ARTIFICIAL NEURAL NETWORKS FOR OPTIMISATION OF TABLET PRODUCTION

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Abstract

Pharmaceutical industry is one of the most regulated industries. Quality by design is a contemporary approach in pharmaceutical development and production.Tablet is the most common pharmaceutical dosage form prepared by compression of dry mixture of powders consisting of active ingredient and excipients into solid compacts. The process of tabletting consists of three stages: a) powder mixture is filled into die; b) compaction, when powder is compressed inside a die by two punches, resulting in plastic and elastic deformation and/or particles fragmentation, and c) ejection, when tablet is ejected from the die and elastic recovery of tablet may occur. Intensive elastic recovery can lead to separating upper part of tablet from the tablet body (capping). Mechanical behaviour of powders during tableting and quality of tablets depend on powder characteristics (formulation) and tableting parameters on tablet press machine.The aim of present study was optimisation of tableting process in order to diminish capping occurrence and variation of tablet mass and crushing strength. Optimisation was performed for the product where 70% of the tablet weight represent active ingredient, on the high capacity rotary-tablet press, in the standard production environment. Artificial neural networks (NN) were used to model the relation between quality and process parameters. It can be concluded that NN can be used to describe relation between raw material characteristics, process parameters and quality of tabletting process. Therefore, it is also possible to find optimal set of process parameters with modelling and simulation, considering the raw material characteristics. Modelling and simulation indicates that it is possible to find process settings for tabletting of non-preprocessed powder such that sufficient quality of tablets can be achieved.

Keywords: tabletting, optimisation, modelling, simulation, artificial neural networks.

Presenting Author's Biography

Aleš Belič received B.Sc and Ph.D. degrees in electrical engineering from the University of Ljubljana, Slovenia in 1994, and 2000 respectively. He is currently Associate Professor at the Faculty of Electrical Engineering, University of Ljubljana. Main areas of his professional interest are artificial intelligence modelling techniques in bio-medical areas. Currently he is involved in modelling of cholesterol pathways in human in the frame of 6th European Framework project STEROLTALK, and in functional analysis of EEG signals.

1 Introduction

Pharmaceutical industry is one of the most regulated industries. The quality should be incorporated into the products. Quality by design is a contemporary approach in pharmaceutical development and production. It presents entire process understanding, using modern analytical methods and optimisation tools (eg.: modelling, artifficial neural network, fuzzy logic ...) in order to optimise product quality and production efficiency during process and diminish quality controls at the end of production.
Tablet is the most common pharmaceutical dosage form prepared by compression of dry mixture of powders consisting of active ingredient and excipients into solid compacts. The process of tabletting consists of three stages: a) powder mixture is filled into die; b) compaction, when powder is compressed inside a die by two punches, resulting in plastic and elastic deformation and/or particles fragmentation, and c) ejection, when tablet is ejected from the die and elastic recovery of tablet may occur. Intensive elastic recovery can lead to separating upper part of tablet from the tablet body (capping).
Mechanical behaviour of powders during tableting and quality of tablets depend on powder characteristics (formulation) and tableting parameters on tablet press machine. In order to assure high and repeatable quality of products the processes and formulations should be optimised. This is specially important on high capacity rotary tablet presses which can produce few hundred thousand tablets per hour and are very sensitive to product and process variables. Special challenge is the large scale production of products in form of tablets where the active drug loading is high (>50% of total mass of tablet). Active drugs as organic molecules very often have inappropriate physical properties which prevent using direct compression of powder mixtures, which is the most economical (shortest process time, minimum cleaning and validation need, low energy consumption, environmentaly friedly). The problem of capping is often observed in production of tablets with high drug loading. This problem can be solved either by formulation or process optimisation.
To find the optimal set of the parameters (main compression force, precompression force, compression speed ...) on tablet press, it is possible to make a few tablets for each set of parameters, and then the operator can decide which settings should work best, and then starts the production. Fine machine setup optimisation must be performed, due to some batch to batch variations of raw materials or some other variables. During setup procedure, many of the tablets do not pass the quality control and must hence be discarded, which can be very expensive, regarding the price of the raw material and the number of trials, needed to find optimal settings. To optimise quality of tablets and to reduce the number of faulty tablets, a modelling and simulation procedures can be used, where a model of quality parameters with respect to process parameters must be developed. The raw materials used in tests should cover all the expected characteristics of raw materials that can be expected to appear in production. With the model, optimal settings of the machine can be found with respect to raw material characteristics, without further loss of raw material.
The aim of present study was optimisation of tableting process in order to diminish capping occurrence and variation of tablet mass and crushing strength. Optimisation was performed for the product where 70% of the tablet weight represent active ingredient, on the high capacity rotary-tablet press, in the standard production environment. Artificial neural networks were used to model the relation between quality and process parameters.

