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.

Keywords: Residence time distribution, flow modelling, axial mixing, stagnant zone, wet granulation

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 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

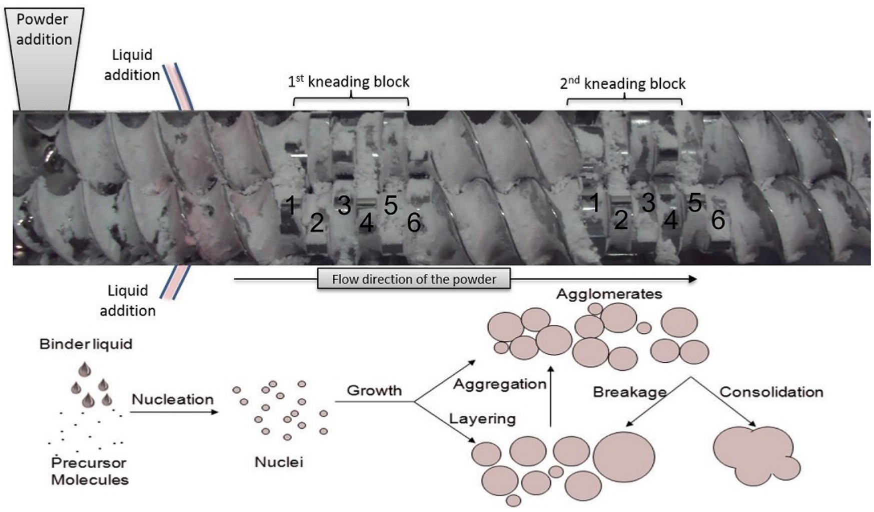

Figure 1: Screw configuration with 12 kneading discs (2 blocks containing 6 kneading discs each) indicating the geometry and flow of material inside the TSG barrel.

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 a twin-screw feeder (KT20, K-Tron Soder, Niederlenz, Switzerland). The granulation liquid was added (11.5% w/w) before the first kneading element by dripping through two liquid feed ports (Fig. 1). Each port was located on the central top of each screw in the barrel. Experimental RTDs were obtained by spiking anhydrous theophylline (2% (w/w) of the actual throughput (g/min)) into the powder inlet port of the granulator. The TSG has an inbuilt torque gauge and the criterion indicating steady state was decided based on the equilibration of the measured torque of the granulator. Spectral images of wet granules were collected using a line-scanning (pushbroom) hyperspectral camera (SWIR, Specim

Ltd., Oulu, Finland). The spatial distribution of theophylline was measured during the first 25 seconds following tracer addition using the spectral matched filter method. Details of the experimental set-up, procedure and DoE have been described earlier by Kumar et al. (2014b).

2.3. Estimation of RTD from experimental data

A RTD was derived by injecting a pulse of tracer into the system at the inlet, and the residence time function, $e(t)$, was calculated as

$$e(t) = \frac{c(t)}{\int_0^\infty c(t)dt} \tag{1}$$

where $c(t)dt$ is the concentration of the tracer at the outlet between time points t and $t+dt$.

This tracer map was then transformed into the exit age distribution curve, i.e. the RTD based on the mean tracer concentration, e(t) between t and $t + dt$, which was then used to calculate the mean residence time ($\bar{t}$) as the ratio of the first and the zeroth moment using equation

$$\bar{t} = \frac{\int_0^\infty t.e(t)dt}{\int_0^\infty e(t)dt} \tag{2}$$

The RTD shape and $\bar{t}$ thus obtained were used to obtain the normalised residence time as $e(\theta) = \bar{t}.e(t)$, where dimensionless time, $\theta = {}^{t}/_{\bar{t}}$.

2.4. Theoretical models for RTD in TSG

In the previous experimental studies, the RTDs obtained for TSG showed intermediate flow characteristics between the two ideal cases, the perfectly-mixed flow and the plug flow (Lee et al., 2012; Kumar et al., 2014b). Therefore, models for non-ideal flow have to be used to describe the material flow inside the TSG. Major considerations for the selection of a flow model are, the physical significance of the model and the number of adjustable parameters.

In order to have a physical significance, the model structure should be able to characterise the real process through its parameters. In this study, three model candidates were selected to simulate the RTD of the twin-screw granulator: the tanks-in-series (TIS) model without a plug-flow volume fraction, the TIS with a plug-flow volume fraction and the TIS including a plug-flow volume fraction and dead zones (Fig. 2). The TIS model without a plug-flow volume fraction is a one-parameter flow model expressed as (Levenspiel, 1999)

$$e(\theta) = \frac{n(n\theta)^{n-1}}{(n-1)!}\exp(\text{-}n\theta) \tag{3}$$

where, n is the constantly stirred tank reactors. The closer the n value to unity, the higher the degree of mixing, and vice-versa. The TIS model containing a plug-flow volume fraction as well is a three-parameter flow model given by (Levenspiel, 1999)

$$\begin{gathered} e(\theta) = \frac{b[b(\theta - p)]^{n-1}}{(n-1)!}\exp[-b(\theta - p)] \\ \text{where, } p = \frac{t_{min}}{\bar{t}} \text{ and, } b = \frac{n}{1-p} \end{gathered} \tag{4}$$

