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

RIJKSUNIVERSITEIT GRONINGEN

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

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Contents

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

Chapter 1

Introduction

Tablets are by far the most popular dosage form for pharmaceutical products for therapeutic use. Tablets are prepared by compressing a powder mixture in a die at high compression force. The powder mixture contains next to the drug generally also filler binders, disintegrants, lubricants, glidants etc. The large scale production of high quality tablets requires a tablet mixture with excellent properties regarding homogeneity, flowability and compactibility. When the powder mixture does not possesses these properties it has to be preprocessed, else direct compression can be used (Table 1). With direct compression the powder mixture is blended during a period of time and can directly be compressed into tablets. Only a lubrication step may be necessary to prevent the mixture from adhesion to the die and punches during compression. Direct compression can be used when the mixture already has good tableting properties of itself. The mixture has to flow easily and give good binding during compaction. Unfortunately, most tablet mixtures lack these properties and a wet granulation step is necessary.

With wet granulation, extra process steps are necessary to produce a tablet mass with sufficient tableting properties. The powder mixture is dry blended to give a homogeneous distribution of all the components in the mixture. Then a binder solution is added to the mixture to moisten the particles. By introduction of the solution, binding between the primary particles improves and stronger tablets can be produced. Mixing is continued until the granulation end point has been reached. The end point may be defined as the mixing time or amount of granulation liquid that produces a certain amount of granules with a specific diameter. The mass is screened to remove large lumps, and dried to remove the granulation liquid. Finally, the granulations may be dry sieved to remove the agglomerates that were formed during drying. Just as with direct compression, lubrication of the granulations may be necessary. There are various techniques of producing granules such as dry and wet granulation, extrusion, or spray drying. Most commonly used is wet granulation. Here the aggregates are produced by agitation of moistened powders [1]. This thesis deals with the wet granulation process as a preprocessing technique for the manufacturing of pharmaceutical tablets.

Table 1: Steps in production of tablets by direct compression and wet granulation.

Direct compression	Wet granulation
Dry mixing of powders	Dry mixing of powders
	Addition of binder solution
	Wet massing
	Wet screening
	Drying
	Dry screening
Lubrication	Lubrication
Compression	Compression

Wet granulation

According to the Encyclopedia of pharmaceutical technology, granulation is a process of size enlargement whereby small particles are gathered into larger permanent aggregates in which the original particles can still be identified [1]. Reviews of pharmaceutical granulation technology have been given by Record, Schwartz and Kristensen *et al*. [2-4]. The very thorough review of Kristensen and Schaefer reviews all aspects of the wet granulation process for high shear mixers and fluid bed granulators. Granulation usually refers to processes whereby agglomerates with sizes ranging from 0.1 to 2.0 mm are produced. The most important reasons for a granulation step prior to tableting are to [2]:

- improve the flow properties of the mix and hence the uniformity of the dose
- prevent segregation of the ingredients
- improve the compression characteristics of the tablet mixture
- reduce dust during handling

The flowability of the tablet mixture improves because the granules are larger and more spherical than the primary particles. Larger particles usually flow better than small particles (e.g. compare the flowability of crystal sugar with powder sugar). In the hopper of tablet machines, small particles tend to segregate from the larger ones because of the vibration of the machine. This causes higher concentrations of small particles at the bottom of the hopper. After granulation all particles are bound tight in the right amount in the granules, which prevents segregation of the small particles.

Instruments

Type of granulators

Until the nineteen sixties, granulation was mainly performed in planetary mixers with low speed and low shear forces. Then, fluid bed granulators were introduced in pharmaceutical industry. Some ten years later, high shear mixers were introduced.

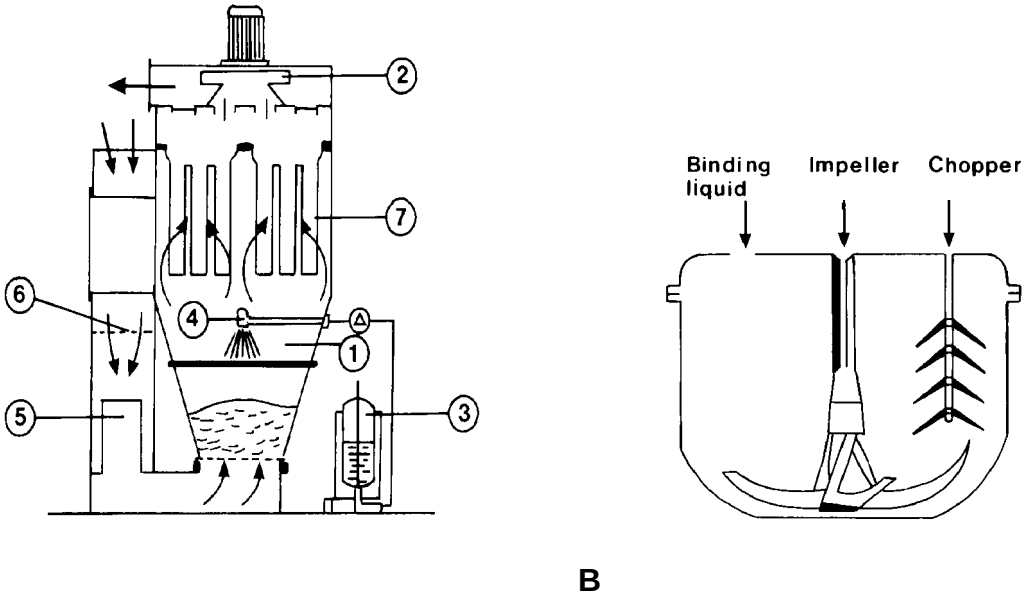

Figure 1: Two types of granulators: A: Fluid bed granulator (1 material container, 2 ventilator, 3 binder solution, 4 nozzle, 5 heating, 6 inlet air filter, 7 outlet air filter). B: Changeable bowl high shear mixer [4].

Figure 1 shows both types of granulators. In fluid bed granulators heated air (40-80°C) is drawn by a ventilator through a material container of a conical shape. The binder solution is sprayed on the fluidising particles that go up in the centre of the container and down again at the wall. After liquid addition has been finished, particles are dried in the same equipment. Granulation in fluid bed granulators is studied by several authors [5-8].

High shear mixers (high speed mixers, high intensity mixers) are large kitchen blenders that give high densification to the granules because of the high rotating speed of the impeller. The binder solution may be poured or pumped into the mixing bowl. When all the liquid is added, mixing is continued for a while (wet massing) to get a homogenous distribution of the liquid and to further densify the granules. This thesis only deals with wet granulation in high shear mixers as a primary step in the manufacturing of pharmaceutical tablets.

The major advantages of these high shear mixers/granulators are the short process time and the production of very dense granules with low porosity. Most high shear mixers are equipped with an impeller and a chopper (Figure 1B). The impeller rotates at a speed of 100 - 500 rpm. and exerts the high shearing and compaction forces on the material. The chopper is a small cutting tool which rotates between 1000 and 3000 rpm. The size of the high shear mixer bowl changes from 5 litres for laboratory scale to 600 litres in production. Extensive lists of different types of high shear mixers used in industry are given by Kristensen *et al.*, Record and by Timko *et al.* [1,2,9].

Dryers

Drying of the granulations can be done in tray ovens or in fluid bed dryers. In tray ovens, the material is dried at a predefined temperature for a specific period of time. In fluid bed dryers heated air is blown through the granulations. Drying may be considered complete when the outlet air temperature is constant. Disadvantage of the granulation in high shear mixers is that the material has to be transferred to a drying equipment. However recently, micro wave equipment has been introduced in the high shear mixer, which allows drying in the same apparatus [10,11].

Granulation mechanisms

The formation of agglomerates and growth of granules can be described by two mechanisms which operate during granulation (Figure 2):

- nucleation of particles
- coalescence between agglomerates

Both grow mechanisms require the presence of a liquid binder to establish bindings with sufficient strength. Knight studied the kinetics of granulation in high shear mixers [12]. The binding strength is a significant factor in granule growth, which depends on the surface tension of the liquid, the contact angle of the particles, particle size diameter and the packing of the spheres [13].

Newitt and Conway-Jones [14] and Barlow [15] described four different states of moist agglomerates having an increased content of liquid phase (Figure 3):

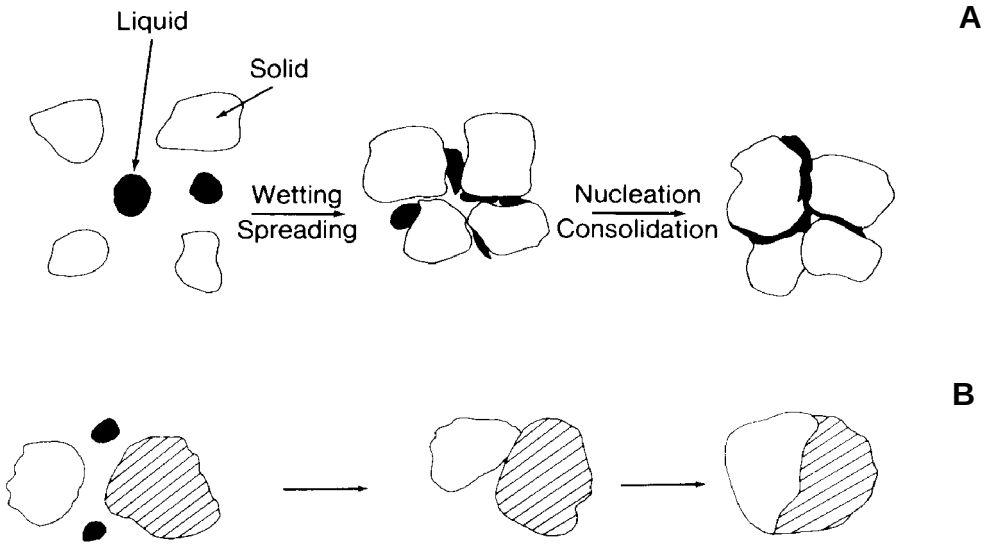

Figure 2: Illustration of granule growth by nucleation (A) and by coalescence (B) [4].

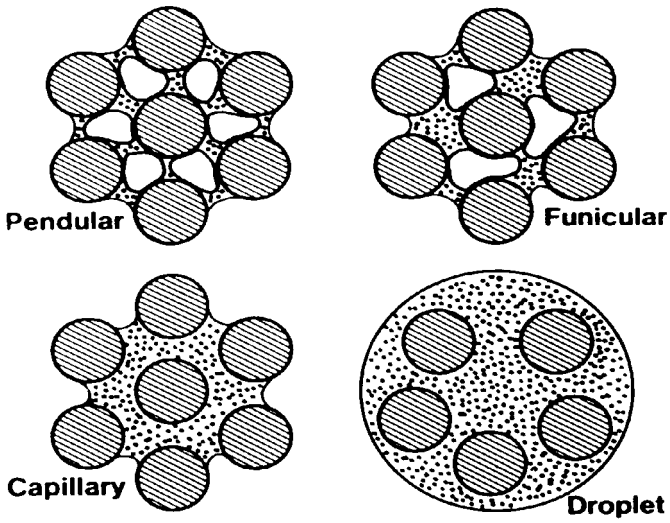

Figure 3: Diagram of bonding mechanism for particles in the presence of liquids. Four different states can be observed: pendular, funicular, capillary and droplet [4].

1) pendular state
2) funicular state
3) capillary state
4) droplet state

The states are distinguished by the amount of liquid phase in the mixture as expressed by the liquid saturation. The liquid saturation *S* is the ratio of the volume of liquid phase to the total volume of the pores. It depends on the amount of liquid and the intragranular porosity (porosity within the granules).

$$S = \frac{H(1-\epsilon)}{\epsilon\rho}$$

H is the ratio of the mass of liquid to the mass of solid particles, ϵ is the intragranular porosity and ρ the particle density. The liquid density is assumed to be unity. The pendular state has a saturation lower than 25%, a saturation between 25%-80% is called the funicular state, and the capillary state has a saturation of more than 80%. When the liquid saturation is more than 100%, the granulation becomes a suspension. Kristensen *et al.* showed that the effects of process conditions upon granule growth could be described by the effect of *S* on the mean granule size [16]. However, the correlation between *S* and the mean granule diameter is a characteristic of the feed material in a particular type of mixer. The correlation is influenced by the particle size distribution of the feed material [17].

Liquid requirements

The granulation process proceeds within a narrow range of liquid content. The amount of liquid required to run an uncritical granulation step depends on feed material properties (particle size distribution, solubility in the liquid and ability to absorb the liquid), liquid characteristics (viscosity and surface tension) and the equipment used [18]. Prediction of the required amount of liquid from knowledge of the feed material has not been successful. From theoretical models, that assume that the amount of liquid saturation should be equal to 100%, predictions could made with an accuracy of about 30% only. Leuenberger *et al.* used a simplified model and took into account that cohesiveness in the wet mass may appear before the agglomerates are fully saturated with liquid [19]. Then predictions agreed better with experiments in planetary mixers. Nowadays, instrumental methods are implemented for the monitoring of the granulation process and used to define the end point of the granulation.

