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Aleš Belič, Igor Škrjanc, Damjana Zupančič Božič, Rihard Karba, Franc Vrečer

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Minimisation of the capping tendency by tableting process optimisation with the application of artificial neural networks and fuzzy models

Aleš Belič [a] Igor Škrjanc [a] Damjana Zupančič Božič [b]
Rihard Karba [a] Franc Vrečer [b,c]

[a] *Faculty of Electrical Engineering, University of Ljubljana, Ljubljana, Tržaška cesta 25, Slovenia*

[b] *Krka d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia*

[c] *University of Ljubljana, Faculty of Pharmacy, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia*

Abstract

The pharmaceutical industry is increasingly aware of the advantages of implementing a quality-by-design (QbD) principle, including process analytical technology, in drug development and manufacturing. Although the implementation of QbD into product development and manufacturing inevitably requires larger resources, both human and financial, large-scale production can be established in a more cost-effective manner and with improved efficiency and product quality. The objective of the present work was to study the influence of particle size (and indirectly, the influence of dry granulation process), and the settings of the tableting parameters on the tablet capping tendency. Artificial neural network and fuzzy models were used for modelling of the effect of the particle size and the tableting machine settings on the capping coefficient. The suitability of routinely measured quantities for prediction of the tablet quality was tested. The results showed that model-based expert systems based on the contemporary routinely-measured quantities can significantly improve the trial-and-error procedures, however, they cannot completely replace them. The modelling results also suggest that in cases where it is not possible to obtain sufficient number of measurements to uniquely identify the model, it is beneficial to use several modelling techniques to identify the quality of model prediction.

Key words: Dry granulation, Tableting, Capping, ANN, Fuzzy models, Mathematical model

1 Introduction

The pharmaceutical industry recognises the advantages of adopting the quality-by-design (QbD) principle together with process analytical technology (PAT) in drug development and manufacturing [1, 2]. Although the implementation of QbD and PAT may be more expensive during product development, large-scale production can be established in a more cost-effective manner and with improved efficiency and product quality. The final goal of PAT is completely automated production, where each significant step is closely monitored and controlled, resulting in the highest possible quality of the product with minimal or no control of the finished product. The main advantage of PAT is its flexibility and ability to immediately adapt to new situations in the process, since the system can detect production deviations and react by adjusting the appropriate process parameters before the deviations can affect the quality of the product.

Tablets are the most common pharmaceutical dosage form. They are produced by compressing a powder mixture containing the active ingredient and auxiliary materials into a solid form. The tablet quality can be described by several parameters such as: accurate tablet mass, hardness, thickness and friability with minimal variations of results. Capping is one of the common technological problems during tableting. It can occur if the intensity of the elastic relaxation overcomes the strength of the inter-particulate bonding formed during compression, leading to separation of the upper part of the tablet from the tablet body. Capping is a serious problem affecting the tablet's mechanical strength and its quality [3].

Many studies on the relationship between the powder's mechanical characteristics, the cohesion, the deformation mechanisms and the elastic recovery of the tablet have been performed in the past [2, 4–14]. However, real multicomponent mixtures of ingredients were rarely evaluated in the published studies. Real pharmaceutical formulations and production equipment are usually complex and practical experiences show that applying models developed in laboratory-scale studies, i.e., [15–18] for large-scale production situations often give unsatisfactory results. The mechanical properties of powder mixtures with a large number of components are too complex to be described in a transparent mathematical model based on theory, thus the mathematical models developed in [4–14] are often not precise enough for the purpose of adjusting the parameters of a tableting machine to inter-batch differences.

The objective of the present work was to study the influence of particle size and the process parameters on the tablet capping tendency. Indirectly, the influence of dry granulation process on the capping tendency was studied through its influence on particle size distribution. We investigated the use of artificial

Email address: ales.belic@fe.uni-lj.si (Aleš Belič).
URL: msc.fe.uni-lj.si (Aleš Belič).

neural networks (ANNs) and fuzzy models for the prediction of the capping coefficient from the routinely measured mechanical properties of the powder mixture and the tableting machine's settings. For the model development we used the capping coefficient (CC) data of tablets produced from powders with different mechanical properties but with the same composition. Model tablets were produced using several different settings of the tableting machine. We also evaluated the efficiency of both model types for the optimisation of the tableting parameters for the known properties of a powder batch as a part of an expert system. The implementation of the expert systems can be very suitable for a better understanding of the process and as a basis for controlling the process in the PAT system [2].

