XII. Péter Kása jr., **Tamás Sovány**, Stane Srcic, Endre Horváth, Zoltán Kónya, Imre Kiricsi, Klára Pintye-Hódi Preparation and investigation of biayer tablets containing theophylline combined titanate nanotubes 1st World Conference on Physico-Chemical Methods in Drug Discovery and Development Rovinj, Horvátország 2009. szeptember 27. - október 2.

XIII. **Sovány Tamás**, Ilija Ilic, Papós Kitti, ifj. Kása Péter, Stane Srcic, Hódi Klára A felületi szabadenergia és a plaszticitás szerepe tablettaformulálás során XIV. Congressus Pharmaceuticus Hungaricus Budapest, Magyarország 2009. november. 13-15.

XIV. Márta Venczel, Gabriella Újhelyi, **Tamás Sovány**, Klára Pintye-Hódi Flow Through Dissolution - a Useful Tool from Discovery Phase to Preclinical Development XIV. Congressus Pharmaceuticus Hungaricus Budapest, Magyarország 2009. november. 13-15.

XV. ifj. Kása Péter, **Sovány Tamás**, Stane Srcic, Horváth Endre, Kónya Zoltán, Kiricsi Imre, Hódi Klára Kétrétegű tabletták előállítása és vizsgálata teofillin tartalmú titán nanocsövekből XIV. Congressus Pharmaceuticus Hungaricus Budapest, Magyarország 2009. november. 13-15.

XVI. P. Kása jr., **T. Sovány**, S. Srcic, E. Horváth, Z. Kónya, I. Kiricsi, K. Pintye-Hódi Formulation and investigation of biayer tablets containing theophylline combined titanate nanotubes 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology Valletta, Málta 2010. március 8-11.



**Summary of Ph.D. Thesis**

# Modelling of the postcompressional properties of scored tablets with the use of artificial neural networks

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**Introduction and Aims**

Despite its considerable difficulty, its increasing importance in paediatrics and the ever stricter requirements of the drug authorities, the subdivision of scored tablets is a poorly studied field. Only a few investigations of the production of scored tablets from technological aspects are to be found in the literature. Most of the articles deal with scored tablets from a clinical point of view. The results show that, although there are studies, which concludes, that tablets with score lines can be split safely, most patients have problems with the breaking of the marketed products. Some of these problems can be corrected through appropriate training of the patients and scored tablets have their therapeutic and economic advantages, but the improvement of breakability remains important, as this in the only way to ensure the uniformity of dosing, especially in the case of modified release dosage forms.

The aims of my studies were as follows:

Primary aim: The *in silico* modelling of the compression of scored tablets, for prediction of the postcompressional properties, and especially the subdivision of the products, with the help of artificial neural networks (ANNs).

Secondary aims: The determination of the best predictable neural model necessitated a better understanding of the effects of material behaviour, and the settings of the tablet presses.




VI. **Sovány Tamás**, ifj. Kása Péter, Pintyéné Hódi Klára Direkt préseléssel készült tabletták felezhetőségének vizsgálata mesterséges neurális hálózatokkal Műszaki Kémiai Napok ’08 Veszprém, Magyarország 2008. április 22-24.

VII. **T. Sovány**, P. Kása jr., K. Pintye-Hódi Comparison of halving of tablets prepared by eccentric and rotary tablet press 7th Central European Symposium on Pharmaceutical Technology and Biodelivery Systems Ljubljana, Szlovénia 2008. szeptember 18-20.

VIII. **Sovány Tamás**, ifj. Kása Péter, Pintyéné Hódi Klára Excenteres és rotációs gépen készült tabletták felezhetőségének összehasonlítása „Gyógyszer az Ezredfordulón VII.” Továbbképző Konferencia Sopron, Magyarország 2008. szeptember 25-27.

IX. **Sovány Tamás**, ifj. Kása Péter, Hódi Klára Préselési ciklusban kifejtett préserő hatása a tabletták textúrájára és tulajdonságaira Műszaki Kémiai Napok ’09 Veszprém, Magyarország 2009. április 21-23.

X. **Sovány Tamás** Excenteres és rotációs gépen készült tabletták oszthatóságának összehasonlítása IX. Clauder Ottó Emlékverseny Budapest, Magyarország 2009. április 23-24.

