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Version: Accepted Version

Article:
AlAlaween, W., Khorsheed, B., Mahfouf, M. et al. (2018) Transparent predictive modelling of the twin screw granulation process using a compensated interval type-2 fuzzy system. European Journal of Pharmaceutics and Biopharmaceutics, 124. pp. 138-146. ISSN: 0939-6411

https://doi.org/10.1016/j.ejpb.2017.12.015

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Transparent Predictive Modelling of the Twin Screw Granulation Process using a Compensated Interval Type-2 Fuzzy System

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Abstract

In this research, a new systematic modelling framework which uses machine learning for describing the granulation process is presented. First, an interval type-2 fuzzy model is elicited in order to predict the properties of the granules produced by twin screw granulation (TSG) in the pharmaceutical industry. Second, a Gaussian mixture model (GMM) is integrated in the framework in order to characterize the error residuals emanating from the fuzzy model. This is done to refine the model by taking into account uncertainties and/or any other unmodelled behaviour, stochastic or otherwise. All proposed modelling algorithms were validated via a series of Laboratory-scale experiments. The size of the granules produced by TSG was successfully predicted, where most of the predictions fit within a 95% confidence interval.

Keywords: Twin screw granulation; Interval type-2 fuzzy logic system; Gaussian mixture model.

1. Introduction

Granulation processes are, more often than not, used to obtain and maintain good specific properties in terms of compressibility, flowability and homogeneity (Iveson, 2001). In

particular, wet granulation processes, both batch and continuous, have been extensively used (Benali et al., 2009; Fonteyne et al., 2014; Litster, 2004). In the pharmaceutical industry, tablets production cycle has been operated in a batch mode. Recently, moving towards a continuous one is considered and investigated, this is due to its potential advantages in time, cost, scalability and controllability (Rogers et al., 2013). Among all the continuous granulation processes, twin screw granulation (TSG) has recently attracted a lot of interest in the pharmaceutical industry, this being due to its flexible design and short residence time (Barrasso et al., 2014; Dhenge et al., 2012; Djuric and Kleinebudde, 2008; Saleh et al., 2015).

Since the granulation process can determine the 'fate' of the produced tablets, several studies have been devoted to understand and model and simulate such a process (Paavola et al., 2013; Saleh et al., 2015; Shirazian et al., 2017). Many research papers have provided a comprehensive understanding of the factors that affect the process mechanisms and the properties of the produced granules (Benali et al., 2009, Dhenge et al., 2012; Kumar et al., 2014; Christian and Markus, 2014; Tu et al., 2013; Vanhoorne et al., 2016). Such an understanding has been further enhanced by developing various predictive models for the granulation process (AlAlaween et al., 2017; Rogers et al., 2013). These modelling paradigms can either be data based (*e.g*. an artificial neural network) or physically-based (e.g. population balance) models (Paavola et al., 2013; Shirazian et al., 2017). Population balance models (PBMs) have been implemented to follow the evolution of the granules with time (Sanders et al., 2003; Ramkrishna, 2000). A one dimensional PBM was typically used to study the granule size (Iveson, 2002). However, the consideration of the other granule properties is really crucial, where these properties can significantly affect the critical quality attributes of the tablets produced (*e.g*. porosity) (Barrasso et al., 2015). Therefore, multi-dimensional PBMs have been employed (Paavola et al., 2013; Pinto et al., 2007; Poon et al., 2008). For instance, a two-dimensional PBM for the continuous TSG process was developed to follow the evolution of

the granule size and the liquid distribution with time (Barrasso et al., 2015). Although, the PBMs have provided a deeper insight into the granulation process at the micro level, all the possible interactions among the process mechanisms, namely, wetting and nucleation, growth and consolidation, and breakage and attrition, have not been fully considered (Iveson, 2002). Therefore, these models have been integrated with various modelling approaches such as Monte Carlo, in order to model a greater number of particle properties, and the discrete element method, in order to model the effect of equipment dynamics (Barrasso et al., 2014; Braumann et al., 2007; Shirazian et al., 2017). Data based paradigms have also been utilized to model the granulation processes by mapping the process inputs to the outputs (*i.e.* the properties of the granules) (AlAlaween et al., 2016; Mansaet al., 2008). For example, for the TSG process, an artificial neural network was presented to predict the granule size, which was represented by the three diameters: D_{10}, D_{50} and D_{90} (Shirazian et al., 2017). In addition, modelling frameworks that integrate data-driven models with physical based ones have also been presented in the related literature (Barrasso et al., 2014). Such an integration can circumvent the potential limitations of implementing each model separately.

