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A data mining approach to optimize pellets manufacturing process based on a decision tree algorithm

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ABSTRACT

The present study is focused on the thorough analysis of cause–effect relationships between pellet formulation characteristics (pellet composition as well as process parameters) and the selected quality attribute of the final product. The shape using the aspect ratio value expressed the quality of pellets. A data matrix for chemometric analysis consisted of 224 pellet formulations performed by means of eight different active pharmaceutical ingredients and several various excipients, using different extrusion/spheronization process conditions. The data set contained 14 input variables (both formulation and process variables) and one output variable (pellet aspect ratio). A tree regression algorithm consistent with the Quality by Design concept was applied to obtain deeper understanding and knowledge of formulation and process parameters affecting the final pellet sphericity. The clear interpretable set of decision rules were generated. The spehronization speed, spheronization time, number of holes and water content of extrudate have been recognized as the key factors influencing pellet aspect ratio. The most spherical pellets were achieved by using a large number of holes during extrusion, a high spheronizer speed and longer time of spheronization. The described data mining approach enhances knowledge about pelletization process and simultaneously facilitates searching for the optimal process conditions which are necessary to achieve ideal spherical pellets, resulting in good flow characteristics. This data mining approach can be taken into consideration by industrial formulation scientists to support rational decision making in the field of pellets technology.

1. Introduction

The multivariate data analysis of manufacturing process is increasingly used in the field of pharmaceutical technology. It is mainly due to the fact of growing need for better understanding of the formulation and process development by pharmaceutical scientists (Djuris, 2013). This approach is consistent with the Quality by Design concept which is currently recommended by the regulatory authorities worldwide (ICH Q8 R2, 2009). It is generally known that research and development stage in the pharmaceutical industry is very expensive and time-consuming, therefore it should be conducted as efficiently as possible. A successful development of a pharmaceutical formulation is dependent on both formulation ingredients and process parameters (Djuris, 2013). Application of chemometric tools such as experimental design and multivariate data analysis enables to increase the product and process knowledge and consequently allows for appropriate excipients selection as well as proper identification and optimization of critical process parameters (Djuris et al., 2012; Ibrić et al., 2002; Petrović et al., 2011; Verma et al., 2009).

Generally, two various approaches in better product and process understanding can be distinguished. One of them is experimental design methodology which seems to be an essential tool for successful building of quality into new pharmaceutical products and processes, especially at the early stage of their development. In this approach, the proper choice of experimental designs and then the data collection according to the generated design matrix are crucial in order to draw valid and objective conclusions. Data from a well-designed experiment are easy to analyze. In many cases, a simple low-order (usually a first-order or a second-order) polynomial model is appropriate to describe in detail the main effects of the investigated factors and their interactions. Furthermore, a better overview can be obtained by plotting

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the model response surface. Despite of many advantages of experimental design approach, sometimes a second-order polynomial model does not have sufficient density in the parameter space to capture the expected nonlinearities of the system (Kristan and Horvat, 2012).

In contrast to experimental design, data mining approach in better product and process understanding differs the manner in which the data were collected. This approach based on multivariate data analysis is usually applied in the quality improvement of existing products and processes. The multivariate methods can be used in manufacturing process analysis to reveal internal structure and identify dependencies in large complex process data sets from historical batch records. Thus, the historical process data sets are analyzed retrospectively in order to better understand the manufacturing process and consequently improve the product quality. A typical multivariate techniques, such as artificial neural networks, support vector machines and partial least squares regression are widely used to model complex relationships hidden in large data sets (Amani et al., 2008; Chansanroj et al., 2011; Lourenço et al., 2011; Mihajlovic et al., 2011; Ronen et al., 2011). These methods can predict successfully the product properties resulting from a given set of ingredients and process conditions. Despite of good predictive abilities of the obtained models, the relationships between the predictor variables and the predicted output value (quality attribute of the final product) are not so easy to interpret and for this reason, the mentioned methods are often considered as black boxes. The use of this kind of multivariate models is not completely in accordance with the Quality by Design concept which requires clear science-based understanding of the mechanics behind the prediction and thus the system being modeled (Polizzi and García-Muñoz, 2011). A good solution can be the application of knowledge discovery methods, such as neuro-fuzzy logic, decision trees or methods based on rough set theory. These exploratory data mining techniques enable to generate easily understandable decision rules which are useful in a manufacturing process optimization as well as a new drug product development (Branchu et al., 2007; Lee et al., 2003; Mendyk et al., 2010; Shao et al., 2006). The ability of the knowledge discovery methods to convert large complex process data sets into information-rich rules and simultaneously their ability to identify the most significant factors affecting the product quality make them suitable for quality improvement of existing pharmaceutical products and processes, according to the Quality by Design principles. The multivariate analysis of historical process data sets can also provide valuable guidance for design of new drug products and processes. This approach seems to be complementary to the experimental design in the pharmaceutical quality improvement strategy. The design approach is particularly relevant and recommended at the early development stage of new pharmaceutical formulations, whereas data mining approach (through a retrospective analysis) seems to be a good solution to extract knowledge from large, complex formulation and process data sets from historical batch records. The significant advantage of this approach is the possibility of uncover interactions and non-linear relationships that might not be easily detectable when small experimental designs are used.