In the mixing process, changes in power consumption occur as a result of a change in the cohesive force of the agglomerates. It should therefore be possible to interpret the power consumption record on the basis of the cohesive forces during the moist agglomeration process. Rumpf *et al*. [20,21] calculated the cohesive forces that exist between two particles. The cohesive force depends on the surface tension of the granulation liquid, the contact angle, the separation between the particles and the particle diameter. They calculated the cohesive forces between two particles for rhombohedral and for cubical packing assuming ideal wettability and no separation between the particles. Using the cohesive forces, Leuenberger *et al.* made a theoretical estimate of the quantity of granulation liquid required in the granulation process [19].

When the powder mixture consists of several components with varying particle diameter and particle shape, the theoretical model for estimation of the required liquid amount cannot be used anymore. Moreover, during the granulation, some particles may dissolve partly in the liquid, which leads to very complicated binding forces between the particles. Therefore, multivariate calibration has to be used to model the required liquid amount. Chapter 3 describes the prediction of the uncritical granulation liquid amount that can be added to a specific mixture.

End point control

The physical changes of the granulations that occur in the high shear mixer during granulation cannot be measured directly. Therefore, it is difficult to determine the granulation end point, which is the processing time and amount of liquid at which the desired granulation quality is achieved. During the last few years much effort has been put in the development of reliable instrumental methods that have the ability of process control. These techniques include measurement of the change in impeller speed during granulation or motor slip [22], measurement of power consumption of the main impeller [23-28], probes in the powder mass [29,30] and torque measurement of the main impeller shaft [31,32]. It has been found that the measured

quantities reflect changes in the rheological properties of the moist mass and that changes are related to the granule growth process. Different techniques for end point control have been compared [33,34]. Corvari *et al*. found a strong correlation between the records of power consumption and torque measurement. In Chapter 3 power consumption measurements are used to determine the optimal liquid amount for several tablet mixtures with different drugs. The techniques mentioned above provide indirect measurement of the changes in consistency of the wet mass. In a series of articles, Leuenberger divided the obtained power consumption curve into several phases [13,19,35,36]. Each phase in the curve can be related to a particular feature of the mixture (Figure 4). Lindberg presented a similar curve when he recorded the change in rotation speed in a Diosna P-25 during granulation of lactose. [37,38]. The characteristic curve can be found in most power consumption records, independently of the mixer. However, the power consumption curve depends on the feed material in the mixer bowl [39]. Correlation between power consumption records and the mean granule size was demonstrated by Holm *et al.* [39,40]. Ritala *et al.* showed correlation between power consumption and granule porosity [41,42].

Physical properties of granulations and tablets

The reason for a wet granulation step is mainly to improve the tableting properties of the powder mixture. This means that the flowability and the compression characteristics of the granules are important. The following characteristics of the

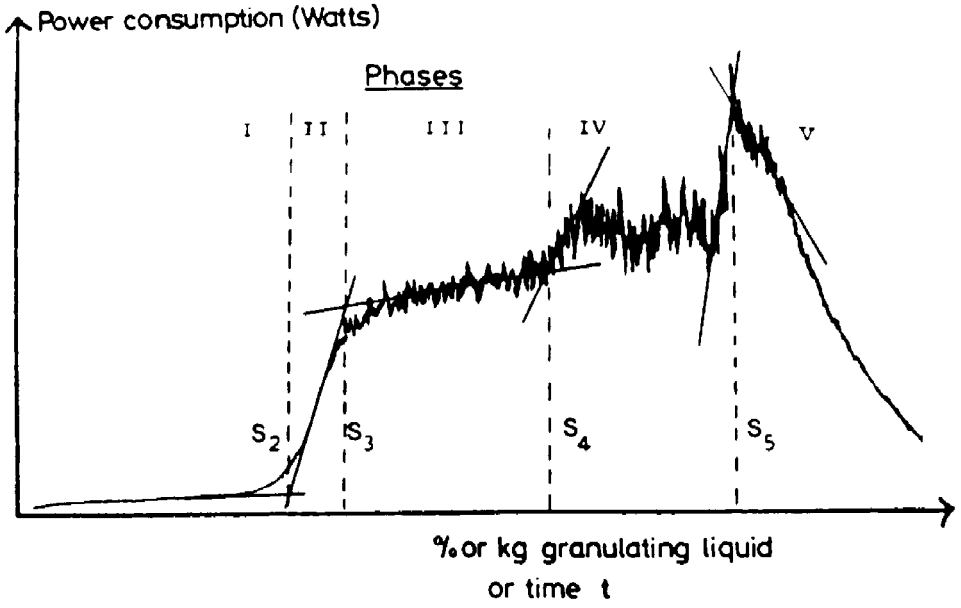

Figure 4: Division of the power consumption curve in 5 phases, according to different states of the powder mixture [4].

granulations are often determined:

- particle size distribution (by sieve analysis or laser diffraction measurement)
- mean granule diameter
- poured and tapped density
- flow rate
- moisture content (by drying or Karl Fisher titration)

The crushing strength (N) of the tablets is measured because tablets need sufficient mechanical resistance to withstand stresses and strains of transportation and storage. For fast dissolution of the pharmaceutical component, the tablet has to disintegrate within a specific period of time. Therefore, the disintegration time (s) is determined.

Systematic optimisation in tablet production

In systematic optimisation two approaches can be distinguished: the sequential approach and the simultaneous approach. Gould calls these methods model independent and model dependent [43]. In the sequential approach no model is developed. It consists of a series of measurements, where each new measurement is defined after the response of the previous experiment is known. Experiments are continued according to a direction in the search space that looks promising until no further improvement of the response variable is found. This is called a hill-climbing method. Sequential methods include the simplex method [44].

In the simultaneous or model dependent approach, experiments are performed according to specified settings of the variables (experimental design). An empirical model is developed according to the results of the experiments. The model can be used to predict the response value at every position in the experimental space. Several steps can be distinguished in the simultaneous approach.

Problem definition

The first step in the optimisation is the definition of the process. Which response variables have to be optimised, which design variables may affect these responses and what kind of relation is expected between the design variables and the response? The selection of the experimental range is of importance. The knowledge of pharmaceutical engineers should be used to define the feasible region.

Reproducibility tests

The reproducibility of the process has to be high to study the effect of design variables on the responses. Several levels of reproducibility can be defined. Therefore experiments have to be repeated on several days and by different analysts. Factors that influence the experiment have to be controlled.

Screening of variables

Screening designs are used to study which variables of a large group indeed affect the responses. Only a small number of experiments is necessary to study the effect of a large number of variables [45]. In screening designs only the main effects of the variables are considered. The first three steps, problem definition, reproducibility tests and the screening of variables must also be used in the sequential optimisation approach.

Design selection

Experimental design techniques were developed to obtain greatest amount of information using the least number of experiments [46,47]. Reviews and tutorials on the use of experimental design and optimisation in pharmaceutical development have appeared [48-50]. Factorial designs are used to study the effect of design variables on the response and the presence of interactions between the design variables [46,47]. Response surface methodology (RSM) uses a particular group of statistical designs to explore the dependency the response surface on independent process variables. The goal of RSM is to obtain a regression model that describes the dependent response variables as a function of the independent variables. The model is used to define the response surface which can be used for optimisation.

Selection of the experimental design is based on the expected relation between the design or independent variables and the responses. The more complicated this relation is, the more design points are necessary to model this relation. Besides the necessary design points, some extra design points are to be measured for the model validation.

Outlier selection

Outliers are caused by errors in the measurement. The recorded response may be incorrect because of unknown factors affecting the measurement, or the settings of the experimental variables may be incorrect. Several methods have been described to detect outlying experiments [51,52,53]. Schofield *et al.* [54] used Cook's distance to determine an outlying experiment. The effect of removing this experiment on the regression coefficients is enormous.

Model selection

The model describes the relation between the dependent response variable and the independent process variables. Not all model terms may be needed to model the response. Only the significant terms have to be selected in the model. Model terms are said to be significant if their effect is at least twice as large as the standard error. Several methods of model selection, such as forward selection and backward elimination are described in literature [52,55,56]. Schofield *et al.* [54] showed model selection by backward elimination of the model terms. The simpler model is judged to be better than the full model.

Model evaluation
The final model for a response can be used for optimisation. Predictions in the whole experimental range are made. Graphical techniques such as surface plots and contour plots can be used to show the relation between the independent process variables and the dependent responses. The model can also be used to acquire knowledge of the process.

Optimisation in direct compression
Several authors investigated the optimisation of direct compression [57-61]. They studied the relation between the composition of the tablet mixture and the physical properties of the tablets. The crushing strength of the tablets and the disintegration time were influenced not only by the type of components used in the mixture, but also by their concentrations. This optimisation was based on the use of mixture designs. In mixtures, the concentrations, *c*, of all components add to 1. Furthermore, the concentration of each component varies from 0 to 1. This causes the experimental space to be limited to (*c-1*) dimensions. The theory of mixture designs and mixture regression models is described by Cornell [62].

During direct compression, also several process variables have to be controlled to obtain tablets with specific characteristics. The crushing strength of the tablets and the disintegration time have to be optimised. The process variables that influence these tablet properties are the mixing time, the compression force etc. The designs for these experiments have to combine both mixture variables and process variables [63-65]. Bos *et al.* used combined designs to optimise direct compression tablet formulations for use in tropical countries [59-61].

Optimisation in wet granulation
Several composition and process variables in the wet granulation process affect the physical properties of the granules and tablets. During the last ten years, much effort has been spent at a more systematic optimisation of the granulation process in high-speed mixers. Aulton and Banks [6] distinguished between three groups of variables that influence the wet granulation process: apparatus variables, process variables and product variables.

Apparatus variables
Apparatus variables such as the size and shape of the bowl, impeller and chopper are dependent on the type of mixer used. Holm [66] showed that the effects of the impeller design in high-speed mixers can be described in terms of volume swept out by the impeller. A high swept volume causes high densification of the agglomerate and narrow granule size distribution. Chopper size and rotation speed had no effect upon the granule size distribution. Schaefer investigated nine types of mixers. The differences in granule growth could be explained by difference in shear, consolidation and particle motion. [67,68]. Schaefer also compared two sets of mixing tools in a Diosna mixer [69]. The standard tools resulted in a considerable

amount of wetted mass adhering to the wall, but with the specialized tools adhesion was prevented.

Process variables

Granulation in a high shear mixer is mainly controlled by the mechanical forces on the moist powder mass by the mixing tools. The most important variables are the impeller speed and wet massing time. The combined effect of these two variables can be understood in terms of liquid saturation. In general, a higher impeller speed leads to an earlier densification of the granules, and longer wet massing times lead to higher densification of the granules. Higher densification of the granules gives higher liquid saturation and therefore an increased granule size. The effect of impeller speed was shown in many papers [16,70-79]. The granulation time was also studied in many papers [73,76-81].

The effect of the impeller speed and wet massing time depends on the physical properties of the materials. If the materials are easily densified, minimum porosity is reached at short wet massing times and at relatively slow impeller speed. In this case, higher speed and longer massing times have no effect on the porosity, and therefore on the liquid saturation and granule growth. For cohesive materials, however, which are difficult to densify, impeller speed and massing time are critical parameters. The chopper design changes with the type of mixer, and therefore, the effect of the chopper speed depends mainly on the type of mixer used.

The method of liquid addition can change from pouring the total amount of liquid at once, to the pumping of liquid for a specific period of time during granulation. When the liquid is pumped into the mass, atomisation may be used to obtain a homogeneous liquid distribution [70].

Product variables

It was shown that the effect of the process variables in granule growth depends on the material used. The effects found in these investigations are only valid for the specific powder mixtures used. The powder mixture consists of several components. Besides the drug, also filler binders, disintegrants and binders are present in the mixture. Batch differences of one or more of the components influence the properties of the mixture. When the composition of the mixture changes, (e.g. more disintegrant is used and therefore less filler binder material) the properties of the total mixture change even more. When a new filler binder or disintegrant is used, the powder properties may vary dramatically. Knowledge of the effects of physical properties of the components (or total mixture) on the process of granulation is therefore very important.

The particle size and solubility in the granulation liquid are the most important properties of the mixture. A small particle size results in a large surface area. Therefore, more liquid is needed to keep the granule size constant [35, 82]. Ritala *et al.* also found the granule friability to increase when smaller particles are used. Kristensen *et al.* found that densification of dicalciumphosphate was dependent on

mean particle size and distribution [16].

When the powder is soluble in the binder solution, the amount of liquid has to be lower since the amount of powder is reduced, and therefore, also the surface area of the mixture [83]. Recrystallisation during drying will increase the strength of the granules. If the starting material is poorly wettable, granule growth is much less. This results in smaller granules [84].

Many studies investigated the effect of the binder concentration in the granulation [85-88]. The binder may be added in dry form to the powder mixture, and then water can be used as granulation liquid. D'Alonzo *et al.* found that dry addition resulted in larger granules. The mean granule size increased with an increasing binder level. The dry addition method also showed a better relation between the concentration and the mean granule size than the wet addition method. Similar findings were reported by Lindberg and Jönsson [38]. When the binder is dissolved, the solution must not be too viscous, because this leads to inhomogeneous distribution of the binder which results in weaker granules [89].