Generally, these modelling paradigms have their own strengths and limitations. On the one hand, data-driven models, as powerful interpolators, can simply interpret the input/output relationships in a way that users can easily understand (AlAlaween et al., 2016). Moreover, they can be utilized to monitor more than three granule properties, which is considered to be computationally taxing task for the physical-based models (Iveson, 2002). On the other hand, the physical-based models can be utilized on a larger scale by using the scaling-up techniques that are proposed in the related literature (Watano et al., 2005). However, none of the presented models can systematically deal with the uncertainties present in both the granulation inputs and outputs. Such uncertainties may be due to the heterogeneous distributions of the binder content and porosity or due to the measurement apparatus or methods (AlAlaween et al., 2016).

Moreover, the majority of the presented models assume that the error residuals are normally distributed (Yang et al., 2012). Such an assumption, which is not usually valid, may lead to unmodelled behaviour, which may consequently result in performance deterioration (Yang et al., 2012).

The main aim of this research is to develop a fast, transparent, more accurate and cost-effective predictive modelling framework for the TSG process. For this purpose, an interval type-2 fuzzy logic system (IT2FLS) is presented to predict the size distribution of the granules produced. Such a model can take into account the uncertainties that surround the TSG process. The Gaussian mixture model (GMM) is then utilized to characterise the error and to account for any unmodelled behaviour. The main 'rationales' behind incorporating the GMM are to compensate for the normality assumption and to improve the predictive performance of the developed model. The rest of the paper is organized as follows: the experimental work that was carried out using the twin screw granulator is described in Section 2. Section 3 presents the theoretical background of the IT2FLS and the model results. The GMM and its results are presented in Section 4. Finally, the concluding remarks are summarized in Section 5.

2. Experimental Work

Microcrystalline cellulose (MCC, Avicel PH 101, FMC Corporation, D_{50}=50μm) was granulated using a co-rotating twin screw granulator (16mm Prism Eurolab TSG, Thermo Fisher Scientific, Karlsruhe, Germany). Deionised water was used as a liquid binder. Both the MCC powder and the liquid binder were fed to the granulator using a gravimetric twin screw feeder (K-PH-CL-24-KT20, K-Tron Soder, Niederlenz, Switzerland) and a peristaltic pump (Watson Marlow, Cornwall, UK), respectively. The twin screw granulator has a length to diameter (L/D) ratio of 25:1 (continuous, open end or die less system). The screw configuration, which consists of conveying and kneading elements, was considered as an input

parameter in addition to three other parameters, namely; liquid to solid (L/S) ratio, feed rate and speed, as summarized in Table 1. The schematic diagram of the twin screw granulator and the different screw configurations considered in this study are shown in Figure 1. Several input parameters can affect the TSG process, however, the aforementioned ones have the most significant effects (Dhenge et al., 2012; Kumar et al., 2014). It is worth mentioning at this stage that the granulator temperature was kept constant at 25^{o} C.

Table 1. The investigated input parameters of the TSG process.

Figure 1. Schematic diagram for the twin screw granulator and the screw configurations: Long pitch conveying element (LPCE, Length=2Diameter), Short pitch conveying element (SPCE, Length=Diameter) and Kneading disc at 60° pitch (K 60° staggering angle, Length=Diameter/4).

A total of 36 experiments were conducted based on a full factorial design of experiments. Once each experiment was completed, the produced granules were left to dry at room temperature. Finally, the size of all the granules was measured using the Retsch Camsizer (Retsch Technology GmbH, Germany), which is a dynamic image analyser, where the size of the free flowing granules is photo-optically recorded and measured.

3. Interval Type-2 Fuzzy Logic systems

3.1 Model Development

With recent advances in computing power, data-driven models have become the type of models that one seeks to represent complex processes (Nunes et al., 2005), in particular, those processes where the physical model does not exist or it is simply too complex to derive (AlAlaween et al., 2016). In spite of the powerful algorithms behind them, some of the data-driven approaches such as neural networks are referred to as black-box approaches (Bishop, 2006). This is because the mechanism that maps the process inputs to its outputs does not provide users with the required information to understand the process. Therefore, a fuzzy logic