2 Materials and Methods

The method for optimising the tableting process using two different mathematical models (ANN and fuzzy) was developed and tested on a high-capacity Killian T300/40 rotary press with formulation containing high amount of active ingredient which exhibits poor flow and compressibility characteristics and intensive capping tendency. A dry granulation of this formulation led to a larger particle size, improved powder flowability, better compressibility properties and a significantly lower capping tendency [19]. Optimisation of tableting setting parameters such as main pressure, pre-pressure and tableting speed can additionally contribute to minimisation of capping tendency. The data was organised in a matrix where each column represented one measured quantity and each row represented one tablet type. The following quantities were measured for all 76 tablet types: powder distribution over eight particle size ranges (d_1 - d_8), main compression force (F), pre-compression force (f), tableting speed (v), and CC. For the model's evaluation a quality-correlation coefficient R^2 was used:

$$R^2 = 1 - \frac{\mathrm{SSE}_M}{\mathrm{SSE}_T} \tag{1}$$

where SSE_M is the sum of the squared error between the model prediction and the target, and SSE_T is the sum of SSE_M and the average of the target values.

2.1 Production of Model Tablets

In order to study the influence of the particle size distribution of powder mixtures on tablet quality, three types of powder mixtures for tableting were prepared:

a) powder mixture for direct tableting (Type: **Direct** - 1 sample),
b) powder mixture prepared by slugging (dry granulation on a rotary tablet press), using different setting parameters of tableting speed and compression pressure (Type: **Slugging** - 4 samples - see Table 1),
c) powder mixture prepared by dry granulation on a roller compactor using different parameters of compacting speed and pressure (Type: **Roller** - 4 samples - see Table 1).

[Table 1 about here.]

The qualitative and quantitative compositions of all the powder mixtures were the same: active ingredient (M-112, provided by KRKA, d.d., Novo mesto), 75% (w/w), microcrystalline cellulose (MCC, Avicel PH 101, FMC, Germany), 15% (w/w), cation exchange resin - Amberlite IRP88 (Rohm and Haas, France), 5% (w/w), talc (Luzenac val Chisone SPA, Italy), 4% (w/w), magnesium stearate (Faci SPA, Italy), 1% (w/w). Drug, MCC and half of the quantities of talc and magnesium stearate were used intragranulary. The rest of talc and magnesium stearate and the whole quantity of Amberlite were admixed extragranulary to the milled and sieved dry granulate. Milling and sieving of the compacts were performed on the Quadro-Comil U20 machine (Quadro, Canada) using a 1.5-mm sieve. Each powder type was characterised with a particle size distribution based on a sieve analysis (Alpine 200LS-N, Hosokawa, Germany) using the following sieve ranges: 0-0.045mm (d_1), 0.045-0.071mm (d_2), 0.071-0.125mm (d_3), 0.125-0.25mm (d_4), 0.25-0.5mm (d_5), 0.5-0.71mm (d_6), 0.71-1.0mm (d_7), and 1.0-1.25mm (d_8). Each powder type was characterised by the proportion of particles belonging to each particle size group (w_i). All powder mixtures were compressed into tablets on a Killian T300/40 (IMA, Germany) rotary tablet press equipped with round, concave punches (Φ=13 mm, R=26 mm) using different combinations of parameters settings: the main compression force, the pre-compression force and the tableting speed (Table 2). The tablet mass was 0.550 g. Due to the high weight fraction of M-112 in the tablet formulation, the particle size distribution of mixture Direct closely resembles the particle distribution of the plain drug (M-112). Approximately 85% of the particles in Direct are < 0.071 mm, the compactibilitiy slope is $1.63 \cdot 10^{-2} \pm 9.60 \cdot 10^{-4}$, and the crushing strength of tablets made of pure M112 is 98.37 N $\pm$ 5.09 N. Detailed analysis of physical properties can be found in [19].

[Table 2 about here.]

Nine powder mixtures (Direct - 1 sample, Slugging - 4 samples and Roller - 4 samples) were compressed at different combinations of parameters settings during the tableting (process parameter combinations 1.-8.). Mixture Direct was compressed also using process parameter combinations 9. - 12. We produced 76 types of tablets, and a sample of 10 tablets was evaluated from each

tablet type.
The tablet types were evaluated in terms of a capping coefficient (CC) during the tablet crushing strength testing. The tablet was considered to have a capping tendency if the upper part of the tablet completely fell apart from the tablet body during crushing strength testing or if typical relief (a significant step form) appeared on the fractured surface of the tablet, which would indicate that there is a large probability that the tablet would break later during the subsequent steps in production [19]. The CC was calculated as a fraction of the tablets with a capping tendency compared to the whole tested number of tablets.
The CC of each tablet type was analysed in accordance to the following experimental values: compression parameters settings (the main compression force, the pre-compression force, the tableting speed) and powder mixture parameters: the Carr index (CI) and the median of the particle size distribution (p) of the powder. The Carr index is a well-established index for describing the compressibility of powders [9] as it represents a measure for volume reduction. The median of the particle size distribution represents a statistically calculated descriptor of powder type based on particle size distribution of the powders involved in the study.