It is difficult to vary the physical properties of the drugs and excipients to be granulated systematically because it is impossible to vary only one property of a substance without changing other properties as well. Kristensen *et al.* [4] already mentioned that the effect of the starting material on granule formation and growth is a complex interaction between different properties. The drug and excipients have several relevant physical properties. It is therefore difficult to draw conclusions about the effect of only one physical property. When only a single parameter is optimised at the time, interactions between parameters cannot be detected. Interactions between parameters are very likely to occur in the granulation process, therefore, a multivariate approach is necessary.

Granulation properties affecting tablets

Kristl [90] shows that tablet crushing strength is influenced by granule diameter and angle of repose, and to a lesser extent by the flow rate of the granules. The liberation constant and the friability of the tablets were also influenced by these granule properties. The fragmentation propensity of the granules is important for the tablet strength just as the distribution of the binder, granule size and the moisture content [91]. The granulation properties can be combined with the process variables of both the granulation and the tableting steps to describe the crushing strength and disintegration time of the tablets [75,92].

Scaling-up of the process

In 1987 Kristensen and Schaefer reviewed the scaling-up of the wet granulation process and concluded that trial and error is still the most widely used technique [4]. Since then scaling-up was investigated more systematically many authors [67,68,94-97]. Neural networks were also used in upscaling of the granulation process [98]. Schaefer used dicalciumphosphate as a model substance. The degree of filling of the bowl, relative amount of binder solution and wet massing time were kept

constant. Scaling up results in a higher porosity of the granules, which is undesirable because it might affect the strength and bioavailability of the final granulation. Besides the increased porosity, scaling up resulted in a slightly inhomogeneous liquid distribution and a wider granule size distribution. Horsthuis *et al*. showed that scaling-up in Gral high shear mixers could be controlled by keeping the Froud number constant. The dimensionless Froud number is the ratio of the centrifugal force to the gravitational force. It can be a criterion for the dynamic similarity of mixers.

Robustness in tablet production

An increasing interest in robust processes has grown in pharmaceutical technology. The ideas of Genichi Taguchi have been used to find one or more optimal combinations of the process variables that would not only lead to the required granulation properties, but also to a stable product of which the properties are not sensitive to noise factors or other causes of variation [77,79,99]. Vojnovic *et al*. used the Taguchi approach to prepare an optimal product that is not sensitive to a change in impeller speed, because the impeller speed cannot be controlled easily during upscaling of the process. De Boer *et al.* introduced a robustness criterion to optimise the robustness of a process [100-102]. This criterion can easily be combined with other responses in a multi criteria optimisation procedure [101]. Hendriks *et al.* reviewed robustness in analytical chemical methods and in pharmaceutical technological development [103].

During the last ten to fifteen years, many systematic optimisations were performed using factorial, fractional factorial, RSM designs, mixture designs and D-optimal designs [49,70-72,75-81,92,96,97,104-116]. These experimental designs have not only been used to optimise the process, but also to validate the operation of wet granulation and tableting. However, in most of these investigations, only one formulation is optimised by varying parameters such as impeller speed, granulation time, moisture level, concentration of binder solution etc. Therefore, the results of these optimisations are only valid for the specific drug under investigation. They are not applicable to the granulation of other drugs and excipients.

In the present thesis different drugs are wet granulated to study the effect of physical properties of a new drug on the process and on the granulation and tablet properties. Multivariate analysis will be used to select a set of model drugs that have a large spread in the drug properties that are assumed to be of importance for the wet granulation process. Multivariate calibration is used to model the relations between the drug properties and the physical properties of the granulations and tablets.

Multivariate analysis

Multivariate analysis deals with data containing measurements of more than one variable for a number of objects [117-119]. Pharmaceutical drugs can be described in various ways by different properties of the drug. Analytical chemists may study the purity of the drug. Pharmacochemists measure the binding affinity of the drug to a certain receptor. Pharmaceutical technologists want to know the particle size distribution of the drug powder and its flowability and compressibility properties. The drugs are characterised in several ways. Multivariate analysis searches for interdependences among all variables. Various methods have been developed for the analysis of the multivariate data.

Multivariate data is often presented in a data matrix. The data is arranged in such a way that each row represents one object, characterised by several variables. Each column represents the same variable for all objects. A (*I***J*) data matrix **X** consists of measurements of *J* variables on *I* objects.

$$\mathbf{X} = \begin{pmatrix} x_{11} & x_{12} & \cdots & x_{1J} \\ x_{21} & x_{22} & \cdots & x_{2J} \\ \vdots & \vdots & & \vdots \\ x_{I1} & x_{I2} & \cdots & x_{IJ} \end{pmatrix}$$

In most cases the data has to be preprocessed to obtain maximal information from the data. Two much used preprocessing methods are centring and scaling of the data. For these methods the mean ($\bar{x}_j$) and variance (s_j^2) of each column of the matrix are calculated.

$$\bar{x}_j = \frac{1}{I} \sum_{i=1}^{I} x_{ij}$$

$$s_j^2 = \frac{1}{I-1} \sum_{i=1}^{I} (x_{ij} - \bar{x}_j)^2$$

The square root of the variance s_j^2, is the standard deviation, s_j, of the columns. With mean centring the mean $\bar{x}_j$ of each column *j* is subtracted from each value in column *j*. The mean of each column will, therefore, be shifted to zero. Mean centring is used because multivariate techniques are usually concerned with relative differences between objects. Scaling of the data matrix is usually done by dividing each column

by its standard deviation. After scaling every column has the same variance, one. Scaling is performed to give each variable equal weight. When the variables are not represented in the same unit, the magnitude of the values may influence the results of the data analysis. When each column of the data matrix is represented in the same unit, e.g. absorbance in a UV or IR spectrum, scaling may not be the right preprocessing method. Often mean centring and scaling are combined and called *autoscaling*.

Latent variables

Multivariate analysis methods search for interdependences between the variables and between the objects. They also give information about outlying objects that do not fit within the group of objects. The data are presented in simple plots to visualize the features that are hidden in the data.

Multivariate methods make use of latent variables which are linear combinations of the original variables. Latent variables in the data are directions that cannot be measured directly, but are principal properties that explain most of the variation between the objects. Latent variables may be defined to be orthogonal, *i.e.* uncorrelated (if **X** is centred). Then each new latent variable describes a direction in the data that is not described by any other latent variable. In Chapter 2, principal component analysis (PCA) is introduced, which is a multivariate analysis method that uses latent variables to describe the variations between drugs in a few orthogonal latent variables. This makes the selection of model drugs much easier.

Multivariate calibration

Multivariate calibration models play an important role in systems with numerous input variables and responses that are difficult or expensive to measure. A mathematical function, the calibration model, is needed to predict the responses for new experiments from data which can be obtained easily or cheaply. Calibration models are often used to predict the concentration of specific compounds in a sample from data measured by an instrument. This can be the absorption of a specific UV wavelength (univariate) or a whole near infrared (NIR) spectrum (multivariate). The calibration model is developed by the results of several experiments that were defined according to an experimental design. These experiments together are called the training set. In developing a calibration model it is assumed that the relation that holds for the model objects is also valid for new objects.

In the granulation process of a new drug the 'hard to measure' variables are the settings of the process variables, and the properties of the produced granules and tablets. These parameters are hard to measure because the amount of new drug available is usually not sufficient for a series of experiments. Therefore, ‘easy to measure’ variables, such as physical drug properties, will be used to predict optimal settings of process variables and the physical tablet properties.

Ordinary least squares

Ordinary least squares (OLS) regression can be used to obtain a linear model between the response **y** and the settings of independent variables **X** that are expected to affect the response. Let **X** be a matrix of *I* observations and *J* variables ($I \geq J$) and **y** is a vector of *I* responses, which is said to be dependent of **X**. Let **X** and **y** be centred.

$$\mathbf{y} = \mathbf{X} \ ,$$

where consists of the *J* regression coefficients for the variables of **X**. An estimation of can be given with OLS,

$$\mathbf{b} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y}.$$

Now,

$$\hat{\mathbf{y}} = \mathbf{X}\,\mathbf{b} + \boldsymbol{\epsilon},$$

where $\boldsymbol{\epsilon}$ is a vector of deviations between the real **y** and $\hat{\mathbf{y}}$ predicted by the model. The deviations are assumed to be independent and normally distributed. **b** is an unbiased estimator, this means that the expected value of **b** equals . The total sum of squares (SS_T) of the data can be divided in a sum of squares due to regression (SS_R) and the sum of squares of the residuals (SS_ϵ).

$$SS_T = (\mathbf{y}_i - \bar{\mathbf{y}})^2,$$

$$SS_R = (\hat{\mathbf{y}}_i - \bar{\mathbf{y}})^2, \text{ and}$$

$$SS_\epsilon = (\mathbf{y}_i - \hat{\mathbf{y}}_i)^2$$

The correlation coefficient R^2 is a much used criterion for the descriptive performance of models. The correlation coefficient only describes linear relations between **X** and **y**.

$$R^2 = SS_R \,/\, SS_T$$

When models with a different number of variables have to be compared, it is better to use the adjusted correlation coefficient.

$$R^2_{adj.} = 1 - \frac{I-1}{I-P}\,(1-R^2)$$

where *P* is the number of coefficients in the model (including $_0$). The adjustment is necessary because R^2 is a nondecreasing function of the number of variables. Both R^2 and $R^2_{adj.}$ can maximally become 1 for perfect relationship between **X** and **y**. $R^2_{adj.}$ can even become smaller than 0 when no relationship exists.

Partial least squares regression

Partial least squares regression (PLS) is, like OLS, a least squares regression method. Several tutorials are found in literature [120,121]. With PLS, the regression of the response **y** is carried out on latent variables of **X**, which are selected to maximise the covariance with **y**. A mathematical description of PLS regression method is presented in Chapter 7.

Validation

The calibration model is validated by a test set. Predictions of the response variable for experiments in the test set are compared to the measured response values. A real test set with new data obtained from the same process gives the best estimation of prediction properties of the calibration model. When a real test set is not available, a part of the training set may be used as a test set. Common practice is to use part of the data for the test set. Both sets of data must be distributed well over the whole experimental space. If only few experiments are available, cross validation can be used. With cross validation one or a few experiments are left out of the training set in the calibration phase and used as a test set. This is repeated with other experiments until all objects have been left out ones. During cross validation each new training set may be centred and scaled but the original centring and scaling may also be maintained.

The prediction error sum of squares (PRESS) is a good criterion for the predictive properties of the calibration model.

$$\text{PRESS} = \sum (\mathbf{y}_i - \hat{\mathbf{y}}_{/i})^2,$$

where $\hat{\mathbf{y}}_{/i}$ is the predicted value fqr **y** when object *i* has not been used in the calibration phase. With PLS, the model with the lowest PRESS will be selected. Besides a PRESS value, the Q^2 criterion can be calculated which is the squared correlation between the measured **y** values and the cross validated predictions $\hat{\mathbf{y}}_{/i}$. Q^2 can maximally be 1 for perfect predictive models, and may even be smaller than 0 for models without predictive quality.

$$Q^2 = \frac{\sum (\mathbf{y}_i - \bar{\mathbf{y}})^2 - \sum (\mathbf{y}_i - \hat{\mathbf{y}}_{/i})^2}{\sum (\mathbf{y}_i - \bar{\mathbf{y}})^2}$$

Multivariate statistical process modelling

During the last few years, the multivariate statistical modelling of large processes received much attention [122-129]. As opposed to fundamental modelling where theoretical models are developed to describe the process, statistical modelling uses the experimental results to develop the models. Processes may be distinguished in batch processes and continuous processes. Batch processes play an important role in chemical, pharmaceutical and food industry. Examples include the manufacturing of pharmaceutical and polymers. Batch processes are characterised by a prescribed processing of materials for a defined period of time or until the product has reached a specified characteristic [128]. It is very difficult to develop fundamental models for batch processes.

Continuous processes are present in chemistry and pharmaceutical technology (continuous granulation). Here flow rates of materials and process variables as the temperature must be controlled to produce the product with a stable purity.

For the modelling of large processes multivariate regression methods such as PLS and principal component regression (PCR) have been used. These methods make use of latent variables because the variables in the processes are numerous. Processes may consist of several steps, with intermediate products that have to be processed further to the final product. Quality variables of the intermediates can be obtained for in-process control. It is also possible that in continuous processes measurements at different parts of the process have been taken. Then a predefined causal relation exists between the measurements of the various intermediates and between measurements at different parts of the continuous process. Multiblock methods have been introduced to deal with these several blocks of data [122,124,130-132]. In multiblock methods the data from several parts of the process or from several intermediates can be separated in blocks. These blocks can be connected according to a predefined pathway according to the process. In the analysis of the data it is possible to zoom in into the blocks to learn more about a specific part of the process. Because of the numerous variables in the process specific information of certain parts in the process will be lost when all data is examined simultaneously. Another advantage of blocking is that the effect of process variables can be set explicitly to the blocks that are influenced.