system (FLS) has been extensively applied in many research areas such as those associated with medical, industrial and academic applications to develop a simple and transparent model (Wang and Mahfouf, 2012). Moreover, this system, as it is well-known, can typically handle uncertainties more efficiently (Mendel, 2001). Generally, the FLS is represented and analysed by fuzzy sets, which are usually described by membership functions. The most common types of the fuzzy sets are type-1 and type-2. A type-1 fuzzy logic system (T1FLS) is the one whose rules' antecedents and consequent are completely described by type-1 fuzzy sets. Whereas the system where at least one of its rules' antecedents or consequent is described by type-2 fuzzy sets is called a type-2 fuzzy logic system (T2FLS). In such a system, the membership functions are themselves fuzzy. Because of the extra degree of freedom, the T2FLS can tackle uncertainties more efficiently compared to its counterpart T1FLS. However, implementing such a paradigm is computationally expensive. Therefore, an interval type-2 fuzzy logic system (IT2FLS) has been widely applied instead. An interval type-2 fuzzy set can usually be given as follows (Mendel, 2001):

$$\tilde{A} = \int_{x \in X} \int_{u \in J_x \subseteq [0,1]} 1/(x,u) \tag{1}$$

where x, X and J_x stand for the primary variable, its measurement domain and its primary membership degree, respectively. The parameter u represents the secondary variable; $u \in J_x$ at each $x \in X$.

Figure 2. The Structure of IT2FLS.

The IT2FLS structure is depicted in Figure 2. First of all, the crisp inputs (x_1, x_2 …x_n) are fuzzified into input type-2 fuzzy sets ($\tilde{A}_j^i$) to determine the upper and lower membership functions $\left[\underline{\mu}_{\tilde{A}_j^i}, \overline{\mu}_{\tilde{A}_j^i} \right]$ where $\tilde{A}_j^i$ is the i^{th} fuzzy set for the j^{th} variable. The most commonly used

membership function is the Gaussian one with uncertain mean, this being due to the continuity and smoothness of the Gaussian function which allow users to use the fuzzy logic systems as a '*universal approximator'* (Wang and Mahfouf, 2012). This membership function can be expressed as follows (Mendel, 2001):

$$\mu_j^i(x_j) = \exp\left[-\frac{1}{2}\left(\frac{x_j - m_j^i}{\sigma_j^i}\right)\right], \quad m_j^i \in \left[m_{j1}^i, m_{j2}^i\right] \tag{2}$$

where m_j^i and σ_j^i are the mean and the standard deviation of the i^{th} set, respectively. The union of the membership functions that lie between the lower and upper ones is called the footprint of uncertainty.

In general, the inference process combines the defined rules to map the input fuzzy sets to the output fuzzy sets. These rules can be provided by experts or can be extracted from a collected data set. Both types can be presented as a collection of IF-THEN statements, as follows:

Rule^i: IF x_1 is $\tilde{A}_1^i$ … and x_n is $\tilde{A}_n^i$, **THEN** y is $\tilde{B}^i$.

where $\tilde{B}^i$ represents the i^{th} output fuzzy set, when a Mamdani IT2FLS is considered. Such a rule has a similar form as T1FLS, the only distinction is associated with the nature of the membership functions, which is a type-2 fuzzy set in this case (Mendel, 2001).

Finally, the type-2 output fuzzy set is processed by two operations. The first operation is to reduce the type-2 fuzzy system into a type-1 one. Most of the computational effort of IT2FLS is incurred by this step, where the left and right points of the interval are found using the Karnik-Mendel (KM) algorithm (Karnik and Mendel, 2001). Such a step is usually followed by a defuzzification process of the output to get a crisp one, this operation can be simply performed by computing the average value (Mendel, 2001).

3.2 Results and Discussion

An IT2FLS model was developed to model the TSG process. The collected data were divided randomly into two data sets: training (30) and testing (6). The training data set, as the name indicates, allows the model to learn the relationships between the inputs and the output by extracting informative rules, whereas the testing data set is used to validate the model by assessing its generalization capabilities. In order to model the TSG process successfully, one should understand the nature of the process input variables (*i.e*. continuous or discrete). In this research paper, all the input variables are continuous except the screw configuration variable, which is considered as a crisp variable. The number of rules that was selected corresponds to the minimum error between the predicted and the experimental output evaluated by the root mean square error (RMSE). For a predefined number of rules, the model parameters were carefully initialized using the interval type-2 fuzzy clustering algorithm presented in (Rubio and Castillo, 2013). The model parameters were then optimized by employing the steepest descent algorithm with an adaptive back-propagation network (Mendel, 2001).