Pharmaceutical literature overview from the last few years indicates that the analysis of the process data seems to be essential in order to gain useful knowledge, improve process understanding and consequently ensure acceptable final drug product quality. The attempt to implement selected algorithms to new pharmaceutics development is completely reasonable and recommended. As there is no literature data on application of a decision trees methodology for characterization of pellets manufacturing process, in this work attention is directed toward the decision tree algorithm as a potentially useful tool for pellet formulation development and optimization. The present study is focused on the thorough analysis of cause–effect relationships between formulation characteristics (pellet composition as well as process parameters) and the selected quality attribute of the final product. The quality of pellets was expressed by the shape using the aspect ratio value. The pharmaceutical pellets should have ideal spherical shape, resulting in good flow properties which ensure reproducible die or capsule filling and consequently good content uniformity (Dukić-Ott et al., 2009). Due to the possibility of generation clear set of decision rules, in this project the tree regression algorithm was applied to find and describe significant relationships hidden in the experimental data set and to build a regression model, providing the pellet aspect ratio based on the formulation composition and process parameters. The aim of a multivariate model construction was to find the optimal formulation composition and extrusion/spheronization parameters for obtaining spherical pellets.

2. Materials and methods

2.1. The data set

The pellet formulation data set containing 224 experimental records was formed based on data described in previously published research articles (Bornhöft et al., 2005; Thommes and Kleinebudde, 2006b, 2007a, 2007b, 2008). All pellets were prepared by extrusion/spheronization technique using eight different active pharmaceutical ingredients (acetaminophen, theophylline, mesalamine, hydrochlorothiazide, phenacetin, chloramphenicol, dimenhydrinate, lidocaine) and various excipients. The active pharmaceutical ingredients (API) were used at fractions of 20%, 40%, 60% and 80% in pellet formulations. Each API molecule was described by water solubility and log *P* value. The influence of two different types of the pelletization aid (microcrystalline cellulose, kappa-carrageenan) on pellets sphericity was investigated. The pelletization aid was used at fraction of 20% in each formulation. Furthermore, four fillers of varied solubility (lactose, mannitol, maize starch, dicalcium phosphate dihydrate) at fractions of 0%, 20%, 40% and 60% were examined. The production parameters during extrusion (screw speed, number of holes), spheronization (spheronizer speed, spheronization time, spheronization temperature) and drying (temperature, time) were varied. All qualitative input variables and minimum and maximum values for the above mentioned quantitative variables describing pelletization process parameters, API and excipients properties are given in Table 1.

A data matrix for chemometric analysis contained 14 input variables (both formulation and process variables) and one output variable (pellet quality attribute). The input variables (also called independent variables) described pellet quantitative and qualitative composition as well as preparation technology (screw speed, number of holes, spheronization speed, spheronization time, spheronization temperature, drying temperature, drying time, water content of extrudate). Whereas the output variable (also called a dependent or target variable) was a pellet aspect ratio value. The ideal pellets should be characterized by spherical shape which is expressed by the aspect ratio value of one.

2.2. Data mining procedure

In this project, CART (Classification and Regression Trees) as one of the most popular methods of decision trees induction was applied to explore the impact of process parameters and formulation composition on the pellet aspect ratio. As a non-parametric method, it does not require any assumptions about the statistical distribution of predictor variables (Mahjoobi and

Table 1
Qualitative input variables, minimum and maximum values for quantitative input variables and the obtained pellet aspect ratios.