2 Production of model tablets

Due to the high drug content and chosen manufacturing procedure (direct compression) changes in raw material characteristics can result in variable crushing strength of tablets, large tablet mass variation and most problematic, intense capping problems. If problems in direct tableting are too intense, dry granulation can be used as an alternative to improve particle compression characteristics. Dry granulation means aggregation of smaller particles using force into bigger compacts, which are milled and sieved afterwards. Next step is tableting.
Three types of mixtures for tableting were prepared:

A) mixture for direct tableting (Type: “Direkt” - 1 sample),

B) granulate prepared by slugging (precompression on rotary-tablet press,), using different parameters of tableting speed and compression force (Type: “Briket” - 4 samples),

C) granulate prepared by precompressing on roller compactor using different parameters of compacting speed and force (Type: “Kompakt” - 4 samples).

The composition of all powder mixtures was the same, milling and sieving of compacts was performed on the same eqiupment. After dry granulation, the particle size distribution is normally shifted toward bigger particles, also capping occurence is often decreased due to change in particle characteristic (flowabilty and compression characteristics). Nine samples were tableteted on rotary- tablet press using different combination of following parameters: compresson speed, precompression force, main compression force. Each of this parameters was set at three levels. Tablets were evaluated according to capping occurence, crushing strength and tablet mass variability.

2.1 Capping coefficient

Capping occurency (capping coefficient, CC) was calculated as the ratio between the number of tablets that have tendency to cap and the number of tablets that have been observed. It was observed visually on each tablet after classical tablet hardness test (Erweka). Tablet was considered to have capping tendency if upper part of tablet falled off from tablet body or if a significant shape (a step-like form) was formed on breaked surface of tablet.

2.2 Experiments on the rotary-tablet press

For experiments on the rotary-tablet press three groups of raw materials were used ("direkt", "briket", "kompact"). Types "kompakt" and "briket" were further divided into four sub-groups depending on combination of compression force and speed during slugging or roller compaction. For each of these raw materials several combinations of settings on rotary-tablet press were set (tableting speed, main compression force, precompression force), produced tablets were controlled afterwards: CC, average crushing strength, standard deviation of crushing strength, average tablet mass and standard deviation of tablet mass. For each raw material and parameter setting, 10 tablets were made and analysed. All together a 76 data points were measured.

3 Modelling

To model the relation between process parameters, raw material characteristics, and quality of the tableting process (CC, standard deviation of mass, standard deviation of crushing strength) it was not rational, to use physical laws that describe operation of the tableting machine, considering the aim. The system characteristics depend on many stochastic processes (particle rearrangement and deformation type, friction, bond-forming between particles, ...), therefore, the model would be too complex for process parameter optimisation. On the other hand, there is relatively large database available, hence, it is more rational to use artificial intelligence methods instead.

3.1 Neural networks

To model the system characteristics, feed-forward neural network (NN) [1] was used, with two to four imputs, depending on the output. For each output (CC, standard deviation of crushing strength, standard deviation of mass), separate neural network was constructed. In case of CC as output, only index of raw material characteristics and main compression force were needed as inputs. If the precompression force and speed were also added as inputs to the NN the prediction quality of the NN was not improved, however, the training procedure needed more iterations to converge. In case of standard deviation of tablet crushing strength, precompression force had to be added. Tableting speed had no influence on the prediction quality of the NN. In case of standard deviation of mass, also tableting speed had to be added as the input, to achieve reasonable prediction quality. Training and simulation of NN was performed in MATLAB [2].

3.2 Index of raw material characteristics

Index of raw material characteristics was calculated as first principal component of material composition regarding particle sizes. Each raw material batch has unique composition of particles, since its production cannot be exactly repeated. The raw material characteristics can be charaterized by the particle size distribution. In this case, the particle sizes were separated in the following 8 subgroups: 0-0.045, 0.045-0.071, 0.071-0.125, 0.125-0.25, 0.25-0.5, 0.5-0.71, 0.71-1.0, and 1.0-1.25mm. The principal components [3] of such decomposition were calculated and the first component was taken as the measure for raw material characteristics.

4 Results

First, neural networks model was designed and validated, next, the model was used find optimal process parameters.

4.1 Modelling

The NN training was repeated approx. 1000 times with different, randomly chosen, trainig and validation sets. It was shown that in most cases the prediction on validation set was consistent with experimental data accuracy. However, if some critical points were omitted from training set, the validation was poor. For final training, the whole data set was used, since, considering rather small dimensionality of the problem, the non-linear input-output relation could be visualy monitored. Visual monitoring showed, that the relation is non-linear but relatively simple, therefore, each repetition of trainig converged to very similar relation. The identified relations can be seen in figures 1 to 3.

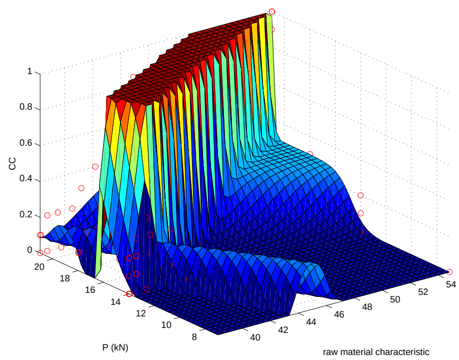

Fig. 1 Capping coeficient with respect to raw material and main compression force (P)

4.2 Optimisation

Using Newton optimisation method with constraints (*fmincon*) optimal parameter were identified, for criterion function

$$J = CC + \frac{\sigma_h}{40} + \sigma_m + \frac{10}{v}, \qquad (1)$$

where CC represents capping coefficient, σ_h standard deviation of crushing strength, σ_m standard deviation of mass, and v tabletting speed. Depending on intial conditions, several optimal parameters could be found (see Table 1).