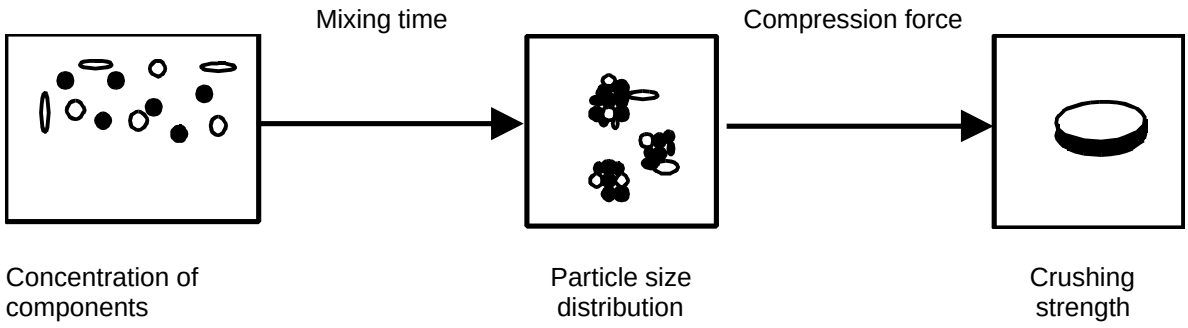

Figure 5: The two-step process of wet granulation and tableting.

The process of tablet manufacturing with a wet granulation step, can be viewed as a two-step process (Figure 5). In the first step, the powder mixture that consists of several components is wet granulated for a specific period and dried to improve the tableting properties such as flowability and compactibility. Physical granule properties such as the particle size distribution can be obtained by measurements to judge if the granulation step was successful. The granulation may be further processed into tablets in the second step of the process with a specific compression force. Crushing strength, disintegration time and other physical tablet properties can be measured to evaluate the tablets.

The aim of this whole process is to produce tablets that meet certain specifications. The quality of the granulations is not the main goal in the process, however, some specifications have to be met.

Scope of this thesis

Wet granulation is a complex process to improve the tableting properties of powder mixtures. It is much used in pharmaceutical industry because the powder mixtures lack characteristics necessary for the large scale production of tablets. When new drugs have been synthesized, the solid dosage form has to be developed. Experiments are necessary to optimise the wet granulation and tableting process for the specific mixture with the new drug. However, only a small amount of the new drug is available for experimentation. Some guidelines are needed in the optimisation of the process to decrease the number of experiments. Physical properties of the new drug may give information for the optimisation strategy.

As indicated in this introduction, many authors studied the influence of process variables in wet granulation on the granule and tablet properties. However, the effects that were found are only valid for the powder mixture that was studied. In most cases the effect of the product variables on the properties of the granules and tablets was studied qualitatively. In this thesis the effect of different drugs on the process is studied quantitatively. Therefore, a number of model drugs must be selected that are representative for a large group of drugs that can be wet granulated. The model drugs must have a large spread in physical properties that are important in the granulation process. Each drug will be described by a number of physical properties. These physical properties are not only related to the tablet and granule properties, but also to the settings of the process variables that control the wet granulation step. These settings, such as the amount of water that can be added during granulation have to be controlled to produce granulations that can be used in the tableting step. Chapters 2-4 describe the selection of the model drugs, the prediction of an uncritical amount of granulation liquid that can be added to the mixture and the multivariate modelling of the wet granulation process for a specific mixture with various drugs.

The whole process of wet granulation and tableting is a two-step process. Variation in the powder mixture, e.g. batch differences or another composition of the mixture, affect not only the granule properties but also the tablet properties. Modelling of this two-step process is necessary to control the production of tablets with specific characteristics. In everyday production of tablets, batch differences and other uncontrolled factors may influence the granule and tablet properties. If this can be detected in an early stage, process variables can be adjusted, to correct for these disturbances in tablet production.

Chapters 5-8 describe the modelling of the two-step process of tablet manufacturing with a wet granulation preprocessing step. Calibration models can be used to predict the crushing strength and disintegration time of the tablets. When the wet granulation has been carried out, physical granule properties can be used to improve the predictive properties of the model.

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Chapter 2

Multivariate design considerations

In multivariate data analysis it is essential that training set systems are selected to provide data with information essential for the construction of calibration models; data should encompass any future situation where the multivariate model is used for predictions. Chapter 2 describes the selection of model compounds that will be used for the multivariate calibration of the process of tablet manufacturing with wet granulation. From a set of potential model compounds physical properties were obtained that, from previous experience, were thought to be important for the wet granulation process. Principal component analysis is used to reduce the dimension of the drug space, to enable a good selection. Eight compounds that are representative for the whole set were selected. In the following chapters these compounds will be used to study the whole process of tablet manufacturing with wet granulation.

Introduction

If a textbook on the art of baking would claim that all types of bread, e.g. loaves of black bread, sponge-cakes and ginger biscuits, should be baked at the same oven temperature and for an equally long time, that book would probably not be a best-seller. Each sort of bread has its own optimal process settings, and they must be compared at their own optimal response values [1].

The process of baking is not very different from the process of granulation. When formulations with new drugs or excipients have to be granulated, it is not likely that the amounts of binder and granulation liquid have to be equal to previous granulations. A comparison of the granulation of various formulations using the same processing conditions would not be fair. Just as the black bread, the cakes and biscuits all have their own optimal oven temperature and baking time, granulations all have different optimal settings of the process variables.

In a process such as baking or granulation we can distinguish two different multivariate spaces, the experimental space and the response space. The experimental space is spanned by the variables that are varied during the experiments. Each point

in the experimental space represents an experiment performed at specific settings of the process variables. In the granulation process the experimental space is spanned with process variables such as the amount of granulation liquid, the granulation time, impeller speed etc. The composition of the formulation (amount of drug, disintegrant and filler binders) is also part of the experimental space. The extremes of this space are set by the limitations of the apparatus, the formulation constraint (amounts of all ingredients sum to 100%) and by what the technician thinks is reasonable.

The response space is spanned by response variables that characterize the product of the experiments. The response variables of wet granulation comprise particle size distribution, flowability and porosity of the granules. Each product can be viewed as a point in the response space. Each point in the experimental space is connected to a point in the response space. The response space may not be continuous; not all combinations of responses are possible. Optimising a process is searching for optimal areas in the response space, and finding areas in the experimental space that are related to these optimal areas.

When a new drug or excipient is used in the formulation, the new experiment does not fit in the original experimental space anymore, because there is no single variable that distinguishes between several drugs. A new experimental space for each new formulation would be needed. This new space is connected to the response space in a different way than the former experimental space. The optimal area in the experimental space might not be the same for the various experimental spaces. If predictions have to be made about the optimal region in the experimental space of a new drug, there must be a relation between the properties of the drug and the optimal region in its experimental space. All drugs can be represented as a point in the drug space. The drug space is spanned by variables that make distinctions between the drugs and are thought to be of interest for the studied process.

In the analysis of multivariate data it is essential that the training set consists of drugs, selected to provide data with essential information for the construction of calibration models, and to represent any future situation where the multivariate model is used for predictions [2]. The model drugs must have a sufficient range of variation in all physical properties considered important in the granulation process. When the model drugs are rather similar, no predictions can be made from the model for a new drug that differs too much from the model drugs. On the other hand, when the drugs are too widely different, a good model may be very difficult to construct. In some papers it seems that the authors have used the "*what could be found on the shelf*" strategy to select their model-objects. This may lead to highly biased information due to the narrow span of important properties of the objects [1].

Before a selection can be made, all potential model drugs have to be described by descriptors that may be of importance for the studied process. Descriptors are variables that describe the properties of the drugs as good as possible in relation to the specific problem. These descriptors can be physical properties (melting point, particle size), chemical properties (pKa, logP) or spectroscopic data (UV, IR). The descriptors span a specific space of drug properties. The dimensionality of this drug space is equal to the

number of descriptors used. All potential model drugs can be described as a point in that space. So *I* drugs give a swarm of *I* points in the same space. If the drugs are similar, the variation will be very small. Correlation can exist between two or several descriptors. The real dimension of the drug space is lower than the number of descriptors. Not every axis in the drug space describes an independent property of the drugs because this may also have been described by another descriptor. If the selection of model drugs is based only on the descriptors, it may be biased. Model drugs that are rather similar may be chosen because correlated descriptors were expected to describe new variation between the drugs. Principal component analysis (PCA) is used to prevent this biased selection. PCA selects orthogonal directions in the drug space.

Principal component analysis

The goals of PCA can be: simplification of the data, data reduction, outlier selection and classification [3]. The central idea of PCA is to reduce the dimensionality of a data set which consists of a large number of interrelated variables, while retaining as much as possible of the variation present in the data set. The orthogonal principal components (PC's) are linear combinations of the original descriptors. Because of the orthogonality each direction in the new space describes a new source of variation between the drugs.

Assume a set of *I* objects has been characterized by *J* descriptors ($\mathbf{X}_1$... $\mathbf{X}_J$). The data can be presented in an *I*J* data matrix. Each object can be described as a point in the *J* dimensional space. The first step of PCA is to determine the direction through the cloud of points along which the data show the largest variation. This is the direction of the first principal component (PC_1). Say this direction is called $\mathbf{h}_1$ then:

$$\mathbf{h}_1 = \mathbf{p}_{11} * \mathbf{X}_1 + \mathbf{p}_{12} * \mathbf{X}_2 + ... + \mathbf{p}_{1J} * \mathbf{X}_J$$

The extent to which a descriptor contributes to this first principal component is called the loading ($\mathbf{p}_{1j}$) of a descriptor. $\mathbf{p}_1$ is the first eigenvector of the $\mathbf{X}'\mathbf{X}$ matrix. The new direction can be seen as a principal property of the objects. This property cannot be measured directly but it explains most of the variation between the objects.

After projection of all data points on the first PC, it is possible to calculate how well this vector describes the data. The sum of all distances between the original point and its projection is a measure of the variation that is not described by the first PC. A second PC can be calculated to describe a part of the remaining variation. The second PC is chosen in a direction that explains the largest part of the remaining variation, orthogonal to the first PC. This can be repeated until all information in the data set is described by *J* PC's. The objects can be displayed in a new *J* dimensional space with orthogonal axes. Using all PC's the total variation in the data is described. Usually the first few PC's describe a large amount of variation, the last *L* ones only describe minor variation. This means that one can describe by only $K=J-L$ principal components almost as much variation as with *J* descriptors. The remaining minor variation can be considered as noise around the important properties. It is, therefore, desirable to subtract it from the total variation in the data.

Plots

From the PC analysis two sets of data are obtained: the coordinates of the objects on the PC's (the scores) and the amount ($\mathbf{p}_{jk}$) that descriptors contribute to the PC's (loadings). A scores plot presents the objects projected on two PC's, and a loadings plot presents the weights of the descriptors on the PC's. When descriptors lie close to each other in the loading plot of PC_1 against PC_2 they are highly correlated provided the total variation explained by the first two PC's is large enough. Descriptors that have a strong contribution on one PC are far away from the origin and lie close to the PC axis. Descriptors that have high influence on several PC's are projected in the quadrants of the loading plot. Descriptors that give no specific information about the objects lie close to the origin.

A two dimensional example

Two physical properties ($\mathbf{X}_1$ and $\mathbf{X}_2$) of 6 objects have been measured and are plotted in Figure 1. The first principal component (PC_1) is chosen in the direction that describes most of the variation. The objects are projected on this PC. A second component (PC_2) is chosen orthogonal to the first in the direction that explains the remaining variation. The two PC's are shown in Figure 2 with the projected objects.

An important result is that we now can describe the main systematic variation (say 75%) in the data using fewer variables (only PC_1) than the J original ($\mathbf{X}_1$ and $\mathbf{X}_2$) descriptors. When there are more than three descriptors it is difficult to visualize the data and, therefore, the selection of objects that give a wide spread in most of the important descriptors is not easy. By the use of principal components analysis, the data can be presented in fewer dimensions. Most of the variation can still be explained and selection of objects is much easier. The remaining variation that is not explained by the principal components can be seen as noise. Figure 2 shows the scores and loading

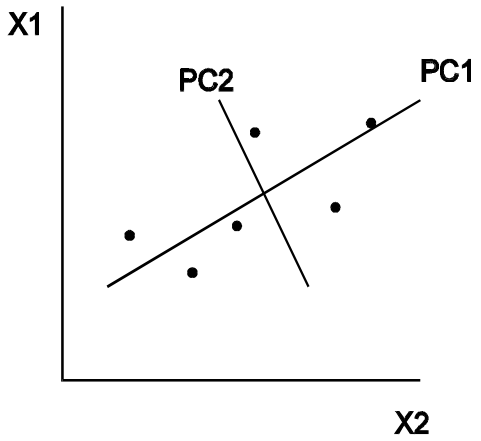


Figure 1: Principal component analysis in two dimensions.