2.2 Principal component analysis

The dimensionality of the problem, can be identified using principal component analysis (PCA) [20]. PCA calculates linear combinations of regressors, called the principal components, in such a way that the components are linearly independent. The variance of each component indicates its importance. The covariance matrix is calculated from the measured data. Let $\boldsymbol{X}$ denote the matrix of the measurements where each column represents one measured quantity and each row represents one time slice of all the measurements. Thus, the covariance matrix $\boldsymbol{C}$ is calculated as

$$\boldsymbol{C} = \boldsymbol{X}^T \boldsymbol{X} \tag{2}$$

where the diagonal values represent the variances of the measurements (the regressors). The singular values (σ) of the matrix $\boldsymbol{X}$ are equal to the eigenvalues of the covariance matrix $\boldsymbol{C}$ and the corresponding eigenvectors of the matrix $\boldsymbol{C}$ form the transformation matrix $\boldsymbol{T}$, each eigenvector representing one column, such that the principal components $\boldsymbol{P}$ are calculated as

$$\boldsymbol{P} = \boldsymbol{X}\boldsymbol{T} \tag{3}$$

An analysis of each component singular value reveals which components can be neglected without any significant loss of information; generally, it is possible to omit the components whose sum of singular values share in the sum of all

singular values is smaller than or equal to the share of measurement-noise in the measurements.

2.3 Artificial neural network model of the CC

To model the system's characteristics a feed-forward ANN [21–24] was used. The neural network consisted of two neurons with a tangent sigmoid transfer function on the first layer and one neuron with a linear transfer function on the output layer. Such minimalistic structure reduces the problems of over-training. The ANN was trained with the Levenberg-Marquadt algorithm. The network was trained several hundred times to analyse the stability of the result and to reduce the luck-of-training effect. The network with the highest value of R^2 was used as a final result.

2.4 Fuzzy model of the CC

Fuzzy models are often used for the modelling of non-linear relations [25–29]; however, their use in pharmacy remains limited. In this study a Takagi-Sugeno-type fuzzy model was used [30]. The model consists of if-then logical statements that represent the partial relations between the input and the output variables of the model. A logical statement consists of a premise or an if-part that defines a region of input space, and of consequence that is, in Takagi-Sugeno type, an arbitrary function of the input variables (y_i). For simplicity of interpretation, however, the output functions are normally linear functions of the input variables. Thus, the Takagi-Sugeno model of a system with 2 inputs x_1 and x_2, where each input is divided between two fuzzy sets, $x_1 \in X_{11}, X_{12}$ and $x_2 \in X_{21}, X_{22}$, and with outputs y_i that are linear functions of input variables with coefficients k_{ij} would look like:

$$\begin{aligned}
&\mathrm{IF}(x_1 \in X_{11}) \cap (x_2 \in X_{21})\mathrm{THEN}(y_1 = k_{11}x_1 + k_{12}x_2 + n_1) \\
&\mathrm{IF}(x_1 \in X_{11}) \cap (x_2 \in X_{22})\mathrm{THEN}(y_2 = k_{21}x_1 + k_{22}x_2 + n_2) \\
&\mathrm{IF}(x_1 \in X_{12}) \cap (x_2 \in X_{21})\mathrm{THEN}(y_3 = k_{31}x_1 + k_{32}x_2 + n_3) \\
&\mathrm{IF}(x_1 \in X_{12}) \cap (x_2 \in X_{22})\mathrm{THEN}(y_4 = k_{41}x_1 + k_{42}x_2 + n_4)
\end{aligned} \tag{4}$$

Each logical statement defines a region of input space and the corresponding output function. Each input variable is first fuzzified, by calculating the memberships of the fuzzy sets that describe the particular input variable. Next, the output of each statement is calculated, and then the outputs are aggregated by calculating the weighted sum of the outputs, the weights being the

corresponding results of the premises.

$$y = \frac{\mu_1 y_1 + \mu_2 y_2 + \mu_3 y_3 + \mu_4 y_4}{\mu_1 + \mu_2 + \mu_3 + \mu_4} \tag{5}$$

Where μ_i represents the result of a premise statement.

$$\begin{aligned}
\mu_1 &= (x_1 \in X_{11}) \cap (x_2 \in X_{21}) = \min(x_1 \in X_{11}, x_2 \in X_{21}) \\
\mu_2 &= (x_1 \in X_{11}) \cap (x_2 \in X_{22}) = \min(x_1 \in X_{11}, x_2 \in X_{22}) \\
\mu_3 &= (x_1 \in X_{12}) \cap (x_2 \in X_{21}) = \min(x_1 \in X_{12}, x_2 \in X_{21}) \\
\mu_4 &= (x_1 \in X_{12}) \cap (x_2 \in X_{22}) = \min(x_1 \in X_{12}, x_2 \in X_{22})
\end{aligned} \tag{6}$$