where, t_{min} is the minimum residence time and p is the fraction of the volume of the TSG that is assumed to correspond to the plug-flow volume fraction. For the TIS model with both plug-flow volume fraction and dead zones, which is a four-parameter flow model, the calculation of $e(\theta)$ and the p in eq. 4 remains the same, whereas the b is modified as (Kumar et al., 2008)

$$b = \frac{n}{(1-p)(1-d)} \tag{5}$$

where, d is the dead zone of continuously-stirred tank reactors indicating the fraction of material which is either excessively back-mixed or spend much longer time than $\bar{t}$ in the stagnant pockets that exist in the TSG. Normally, this material spends more than twice the $\bar{t}$, and the average velocity is much smaller compared to the well mixed region, leading to a long tail in the RTD. Hence, the four parameters that are present in these models are $\bar{t}$, n, p and d. tendency for

Regarding the number of adjustable parameters, the heuristic rule is to use the model

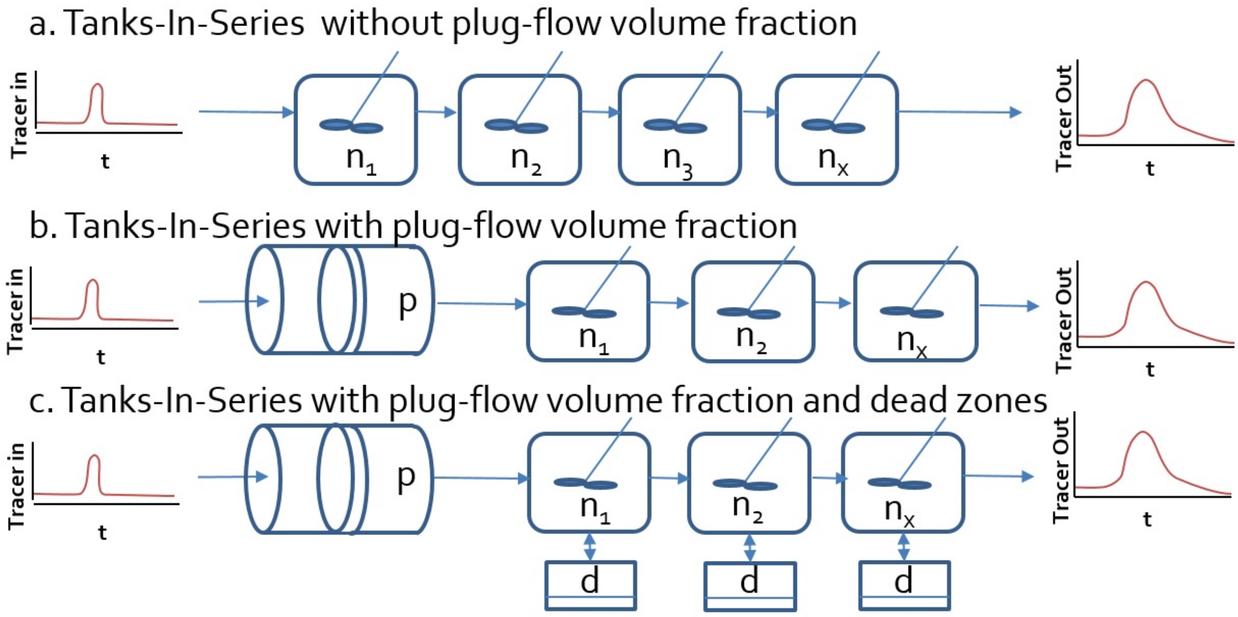

Figure 2: Schematic diagram of three conceptual models based on non-ideal flow for the RTD in a TSG with a series of continuously stirred tank reactors (a) without a plug-flow volume fraction , (b) with a plug-flow volume fraction , and (c) with plug-flow volume fraction and dead zones.

with the lowest number of parameters. Since the TIS model with both plug-flow volume fraction and dead zones contained four adjustable parameters, practical identifiability was studied in order to verify the reliability of parameter estimates and their functional relation. The collinearity analysis was used to detect practical identifiability problems over the complete parameter space **S**. Columns of a matrix **S** are called near collinear if there exists a vector β such that $\parallel \beta \parallel \neq 0$ and $S\beta \approx 0$. The collinearity among columns $\mathbf{S}_k$= 1, 2, ..., m, of **S** was tested by inspecting the smallest eigenvalue λ_m of the normalised sensitivity matrix, $\tilde{\mathrm{S}}$. For details see Brun et al. (2001). Finally, the collinearity index, γ was calculated as

$$\gamma = \frac{1}{\min_{\|\beta\|=0} \parallel \tilde{\mathrm{S}}\beta \parallel} = \frac{1}{\sqrt{\lambda_m}} \qquad (6)$$

A high collinearity index indicates correlation among the parameters. Parameter subsets with collinearity index smaller than 5 are considered as identifiable and collinearity index values above 20 are considered non-identifiable (Brun et al., 2001).