XI. **Tamás Sovány**, Ilija Ilic, Kitti Papós, PéterKása jr., Stane Srcic, Klára Pintye-Hódi The role of surface free energy and plasticity of the materials in tablet formulation 1st World Conference on Physico-Chemical Methods in Drug Discovery and Development Rovinj, Horvátország 2009. szeptember 27. - október 2.

**Presentations**

I. Kása Péter, **Sovány Tamás**, Pintyéné Hódi Klára, Szabóné Révész Piroska Diltiazem-klorid tartalmú pelletek formulálása mesterséges neuráli hálózat segítségével XIII. Congressus Pharmaceuticus Hungaricus Budapest, Magyarország 2006. május 25-27.
II. Kása Péter, **Sovány Tamás**, Pintyéné Hódi Klára, Szabóné Révész Piroska Mesterséges neurális hálózattal támogatott diltiazem-klorid tartalmú pelletek formulálása Gyógyszerkutatási Szimpózium 2006 Debrecen, Magyarország 2006. november 24-25.
III. **Sovány Tamás** Mesterséges neurális hálózatok alkalmazása granulátumok formulaoptimalizálásában Magyar Tudomány Ünnepe 2007 Szeged, Magyarország 2007. november 6.
IV. **Sovány Tamás**, ifj. Kása Péter, Pintyéné Hódi Klára Pelletformulálás optimalizálása mesterséges neurális hálózatokkal Gyógyszerkutatási Szimpózium 2007 Szeged, Magyarország 2007. november 9-10.
V. **T. Sovány**, P. Kása jr., K. Pintye-Hódi Dividability of tablets prepared by direct compressed binary powder mixtures 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology Barcelona, Spanyolország 2008. április 7-10.



The relationship between the structure and the breaking properties of tablets also formed an important part of the study.

**Methods and materials**

Drotaverine HCl was used as model API, microcrystalline cellulose (Vivapur 102, JRS Pharma, Germany) was applied as dry binder, and two filler materials spray dried mannitol (Pearlitol SD 200, Roquette Pharma, France) and agglomerated lactose (Tablettose, Meggle Pharma, Germany) was used in the experiments.

Korsch EK0 (E. Korsch Maschienenfabrik, Germany) eccentric and a Ronchi AM8S (Officine Meccanice F.lli Ronchi, Italy) rotary tablet press mounted with strain gauges were applied for tablet compression, with flat with a bisecting line.

For measurement of the force required to break the tablets into halves, a laboratory-constructed hardness tester was utilized, with three-bend tablet hardness testing.

The modelling was done with the Neural Network module of the StatSoft Statistica 6.1 software (StatSoft Inc., Tulsa, Oklahoma, USA). The prediction performances of the different models were compared with the non-parametric Kruskal-Wallis test, with the use of post-hoc comparisons. The statistical analysis was performed with the StatSoft Statistica 8 software.

**Results and discussion**

In the first step of the study, Samples binary mixtures of microcrystalline cellulose and spray-dried mannitol were compressed with eccentric press at 3 compression forces. Parameters which describe the compression process (elastic recovery, plasticity, friction work and lubrication coefficient) were recorded in the case of each compressed tablet. The changes in these parameters and some postcompressional properties, such as hardness, density or tendency to accurate halving, were studied with ANNs. The observed vs. predicted correlation coefficients were used to select the best type and structure of the possible ANNs. Four type of ANNs were studied linear model was used as reference, and compared with the predictive ability of radial basis function (RBF) networks, generalized regression neural networks (GRNN), and multilayer perceptrons (MLP). Linear and GRNN models established inappropriate predictions for output parameters. RBF networks and MLPs provided statistically significant better results, based on nonparametric Kruskal-Wallis test. Despite the good correlations, the usefulness of the developed model is strongly limited, because of the poor descriptive power of the selected input parameters. The lack of the appropriate characteristics of the applied materials and the inappropriate description of the compression process caused the dramatic decrease in the accuracy