2.5 Optimisation

To find the optimal setting for the tableting machine with respect to the powders' mechanical properties, the inputs to the model, representing the powders' properties, must be fixed to the values of the current batch, while the tableting machine's settings can be freely changed within the limits of the machine and the tableting process. As the model represents the effects of the powder characteristics and the tableting machine's settings on the CC, it is possible to find the tableting machine settings that result in the CC being a minimum. The training and simulation of the models as well as the optimisation of the settings were performed in MATLAB (The MathWorks, Natick, MA, USA) [31]. To find the optimal setting with respect to the minimum CC, a simplex optimisation method [32] that was implemented in MATLAB's *fminsearch* function was used. Since the simplex optimisation method is programmed to search for a minimum, the output of the model was used as a criterion function.

3 Results

3.1 Identification of the data's dimensionality

Using a PCA on all the input data (all the data without a CC) showed that there are two significant components in the data. Since the measurement noise could not have been estimated, the significance of principal components was set to 95% of the sum of all singular values of the measurements. The sum of singular values of the first two principal components was already larger than 95% of the sum of all singular values, which means that all the input data could be reduced to two principal components with only 5% loss of information in the measured data, indicating that the dimensionality of the problem

is most likely 2. However, it must be stated that the PCA can be used for the identification of linearly independent variables, and if the relationship between the variables is non-linear, this can result in an underestimation of the dimensionality. Next, we checked if any pair of the measured quantities could represent a suitable input for the model. The best candidates were the Carr index and the main compression force. It would also be possible to use the two most important principal components; however, since they are a combination of all the measured variables this would represent a problem during the optimisation procedure. Calculation of the original variable from the principal component, when only a few of the most significant components are used, is no longer unique and it would not be possible to calculate the optimal components from the result. The Carr index is used for identifying the compressibility properties of the powders; however, the problem was that there were several powder types with the same Carr index, while the CC for those powders was significantly different. This can either indicate that some necessary information about the system is missing or that the Carr index is not suitable information for a prediction of the CC for the studied formulation. First, we added the pre-compression force and tableting speed as the inputs to the model, but the quality of the model prediction was not improved. This means that the available information does not solve the problem of the ambiguity of the CC with respect to the Carr index. Second, we replaced the Carr index (CI) with the median of the particle size distribution of the powders. The median p was calculated as

$$p = \frac{\sum_{i=1}^{8} d_i w_i m_i}{\sum_{i=1}^{8} w_i d_i}. \tag{7}$$

In equation (7) d_i represents the particle size range, w_i is the portion of the particles within the particle size range, and m_i is the median of the particle size range. This solved the ambiguity problems and the model's prediction was significantly better. It must be stressed that p distinguishes between Direct type and both dry granulated powder type (Slugging and Roller) which is not the case for the CI. The median of the particle size distribution of powders from Slugging group are between 0.0657 mm – 0.0541 mm, in Roller group the values of p are between 0.0632 mm – 0.0557 mm, while the value for the Direct powder type is much lower: 0.0028 mm (Table 3).

[Table 3 about here.]

Finally, the ANN and the fuzzy models for the CC prediction were identified with the following inputs: the median of the particle size distribution of the powder (p), and the main compression force. The tableting speed (v) and pre-compression force (f) have no significant effect on the capping coefficient in the selected range of machine settings.

3.2 Model prediction

Both models (the ANN and the fuzzy) were identified with the same data set. For validation purposes a variant of the leave-one-out procedure was used; however, for the final results, all the available data were used for the identification. The surfaces, describing the relation between the main compression force, the median of the particle size distribution and the CC, that were identified with a subset of a complete data set were very similar to the surfaces identified with complete data set.

3.2.1 ANN model

The identification of the ANN's parameters resulted in the nonlinear relation presented in Figure 1. Several repetitions of the ANN's training produced similar results.

[Figure 1 about here.]

The quality of the training process was assessed by a calculation of the correlation coefficient, R^2, which was 0.7 for the ANN model (Figure 1). The reliability of the model for the CC prediction was, after considering the reliability of the CC measurement, estimated to be ± 0.3.

3.2.2 Fuzzy model

The identified model described the input-output relation with two fuzzy sets for each linguistic variable on the input, resulting in four logical statements. The linguistic variable, the median of the particle size distribution was described by two sets that were be named, *fine* and *coarse*, while the main compression force was described with the sets that were named *high* and *low*. The naming of the sets was chosen according to the interpretation of the identified membership functions. The membership functions for the fuzzy sets were identified with the MATLAB's function *anfis*, and are presented in Figure 2.

