wiping screws. At the entrance, raw materials are fed into the transport zone and the granulation liquid is added via two nozzles, one for each screw, before the material reaches the mixing zone which consists of kneading discs (Fig. 1). The modular structure of the screws allows changing the number of kneading discs, hence the length of the mixing zone. The powder is hence wetted by the granulation liquid in this region. Further down, since the granulation occurs by a combination of capillary and viscous forces binding particles in the wet state, the wetted material is distributed, compacted and elongated by the kneading discs of the mixing zones, changing the particle morphology from small (microstructure) to large (macrostructure). It is believed that the material is mixed, compacted and chopped to form irregular and porous granules by the succeeding transport elements and kneading blocks (Vercruysse et al., 2012). The rotation of the screws conveys the material in axial direction through the different zones of the TSG by the drag and flow-induced displacement forces and thus causing mixing and granulation. The rheological behaviour of the material also changes based on liquid-to-solid ratio (L/S) (Althaus and Windhab, 2012).

2.2. Experimental determination of RTD

The RTD experimental data for the twin-screw granulation were obtained using a 25 mm diameter co-rotating twin screw granulator, which is the granulation module of the ConsiGma-25 unit (GEA Pharma Systems, Collette™, Wommelgem, Belgium). The granulator screw has a length-to-diameter ratio of 20:1. The barrel jacket was preheated to 25 °C. During processing, pure α-lactose monohydrate was gravimetrically fed into the granulator by using