2.5. Parameter estimation

$\bar{t}$ and p were estimated from the RTD measurement data using eqs. 2 and 4 respectively. The estimation of the other two parameters of different TIS models, n and d was done using the residual sum of squares (RSS) as an objective function (eq. 7), which was minimised. In order to find the global minimum of the objective function, the "brute force" method was used, which computes the objective function's value at each point of a multidimensional grid of points, to arrive at the global minimum of the function. This multidimensional grid contained ranges of n (1 to 10), p (0 to 0.75) and d (0 to 0.75) with linear step length of 1, 0.005 and 0.005, respectively. Later, to obtain a more precise (local) minimum near brute's best gridpoint, the downhill simplex algorithm was used applying the result of "brute force" minimization as initial guess (Nelder and Mead, 1965).

$$\mathrm{RSS} = \sum (e(\theta)_{\mathrm{exp}} - e(\theta)_{\mathrm{sim}})^2 \tag{7}$$

2.6. Model analysis

The RSS values were obtained by comparing experimental data, $e(\theta)_{\mathrm{exp}}$ with the simulated data, $e(\theta)_{\mathrm{sim}}$ of the conceptual models presented in section 2.4 (Fig. 3, 4, eq. 7). Two different techniques are used to find if the model is adequate to describe the RTD and hence transport and mixing inside the TSG. First, the coefficient of determination (R^2) was used, which is a statistical measure of how well the simulated data points approximate the real measurement data points. Acceptable values of R^2 (close to 1) imply that the respective model defines the true behaviour of the system. Second, RSS was used which is a measure of the discrepancy between the experimental data and an estimation model. A small RSS indicates a close fit of the model to the data.

The calculations for parameter estimation and model analysis were performed using the Python programming language, employing built-in functions in scientific libraries NumPy and SciPy (Oliphant, 2007). If a conceptual framework for RTD could demonstrate a high R^2 value and RSS for a broad spectrum of process conditions, this would form a strong indication that the model is suitable and thus can be used for interpolation in the experimental domain.

3. Results and Discussion

3.1. Comparison of models based on the goodness-of-fit

Tanks-in-series (TIS)

This model allowed estimation of the axial mixing of the bulk material stream under a non-ideal mixing condition in terms of n (eq. 3) (Levenspiel, 1999). The RSS between the experimental data and the model prediction was calculated for the n values ranging from 1–50. The parameter n that gave the least RSS varied from 2 to 30 for the different runs (Fig. 3). The n increased with an increase in $\bar{t}$. An increase in number and stagger angle of kneading discs and a reduction in screw speed led to an increase in the $\bar{t}$. However, there was a significant lack of fit obtained for this model as the R^2 for the different runs for this model varied from 0.50–0.94. Also, the RSS was found to be between 54–265. This suggests that this model structure was not suitable to conceptually describe the RTD in the TSG. The high value of n estimated by this model also indicates that axial mixing in the TSG was non-ideal. Therefore, in order to improve accuracy in simulating the flow behaviour of the material in the TSG, a plug-flow volume fraction was needed to be introduced in the TIS model (eq. 4). In lack of axial mixing, the flow in a plug-flow volume fraction rely on the conveying rate only. Hence, it is a cause of delay in the appearance of the tracer in the outlet.

TIS with plug-flow volume fraction

This model structure contained two physically significant parameters (p and n) thus allowing the quantification of the plug-flow volume fraction along with the degree of mixing, respectively. As for the TIS without a plug-flow volume fraction, the estimated parameters of the TIS with a plug-flow volume fraction also suggest a deviation from the ideal-plug and mixed flow behaviour in the TSG. Including the p as model component caused a significant reduction in the value of n, which now ranged between 2–21. The value of p for different runs were obtained between 0.2–0.65. The existence of a plug-flow regime was clearly identified by this model, and resulted in a lower RSS and higher R^2 ranges compared to the TIS without a plug-flow volume fraction. The RSS and the R^2 were obtained between 42–305 and 0.73–0.97,