[Figure 2 about here.]

The logical statements describing the model are as follows:

$$\begin{gathered}
\text{IF}(p \in fine) \cap (F \in low)\text{THEN}(CC_1 = -0.001p + 0.042F - 0.296) \qquad (8)\\
\text{IF}(p \in fine) \cap (F \in high)\text{THEN}(CC_2 = -0.011p - 0.225F - 3.75)\\
\text{IF}(p \in coarse) \cap (F \in low)\text{THEN}(CC_3 = -0.067p + 0.003F)\\
\text{IF}(p \in coarse) \cap (F \in high)\text{THEN}(CC_4 = -11.81p - 0.031F + 1.4796)
\end{gathered}$$

while the output of the fuzzy model is:

$$CC = \frac{\mu_1 CC_1 + \mu_2 CC_2 + \mu_3 CC_3 + \mu_4 CC_4}{\mu_1 + \mu_2 + \mu_3 + \mu_4} \tag{9}$$

where μ_i is a value of the fuzzy intersection for the premise of each statement. The resulting relation for the CC identified with the fuzzy model is presented in Figure 3.

[Figure 3 about here.]

The quality of the fuzzy identification process was assessed by a calculation of R^2. The coefficient R^2 for the fuzzy model was 0.7 (Figure 3). The reliability of the model for the CC prediction was, after considering the reliability of the CC measurement, estimated to be ± 0.3.

3.3 Optimisation

The optimisation was performed only for the Direct system, since this is the technologically and economically optimal method for production. When optimising the tableting machine settings, the mechanical properties of the powder are a-priori known, therefore, only a part of the modelled surface (Figures 1 and 3) at the value of p_1 that describes the particle distribution of the actual powder is relevant. In our models, once the particle distribution is known, the capping coefficient (CC) becomes only a function of the main compression force. Figures 4 and 5 show the CC as the function of the main compression force for the Direct powder type. The difference between the predicted values of the CC for the selected main compression force obtained from the two models is a measure of the prediction quality for the selected value of the main compression force (Figure 6).

[Figure 4 about here.]

[Figure 5 about here.]

[Figure 6 about here.]

In Figure 4 the optimal setting for the main compression force is located below 15kN while in Figure 5 we can observe two optimal regions, at approx. 7kN and at approx. 15kN. However, in both cases the prediction for CC is not higher than 0.3 for the main compression force values that are below 18kN. The pre-compression force (f) and tableting speed (v) have no significant effect on the CC.

4 Discussion

The most important issue during modelling is the model validation. The validation of models that were built exclusively on data (identification) is usually done by testing the model's predictive power. In our case a variant of the leave-one-out procedure was used. Thus, for each identification-validation cycle, 61 randomly chosen tablet types out of 76 were used for the identification, while the model was validated on the remaining 15 tablet types. Validation with the leave-one-out method showed that the relationship between the first principal component of the particle size distribution, the main compression force, and the CC is relatively simple and that the model is capable of extracting the general shape of the relation from the data, regardless of how the identification and validation data were chosen. The only exceptions occurred when the critical data points were selected for the validation set and were thus missing from the identification data set. The critical data points are the data that describe the relationship in areas of the experimental space that were poorly sampled. Therefore, it is clear that the removal of such points from the identification data sets also removes all the information about the relation in such specific areas of the experimental space. The reasons for the occurrence of the critical data points are often linked with the technical problems of studied processes. In our case it was not possible to produce stable tablets for several settings of the tableting machine. Similarly, the production of powder mixtures with specific particle size distributions with standard industrial procedures by targeting the parameters settings during dry granulation is very difficult. Thus not all the areas of the experimental space were equally sampled. On the other hand, such areas are not interesting as possible operation settings for the machine and poorer model prediction in the areas is not a problem (e.g. very low or high main compression force, because they result in tablets with inappropriate tablet hardness). While comparing the prediction surfaces obtained by ANN and fuzzy model (Figures 1 and 3) differences can be observed, however in the areas where the number of measurements is higher the predictions of both models are similar and thus more reliable (Figure 6). In the areas, where measurements are sparse the predictions of both models are different, governed rather by the properties of the models than the properties of the modelled process. That is a clear evidence that some areas of the experimental space have not been adequately sampled and that the model can interpolate the relation in the area using mostly the properties of its mathematical description and not the properties of the measured data.