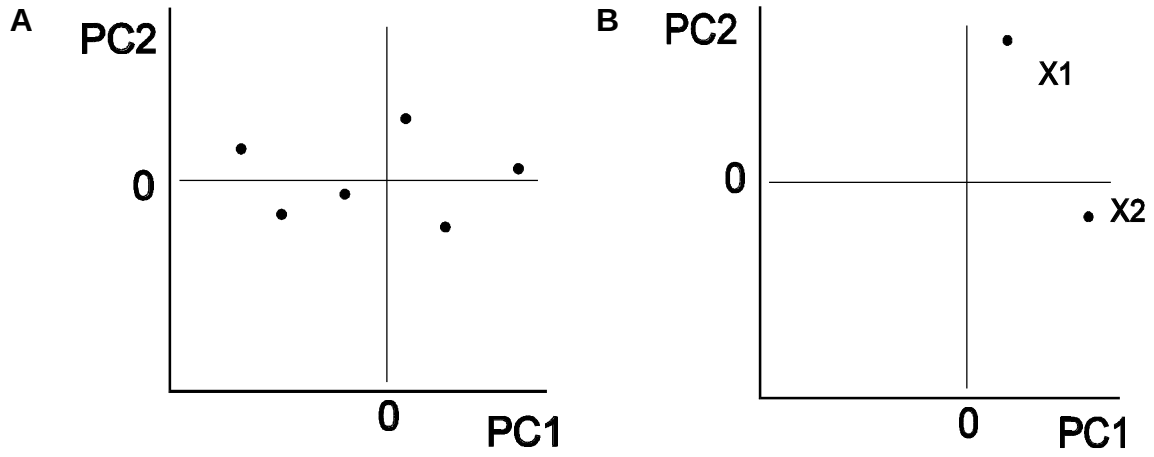


Figure 2: The scores of the objects (A) and the loadings of the variables (B) on the first two principal components.

plots of the data given in Figure 1.

In the scores plot (Figure 2A) we see that the variation in the PC_1 direction is the largest. In some software programs the scores plot shows equal spread in both directions, even when higher order PC's are shown. The axes have equal length, but are scaled differently. Therefore, the importance of the higher order PC's is visually exaggerated by the plot. It must always be kept in mind the amount of variance that is explained by a given PC. The loading plot shows the weights of the descriptors $\mathbf{X}_1$ and $\mathbf{X}_2$ on the PC's. Along the positive direction of PC_1 (in Figure 1, left under to upper right) we see that both descriptors $\mathbf{X}_1$ and $\mathbf{X}_2$ increase but $\mathbf{X}_2$ increases more than $\mathbf{X}_1$. Therefore, $\mathbf{X}_2$ has a higher weight on the first PC (Figure 2B). The second PC shows that $\mathbf{X}_1$ has a high positive and $\mathbf{X}_2$ a small negative weight. The advantages of PCA become more clear when it is used for larger data sets with more descriptors where the dimension reduction is more obvious than it is for the two descriptor case.

Calculation of principal components

PCA can be computed in several ways. Here the singular value decomposition (SVD) of the **X** matrix will be shown. The use of SVD for calculating PC's is well described in literature [3–5]. Carlson visualizes PCA with many pictures [1]. Other methods that can be used are the eigenvector analysis [1,4,5,6] that handles the symmetric (**X'X**) matrix, and the NIPALS (nonlinear iterative partial least squares) algorithm. NIPALS is an iterative method to calculate SVD.

The *I*J* **X**-matrix can be decomposed according to the singular value decomposition ($I \geq J$):

$$\mathbf{X} = \mathbf{UDV'} = d_1\mathbf{u}_1\mathbf{v'}_1 + d_2\mathbf{u}_2\mathbf{v'}_2 + \ldots + d_J\mathbf{u}_J\mathbf{v'}_J$$

with $\mathbf{U'U}=\mathbf{I}_J$ and $\mathbf{V'V}=\mathbf{VV'}=\mathbf{I}_J$, and **D** diagonal with nonnegative diagonal elements ($d_1 \ldots d_J$;

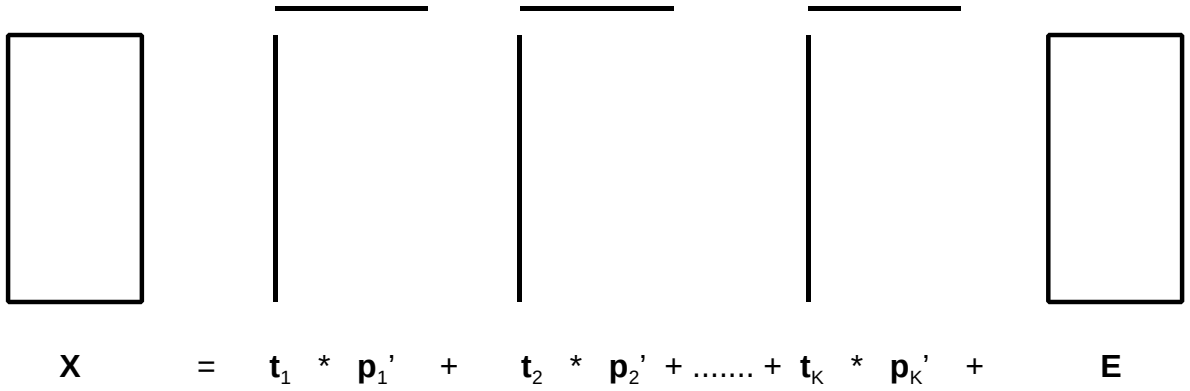


Figure 3: The building up of **X** with the principal components that consist of the scores $\mathbf{t}_1$...$\mathbf{t}_K$ and the loadings $\mathbf{p}_1$...$\mathbf{p}_K$. **E** consists of the residuals.

singular values) arranged from high to low and $\mathbf{X}'\mathbf{X} = \mathbf{V}'\mathbf{D}^2\mathbf{V}$. The columns of **U** and **V**' are called the left and right-hand singular vectors of **X** respectively. The relation of SVD with PCA becomes clear when **V'** equals the loadings **P'** and **UD** equals **T**, the scores of **X**, which gives **X**=**TP'**.

When only *K* columns of **T** are used, some variation is not be described: $\mathbf{X}=\mathbf{T}_K\mathbf{P}_K'+\mathbf{E}$, where **E** contains the unexplained variation. In Figure 3 we see that the **X**-matrix is built up from several PC's where each PC is again built from the outer product of a column-vector $\mathbf{t}_k$ of the **T** matrix times a row-vector $\mathbf{p}_k'$ of the **P**' matrix which gives an estimation of the **X**-matrix. All these estimates are mutually independent (because of the orthogonality) and can be added together to produce **X**.

Selection of model drugs from the PCA plots

The selected model-drugs should have maximal spread in all their properties. Such a selection is accomplished by choosing objects projected at the borders of the score plot and as far as possible from each other. Some caution, however, must be exercised: one must be careful not to choose outliers. Besides objects at the borders it is wise also to take some random objects. The objects selected from the plot of PC_1 against PC_2 must also have a good spread in all the other PC score plots to make sure that enough information is caught. When some obvious classes of objects that belong together can be discerned, it is wise to select representatives from those classes [7]. Representatives of classes or typical objects lie close to the middle of the class.

Materials

A set of 42 potential model drugs were selected by considering first their price.kg^{-1}, because large amounts of drug are used during the experiments. The drugs were also selected to have a broad range in the solubility in the granulating liquid. Some model drugs, that were suspected to give problems in the granulation experiments, were removed from the list. From the final nineteen potential model drugs, descriptors were obtained by measurement and from literature.

It is important to remember that the selected model drugs represent just a set of physical properties. The name of the drug represents a property that says only little about the drug considering its behaviour in the granulation process (*e.g.* paracetamol 45µm and paracetamol 180µm are two different model drugs that have the same name but a different particle size, and therefore a different compactibility, poured density etc.) For the selection of the model drugs, the following easy to obtain descriptors were selected that were thought to be important for the calibration of the granulation process.

Solubility: The solubility of the drugs in the granulation liquid is of main importance [8,9]. When a drug dissolves well in the granulating solution, it cannot take part in the granulation process. A relatively small amount of solution can lead to over wetting. In our case the granulation liquid will be water. The solubility of the drugs in water is given.

Compactibility: The compactibility of the drug is especially important for tableting of the granulation. It is a measure for several aspects that involve the binding between particles. The specific surface area is important for the mechanical strength of the tablets. This area is affected by physical properties of the drug such as particle size and shape, but also by fragmentation or plastic deformation occurring during compaction.

Thickness tablet: The thickness of the tablets of the pure drugs is influenced by the crystal form and poured density of the drug and the particle size, the particle size distribution and the poured density of the granulation. The thickness must be related to the weight of the tablets.

Poured density: The poured density gives in combination with the tapped density an idea about the flowability and the porosity of the starting material. The tapped density is the density of the bulk after 500 taps in a tap apparatus (J. Engelsman, Ludwigshafen a. Rhr).

Hausner ratio: The Hausner ratio is defined as the poured density divided by the tapped density. It measures of flowability of the drug. A low Hausner ratio means that the drug has a high flowability.

Contact angle: The contact angle is a measure for the wettability of the material. If drugs are easily wetted, granule formation is much faster. The contact angles were measured with the h-ϵ method [10]. The influence of the wettability was already described by Jaiyeoba *et al.*[11].

Particle size: The particle size of the drugs is of main importance. It is a measure for the relative surface of the drug. It affects the speed in which the drug dissolves, the poured density, the compactibility etc. The particle size was not actually measured at first but the substances were classified to have a large or a small particle size. Most of the drugs have a small particle size. Ascorbic acid, paracetamol cryst. and

dicalciumphosphate have a large particle size.

Table 1 shows the data set used. The solubility of the drugs is given as the logarithm of the parts of water needed to dissolve 1 part of drug. The logarithm is used because the original values do not have a normal distribution. High values stand for low solubility. Tablets (13 mm, 500 mg, 20 kN) were compressed using a hydraulic one punch tablet press (Mooi / ESH). The compactibility is given as the crushing strength of a tablet of the pure drug (mean of 10 measurements). The poured density is given in ($g.ml^{-1}$) and it is the mean of 5 experiments. The Hausner ratio is determined as the ratio of the volume of 100 g drug before and after 500 taps. The contact angle is measured using the 'h-ϵ' method. The cosine of the values is given. Ascorbic acid, nicotinamide and thiamine.HCl were known to have low contact angles [12]. The contact angle of these drugs were set to the lowest available value of 48^o.

The open places in the table are caused by missing values. Missing values in the tablet thickness are caused by the fact that it was not possible to produce tablets of some drugs. The table of Lagas [11] with contact angles did not contain all substances used in the experiments. For the calculation of the principal components the column means are used for the missing values.

Table 1: The dataset used in the principal component analysis. The solubility of the compounds in water (Sol.), the compactibility (Comp), the thickness of the tablets (Thick.), poured density (Bulk), Hausner ratio (Haus), cosine of the contact angle (Cos θ) and the particle size (Size) are given. Large particles are indicated with a 1, and small particles with a 0. The open places are caused by missing values. In the calculations, column means were introduced for the missing values.

nr	Compounds	Sol.	Comp	Thick.	Bulk.	Haus.	Cos θ	Size
1	Ascorbic acid	0.544	0	2.59	0.909	1.13	0.67	1
2	Salicylic acid	2.700	96	3.20	0.588	1.24	-0.22	0
3	Aluminum oxide	4.300	145	3.39	0.208	1.39		0
4	Carbromal	2.700	54	2.50	0.435	1.20		0
5	Diprophylline	0.700	90	2.73	0.400	1.47		0
6	Ferrousfumarate	2.700	8	2.07	1.111	1.21		0
7	Isoniazid	0.903	29	2.87	0.625	1.23	0.66	0
8	Lithiumcarbonate	2.700	0		0.385	1.57	0.64	0
9	Meprobamate	2.700	100	3.21	0.417	1.29	0.12	0
10	Sodiumsalicylate	0.000	57	2.60	0.263	1.39		0
11	Nicotinamide	0.000	24	3.03	0.400	1.45	0.67	0
12	Paracetamol	1.845	0	3.46	0.244	1.40	0.50	0
13	Paracetamol cryst.	1.845	0	3.21	0.667	1.13	0.50	1
14	Phenobarbital	3.000	0	3.24	0.435	1.51	0.24	0
15	Phenytoin sodium	1.300	260	2.92	0.278	1.53		0
16	Sulfadimidine	3.700	32	2.98	0.385	1.59	0.67	0
17	Sulfamethizole	3.300	0		0.435	1.63	0.54	0
18	Thiamine.HCl	0.000	146	2.94	0.222	1.59	0.67	0
19	Dicalciumphosphate	4.300	37	2.06	0.833	1.15	1.00	1

Results and discussion

The results of the PCA were calculated using the PLS toolbox [13] for Matlab [14]. The first three PC's explain about 74% of the variation in the data. These three PC's were used for the selection of the model drugs. Table 2 shows the loadings of the descriptors on the first three PC's and the percentage of variance explained by each PC.