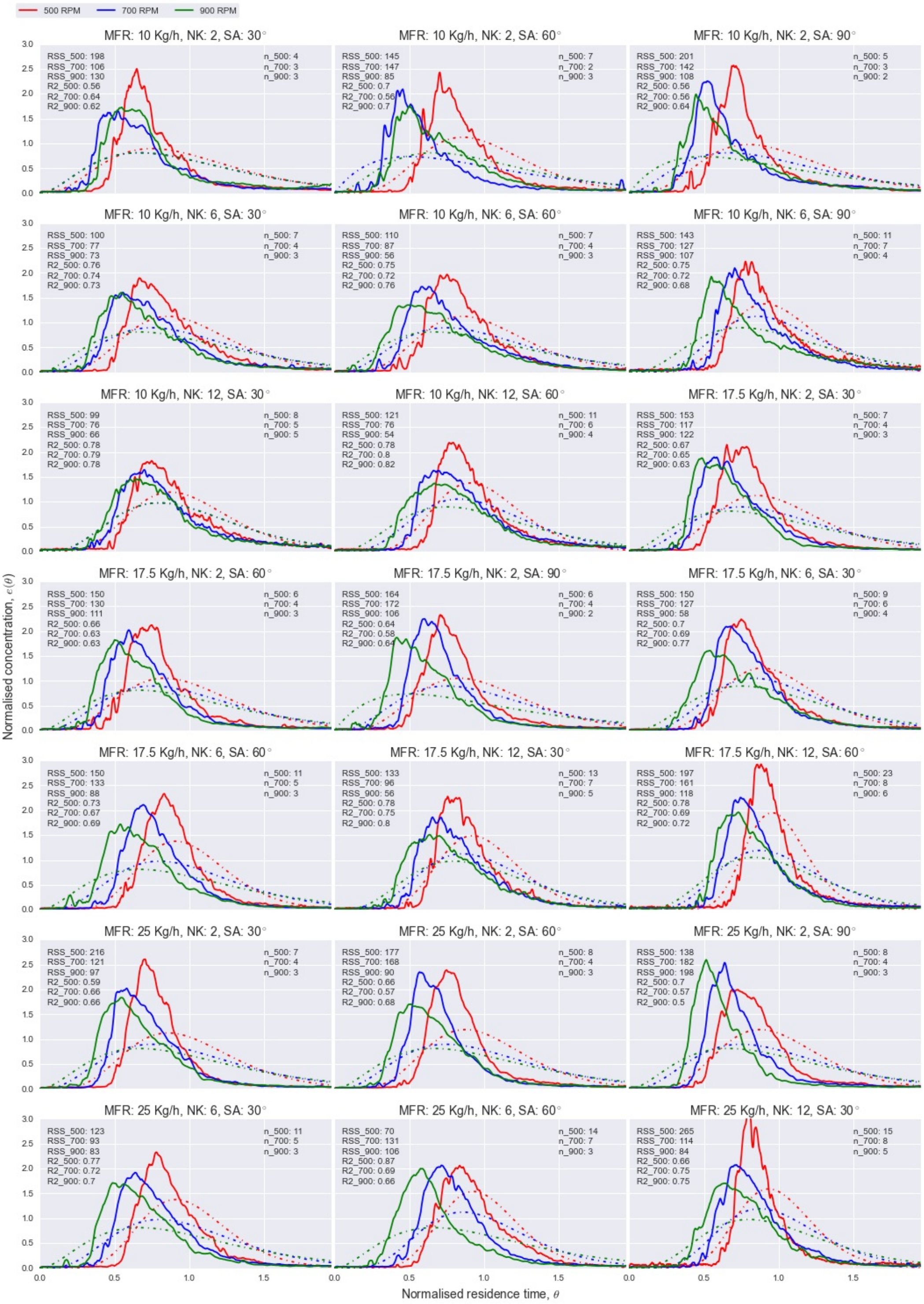

Figure 3: Experimental (—) vs. predicted (-.-) RTD by a TIS model at different screw speed (500, 700, 900 RPM), powder feed rate (10-25 kg/h), number of kneading discs (2, 6, 12) and stagger angle (30-90°) [SA: stagger angle (°), NK: number of kneading discs (-), MFR: powder feed rate (kg/h)].

respectively. However, as the fit between the experimental and predicted RTDs was poor, this model failed to represent the mixing properly resulting in an exceptionally low value of n for all the runs (Fig 4). This situation arises when there are dead or stagnant pockets in the system along with the dispersion effects leading to a long tail in the RTD (Fogler, 2006). Therefore, for a further change in the model structure the conceptual model proposed by Kumar et al. (2008) including the p and d was used to define the RTD in the TSG (eq. 5).

TIS with plug-flow volume fraction and dead-zones

This model allowed estimation of the plug-flow volume fraction (p) and degree of mixing in terms of a finite constantly stirred tank reactors (n) having dead zones (d) (Fig. 2). A significant improvement in the fit between the experimental and estimated RTD data was established by introducing the dead zones (d) in the model structure (Fig. 5). The RSS for different runs varied from 5 to 60 and the R^2 between 0.93 and 0.99, which is much better than observed for the other model structures. This also suggests that the TIS model with plug-flow volume fraction and dead zones is the most suitable to conceptually define RTD in the TSG and can flexibly reflect the behaviour of the system in the domain of the experiment. The obtained p values are found between 0.2–0.65, similar to the TIS model with plug-flow volume fraction only. The values of n and d ranged from 2 to 6 and from 0.01 to 0.54, respectively. Due to a very good fit between the experimental and estimated RTD by this model, the calculated values for the parameters can be reliably used for characterisation of residence time and mixing in the TSG.

Therefore, based on the parameters estimated by this model, further detailed analysis of the twin-screw granulation system will be presented in the next section. A complete list of parameter sets, RSS and R^2 values at different process conditions for all three model configurations is provided as supplementary data (Table S1).