**Publications related to the thesis**

I. **T. Sovány**, P. Kása jr., K. Pintye-Hódi.: *Comparison of halving of tablets prepared with eccentric and rotary tablet press* AAPS PharmSciTech, 10 (2009) 430-436
II. **T. Sovány**, P. Kása jr., K. Vakli, K. Pintye-Hódi.: *X-ray computed microtomography for the determination of the realtionships between structure and breaking of scored tablets* X ray Spectrometry 38 (2009) 505-509
III. **T. Sovány**, P. Kása jr., K. Pintye-Hódi.: *Modeling of subdivision of scored tablets with the application of artificial neural networks* Journal of Pharmaceutical Sciences (2010) 905-915

**Other publications**

I. Kása P., **Sovány T.**, Hódi K.: *Pelletek formulálásának optimálása mesterséges neurális hálózatok segítségével*, Acta Pharmaceutica Hungarica 77. 116-122. 2007.
II. **T. Sovány**, K. Nikowitz, G. Regdon jr., P. Kása jr., K. Pintye-Hódi: *Raman spectroscopic investigation of film thickness* Polymer Testing, 28 (2009) 770-772

- The applied mathematical models facilitate an understanding of the *differences between eccentric and rotary presses*, which simplifies data transfer between the different tablet presses. The understanding of the structural differences between the tablets with various properties can lead to a significant improvement in the breaking accuracy and reliability of the marketed products.
- The recognition of the *importance of the surface properties* of materials in the field of direct compression contributes to the description of the behaviour of the materials during compression, and to predictability of the postcompressional tablet properties. However, an exact description as to how the properties of the components determine the properties of a binary or higher order mixture requires further investigations.



of the predictions when we added other materials with the mixtures or compressed them on different tablet presses.

The next step of the study was a deeper investigation and comparison of the compression mechanism on eccentric and rotary tablet presses. The primary aim of this work was to find and quantify the differences between the characteristic parameters of the different tablet presses, which have significant effects on the properties of the tablets. We used the models of Walker, Heckel and Kawakita to describe the powder densification, and sought relationships with the halving properties of the tablets. The results calculated from Walker and Kawakita equations suggested a considerable difference in the energy consumption during the compression of the different mixtures. The lower energy consumption suppose a smooth compression, resulted in tablet structure free from defects, resulted in appropriate breaking of the tablets. The models of Walker and Kawakita describe these processes well and furnish a better prediction of the halving properties. In contrast, the Heckel model does not give such unanimous results and should be utilized with caution. Another conclusion, that considerable difference was visible between the results of the eccentric and rotary press, which certified that the eccentric presses cause two-three times higher stress on the compacted powder. Because of the breaking result depends mainly on the hardness of the tablets it could be an important descriptor in the neural modelling. However, the breaking is additionally

influenced by the internal structure of the tablets. To support the above-mentioned consequences and to clarify the reasons for the differences in mechanical behaviour of tablets prepared with different tablet presses, the texture of some of the compressed tablets was studied by X-ray microtomography.

It was clearly visible that, despite the differences in the physicochemical parameters the investigated tablets appeared to have essentially similar structures. Their density increases from the centre to the edges, which is a result of the radial movement of the particles. However, in spite of these similarities, the microstructures of the samples reveal important differences. Tablets with high porosity, exhibits poor breaking properties, because of the rich pore network allows breaking in many ways, which usually results in a rough breaking surface susceptible to crumbling. Less porous tablets reveal better breaking properties when the low density area under the score line is associated with the vertically rearranged particles. Otherwise, such in the case of the tablets prepared with the rotary press the bidirectional compression force, or the tilting of the punches results in an oblique pore structure, which leads to breaking into unequal halves.

As it was mentioned structural defects caused by the extensive friction or elastic recovery after compression, have a significant influence to the breaking properties. This makes the characterisation of the behaviour of the applied powder mixtures necessary. Materials with higher surface free energy show high



- The *type of the tablet press* is also of appreciable importance not only because of the compression time differences, but the direction of action exert a significant influence on the rearrangement of the particles and the lines of the forces. These effects could be investigated well by means of *computer microtomography*.

**Practical usefulness**

- The *in silico modelling* of the production processes is of ever greater importance in the pharmaceutical industry. The increasing time and costs of the development of a new drug, and the increasing strictness of the drug authorities, necessitates the deep planning and the use of cost saving methods.
- The *ICH Q8 guideline* requires the demonstration of “an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters”, which can be supported with the developed neural model.
- Furthermore, this model is *able to predict* the probable postcompressional properties of scored tablets, from preformulation data on the applied powder mixtures, which is a useful tool in the reduction of the number of required experiments.

taken into account for the development of a universally functioning neural network.