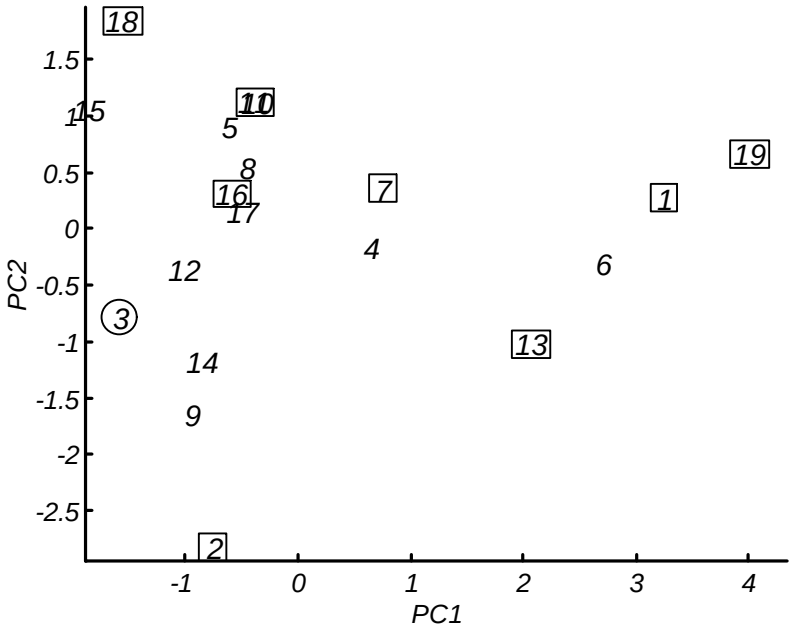
The method used is rather rough because only few drug descriptors were used to separate between the drugs. Figures 4A-C show score plots of the first three PC's. Each plot shows the score values of two PC's. The numbers marked within a square (1,2,3,7,11,13,16,18) are selected as model drugs. The selection was done on sight from all three score plots. Experiments showed that model component number 3 (aluminium oxide; marked with a circle) could not be used in the Gral high-speed mixer. Therefore, another substance far away from object 3 in the multivariate space (19, dicalciumphosphate) was selected. In the first analysis, dicalciumphosphate was not taken into account. The figures show results from the analysis which included calcium phosphate. Aluminium oxide is still presented to show its position in the drug space. According to the score plots it is not outlying object, and its strange behaviour in the granulation process cannot be explained from its position in the drug space.

The first step was the selection of the outer corner points in all plots: 2, 18 and 19 in Figure 4A and 1 and 16 in Figure 4B. Object 15 in Figure 4B is close to objects 2 an 18 and was, therefore, not selected. Object 7 is selected because it is in the middle of each score plot. Objects 11 and 13 were selected to complete the eight model drugs. The selected drugs have a good spread in all PC's. The first PC gives the spread of the drugs in particle size and poured density. The contact angle dominates the second PC and the variation in the third PC is mainly caused by the solubility of the drugs. The selected drugs have enough variation in these important variables. Three drugs with large particles and zero compactibility were selected (1, 13 and 19), one drug with high contact angle (2) and two drugs with very low solubility (16 and 19). Two drugs (7, 11) have intermediate score values on each PC. The selected substances that will be used in following experiments are: ascorbic acid, salicylic acid, isoniazid, nicotinamide, paracetamol cryst., sulfadimidine, thiamine.HCl and dicalciumphosphate.

Table 2: Loadings of the descriptors on the principal components and the percentage of variance explained by each PC.

drug descriptors	PC1 (42%)	PC2 (18%)	PC3 (14%)
Solubility	0.07	-0.45	0.75
Compactibility	-0.30	0.13	-0.41
Thickness tablet	-0.41	-0.36	-0.04
Poured density	0.52	-0.18	-0.06
Hausner ratio	-0.44	0.35	0.40
Cos (θ)	0.24	0.71	0.31
Size	0.46	-0.01	-0.13

A



B

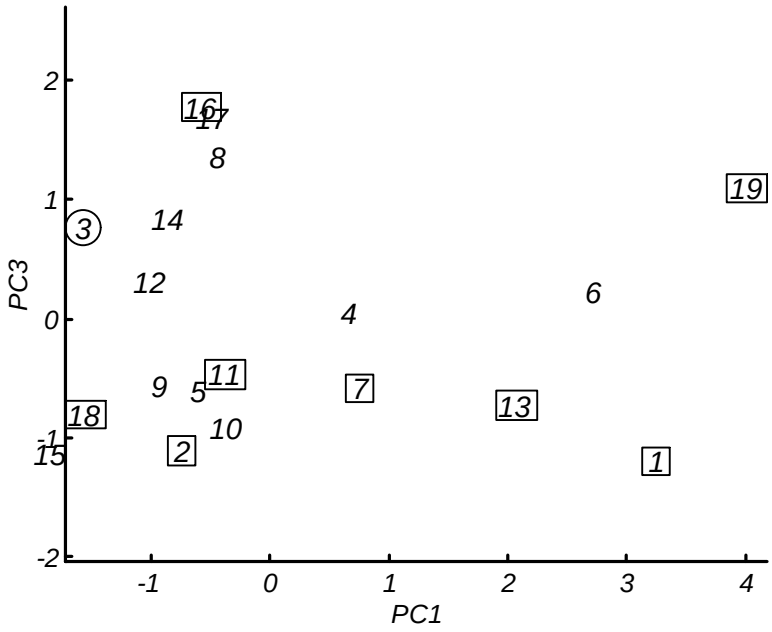


Figure 4: The scores of the compounds on PC1 and PC2 (**A**) and on PC1 and PC3 (**B**). The compounds are represented by the corresponding numbers. The selected model drugs are presented in a square. Compound 3, (aluminum oxide) indicated in a circle could not be used in the GRAL granulator.

C

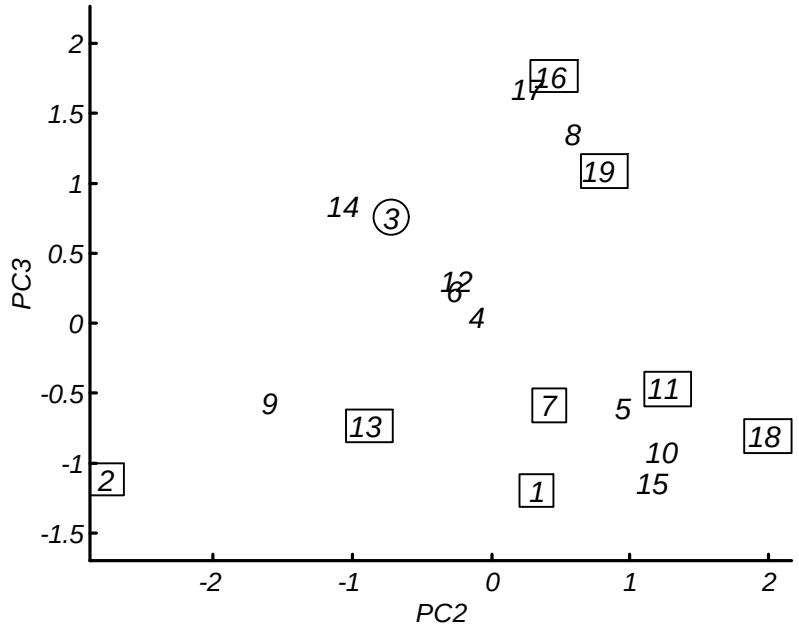


Figure 4C: The scores of the compounds on PC2 and PC3 are represented by the corresponding numbers. The selected model drugs are presented in a square.

Conclusion

In the multivariate calibration of the granulation process a calibration model has to be developed that predicts the settings of process variables of the granulation and physical properties of the granulation to produce tablets of new drugs. To develop the calibration model, some model drugs are needed. The selection of the model drugs for experimentation has to be based on information relevant for the specific process. Because of possible interaction effects all properties must be considered simultaneously. Multicollinearity can bias the selection of the model drugs. Principal component analysis simplifies the problem of selection, because it searches for new orthogonal directions in the drug space. The spread in the properties of the model drugs, should guarantee the validity of the calibration model for the granulation process over a large area in the drug space. In this application only few and easy to obtain variables were used to separate between the drugs. In the calibration of the tablet manufacturing process, in the following chapters, more physical properties of the selected drugs will be used to relate to the characteristics of the granulations and tablets.

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Chapter 3

Prediction of the uncritical liquid amount in wet granulation

Granulation of the model drugs, selected in Chapter 2, is examined. Due to the large differences in physical properties between the selected drugs, the design levels of the process variables of the granulation process have to be varied also. The amount of water added during granulation has to be adjusted for each drug to produce granulations that can be further processed into tablets. Chapter 3 describes the determination of an uncritical amount of granulation liquid that can be added to a specific formulation containing lactose, corn starch, polyvinylpyrrolidone and a model drug. Wet granulation proceeds by agitation of a powder mixture in the presence of a liquid. Granules are formed and grow because of effects of mobile liquid bonds formed between the primary particles. Wet granulation in high-shear mixers proceeds within a narrow range of liquid amount. When too much liquid is added, the powder mixture becomes overwetted and cannot be used for tableting. When too little liquid is added, a large percentage of primary particles is still present in the mixture and the granules disintegrate during drying. The uncritical liquid amount could safely be added to the mixture without causing overwetting and the percentage of primary particles decreased to a small amount. The uncritical liquid amount is determined from the power consumption curve of the impeller, obtained during continuous addition of granulating liquid. It is defined as the middle of stage three, according to Leuenberger's division of the power consumption curve. In the present chapter the uncritical liquid amount is related to physical properties of the model drug. For drugs with a low solubility in the liquid and for drugs that have a large surface area, extra granulation liquid is necessary to produce granules that can be further processed into tablets.

Introduction

In pharmaceutical practice it is well known that wet granulation in high-shear mixers proceeds within a narrow range of liquid contents. The liquid saturation S is claimed to be the major controlling factor for the granule growth process [1–3]. It expresses the

degree of filling the intra granular voids with the binder liquid. It depends on the moisture content relative to dry material of the agglomerates (H), the particle density (ρ) and the porosity (ϵ). When the powder dissolves partly or totally in the liquid, the relation becomes invalid because the porosity of the particle and the intra granular voids increase.

$$S = \frac{(1-,)}{} HD$$

According to Kristensen and Schaefer, the liquid amount required to run an uncritical granulation process depends on a large number of factors which include feed material properties, such as the particle size distribution, solubility in the liquid and ability to absorb the liquid [4]. Paris and Stamm also showed the influence of powder quantity, particle size, solubility and the type of granulation liquid on the amount of liquid [5,6]. Prediction of an uncritical amount of granulation liquid on the basis of knowledge of the feed material has not been very succesful. Rumpf *et al.* calculated the cohesive forces that exists between two particles for rhombohedral and for cubical packing assuming ideal wettability and no separation between the particles [7,8]. The cohesive force depends on the surface tension of the granulation liquid, the contact angle, the separation between the particles and the particle diameter. With the cohesive forces, Leuenberger *et al.* made a theoretical estimate of the quantity of granulation liquid required in the granulation process [9].

For some time now, instrumental techniques have been used to determine an uncritical liquid amount. These techniques include measurement of temperature of the granulation, change in impeller speed during granulation or motor slip [10–13], measurement of power consumption [3,5,6,9,14–20], probes in the powder mass [21] and torque measurement of the main impeller shaft [22,23]. It is found that the measured quantities reflect changes in the rheological properties of the moist mass and that changes are related to the granule growth process. In some papers several techniques for end point control have been compared [24,25]. Corvari *et al.* found a strong correlation between power consumption and torque measurement.

In a series of articles Leuenberger *et al.* showed the relation between the power consumption profile of the impeller shaft and the physical properties of the moist mass [9,14-16]. In the power consumption record five different phases can be observed. Figure 4 of Chapter 1 shows a typical power consumption profile given for a lactose/corn starch powder mixture. In the first phase no increase of power consumption is observed because components in the powder mass can take up water and, therefore, no interparticulate liquid bridges are formed. The second phase shows a fast increase of power consumption as liquid bridges are formed. The mass becomes much more cohesive. During phase three the interparticulate void space is filled with granulating liquid. No increase of the power consumption is observed. Within phase three granules can be obtained that differ in their properties. At the start of phase three, porous and

fragile granules will be formed where at the end of the plateau, the granules will be more dense and thus harder. After phase three, parts of the powder mix will be saturated with liquid. This produces lumps in the mixture which causes the power consumption to fluctuate. Finally, the whole mix will be saturated and a suspension will be formed and the power consumption decreases rapidly. The 100% saturation may give a peak in the power consumption profile depending on the type of granulator and material used. In high shear mixers this peak may not be as obvious as in planetary mixers. For the definition of the degree of liquid saturation it is essential to measure the total power consumption profile till the state of a suspension is obtained. Then it is possible to define a normalized value S* of the liquid saturation of the interparticulate void space:

$$S^* = \frac{S - S_3}{S_5 - S_3}$$

Here S is the amount of liquid at a certain point in the curve between S_3 and S_5, where S_3 and S_5 are the boundaries between phase two and three and between phase four and five respectively. S* is the percentage the granules are filled up with liquid. Several papers have shown that usable granulations should be obtained at phase three of the typical power consumption profile [5,6,15,17-20,24]. Leuenberger showed the increase of the mean granule diameter, and the decrease of the percentage of fines and granule friability in the range from phase S_3 to S_4 [15]. Holm *et al.* showed that the typical power consumption record only holds for lactose and not for other formulations such as dicalciumphosphate or mixtures of dicalciumphosphate and corn starch [17]. Power consumption profiles vary from product to product. This must be caused by differences of the energy required to rearrange and compact the particles composing the moist agglomerate. The start of the rapid grow of granules, caused by partial saturation of the interparticle voids happens at different liquid saturation levels for different materials. Leuenberger stated that pharmaceutical granules can only be obtained for an amount of granulation liquid in a range up to a degree of saturation of about 60% of the interparticulate void space [15]. Beyond the 60% of liquid saturation the granule size increases exponentially, and lumps will be formed. The same amount is found for a Fielder PMAT 25 VG high-speed mixer [17]. The 60% liquid saturation, however, is only valid for lactose. Holm *et al.* showed that for other substances, the granule size increases in the same way at other values for the liquid saturation. Dicalciumphosphate has a saturation limit of 70%, dicalciumphosphate/corn starch (85:15) of 85% and dicalciumphosphate/corn starch (55:45) of 90%.