Qualitative input variables			
Excipients properties	Type of filler	Lactose, mannitol, maize starch, dicalcium phosphate dehydrate	
	Type of pelletization aid	Microcrystalline cellulose, kappa-carrageenan	
	Parameters	MIN	MAX
Quantitative input variables			
API properties	Log*P*	−0.39	2.44
	Solubilty (g/L)	0.72	14.30
	Fraction of API (%)	20	80
Excipients properties	Fraction of filler (%)	0	60
Extrusion	Screw speed (rpm)	50	200
	Number of holes	3	23
Spheronization	Speed (rpm)	500	1000
	Time (s)	15	300
	Temperature (°C)	15	45
Drying	Temperature (°C)	60	105
	Time (h)	0.17	24
LOD (%)*		34	125
Quantitative output variable			
Aspect ratio		1.05	1.89

* LOD – loss on drying; the water content of the extrudates was calculated in % (w/w) based on dry mass.

Etemad-Shahidi, 2008). A significant advantage is also that both quantitative and qualitative data can be used as inputs to form the decision tree. CART algorithm creates binary trees from studied data, thus each internal node has exactly two outgoing branches. The important inputs are selected as the splitting criteria in forming the shape and sequence of branches. The goal is to produce subsets of the data which are as homogeneous as possible with respect to the target variable (Mahjoobi and Etemad-Shahidi, 2008). The decision tree criteria separate important from unimportant branches so only strong relationships between inputs and the target variable are retained (de Ville, 2006). Thus, the decision tree is useful as an exploratory data mining technique. Thanks to clear set of decision rules, it is possible to discover cause–effect relationships hidden in a large studied data set.

Because of predictive abilities, a tree model provides the target variable based on the values of predictor variables. If the target variable is continuous, CART algorithm produces a so called regression tree model. In this model, each terminal node's predicted category is the mean of the target values for records in the node (Mahjoobi and Etemad-Shahidi, 2008). A tree model complexity has a crucial effect on its accuracy. Too complicated trees with too many nodes should be avoided because of a lack of transparency and difficulties with useful graphical representation (Rokach and Maimon, 2008). The cross-validation was applied to assess the optimal model complexity and minimize the risk of overfitting. Furthermore, to avoid undesired model complexity, in our work the minimum size of each node which was divided into child nodes was defined as 22 cases (i.e. 10% of all cases in the studied data set). It means that any split of a node containing less than 22 cases was not accepted.

Detailed description and theoretical concepts related to this data mining technique can be found in references (de Ville, 2006; Grąbczewski, 2014; Rokach and Maimon, 2008). In our project, all calculations were performed with the use of STATISTICA® 10 software (StatSoft, Tulsa, Oklahoma, USA).

3. Results and discussion

A complex multivariate dataset (224 pellet formulations described by 14 independent variables) was formed and then the tree regression algorithm was applied in order to find the best set of decision rules and simultaneously to investigate whether the pellets quality can be successfully predicted based on a formulation composition and preparation technology. In this study, the pellet quality was characterized by the shape (expressed as aspect ratio). The pellets for pharmaceutical applications should have spherical shape. The spherical pellets are expected to have better flow characteristics. It is assumed that the aspect ratio lower or equal to 1.1 is acceptable for pharmaceutical pellets whereas ratios above this value are considered as insufficient (Bornhöft et al., 2005; Thommes and Kleinebudde, 2006a, 2007a; Thommes et al., 2009). A good data mining model, according to the Quality by Design concept, should facilitate finding the optimal formulation composition and extrusion/spheronization parameters for obtaining desired spherical pellets.

In order to construct a reliable chemometric model, the data set was randomly divided into training and testing subsets. The training subset containing 75% of all cases was used for a model construction, whereas the testing subset (25% of all cases) was required to test a predictive ability of the calibration model. During the model construction, data space was divided into mutually exclusive regions, containing homogeneous groups of objects according to the pellet aspect ratio (a target variable). Two child nodes were formed in each division, thus a binary decision tree was finally obtained. As shown in Fig. 1, the decision tree consists of nodes, which are connected by branches representing the explanatory variables.

The influence of process parameters on pellet sphericity is depicted in the form of a tree graph (Fig. 1). The obtained model gives insight into the mutual relations hidden in the complex studied pelletization process data set. As it can be seen, variables describing spheronization conditions such as speed and time are directly responsible for the pellet aspect ratio. These are variables with very high predictive value. Furthermore, number of holes during extrusion and water content of extrudate have been also recognized as key factors influencing pellet shape. Information extracted from the tree model shows that a larger number of die holes applied during pellet manufacturing process leads to pellets with the lower aspect ratio value. The type and fraction of the active pharmaceutical ingredient as well as the type and fraction of excipients were not found significant. The analysis of the tree graph implies explicitly that the pellets sphericity is determined mainly by the extrusion/spheronization process conditions. The