An additional problem for the model identification was created by combining the data from the dry granulated powders and the data from the Direct powder in the same data set. It was discovered in the subsequent studies [19] that the two types of powders have different compaction characteristics, and therefore, it would be sensible to make separate models for the dry granulated mixtures

and the Direct mixture, however, there was not enough existing data for the identification of two separate models. This discussion can be supported by the results of the separate study [33] on the studied formulation which indicated that an interesting phenomenon occurred during tableting and dry granulation. The transformation of a typical crystalline structure of used active ingredient into a more amorphous form occurs during the compression. The extent of amorphisation depends on physical load, which means that amorphisation is more intensive at tablets made from dry granulated system, as physical load of material is higher than in a case of direct tableting. This transformation favourably influences the stronger bonding between the particles during compression and minimises the capping tendency [19]. The median of the particle size distribution of the powder p partially solved the problem of combination of data collected from the two systems. Dry compacted powders have typically different particle size distributions than Direct powders and using p as regressor, the two systems could clearly be separated. Selection of regressors is always very sensitive procedure that is governed by several factors. Ideally, all the important regressors should have been measured, however, that is either not possible or is not cost effective in industrial environment. Complex compression characteristics of the studied powder mixture nevertheless represent severe difficulty for combination of the data. The presented approach is also a test, if routinely measured powder properties can be used as regressors although they are in some cases only indirectly related to the studied process. Combination of data, collected from different powder types, represents a reduction of measurement costs with not significantly reduced prediction quality.

5 Conclusion

The models developed in the present study (ANN and fuzzy model) are suitable for implementation into the PAT concept and can become an important part of a QbD approach. The identified input-output relation is specific to the tableting machine and its equipment used in the study and cannot be generalised to all tableting machines of the same model and equipment. However, the presented procedure of model identification is generally applicable to all tableting procedures and machines.

Fuzzy models are not very often used in the field of pharmaceutical technology; however, they have some significant advantages over ANNs. Most importantly, it is possible to use other knowledge than just the measured data for their identification, which reduces the need for large quantities of data when identifying non-linear relations. The fuzzy model can be built on the basis of piece-wise linear models that are often used in pharmacy. Thus, we also obtain better model transparency, which is very important for the understanding of complex

non-linear relations.

Although the surface of the identified relation is not equal for both models and, therefore, completely automated setting of the tableting machine, with respect to a powder batch is not possible, the model represents valuable information for the operator, about useful ranges of machine settings with respect to the physical properties of the powder. Using a model is also more cost effective than a trial-and-error approach. Optimisation of the tableting machine's settings by trial and error produces a relatively large number of faulty tablets and is very time consuming, especially when the starting settings of the machine were poorly guessed, and the procedure has to be repeated for each new powder batch characteristics. In an industrial environment with a PAT system implemented the development of the model would have to be divided into two stages. First, the data generation for building the model would be organised as a dedicated experiment that should cover the area of interest described by machine's setting parameters and the properties of the powder. For the modelling, the machine's settings must be systematically chosen to cover the whole area of interesting values and tested for several batches. Next, the model would be validated and further developed with data from large-scale production. Production monitoring data typically contributes relatively dense data points from the near-optimal areas of the experimental space that were not included at the beginning in the experimental plan. The experiments for modelling purposes are more expensive than the ones for optimisation with trial and error; however, the model can be used for the prediction of optimal settings for new batches, which substantially shortens the time for optimising the machine with respect to a new batch and reduces the number of faulty tablets. In any case, the models that will be built on the contemporary routinely-measured quantities will most likely never be precise enough for a completely automated adaptation of the machine settings as a compensation for a batch-to-batch differences, but they can serve as a significant improvement of the trial-and-error procedure.

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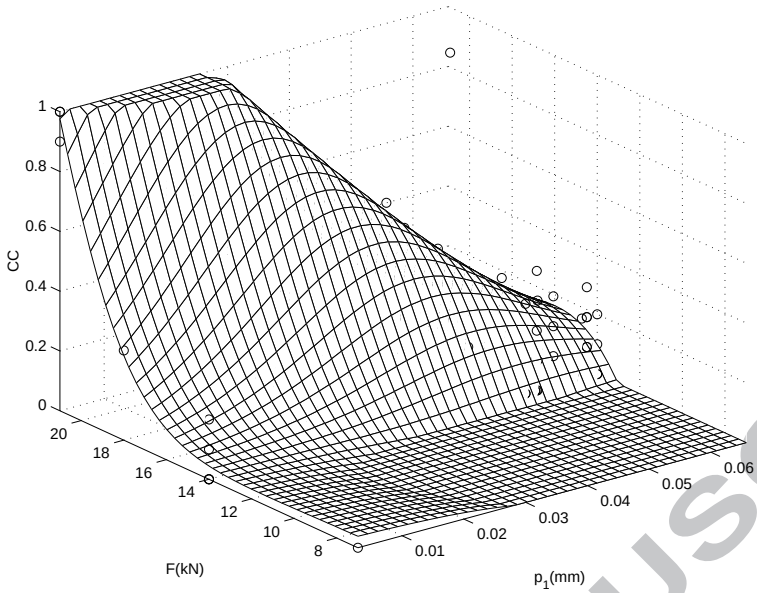

Figure 1. Non-linear relation between the main compression force (F), the median of the particle size distribution of the powder (p) and the capping coefficient (CC). The circles represent the measurements; the surface represents the prediction of the ANN model.