- The *adhesion and friction* to the die wall, and the *elastic recovery* are perhaps the most important physical phenomena in respect of the postcompressional properties of the tablets. The *adhesion work* influences both the flow properties/die filling and the friction work during the ejection of the tablet. This parameter could be calculated from the *surface free energy* of the materials or mixtures. However, prediction of the surface energy of the powder mixtures from the parameters of the mixed components is a very complex problem. Besides the adhesion force and the spreading coefficient, the size and shape of the particles have significantly influence the arrangement in the mixture, which will determine the overall behaviour during compression. The exact description of these relationships requires further investigations.
- The *plasticity* of the different materials shows a certain dependency on the compression force. If this dependence is considerable, the hardness-compression force functions will be curved, and the prediction of the postcompressional properties will be more difficult.
- The applied *compression force* probably has the most significant effect on the postcomprompressional properties of the tablets. However, the effective load has other components, such as the *time of compression*, as suggested by the results of the mathematical models of compression.



adhesion to the stainless steel parts of the tablet presses. This will influence both the filling of the die and the friction during the ejection of the tablet. The high adhesion will hinder the free flow of the materials, and cause serious problems during compression. These materials or mixtures can not be compressed at low compression forces, because the adhesion to the punches is greater than the interparticulate binding forces, and the tablets show strong lamination and capping. Nevertheless, these problems can be corrected by the addition of lubricants. However, it should be used with cautions, because they can change compression force dependency of the plastic-elastic behaviour of other materials and mixtures. A decreasing value of the plasticity indicates the increasing resistance of the materials against the increasing load. The increasing slope of the plasticity-compression force functions or turning into a power curve, which means a greater decrease in plasticity at lower compression forces will influence the postcompressional properties. When the compression force dependency is low, the hardness of the tablets exhibits a linear increment with increasing compression force. In contrast, materials with a higher compression force dependence demonstrate a non-linear increment in tablet hardness or in extreme cases, the hardness of the tablets can decrease above a given compression force, because of the extremely high elastic recovery, and the breaking up of the interparticulate bonding. Based on the results of the above-mentioned studies, a new neural model was developed.

The results suggested that besides the applied compression force, the time of compression and the type of tablet press are also important parameters. For characterization of the applied materials, the surface free energy, the polarity index, and the slope and intercept of the plasticity function should be appropriate parameters. Because of the difficulties in the modelling of the behaviour of complex systems, the properties of the compressed mixtures were used for the training of the new model. However, the external validation tests showed very poor predictive force. The system made no differentiation between tablets prepared at different compression forces; only the change between samples was visible. The application of less information in such a complex model should be avoided, so combination of the different parameters appeared be more advantageous. The surface free energy and polarity index of the materials were replaced with the calculated adhesion force against stainless steel, while the slope and intercept of the plasticity function were replaced by the calculated plasticity value corresponding to the applied compression force.

The results of the internal testing demonstrated appropriate observed vs. predicted correlation coefficients However, the extrapolated data were considerably overestimated and displayed negative correlation. The developed ANN seems to be an appropriate model for prediction of the postcompressional properties of scored tablets, even despite the poorer correlations of extrapolated data. The difference between results of interpolated



and extrapolated data suggests that these problems can be easily solved by increasing and widening of the training data set. However, this requires a large number of further experiments.

**Major conclusions:**

- The *artificial neural network* is a useful modelling technique in pharmaceutical research and development. The *Multilayer Perceptron* seems to be the best type of neural network because of its high flexibility.
- *Gradient-based algorithms* show an inappropriate learning performance as compared with *back-propagation-based algorithms*, but the combination of the two types could result in a significant improvement in the predicted data. Improved back-propagation algorithms, such as quick-propagation or Delta-bar-Delta, displays faster convergence to the minimum error, but the faster working sometimes results in less accuracy.
- Care must be taken as concerns the selection of the data for the input data set: unbalanced data can cause serious problems in the functioning of the neural networks, which can lead to inappropriate predictions.
- Numerous *physicochemical properties* of the applied materials and operational parameters of the tablet press must be