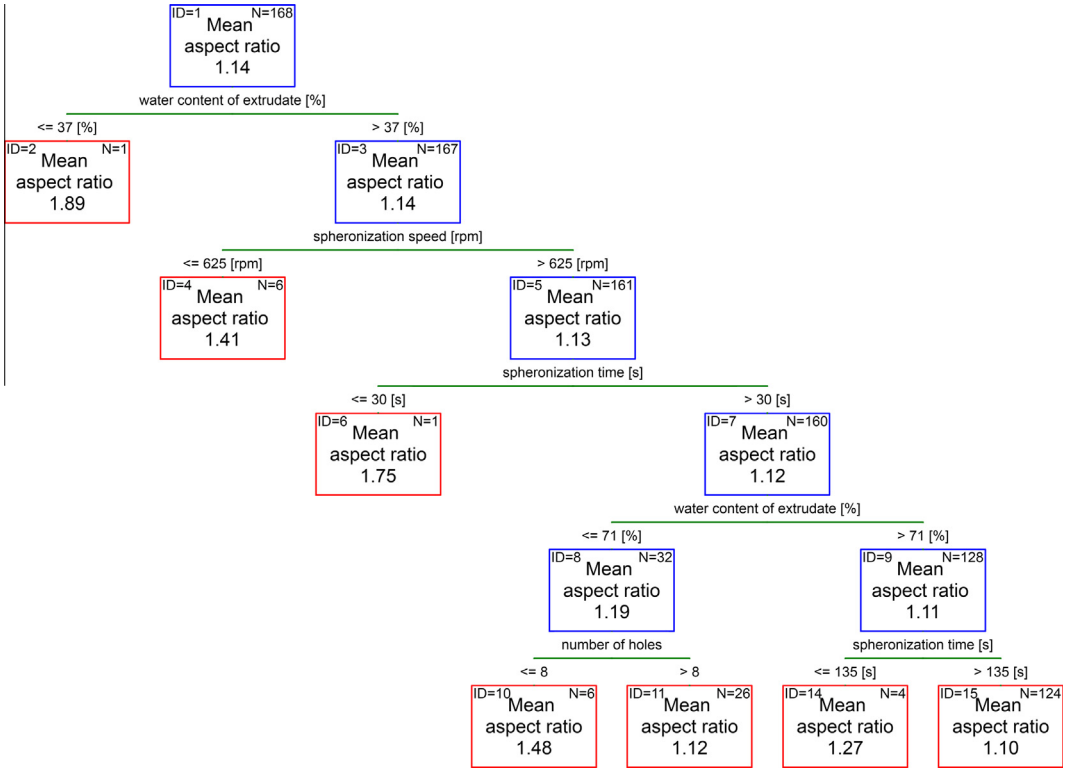

Fig. 1. Regression tree model generated by CART algorithm, *N* is the number of cases in each node.

pellet shape seems to be independent of drying parameters (such as temperature, time) and the formulation composition.

Pellets with the lowest aspect ratio were defined as optimum. The most spherical pellets were achieved by using a spheronizer speed higher than 625 rpm and spheronization time longer than 135 s. As it can be seen, if spheronization speed is less than 625 rpm, the pellet aspect ratio tends to be high (1.41). Non-spherical pellets with high mean aspect ratio value (1.75) were also obtained when spheronization speed was higher than 625 rpm and simultaneously spheronization time was shorter than 30 s. The unacceptable pellet shape was achieved when water content of extrudate was less than or equal to 71% and when less than 8 die holes were applied during extrusion, despite of using a higher speed (>625 rpm) and longer time of spheronization (>30 s). Thus, it seems that the number of holes during extrusion process is preferred to be larger than 8.

The results of the study confirm clearly that the pellet sphericity is mainly related to the selected pelletization process parameters. Four of the eight investigated process parameters (water content, one extrusion and two spheronization variables) affected the pellet shape, markedly. The types and ratios in which the ingredients were combined did not influence the pellet shape significantly. The analysis of the decision tree structure indicates that pellet sphericity could be improved by changing the spheronization (speed, time) and extrusion (number of holes) conditions or water content of extrudate. An increase in the number of holes, time and speed of spheronisation process resulted in pellets with lower aspect ratios. Furthermore, most of the investigated formulations (mainly containing carrageenan as the pelletization aid) required a higher water content to produce spherical pellets. The results of our preliminary research work have indicated the possibility of application of a decision tree methodology to better pelletization process understanding and consequently to appropriate design manufacturing process in order to achieve a desired pellet shape. As shown in Fig. 1, spheronisation time longer than 135 s should be recommended, shorter spheronisation time has a negative effect on the sphericity and leads to pellets with higher aspect ratios. The combination of spheronization speed higher than 625 rpm, spheronization time longer than 30 s and a number of holes less than 8 should be avoided. Decreasing the number of die holes for extrusion clearly resulted in pellets with unacceptable aspect ratio value.