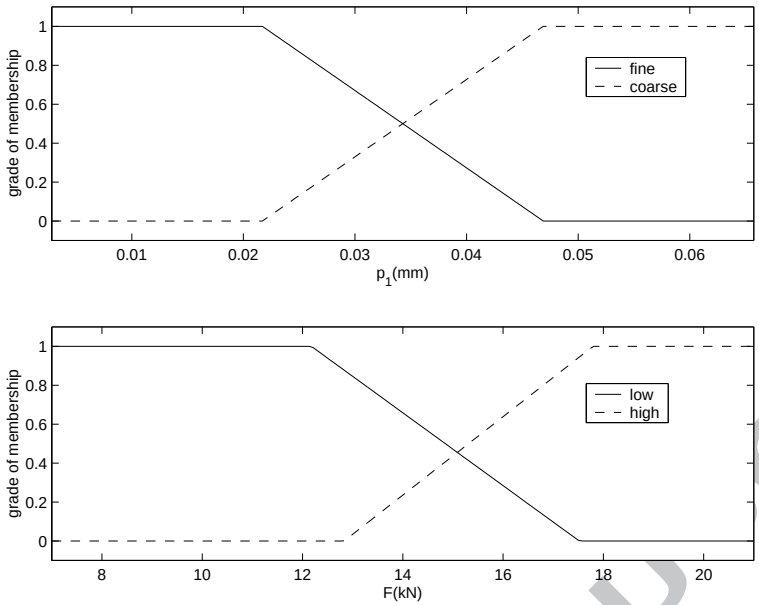

Figure 2. Membership functions for the linguistic variables: a) the median of the particle size distribution (p), b) the main compression force (F)

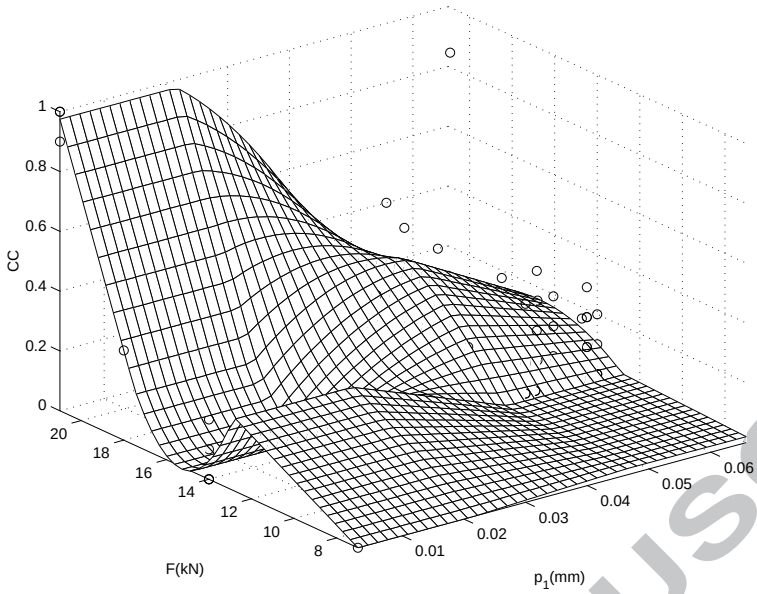

Figure 3. Non-linear relation between the main compression force (F), the median of the particle size distribution (p) and the capping coefficient (CC). The circles represent the measurements; the surface represents the prediction of the fuzzy model.