Figure 3. The IT2FLS for D_{50}: (a) Training, (b) Testing (with a 90% confidence interval).

Figure 3 shows the model performance for D_{50} for both the training and the testing data sets using 5 rules, the RMSE values for the training and testing sets are 64μm and 135μm, respectively. It is noticeable that the RMSE value for the testing set is approximately twice the value for the training set, this can be an indication of over training problem. However, it seems not to be the case in this work, where such a difference is due to the D_{50} values; most of the values in the training set are less than 1000μm, whereas, in the testing set, three values out of a total of six are greater than 1000μm, thus, an error value of approximately 100μm is actually less than 10% of the target value. This can be clearly evidenced by looking at the coefficient of determination values, R^2 (training, testing) = [0.880 0.866]. Moreover, it is worth noting that

most of the predictions fit within a 90% confidence interval. Two sample rules out of a total of five are illustrated in Figure 4, where the shaded area represents the footprint of uncertainty, and their corresponding linguistic forms read as follows:

Rule* 1:** ***IF *L/S ratio is small and feed rate is small and screw configuration consists of conveying and 16 kneading elements and speed is small,* ***THEN*** *the* D_{50} *is small.*

Rule 2: ***IF*** *L/S ratio is medium and feed rate is medium and screw configuration consists of conveying elements and speed is medium,* ***THEN*** *the* D_{50} *is medium.*

Figure 4. The rule base of IT2FLS for D_{50}.

Table 2 summarizes these rules for D_{10}, D_{50} and D_{90}, whereas the linguistic labels for the inputs and the three diameters are presented in Table 3. For the first rule, one can expect a narrow and perhaps unimodal size distribution, since these diameters are small, similarly to what was previously concluded by Dhenge et al. (2012). For the second rule, the size distribution can be wide because of the difference between the D_{90} and D_{10}.

Table 2. The rule base of IT2FLS for D_{10}, D_{50} and D_{90}*.

Table 3. The linguistic labels of the inputs and the three diameters.

In a similar manner, the model was used to predict the whole size distribution. Figure 5 shows the predicted and the experimental distributions for three experiments, which were carried out under varying operating conditions. Table 4 summarizes the performance measures, which are represented by the RMSE and the R^2 values.

As the IT2FLS is considered more computationally demanding compared to T1FLS, this raises the question whether this complexity led to a superior model for the TSG process. Therefore, the T1FLS was implemented to model this process. The overall performance for the T1FLS is $R^2 = 0.783$. The performance measures for the T1FLS are listed in Table 4. This

demonstrates that the prediction performance of the IT2FLS is superior to that of the T1FLS, with an overall improvement of approximately 14% in R^2. This indicates that the IT2FLS can handle uncertainties surrounding the granulation process systematically and more efficiently when compared to the T1FLS. For comparison purposes, a multiple linear regression model was also implemented to model the TSG process. The performance of such a model measured by the R^2 value is 0.369. It is apparent that the performances of the fuzzy models are at least twice the one of the regression model. In addition, an ensemble model based on 10 neural networks was also implemented to represent the TSG process, the performance measures of such a model are presented in Table 4. In addition to being an interpretable model, it is noticeable that the IT2FLS outperformed the ensemble model.

Figure 5. The IT2FLS: the predicted (o) and the experimental (*) distributions for the size (a) using L/S ratio=0.94, feed rate=1Kg/h, Screw configuration consists of conveying and 16 kneading elements and speed=750rpm; (b) using L/S ratio=1.25, feed rate=4Kg/h, Screw configuration consists of conveying and 32 kneading elements and speed=250rpm; (c) using L/S ratio=1.25, feed rate=4Kg/h, Screw configuration consists of conveying elements and speed=250rpm.

Table 4. The performances of the models represented by RMSE* and R^2.

4. Gaussian Mixture Model

4.1 Model Development

In general, the majority of the predictive paradigms implicitly assume that the modelling error residuals follow a normal distribution (Yang et al., 2012). In reality, such an assumption may not be valid, in particular, when the process to be modelled is complex and with measurable but noisy or non-measurable factors. In such a case, the normality assumption may result in losing useful information and, consequently, lead to a model with sub-optimal parameters (Yang et al., 2012). Hence, a plethora of different modelling strategies has been presented to refine these models by extracting the information that may be hidden behind the

error (Mauricio, 2008; Oliveira and Pedrycz, 2007; Yang et al., 2012). The algorithm that depends on the Gaussian mixture model (GMM) has been widely used in many applications; this being due to the ability of the Gaussian model to provide a deeper insight into the density function, and due to its ability to accurately approximate any density function using the best number of Gaussian components (Bishop, 2006). Therefore, such an algorithm can lead to the best model refinement (Yang et al., 2012). However, in fuzzy logic systems, using these paradigms, including the GMM, will change the rules extracted from the process data, in other words, the rules cannot be accurately used to represent the process. Therefore, in this research, the GMM is modified to refine the rules of the fuzzy system instead of the data points.