Shiraishi *et al.* granulated a mixture of theophylline, lactose and corn starch and stopped liquid addition at several points in the power consumption curve [19,20]. Granulation stopped at the start of phase 3 resulted in tablets with the lowest friability and disintegration times. When more water was added, tablet disintegration times increased. Stamm and Paris studied the influence of technological factors and physical

properties of the solvents and products used on the optimal granulation liquid requirement measured by power consumption [5,6]. The optimal liquid amount was calculated according to Leuenberger's formula: $S=½(S_3+S_4)$, which corresponded to the liquid amount as determined by particle size investigation. The flow rate showed no influence on the optimal amount. The optimal liquid amount decreases when particle size of the mixture increases. Powders having the same solubility need the same amount of liquid, but granule properties may change due to different wettability properties.

Theoretical evaluations of the maximal liquid saturation are given, but they assume perfect spherical particles [15]. The influence of the various substances on the critical saturation amount can be fairly large. When mixtures of several compounds are granulated, the estimation of the uncritical liquid amount becomes even harder due to large number of factors and the unknown interactions between the various particles. During the granulation, some particles may dissolve partly in the liquid, which leads to very complicated binding forces between the particles. The theoretical model becomes too complicated for common use. Therefore multivariate calibration will be used to model the required liquid amount for several mixtures of lactose and corn starch with varying drugs. The model makes use of the important physical properties of the drugs, under which the particle size distribution, contact angle and solubility in the granulation liquid.

Multivariate calibration

Partial least squares regression (PLS) is a biased multivariate calibration technique much used in the field of chemometrics. It can be used instead of ordinary least squares regression (OLS) when serious multicollinearity exists between the descriptor variables or when the number of descriptors exceeds the number of objects. PLS is used to model relations between predictors and response variables and to make predictions. Tutorials on PLS were given by Geladi and Kowalski [26] and by Höskuldsson [27]. PLS finds latent directions in the descriptor data set that have a good relation with the response variable. In Chapter 7, PLS regression will be introduced in detail. Multivariate analysis and calibration in pharmaceutical development work have recently been reviewed by Lindberg and Lundstedt [28].

In the present chapter multivariate calibration is used for the modelling of the uncritical liquid amount (ULA). This amount is defined as $ULA= ½(S_3+S_4)$, where S_3 and S_4 are the start and the end of phase three in the power consumption profile. The profiles were obtained from several powder mixtures consisting of lactose, corn starch and one of the selected model drugs at concentrations of 5% and 50%. The mean granule diameter and the percentage of fines were also measured during stage three of the records. The model can be used to predict uncritical amounts of water that can be added to mixtures of lactose 200 mesh, corn starch, polyvinylpyrrolidone with a new drug.

Experimental

Mixtures of lactose 200 mesh (DMV,Veghel), corn starch (AVEBE) and polyvinylpyrrolidon (PVP 25k, Brocacef) were combined with the model drugs: ascorbic acid, dicalciumphosphate, isoniazid, nicotinamide, paracetamol, salicylic acid, sulfadimidine and thiamine.HCl (Pharmachemie). Paracetamol was milled to study the effect of particle size on the uncritical liquid amount From the eight selected model drugs two different formulations (A and B) were made. Further, a third mixture containing no model drug (C) was granulated. Table 1 shows the percentages of substances in the formulations. Mixture C was considered as mixture A or B with lactose 200 mesh as the model drug.

Power consumption records were obtained from a GRAL 10 high-speed mixer with power consumption measurement supply. Power consumption was measured during continuous liquid addition of water to the mixture. PVP was dry added and water was used as the granulation liquid. Water was added with a peristaltic pump at 30 $ml.min^{-1}$. During granulation the impeller speed was maintained at 300 rpm and the chopper speed at 1500 rpm. For each experiment 1.5 kg material was used. The records were evaluated and phase three was determined for each mixture. During new experiments, samples were taken from the mixture at several positions in the third phase of the power consumption record. The samples were dried for at least eight hours at 40°C in a tray oven. The samples were screened (2mm) and particle size distribution was obtained by sieve analysis (1.40, 1.12, 0.85, 0.60, 0.425, 0.30, 0.15, 0.00 mm).

Table 2 shows the physical properties of the model drugs that were used for the calibration of the ULA. Sol is the logarithm of the amount of water (g) needed to dissolve 1 g. of drug. The particle size distribution of the drugs was measured by laser diffraction (Sympatic Helos). 10%, 50% and 90% are the boundaries in the particle size distribution curve that indicate that 10%, respectively 50% and 90% of the particles have a smaller particle diameter than the value given. S_v is the surface area ($m^2.cm^{-3}$) based on the bulk of the material. The poured and tapped density ($g.cm^{-3}$) were measured for all drugs. The surface area was also determined by adsorption of N_2 (BET). Here also the internal surface area of the pores is included. The contact angle θ of the drugs was measured by the h–ϵ method [29]. Lactose 100 mesh is used as a test drug and will not be used in the calibration. The PLS toolbox [30] for MATLAB [31] was used for the calibration calculations of the uncritical liquid amount.

Table 1: Composition of the powder mixtures used in the experiments with 5% drug (A), 50% drug (B) or without drug (C).

Component		A	B	C
model drug	(%)	5	50	0
lactose 200 m	(%)	81	36	86
corn starch	(%)	10	10	10
PVP 15k	(%)	4	4	4

Table 2: Physical properties of the model drugs used in the calibration of the uncritical liquid amount and the range. The descriptors are explained in the text.

Compound	Sol	10%	50%	90%	S_v	Bulk	Tap	Th.	BET	Cos θ
ascorbic acid	0.54	81	216	398	0.07	0.91	1.00	5.63	0.06	0.78
dicalciumphosphate	3.70	88	242	375	0.14	0.87	1.00	4.12	0.32	1.00
isoniazid	0.90	10	39.5	89.0	0.41	0.58	0.78	5.78	0.19	0.66
nicotinamid	0.00	8.0	25.9	62.3	0.53	0.46	0.68	6.02	0.18	0.70
paracetamol	1.85	37	360	570	0.11	0.69	0.77	6.56	0.03	0.50
salicylic acid	2.70	3.0	12	24	1.08	0.28	0.43	5.63	0.41	-0.22
sulfadimidine	3.70	9.9	54.5	140	0.33	0.58	0.78	5.77	0.07	0.67
thiamine.HCl	0.00	4.3	20.7	55.0	0.69	0.26	0.43	5.81	0.39	0.64
lactose 200 mesh	0.70	2.2	26.6	77.3	0.93	0.55	0.85	5.81	0.50	0.80
lactose 100 mesh	0.70	25	134	223	0.25	0.75	0.85	5.61	0.18	0.80

Results and discussion

Large deviations were found between the power consumption records when the mixture consisted of 50% model drug. When 5% drug was used, only minor differences were found between the records. Therefore, only the 50% mixtures will be considered. Most power consumption records seemed to follow the record of Leuenberger. However, the power consumption records of salicylic acid and milled paracetamol deviated too much from the typical curve of Leuenberger. Both model drugs had very small particles and could not be wetted easily. For these two model drugs, it was not possible to define the start and end of either phase. Therefore, the records of these two model drugs were not used in the calibration.

In the Appendix of this chapter the power consumption records of the model drugs, the mean granule diameter (d_{gw}, mm) at certain stages of the curve and the percentage of fines at the same stages are shown. Samples were taken from the start of phase three with steps of about 1.5 % water until the particle size was too large to fit through the 2 mm screen. The mean granule size at that latest point was set to 3 mm. The percentage of fines (✳; <150 µm) of the samples is given for all model drugs. For model drugs with a large particle size, the percentage of fines is also given for a larger particle size dependent on the size of the specific drug (o), (lactose 100 mesh, <300 µm; ascorbic acid, <425 µm; dicalciumphosphate, <425 µm; paracetamol, <600 µm).

In each power consumption profile, the five phases can be determined. Large differences exist between the start and end of each phase for the various model drugs. The rise in power consumption in phase two may be steep, as with isoniazid, or may be rather weak as with lactose 200 mesh. The precise start and end of phase three is not always easy to detect from the curves. Phase three starts at the end of the first increase of the power consumption. At the end of phase three the power consumption drops and rises again with more noise than in phase three. For model drugs with small particle

size, a peak arises before the drop in power consumption. For model drugs with a larger particle size, the peak disappears, however, lactose 100 mesh also shows a small peak at the end of phase three. The same peak at the end of phase three was already mentioned by Shiraishi *et al.* [19]. The end of phase three corresponds well with the exponential growth of the mean granule diameter. In most cases of the drugs with small particle size, the peak at the end of phase three gives overwetting of the mixture. However, for sulfadimidine and lactose 200 mesh this position still gives usable granulations.

For the dicalciumphosphate mixture, only the small particles agglomerate at the beginning of phase three. Dicalciumphosphate does not participate in the agglomeration until the second half of the third phase. Then the amount of particles smaller than 425 µm starts to decrease below 20%. Dicalciumphosphate has a large range of phase three, but good granules can only be obtained at the second half of phase three. The plots of nicotinamide, thiamine.HCl and also ascorbic acid show that before phase three is reached, there is still a large percentage of fines in the mixture. In all of these latter cases the first sample was taken in phase two.

The uncritical liquid amount (ULA = ½(S_3+S_4)) is defined, which is the amount of water that can be safely added to a mixture with lactose 200 mesh, corn starch, PVP and a drug without causing overwetting of the mixture and providing only a small percentage of fines. The figures in the appendix of this chapter show that for all model drugs, the percentages of fines at the ULA is small. For drugs with large particle sizes, the drug particles also take part in the granulation at the ULA. Table 3 shows the mean of two ULA values all model drugs.

Paracetamol was milled to study the effect of particle size reduction. However, the milled paracetamol could not be used in the calibration because of the power consumption record deviation caused by cohesiveness of the material. Therefore, lactose 100 mesh was used to study the effect of particle size reduction on the granulation. For lactose 100 mesh, phase three was reached with less water. The total amount of water to reach phase four is only a little less than for lactose 200 mesh.

Table 3 ULA for mixtures with 50% model drug

model drug	ULA 50%
ascorbic acid	8.4
dicalciumphosphate	13.6
isoniazid	12.6
nicotinamid	9.6
paracetamol	9.2
salicylic acid	*
sulfadimidine	14.1
thiamine.HCL	11.9
lactose 200 mesh	15.3
lactose 100 mesh	12.1 / 11.5

Table 4: Results of the calibration of the uncritical liquid amount of granulation liquid

% Explained	%**X**	%**y**
1	43	62
2	77	84
3	87	94
RMSE	0.6	
RMPRESS	1.1	
s	0.6	
Q^2	0.8	

PLS regression was used for the calibration of the amount of water to reach the ULA. The descriptor variables were autoscaled so they all would have the same weight. The ULA values were mean centred. Table 4 shows the results of the calibration.

For the PLS model of the uncritical liquid amount, three PLS factors were selected with cross validation, which explained 94% of the variance in the response variable. The root mean squared error (RMSE) of the model is comparable to the experimental error (s). RMPRESS is somewhat higher. Q^2 gives the squared correlation between the leave one out predictions and the measured ULA values. The separate training sets in the cross validation steps were not mean centred. This would increase the extrapolation of the models because only eight, rather different, drugs were used in the modelling. Three PLS factors are rather high for the model, however, PRESS kept decreasing when more factors were included. Figure 1 shows the predicted *vs.* observed ULA. Lactose 100 mesh was also used as a test drug for the calibration. The measured ULA values were compared with the predicted values by the PLS model. The predicted ULA values of lactose 100 mesh are also given (✳). The predicted value corresponds rather well with the measured ULA values.

Table 4 also shows the regression coefficients that were calculated from the PLS factors. The ULA can be predicted according to the next formula:

$$\textbf{ULA} = 11.8 + 1.8\,(\text{Sol}) - 0.8\,(10\%) - 0.3\,(50\%) - 0.3\,(90\%) + 0.7\,(S_v) + 0.5\,(\text{Tap}) - 0.3\,(\text{Thick}) + 0.8\,(\text{BET})$$

A strong relation exists between the amount of water that can be added to the mixture and the surface of the specific drug during granulation. The surface area comprises the outer and inner surface of the particles. Drugs with large surface area (high S_v and BET) have high ULA values. The negative sign of the regression coefficient of (10%) indicates that drugs without small particles need less water than drugs with small particles. Drugs that dissolve easily in the liquid (low sol) only need a small amount of water to reach the ULA. During water addition, part of the model drugs may dissolve in the water. This leads to a decrease of the surface area.

