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Short communication

Application of classification trees technique in optimization of parameters of production of film-coated tablets

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Introduction

It is relatively easy to analyze data obtained in a design of experiments and when it is possible, to describe evaluated system by using the first or second order model. When higher order models are required to describe nonlinearity of the system, or when data are not gathered in a statistical design of experiments it can be practical to apply one of data mining techniques to develop models (Kovačević et al., 2022, Mihajlović et al., 2011). Data mining is a branch of computer science that is involved in untrivial extraction of implicit, previously unknown and potentially useful information from data bases. It combines techniques of machine learning, artificial intelligence, pattern recognition and is also known as data driven discovery. Data mining techniques that can be employed are: regression and classification trees, artificial neural networks, genetic algorithms and fuzzy systems (Maimon and Rokach, 2009). The aim of this work was to apply data mining technique in evaluating effects of input factors on the dissolution profile of film-coated tablets. During the production of development batches, it was observed that after film-coating, dissolution rate increases for some batches and for the others it decreases.

Materials and methods

API belongs to BCS class III. Tablets were produced by either direct compression or dry granulation and coated with the same film.

Table 1. Input and output variables used for modelling

Continuous input variables	range
Average core hardness	90 - 125 N
Core disintegration	40 - 125 s
Inlet air temperature (spraying start)	48 - 52°C
Inlet air temperature (spraying end)	49 - 53°C
Suspension flow rate	7 - 8 g/min
Outlet air temperature spraying (start)	38.0 - 43.0°C
Outlet air temperature spraying (end)	37.5 - 40.5°C
Spraying time	20 - 48 minutes
Inlet air temperature (drying)	50 - 51°C
Outlet air temperature (drying)	43 - 45°C
Time of drying	2 - 5 minutes
Categorical output variable	range
Dissolution rate	increase / decrease

Data analysis was performed by using software JMP® Pro version 17 (JMP Statistical Discovery LLC, USA). Decision tree algorithm was employed to analyze data. Historical data set from 19 experiments that were not carried out according to factorial or fractional factorial experimental plan was used for modelling. 11 continuous inputs and one categorical output variable that were included in the modelling are presented in the Table 1.

Dissolution profile is tested by using 900 ml of Phosphate buffer pH 6.8 at 37 °C, and paddle apparatus at

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speed of 50 rpm at time points: 5, 10, 15, 20, 30, 45 and 60 minutes.

Results and discussion

Graphical overview of classification of batches, where increase or decrease of dissolution rate was observed, is presented in Figure 1. Partition based model identified that the factor with most significant effect on dissolution profile after film-coating is the hardness of tablet cores. After film-coating of tablet cores with average hardness higher than 106.8 N, in 7 out of 8 observed cases decrease of dissolution in the first time points was observed. Out of 11 batches for which increase in the amount of dissolved API after 5 and 10 minutes was observed, ten had average hardness of cores lower than 106.8 N.

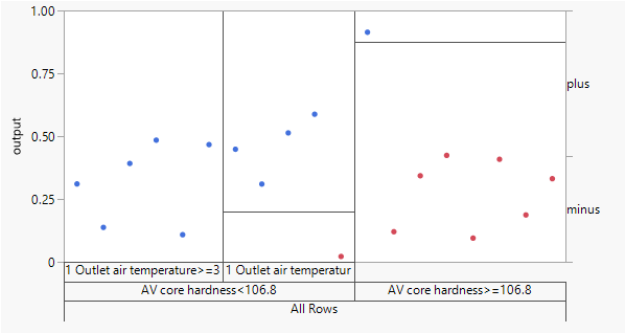

Fig. 1. Graphical overview of classification of evaluated trials

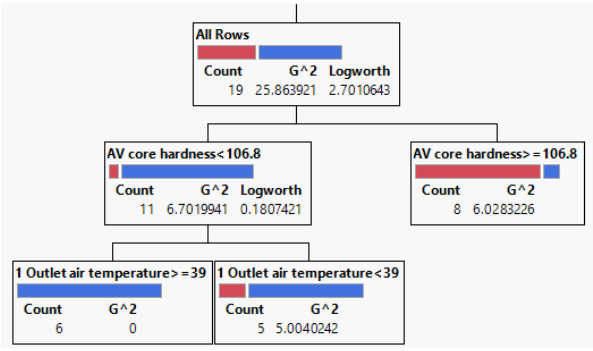

Fig. 2. Tree diagram describing how different batches were split according to effect of significant input factor

In addition, trials for which increase of dissolved amount of API in the first two time points was observed, could further be split into two categories depending on the outlet air temperature during the spraying phase. By applying prediction profiler function of the used software, developed model can be applied so as to define values of process and in-process control parameters of tableting and film-coating steps of production process, in order to achieve target release of API from finished film-coated tablets as it is presented in Figure 3.

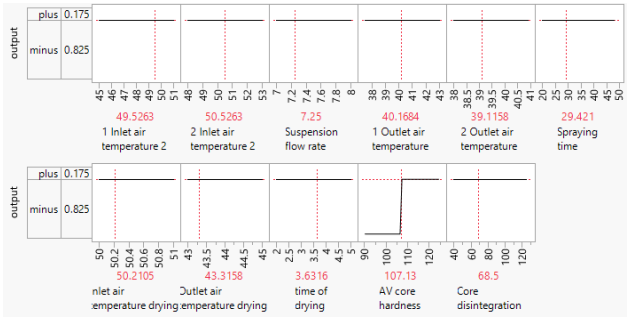

Fig. 3. Prediction profiler function of the software showing how process and in-process parameters should be set, in order to achieve desired release of the API

Conclusion

Classification (decision) tree technique was applied to evaluate the effect of process and in-process control parameters on the results of dissolution after film-coating of tablets. Historical data were used for model development. Developed model can be used for optimization of production process, so as to achieve target release.

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