The principal cause–effect relationships obtained in this study are also in agreement with the results described by Bornhöft et al. (2005), Thommes and Kleinebudde (2006b, 2007a, 2007b, 2008), which additionally confirms the model usefulness. Mendyk et al. (2010) have applied neural networks and sensitivity analysis to identify crucial variables influencing the pellet aspect ratio. Their study also revealed the importance of spheronization parameters such as rotational speed and time of the process. Whereas, variables describing formulation composition were confirmed to be less significant than preparation technology. Thus, the pellet aspect ratio seems to be much more dependent on the process variables than properties of ingredients.

In order to evaluate the accuracy of prediction, aspect ratio values predicted by the model were compared to experimentally obtained values by using correlation coefficient. These coefficients were determined both for the training ($r = 0.8726$) and testing ($r = 0.8013$) subset. As shown in Fig. 2, the predicted pellet aspect ratios were comparable to the actual measured values which confirmed model usefulness.

The model performance was also estimated as the mean squared error (MSE) and the root mean squared error (RMSE) for the training and testing subsets (Table 2).

The results of this study confirm good predictive and describing abilities of decision trees in terms of pellets preparation technology. The obtained tree model provides constructive conclusions about the impact of process parameters on the pellet sphericity. The significant advantage of the model is undoubtedly easy visualization of the complex pelletization process data and

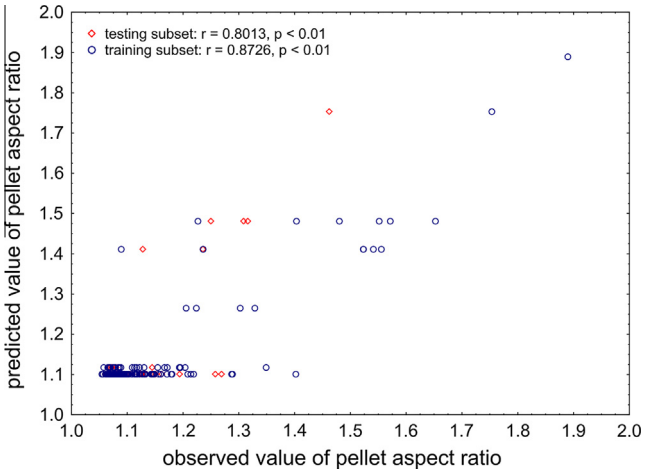

Fig. 2. Comparison between observed and predicted pellet aspect ratios by regression tree model (CART algorithm) for testing and training data.

Table 2
Estimation of the regression tree model performance.

	Training subset	Testing subset
MSE	0.0044	0.0073
RMSE	0.0661	0.0855

interpretability of the results because of a clear set of decision rules. In contrast to so called black box models (such as artificial neural networks), the decision tree methodology allows not only to predict but also explain and describe relationships between the preparation technology and the final product quality attribute. A series of *if-then* rules provide deeper understanding and knowledge of factors affecting the pellet aspect ratio. This approach is highly in accordance with the Quality by Design concept because it assumes designing manufacturing process to ensure predefined product quality. Better pelletization process understanding can directly lead to pellets sphericity improvement. The use of decision tree methodology as a decision-support tool makes it possible to choose optimal process parameters that are necessary in order to achieve a desired quality of final drug product.

4. Conclusions

This study indicates that the multivariate calibration technique such as the tree regression algorithm is capable to find crucial cause–effect relationships hidden in a large complex data set, describing pellets composition and their preparation technology. The significant advantage of this approach is undoubtedly the interpretability of the regression model because of simple, informative and statistically meaningful rules which can be used to support rational decision making in the field of pellets technology. In contrast to so called black box models, the described approach is completely in accordance with the Quality by Design concept because of the transparency of mechanics behind the prediction.

To sum up, the decision tree method as an effective data mining tool is expected to gain much interest in the field of industrial pharmaceutical technology. This data mining approach could increase knowledge of the formulation and it also provides useful clues for industrial formulation scientists. The extracted information could directly lead to the quality improvement of existing products and processes as well as could speed up the development process in the pharmaceutical industry, significantly.

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