Generally, the GMM is a stochastic model which is usually expressed as a linear combination of its components. Each component has its own parameters (*e.g.* mean and covariance). In order to obtain the best model, these parameters need to be optimized by maximizing the log likelihood function. These parameters can be expressed as follows (Bishop, 2006):

$$\psi(z_{dj}) = \frac{\gamma_j \mathrm{N}\left(x_d^e \mid \mu_j^e, \Sigma_j^e\right)}{\sum_{j=1}^{J} \pi_d \mathrm{N}\left(x_d^e \mid \mu_j^e, \Sigma_j^e\right)} \quad , \qquad \forall j$$

$$\left\{ \begin{array}{l} \mu_j^e = \dfrac{\sum_{d=1}^{D} \psi(z_{dj}) x_d^e}{\sum_{d=1}^{D} \psi(z_{dj})} \\ \Sigma_j^e = \dfrac{\sum_{d=1}^{D} \psi(z_{dj}) \left(x_d^e - \mu_j^e\right)\left(x_d^e - \mu_j^e\right)^T}{\sum_{d=1}^{D} \psi(z_{dj})} \\ \gamma_j = \dfrac{\sum_{d=1}^{D} \psi(z_{dj})}{D} \end{array} \right\} , \qquad \forall j \tag{3}$$

where x^e is the data included in the error residuals characterization. The parameters γ_j, μ_j^e and Σ_j^e represent the mixing coefficient, the mean and the covariance of the j^{th} Gaussian component, respectively. The probability of the d^{th} data point belongs to the j^{th} component is expressed by the parameter $\psi(z_{dj})$. Finally, z_{dj} is a J-dimensional binary variable that is equal to 1 when the d^{th} data point belongs to the j^{th} Gaussian component where the other elements are zero. Solving such an optimization problem analytically is not as easy as it may seem. Therefore, the Expectation Maximization (EM) algorithm is commonly utilized to find the optimal values for these parameters (McLachlan and Krishnan, 2008). The parameters γ_j, μ_j^e and Σ_j^e are carefully initialized using the K-means clustering algorithm, followed by estimating $\psi(z_{dj})$, this step is referred to as E-step. In the M-step, the $\psi(z_{dj})$ value is used to re-estimate the parameters, followed by using the revised parameters to update the $\psi(z_{dj})$ value. Such an iterative procedure is terminated when either the algorithm converges, or the maximum predefined number of iterations is reached (Bishop, 2006).

The procedure provided above is for a defined number of Gaussian components. However, in reality, such a number is unknown in advance. In this research paper, Bayesian information criterion (BIC) is adopted as a performance measure for choosing the optimal number of components (Simon and Girolami, 2012). Once the optimal parameters are defined, the calculated conditional mean is added to the consequent mean of the corresponding cluster; in order to compensate for the bias. This step is followed by defuzzifying and estimating the output. The steps of the error characterization algorithm are summarized in Figure 6.

Figure 6. Flowchart of the error characterisation model.

4.2 Results and Discussion

Since the main effect of the granulation input variables were already included when the IT2FLS was developed, only two of them were utilized here to refine the IT2FLS performance by implementing the GMM algorithm illustrated in Figure 6. The combination that was selected is the one that led to the minimum RMSE value (*i.e*. the maximum error compensation). Consequently, the L/S ratio, speed and the error residuals were utilized to develop the error characterization model. The GMM was trained using the training data set. By using 6 Gaussian components, Figure 7 shows the model performance for D_{50} for both the training and the testing data sets after bias compensation. The root mean square error values for the training and testing sets are 40 µm and 59µm, respectively.

Figure 7. The prediction performance for D_{50} after bias compensation (with a 95% confidence interval).