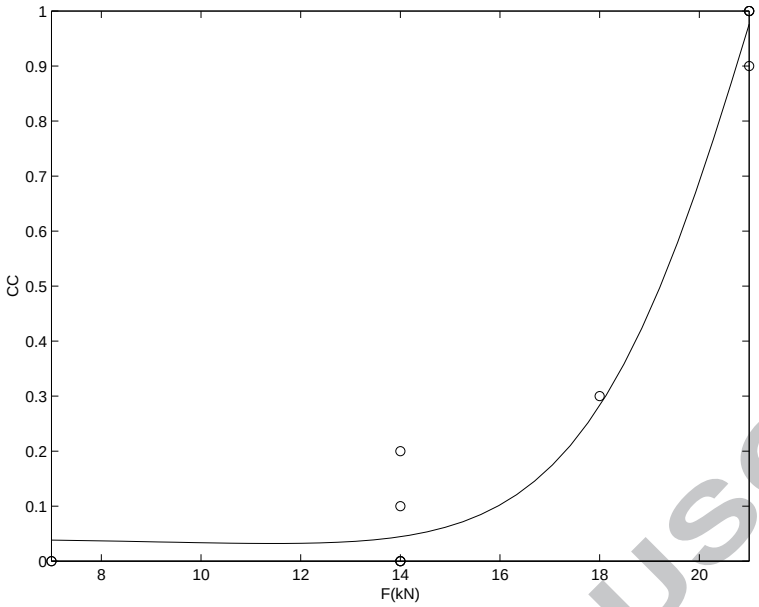

Figure 4. CC with respect to the main compression force (F) for the Direct powder as identified with the ANN. The circles represent the measurements; the surface represents the prediction of the model.

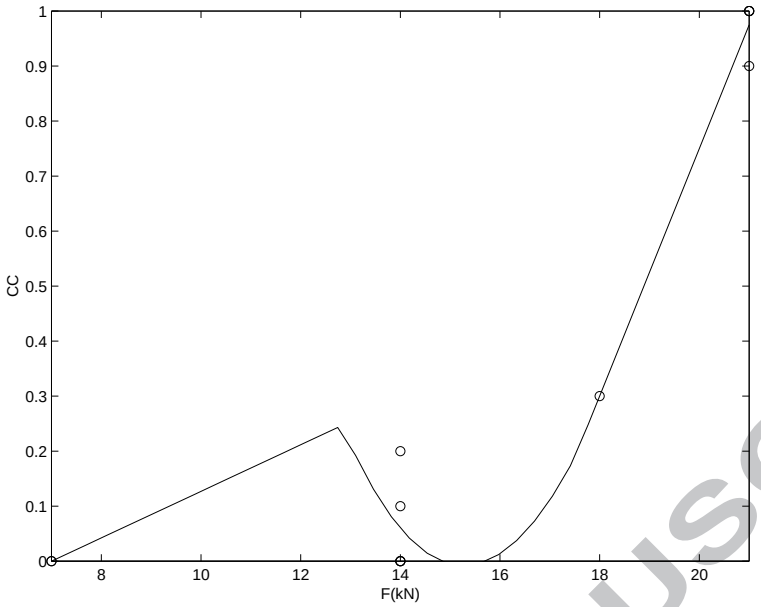

Figure 5. CC with respect to main compression force (F) for the Direct powder as identified with the fuzzy model. The circles represent the measurements; the surface represents the prediction of the model.

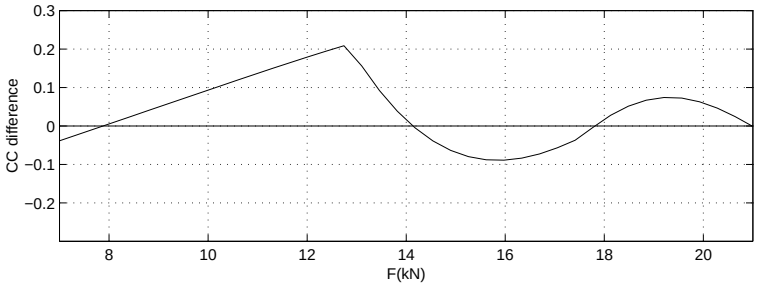

Figure 6. The difference of the predicted CCs between ANN and fuzzy model.

List of Tables

Table 1
Process parameters for dry granulation on a rotary tablet press (Slugging) and on a roller compactor (Roller)

Slugging			Roller		
label	speed (x1000 tbl/h)	compression force (kN)	label	speed (x1000 tbl/h)	compression force (kN)
S26/21	26	21	R12/60	12	60
S100/21	100	21	R20/60	20	60
S26/14	26	14	S16/85	16	85
S100/14	100	14	S20/85	20	85

Table 2
Combinations of the process parameters settings

Process parameters combination	Main compression force (kN)	Pre-compression force (kN)	Tableting speed (x 1000 tbl/h)
1.	21	5	26
2.	21	9	26
3.	14	9	26
4.	14	5	26
5.	18	7.5	40
6.	14	7.5	40
7.	14	9	67.5
8.	14	9	100
9.	21	5	100
10.	21	9	100
11.	7	5	100
12.	7	5	26

Table 3
Comparison of the Carr index (CI) and the median of the particle size distribution (p)

	Direct	R16/85	R20/60	R12/60	R20/85	S26/21	S100/21	S26/14	S100/14
CI	33	27	35	30	33	21	21	20	20
p(mm)	0.0028	0.0586	0.0560	0.0632	0.0557	0.0657	0.0541	0.0559	0.0640