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Research Paper

Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging

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ABSTRACT

Twin-screw granulation is a promising continuous alternative for traditional batch high shear wet granulation (HSWG). The extent of HSWG in a twin screw granulator (TSG) is greatly governed by the residence time of the granulation materials in the TSG and degree of mixing. In order to determine the residence time distribution (RTD) and mixing in TSG, mostly visual observation and particle tracking methods are used, which are either inaccurate and difficult for short RTD, or provide an RTD only for a finite number of preferential tracer paths. In this study, near infrared chemical imaging, which is more accurate and provides a complete RTD, was used. The impact of changes in material throughput (10–17 kg/h), screw speed (500–900 rpm), number of kneading discs (2–12) and stagger angle (30–90°) on the RTD and axial mixing of the material was characterised. The experimental RTD curves were used to calculate the mean residence time, mean centred variance and the Péclet number to determine the axial mixing and predominance of convective over dispersive transport. The results showed that screw speed is the most influential parameter in terms of RTD and axial mixing in the TSG and established a significant interaction between screw design parameters (number and stagger angle of kneading discs) and the process parameters (material throughput and number of kneading discs). The results of the study will allow the development and validation of a transport model capable of predicting the RTD and macro-mixing in the TSG. These can later be coupled with a population balance model in order to predict granulation yields in a TSG more accurately.

1. Introduction

In the pharmaceutical industry, the main purpose of granulation is to enlarge particles to improve flowability for better downstream processing, while reducing the variability in the formulation mixture. Twin-screw granulation, which is seen as a promising continuous alternative for traditional batch (HSWG), allows a relatively high material throughput with a short residence time (typically few seconds) [1]. In a (TSG), besides homogeneous distribution of granulation material, the aim is also to achieve mixing within the shortest screw lengths and at minimum required power input. This is important to govern the extent of different rate processes such as wetting, growth and breakage, which ultimately determine the characteristics of the produced granules. It is evident from several studies that the (t_m) in a TSG (which is few seconds) is much shorter compared to the granulation time in a typical batch granulator, which is in the order of minutes. Although from a productivity point of view, this time gain is preferred, its implications on the granulation rate processes needs to be examined [2]. The mixing inside the granulator is related to the functional role of the screw configuration as well as process parameters. Feeding rates of the

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Nomenclature

σ_θ^2	normalised variance	Pe	Péclet number
$\sigma_{t_m}^2$	mean centered variance	PEPT	positron emission particle tracking
t_m	mean residence time	PFR	plug-flow reactor
API	active pharmaceutical ingredient	PLS	partial least squares
GSD	granule size distribution	PLS-DA	partial least squares discriminant analysis
HSWG	high shear wet granulation	RTD	residence time distribution
NIR	near infra-red	SNV	standard normal variate
PBE	population balance equation	TSG	twin-screw granulator

granulation material, the screw speed and the screw configuration can be independently chosen to yield desired mixing levels of the material.

In the high-shear environment of TSG, a good axial mixing in addition to the radial mixing during granulation in TSG is required to avoid the effect of any inhomogeneities at the inlet on the produced granules. A mixing region in a TSG screw contains blocks of several kneading discs with grooved flights, which cause a broadening of the residence time distribution (RTD). A broad RTD indicates good axial mixing in a TSG, and hence has a favourable effect on product quality by avoiding inhomogeneities in the final product. The RTD of the material is determined by the bulk flow profiles in the screw channels, generation of partial flows in flow-restrictive zones (e.g., in kneading blocks), and reverse flow in the gaps at the flight tips and in the inter-meshing zone as well as in mixing zones (Fig. 1). However, this leads to another optimisation challenge regarding the most-suitable screw configuration.

In recent years, pharmaceutical continuous twin screw granulation has received increased attention and several researchers have investigated various aspects including the effect of key formulation variables [2–5] and screw configurations [6–8]. Similar to the regime map approach applied in batch wet granulation, an effort has been made to implement the regime map in TSG to predict a priori the response of the change in the process parameters on the granule size distribution (GSD) characteristics [9]. The population balance equation (PBE) is a mathematical framework typically used for model-based analysis and to improve understanding of the HSWG process [10]. A better description of the flow properties within the granulator is required for an advanced PBE framework towards understanding the effects of the control variables in the TSG during granulation and track or predict the characteristics of the GSD produced as a function of space and time. Besides, the RTD exhibited by a given system yields distinctive clues regarding the type of axial mixing occurring within the system and is one of the most informative characterisation methods of the system [11].

Dhenge et al. [12] measured the RTD using the impulse-response technique under different processing conditions and showed the variation in the RTD depending on formulation and process parameters. El Hagrasey et al. [2] applied the same RTD measurement approach to estimate the response to changes in formulation properties such as raw material attributes as well as granulating liquid properties on granule properties. However, due to the difficulty to visualise the material flow in the barrel, little efforts have been made towards understanding the mixing of the material inside the TSG barrel, which is essential for the optimisation of the obtained granule properties. In a recent attempt, Lee et al. [13] obtained the RTD using positron emission particle tracking (PEPT) to study the axial mixing. Although this is a very powerful technique, this approach requires several manipulations in the equipment and the process (e.g. thinner TSG barrel wall to make sure that the gamma rays can penetrate the construction material, but it limits the shear handling capability of the barrel). Therefore, it would be beneficial to have a measurement method allowing RTD measurements without the need of manipulation of the equipment. Also, the PEPT involves single particle tracking, which is limited by the number of tracer passes to study the complete RTD adding operational variability to the RTD study. The circulated tracers in the PEPT study may not provide information on the total flow behaviour as some material paths are so rare that they will not be followed by the finite number of tracer paths through the equipment. Therefore, only distributions of passage time rather than true RTD can be measured using the PEPT [14]. Vercruysse et al. applied near infra-red (NIR) chemical imaging to evaluate the influence of the liquid addition method, screw configuration, moisture content and barrel filling degree on the moisture homogeneity during TSG [15].

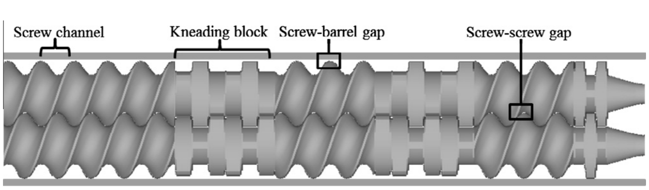

Fig. 1. Screw configuration with 12 kneading discs (2 blocks) used in the twin screw granulator during the study.

In this study, a novel sample preparation and an image data collection method based on NIR chemical imaging has been used as an analytical technique to characterise the flow and axial mixing of material in the TSG qualitatively and quantitatively. The study presented here examines the axial mixing inside a continuous TSG based on the characteristic RTD of the tracer component. NIR chemical imaging was used to investigate the residence time of tracer inside the barrel and its distribution as a function of process (screw speed and material throughput) and equipment parameters (number and stagger angle of kneading discs in screw configuration).

2. Materials and methods

2.1. Pharmaceutical formulation

α-Lactose monohydrate (Pharmatose 200M, Caldic, Hemiksem, Belgium) was used as a model excipient. Distilled water was added as granulation liquid. To evaluate the residence time of material inside the barrel, theophylline anhydrate (Farma-Química Sur, Malaga, Spain) was used as tracer component.

2.2. Continuous twin screw granulation

Granulation experiments were performed using a 25 mm diameter co-rotating twin screw granulator, which is the granulation module of the ConsiGma-25 unit (GEA Pharma Systems, Collette™,