The overall improvement achieved by applying the GMM is of approximately 7.6% in R^2. This demonstrates the ability of such an algorithm to compensate for bias by detecting the unmodelled stochastic (*i.e*. non deterministic) behaviour. The rules after bias compensation are illustrated in Figure 8, where one can notice that the antecedents are similar to the ones presented in Figure 4 but the consequent is slightly different. The consequent mean values for Rule 1 and Rule 2 were refined by approximately 25µm (to the left) and 150µm (to the right), respectively. Such slight changes in the mean values did not actually change the linguistic forms of these rules. It is worth mentioning at this stage that the prediction performance of the modified GMM is superior to that of the traditional GMM presented in (Yang et al., 2012), with an overall improvement of approximately 2% in R^2. Moreover, as stated previously, these simple but informative rules can be accurately used to represent the TSG process.

Figure 8. The rule base of IT2FLS for D_{50} after bias compensation.

The refined predicted size distributions from the GMM for the three experiments are shown in Figure 9, where the areas where significant improvements can be noticed are highlighted by arrows. Different numbers of Gaussian components were assigned to the various size classes, these numbers were in the range of 4 to 9. The performance measures for the GMM are listed in Table 4, these values demonstrate the ability of the proposed framework; the IT2FLS followed by the GMM, to successfully predict the size distribution of the granules produced by the TSG process. Moreover, the IT2FLS provided users with a simple understanding of the process, such an understanding was retained during the error characterization model. For comparison purposes, the modified GMM was adopted to refine the T1FLS, leading to a significant improvement, as summarized in Table 4. However, it is apparent that the proposed framework outperforms the model incorporating the T1FLS and the GMM, where the overall improvement is of approximately 19%.

Figure 9. The proposed framework: the predicted (o) and the experimental (*) distributions for the size (a) using L/S ratio=0.94, feed rate=1Kg/h, Screw configuration consists of conveying and 16 kneading elements and speed=750rpm; (b) using L/S ratio=1.25, feed rate=4Kg/h, Screw configuration consists of conveying and 32 kneading elements and speed=250rpm; (c) using L/S ratio=1.25, feed rate=4Kg/h, Screw configuration consists of conveying elements and speed=250rpm (arrows are used to highlight the areas where significant improvements can be noticed).

Since the main of this research work is to develop a model that can successfully represent the TSG process, the proposed modelling framework was utilized to predict the size distribution for a new set of operating conditions, which are within the examined ranges. Then, the predicted size distribution was compared with the measured ones. Figure 10 shows that the proposed model was able to predict the size of the granules successfully. Such results indicate that the modelling framework can be used to predict the properties of granules. Therefore, by carefully training the proposed model on a relatively large-scale (industrial scale), it can be used, in some cases, instead of actual experiments throughout the process development. It can

also be used to enhance the process understanding, explore the design space and define the critical process parameters. Moreover, such a framework can pave the way for developing a cost-effective product, improving the supply chain management, minimizing the waste and recycling ratios, enhance the competitiveness of a company in the market and minimize new drug development time.

Figure 10. The validation experiment: the predicted (o) and the experimental (*) distributions for the size using L/S ratio=1.1, feed rate=1Kg/h, Screw configuration consists of conveying and 16 kneading elements and speed=350rpm (a) the IT2FLS and (b) the IT2FLS with bias compensation.

5. Conclusions

The ultimate aim of this research was to develop a fast, transparent, more accurate and cost-effective predictive modelling framework for the twin screw granulation (TSG) process. Such a modelling framework integrated an interval type-2 fuzzy logic system (IT2FLS) and a Gaussian mixture model (GMM). First, the IT2FLS was utilized to model the TSG process. Such a model mapped the granulation input variables to the granule size by extracting linguistic rules from a collected data set. The IT2FLS predicted the size distribution of the granules successfully. In addition, the informative rules extracted from the data can help user to understand and consequently to control the process. The error residuals were then characterized using the modified GMM algorithm, such a model was implemented in a way by which the extracted rules were refined to compensate for any potential bias, which would result from such unmodelled behaviours. Significant improvements were gained by implementing the GMM, it was also shown that most of the predictions fit properly within a 95% confidence interval.

In summary, the proposed modelling framework is a promising development in the granulation process, as it was able not only to predict the granule size successfully, but also to

deal with the uncertainties surrounding such a process. In the future, such a modelling framework can also be adopted to represent the production cycle of pharmaceuticals; by developing a model for each unit operation, followed by connecting these models into one single modelling framework. Therefore, the proposed structure can pave the way for (i) a systematic process control and optimization of the quality of the granules and the downstream product, (ii) the so-called right-first-time production of granules as well as tablets, and (iii) reducing waste and recycling ratios.

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