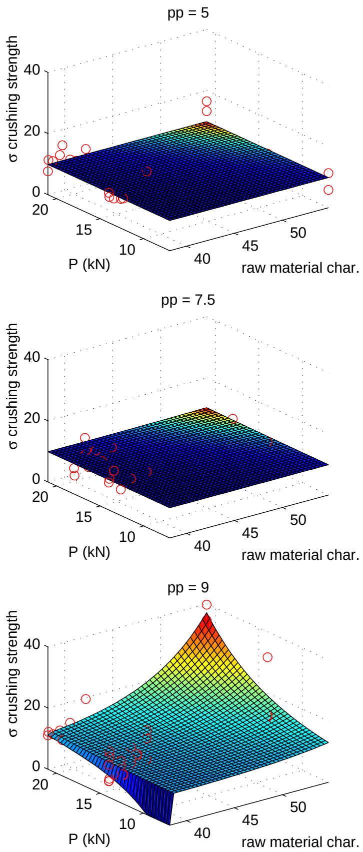

Fig. 2 Standard deviation of crushing strength with respect to raw material, main compression force (P), and precompression force (pp)

Tab. 1 Optimal settings for ”direkt” powder with respect to different initial settings

initial values			optimal values			criterion		
P	pp	v	P	pp	v	CC	σ_h	σ_m
21	9	50	7.0	5.0	100.0	0.0	10	0.005
21	9	100	19.3	5.3	100.0	0.3	10	0.005
15	9	100	9.5	5.0	100.0	0.0	10	0.005
15	5	100	8.7	6.4	100.0	0.0	10	0.005
17	6	100	19.4	5.0	100.0	0.3	10	0.005

5 Conclusion

It can be concluded that NN can used to describe relation between raw material characteristics, process parameters and quality of tabletting process. Therefore, it is also possible to find optimal set of process parameters, considering the raw material characteristics. Since the relation is rather simple, and the shapes of corresponding functions has large flat areas, the optimisation algorithms would not be able to perform better than visual observation and manual identification of optimal setting.Modelling and simulation indicates that it is possible to find process settings for tabletting of non-preprocessed powder such that sufficient quality of tablets can be achieved.

6 References

[1] Martin T. Hagan, Howard B. Demuth, and Mark Beale. *Neural Network Design*. PWS Publishing Company, Boston, 1996.

[2] Mathworks. *Using Matlab version 5*. The Mathworks Inc., Natick, 1998.

[3] J. Edward Jackson. *A User Guide to Principal Components*. John Wiley & Sons, inc., New York, 1991.

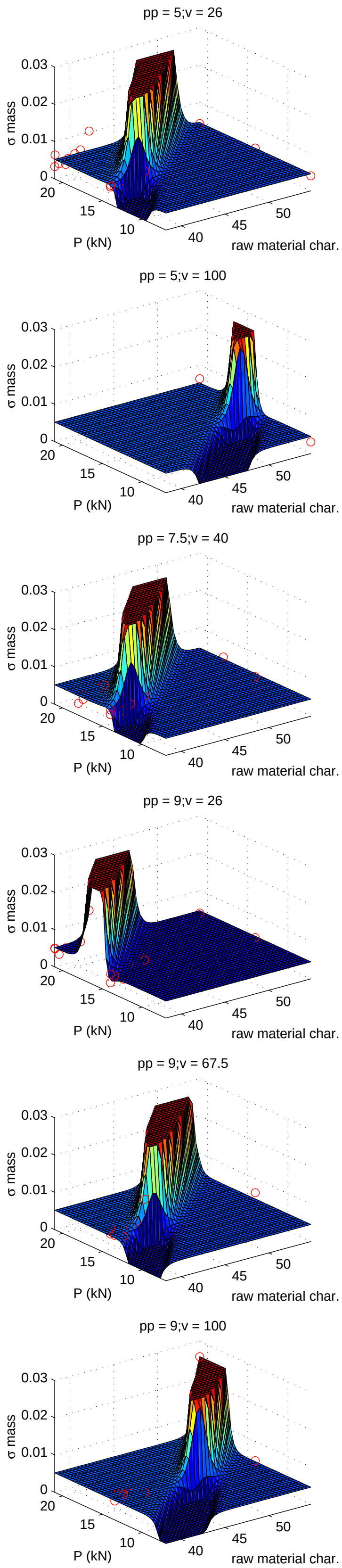

Fig. 3 Standard deviation of mass with respect to raw material, main compression force (P), precompression force (pp), and speed (v)