3.2. Analysis of RTD using TIS model with plug-flow and dead-volume fractions

Prior to a comprehensive analysis of modeling results it is indispensable to know how reliable the parameter estimates are. Although only certain numerically estimated parameter combinations for the model could closely reproduce the experimental RTD of the process,

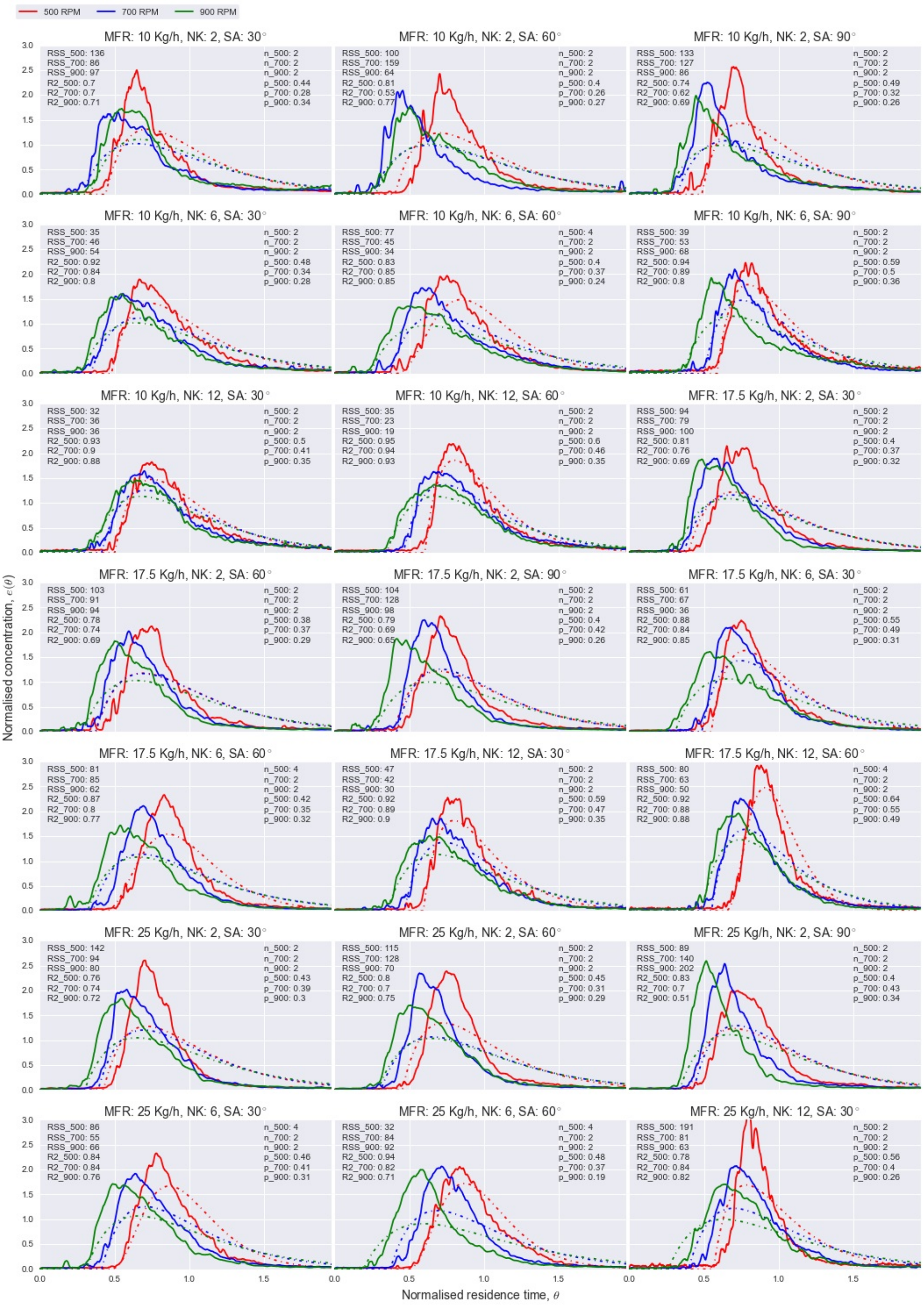

Figure 4: Experimental (—) vs. predicted (-.-) RTD by a TIS with plug-flow volume fraction model at different screw speed (500, 700, 900 RPM), powder feed rate (10-25 kg/h), number of kneading discs (2, 6, 12) and stagger angle (30-90°) [SA: stagger angle (°), NK: number of kneading discs (-), MFR: powder feed rate (kg/h)].

