Multivariate statistical modelling of the pharmaceutical process of wet granulation and tableting

Westerhuis, Johannes Arnold

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RIJKSUNIVERSITEIT GRONINGEN

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PROEFSCHRIFT

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. van der Woude,
in het openbaar te verdedigen op
maandag 22 september 1997
des namiddags te 4.15 uur

door

Johannes Arnold Westerhuis

geboren op 1 juni 1966
te Groningen

Promotores:

Prof. dr. D.A. Doornbos
Prof. dr. ir. C.F. Lerk

Co-promotor:

Dr. P.M.J. Coenegracht

Promotiecommisie:

Prof. dr. H.E. Junginger
Prof. dr. J.F. MacGregor
Prof. dr. A.K. Smilde

Paranimfen:

Mirjam Koetse
Betty Westerhuis

Acknowledgement:
The research in this thesis was sponsored by three Dutch pharmaceutical companies. Pharmachemie (Haarlem, the Netherlands) is thanked for supplying of the model drugs. Power consumption records were obtained at Solvay Duphar (Weesp, the Netherlands). Organon NV (Oss, the Netherlands) is thanked for the experimental effort and guidance for the research presented in Chapter 5, which resulted in the corresponding paper.

The studies in this thesis were carried out at the Groningen Utrecht institute for drug exploration (GUIDE).

ISBN 90-3670797-8

An electronic version of this thesis in Adobe-format is available on:
http://docserver.ub.rug.nl/eldoc/dis/science/j.a.westerhuis/

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Preface

This thesis is the result of a combined project between the research group of chemometrics (Prof. Doornbos) and the department of pharmaceutical technology (Prof. Lerk), both at the University Centre for Pharmacy at the University of Groningen. The cooperation between these two groups earlier resulted in the theses of van Kamp, Bos, de Boer and Duineveld [1–4]. They all describe the use of chemometrical techniques for the development of pharmaceutical dosage forms.

The cooperative research of the two groups was mainly focussed on the relation between the components in tablet mixtures and physical properties of the tablets such as crushing strength and disintegration time. The theses of van Kamp, Bos, de Boer and Duineveld all applied the direct compression method for the production of pharmaceutical tablets. Van Kamp investigated the relation between the composition of the tablet mixture and the tablet properties. This was done with use of mixture designs and mixture regression models. Experiments were carried out with specific concentrations of the mixture components according to a mixture design. Mixture regression models were developed that fitted the physical properties very well. By use of optimisation techniques settings for the concentrations of the components could be found to give tablets with optimal physical properties

De Boer extended the research with multi criteria optimisation. Optimal crushing strength and disintegration time required a different composition of the mixture. Therefore, regions in the mixture space had to be found where both the crushing strength and the disintegration time were within a specified range. Pareto optimality and overlay contour plots were used to find these regions in the mixture space. De Boer also studied the robustness of mixtures. When small changes in the mixture composition have a large effect on the tablet properties, the mixture is not robust, and another mixture composition should be used for the large scale production of tablets. The robustness was also combined with the tablet properties in a multi criteria optimisation to find tablet mixtures that are robust to small changes and give tablets with specified properties.

Next to the composition of the mixture, the process variables also influence the physical properties of the tablets. Mixing time and compression force are process variables that have a strong effect on crushing strength and disintegration time of the tablets. New designs were developed that combine the mixture variables and process variables. This is necessary because interactions may exist between the mixture components and the process variables. These combined designs and the associative regression models were investigated by Duineveld.

Bos used these combined designs for the optimisation of direct compression tablet formulations for use in tropical countries. Several mixtures of three components were lubricated and compressed, both at two levels according to a 2^2 factorial design. Furthermore, the tablets were stored at two different temperatures and relative humidities also according a 2^2 factorial design.

In the present thesis different drugs were selected to investigate the effect of drug properties on the physical properties of the tablets, with wet granulation as the preprocessing method. Because it is not possible to vary only the solubility or the wettability of a specific drug on several levels, an experimental design for drug properties cannot be used. Therefore, experiments have been carried out according to a multivariate design. The regression models are developed with multivariate regression techniques because the properties of the drugs are correlated. Partial least squares regression (PLS) is a multivariate regression method used to construct models between physical properties of the drugs, such as the solubility and particle size, and physical granule and tablet properties.

In the wet granulation process, granulations are produced that will be processed further into tablets. Physical properties of the granulations affect the properties of the tablets. The multivariate calibration of the whole tablet manufacturing process with a wet granulation step deals with several blocks of physical properties, i.e. drug, granule and tablet properties. Multiblock PLS methods are used to deal with these blocks of data.

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List of symbols and abbreviations

X	data matrix or design matrix
X'	transpose of **X**
I	number of objects or experiments (*i*=1...*I*)
J	number of variabelen (*j*=1...*J*)
K	number of PC's or PLS factors (*k*=1...*K*)
y	response
Z	response
D	block with design variables
G	block with granulation properties
$\mathbf{t}_k$	k^{th} score vector
$\mathbf{u}_k$	k^{th} score vector of response
$\mathbf{w}_k$	k^{th} weight vector
$\mathbf{p}_k$	k^{th} loading vector
β	population model coefficients
b	estimation of β with the OLS method
$\mathbf{b}_{PLS}$	estimation of β with the PLS method
s	standard deviation, reproducibility

OLS	ordinary least squares regression
PLS	partial least squares regression
MBPLS	multiblock partial least squares regression
PCA	principal component analysis
RMSE	root mean squared error
PRESS	predictive residual error sum of squares of leave one out predictions
Q^2	squared correlation between measured values and leave one out predictions

CS	crushing strength
DT	disintegration time
EF	ejection force

PVP	polyvinylpyrrolidone
MCC	microcrystalline cellulose
HPC	hydroxypropyl cellulose