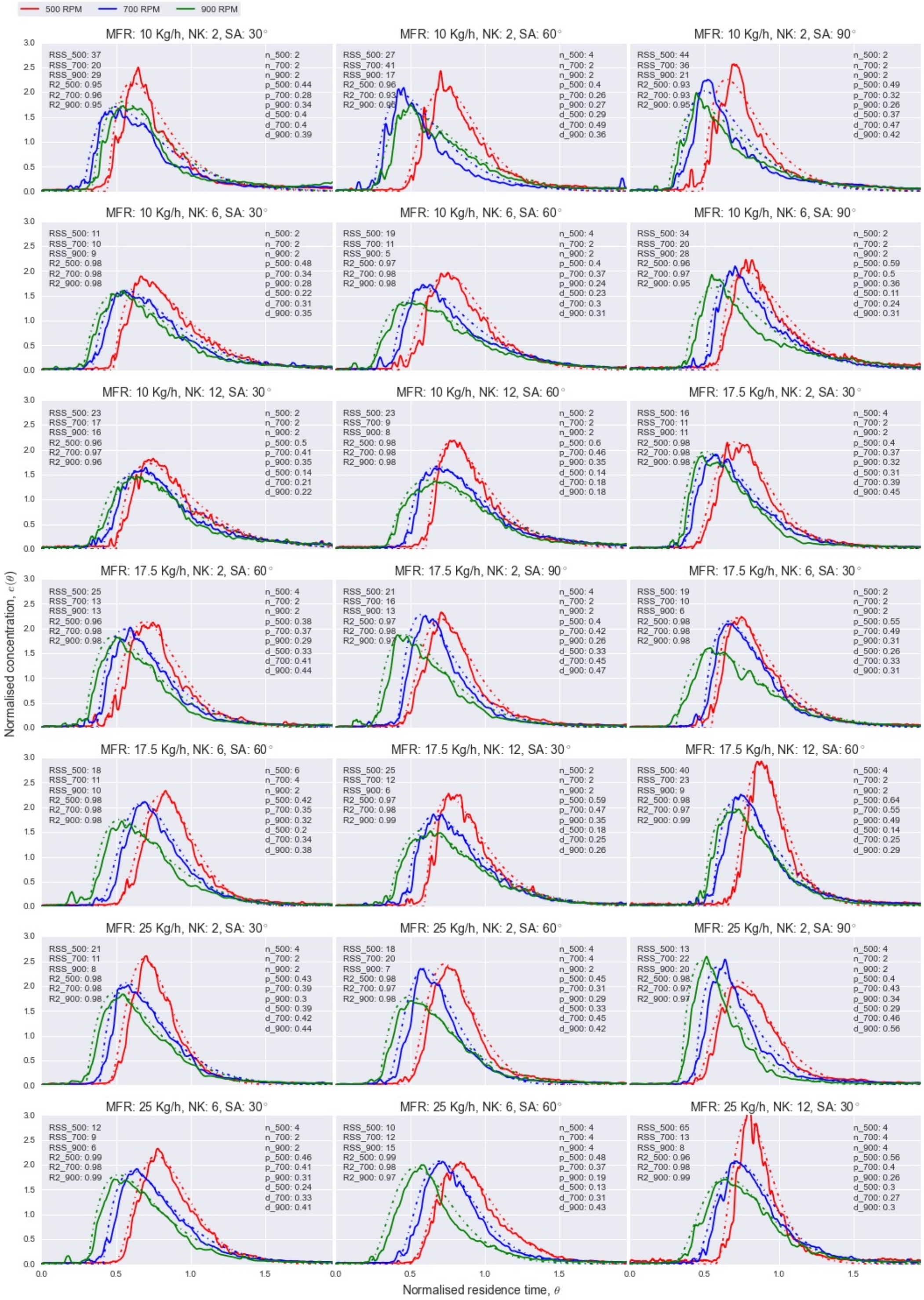

Figure 5: Experimental (—) vs. predicted (-.-) RTD by a TIS with plug-flow and dead-volume fractions model at different screw speed (500, 700, 900 RPM), powder feed rate (10-25 kg/h), number of kneading discs (2, 6, 12) and stagger angle (30-90°) [SA: stagger angle (°), NK: number of kneading discs (-), MFR: powder feed rate (kg/h)].

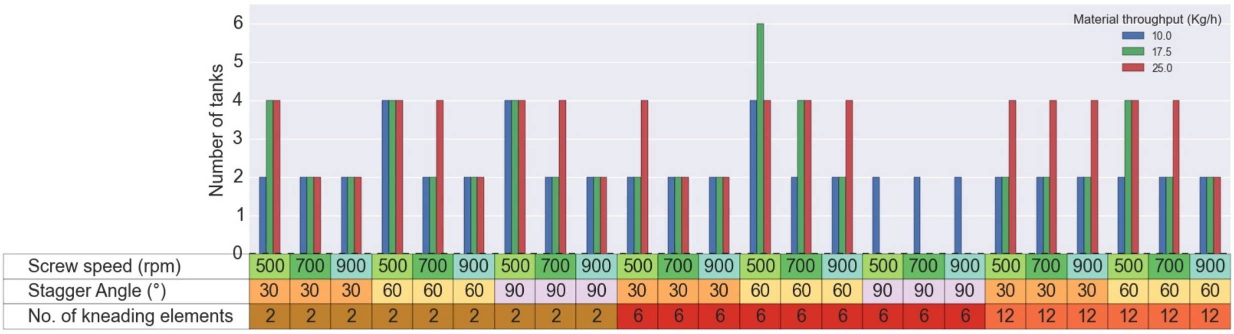

Figure 6: Effects of change in the process conditions on the plug-flow volume fraction as predicted by the TIS model with plug-flow volume fraction and dead zones.

ignoring the dependencies among the estimated parameters may lead to an identifiability problem and meaningless estimates which severely reduces the prediction power of the model. Therefore, practical identifiability was analysed globally over the complete parameter space by the collinearity analysis. The collinearity index (eq. 6) was found to be 1.87, which is sufficiently low to suggest that there was no significant interrelation between parameters.

3.2.1. Effect of process settings on plug-flow volume fraction in the TSG

The effect of powder feed rate (10-25 kg/h) on the plug-flow volume fraction (p) was very low for a lower number of kneading discs, however, for 6 and 12 kneading discs, the plug-flow volume fraction increased with an increase in powder feed rate (Fig. 6). Similarly, increasing the number of kneading discs caused an increase in the plug-flow volume fraction in the TSG. Also, the effect of a change in stagger angle was less prominent for a low number of kneading discs. However, for 6 and 12 kneading discs, the plug-flow volume fraction increased significantly when stagger angle increased from 30° to 60° and then to 90°. The effect of screw speed was most dominant, and therefore, the plug-flow volume fraction always reduced with the increase in the screw speed (500 to 700 and 900 rpm) irrespective of other process settings.

These results suggest that kneading blocks in the TSG screws act like a plug-flow region and the fill ratio in this region is critical. An increase in powder feed rate led to a high fill ratio due to a higher material flux, whereas the increase in screw speed increased conveying rate leading to reduction in the fill ratio. Since the p is the ratio between minimum residence time (t_{min}) and mean residence time ($\bar{t}$) (eq. 4), and since we know from a previous experimental study (Kumar et al., 2014b) that an increasing powder feed rate and screw speed cause a reduction in $\bar{t}$, it can be inferred that an increase in powder feed rate causes a relatively greater reduction in $\bar{t}$ than t_{min} (narrowing of the RTD) and hence a higher p. However, when the screw speed was increased the relative reduction in t_{min} was greater than $\bar{t}$ (broadening of the RTD), leading to a lower p. Hence, powder feed rate and screw speed, despite having the same effect on $\bar{t}$, have an opposite influence on the axial mixing.

3.2.2. Effect of process settings on axial mixing in the TSG

Mixing of the material within the shortest possible granulator length is of key importance in TSG. Beside the indirect measurement of axial mixing in terms of the ratio between t_{min} and $\bar{t}$, in the TIS model with plug-flow volume fraction and dead zones the axial mixing is directly quantified in terms of the constantly stirred tank reactors (n). The trend of change in n at various process settings suggests that the level of axial mixing was most dominantly controlled by the screw speed (Fig. 7). At a low screw speed (500 rpm), the value of n was mostly 4 compared to the experiments with a high screw speed (900 rpm) where it was 2. Also, a high powder feed rate along with a low screw speed, i.e., the high fill ratio condition, led to reduction in axial mixing. At a high powder feed rate, an increase in the number of kneading discs from 2 to 6 and then to 12 as well as a change of the stagger angle (30° to 60°) also caused a reduction in the axial-mixing level despite a high screw speed (900 rpm), and the n increased to 4. The runs for 90° stagger angle could not be performed due to low axial mixing, which caused jamming of the granulator. However, an increase in the screw speed to its maximum (900 rpm) mostly resulted in resetting of the axial mixing to the same level ($n = 2$).

These results suggest that powder feed rate and screw speed together dictate the axial mixing. Therefore, a balance between the throughput force and conveying rate is needed to obtain good axial mixing inside the TSG. At a high conveying rate, material thoughput can be increased without loss in mixing, however, an increase beyond the conveying capacity of

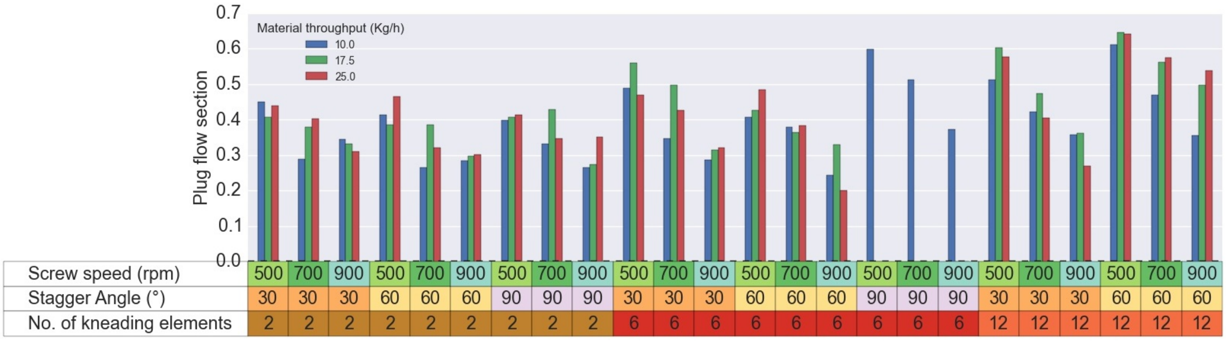

Figure 7: Effects of change in the process conditions on the number of TIS as predicted by the TIS model with plug-flow volume fraction and dead zones.

the screw may lead to a sudden change in flow regime to plug-flow and complete jamming of the granulator (Kumar et al., 2014b).

3.2.3. Effect of process settings on dead zones in the TSG

Although axial mixing reflected by broadening of the RTD is necessary to compensate for process variations (Kumar et al., 2014b), the excessive broadening in the tail region of the RTD may also result from a stagnant region and excessive backing inside the TSG. Such a desirable region may lead to build-up of material in long runs and is therefore estimated by the dead zones (d) in the model. The value of d was primarily influenced by the screw speed and the number of kneading discs (Fig. 8). When the number of kneading discs increased in the screw configuration, d decreased monotonically. Furthermore, an increase in screw speed caused a reduction in d. In contrast, for a higher number of kneading discs (6 and 12), an increase in powder feed rate caused an increase in d. This change is once again related to the higher throughput force by the increased material flux.

These results indicate that the kneading blocks, which normally work under a more filled channel condition than the transport screws, prevent excessive back-mixing in the TSG. Also, increasing fill ratio reduces the stagnant region and consequently lowers the dead zone inside the mixed flow section of the TSG. However, when the slippage rate increases due to an increase in screw speed, there is a greater possibility of back-mixing, hence an increase in d. Also, the conveying force helps in clearing the flow in the kneading blocks leading to

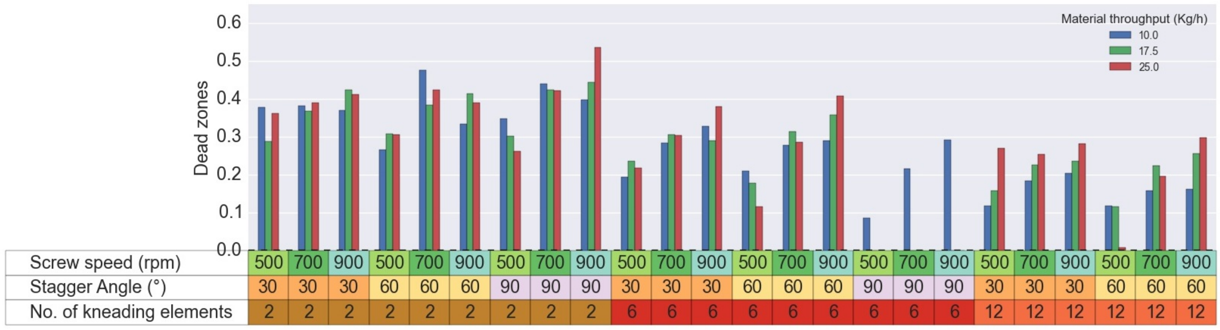

Figure 8: Effects of change in the process conditions on the dead-volume fractions inside the TSG barrel as predicted by the TIS model with plug-flow volume fraction and dead zones.

more back-mixing.

Beside the modelling and system identification owing to a good agreement between the simulated and the experimental RTD data, this study also established that the combination of modelling and dedicated experimental data collection is very effective for gaining an improved insight into the transport and mixing characteristics of material in the TSG. Although the presented study is not "generic" to all formulations due to the likely difference in the granulation behaviour of different excipients (such as microcrystalline cellulose and dibasic calcium phosphate), the method used in this study (both data collection and modelling) is generic and can be repeated for other excipients. The knowledge gained from this study can now be used as the basis for future extensive numerical simulation of flow and transport in the TSG using Discrete Element Method (DEM). The, DEM requires enormous numerical and computational effort due to the large number of equations, the strong coupling between various physical processes and the difficulties to resolve boundaries of the flow domain in the intermeshing twin-screw involved. However, these models are necessary for complete understanding of the multiphase flow and mixing of wetted powder such as local residence time and impact speed of colliding granules in the screw zones, which are important for understanding the granulation mechanism in the TSG. Till an extensive DEM model is developed, the best-fit conceptual model consisting of algebraic equation to describe a plug flow in series with a finite number of constantly stirred tank reactors having dead volume fractions can be applied for representation of the RTD in a TSG with a reasonable accuracy along with simplicity and computational advantages.

4. Conclusions

In this study, a systematic evaluation of the performance of three different conceptual models for the description of the residence time distribution in a twin-screw granulator has been performed. The suitability of the model framework was examined using the statistical difference between the experimental and estimated residence time distribution for runs with different screw configurations and process settings. The TIS model assuming plug-flow volume fraction in series with a finite constantly stirred tank reactors with dead zones was found to be the most suitable conceptual model for describing the experimentally measured residence time distribution in a twin-screw granulator. As estimated by this model, the kneading block in the screw configuration significantly stimulates the plug-flow transport of material inside the granulator. Furthermore, the results showed that mixing and dead zones are generally affected by the fill level inside the twin-screw granulator barrel, thus a good balance between the throughput force and the conveying rate is necessary for a good axial mixing and reduction in the stagnant regions inside the twin-screw granulator. The steady-state models consisting of algebraic equations rather than the physical models containing differential equations, achieve a reasonable accuracy in representation of the RTD along with the simplicity of implementation and computational advantages. Therefore, the conceptual TIS model describing RTD as a plug flow in series with a finite number of constantly stirred tank reactors having dead volume fractions was suggested for improved understanding the mixing and transport of material in the twin-screw granulator. Future experiments and modelling studies should investigate the effect of other formulations with significantly different raw material properties.

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List of symbols and abbreviations

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

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