The total range of phase three (Range=S_4-S_3) could not be described by the physical properties of the model drugs. No explanation could be found why some drugs start to

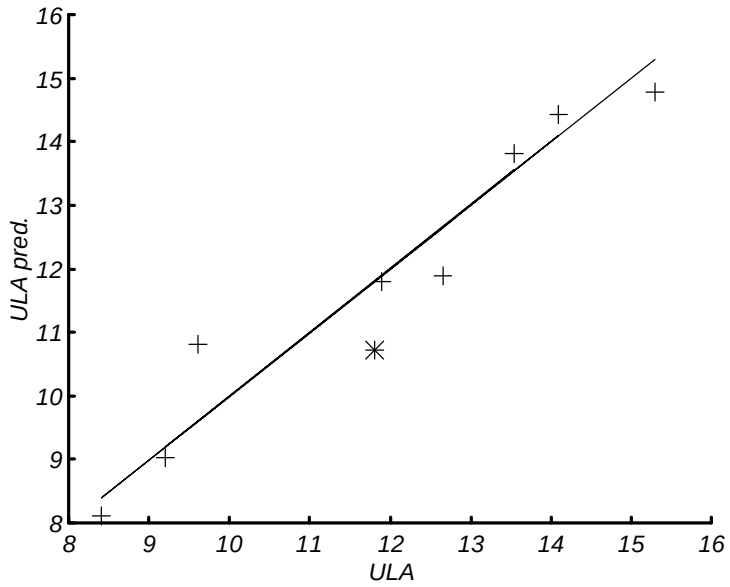

Figure 1: Predicted *vs.* observed uncritical amount of granulation liquid (ULA) for the model drugs (+). The measured ULA values were compared with the predicted values by the PLS model. The predicted ULA value of lactose 100 mesh is also given (✳).

agglomerate earlier than others. The comparison between lactose 100 mesh and lactose 200 mesh shows that the first starts to agglomerate with less water than lactose 200 mesh.

The ULA for mixtures with lactose 200 mesh, corn starch, PVP and a drug can be predicted rather well with the model. One must keep in mind that only 8 model drugs are used in the calibration, however these drugs were selected to have a broad range in physical properties. For a better prediction model, more drugs are to be used, or the drugs have to be more similar. A limitation however is that for drugs with very small particle size (such as salicylic acid and milled paracetamol) the model cannot be used. The power consumption records for such drugs were too different from the regular curve given by Leuenberger, that was found for the rest of the model drugs.

Conclusion

Mixtures of lactose 200 mesh, corn starch, PVP with several model drugs at the 50% level have been studied. Power consumption curves have been recorded for several drugs that were selected to have large spread in physical properties. In was shown that during phase three of the records, the mean granule size increases and the percentages of fines decreases. An uncritical liquid amount (ULA) was defined to be in the middle of phase three. The ULA is the safe amount of water that can be added to the powder mixture without causing overwetting of the mass. The percentage of fines

at the ULA was very small for all model drugs. The ULA was related to physical properties of the drugs that were used. The surface area of the particles and the solubility of the drugs are of main importance for the amount of water that can be added. Drugs with a large surface area can take much water before overwetting will occur. Drugs with high solubility in the liquid, tend to dissolve during granulation. Therefore, the surface area of the powder mixture decreases and only a small amount of water can be added. The calibration model can be used for prediction of liquid amount that can safely be added to mixtures of lactose 200 mesh, corn starch, PVP and a new drug.

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Appendix

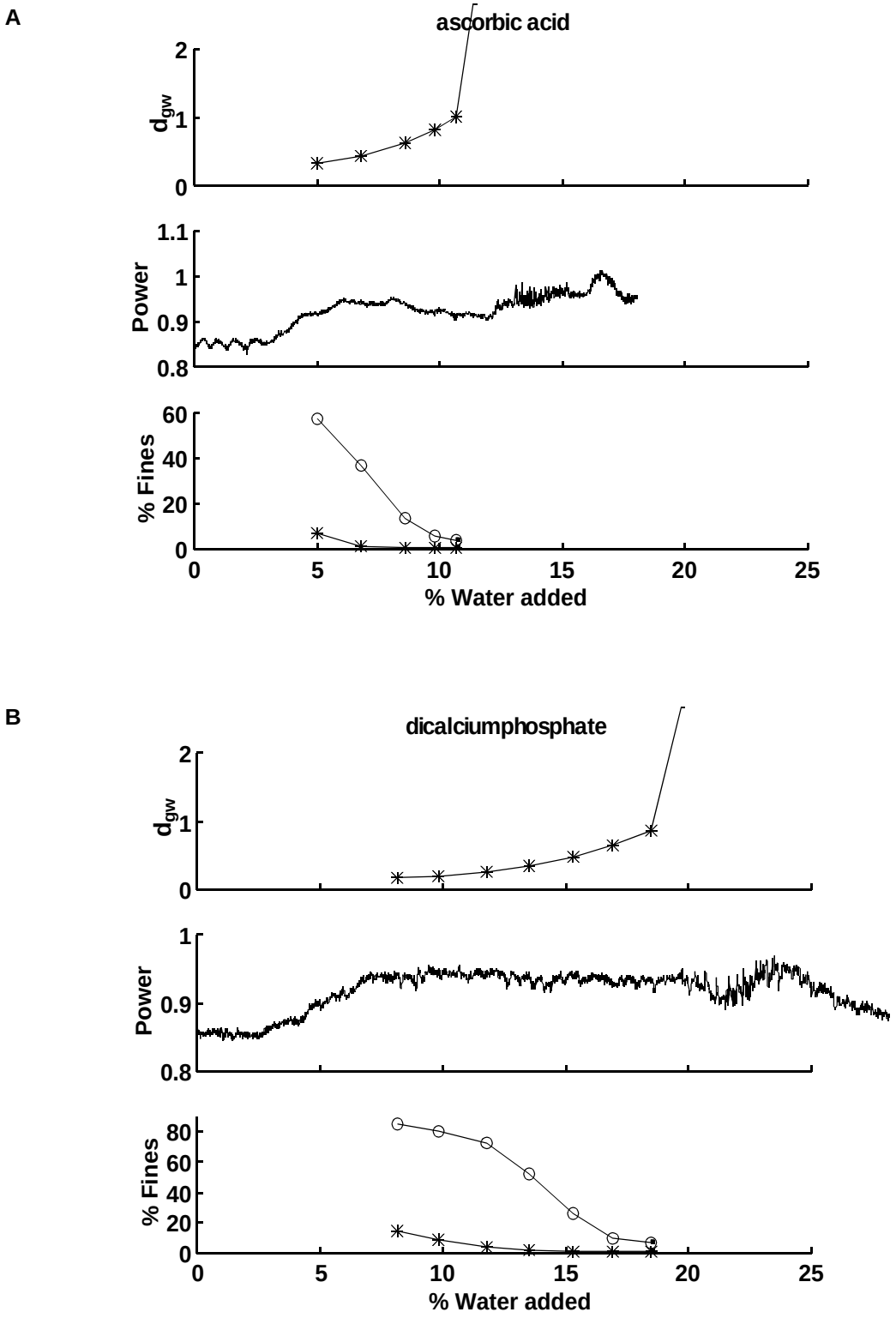
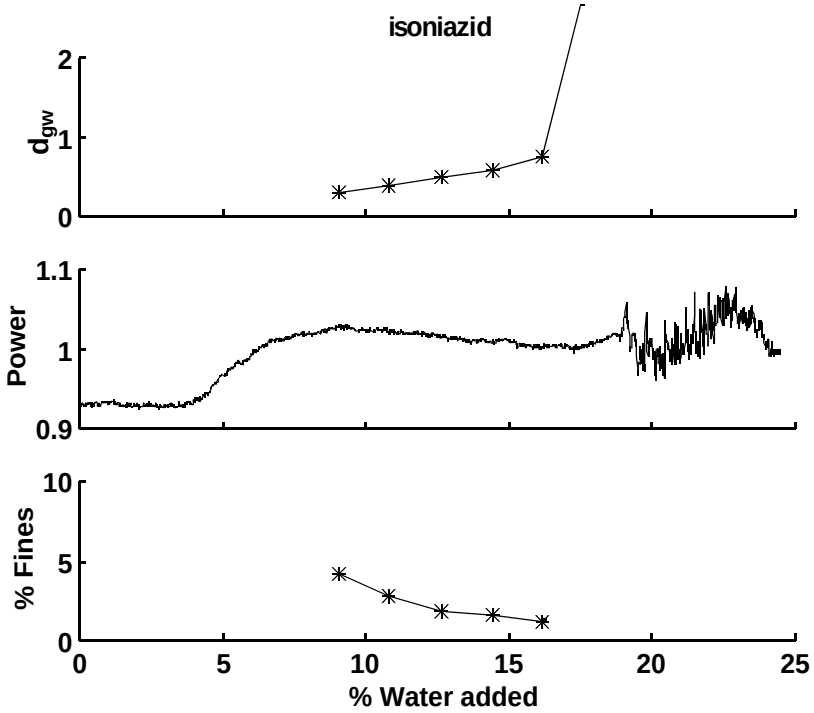


Figure A and B: Mean particle size, power consumption profile and percentage of fines (✳=<150µm, o=<425µm) for ascorbic acid and dicalciumphosphate.

C



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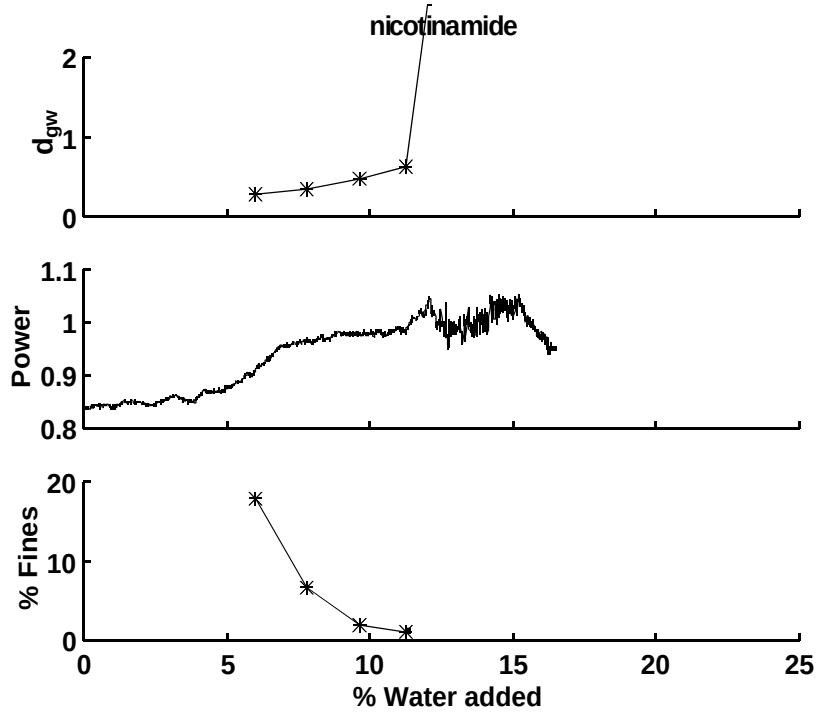
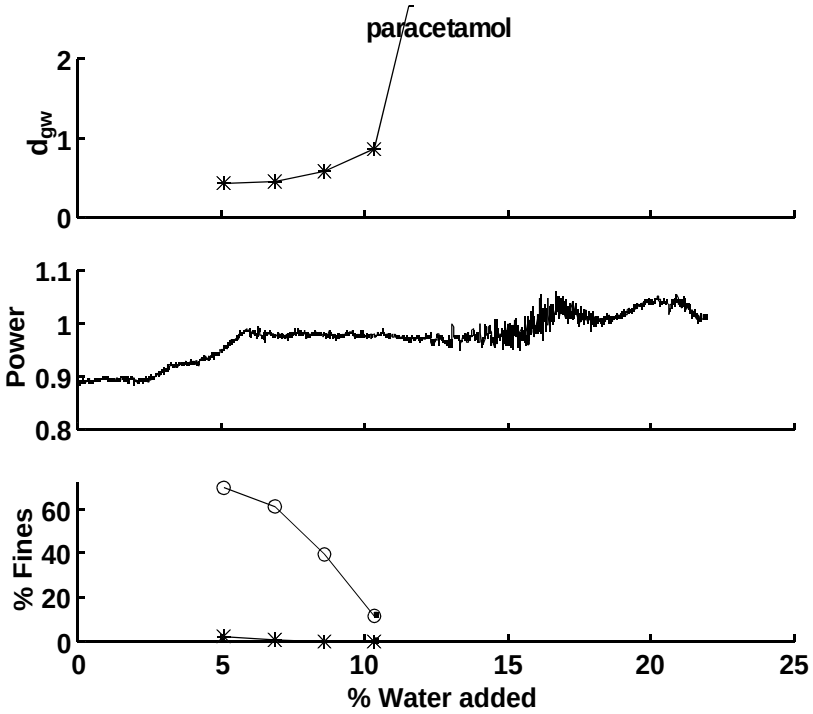


Figure C and D: Mean particle size, power consumption profile and percentage of fines (✳=<150µm) for isoniazid and nicotinamide.

E



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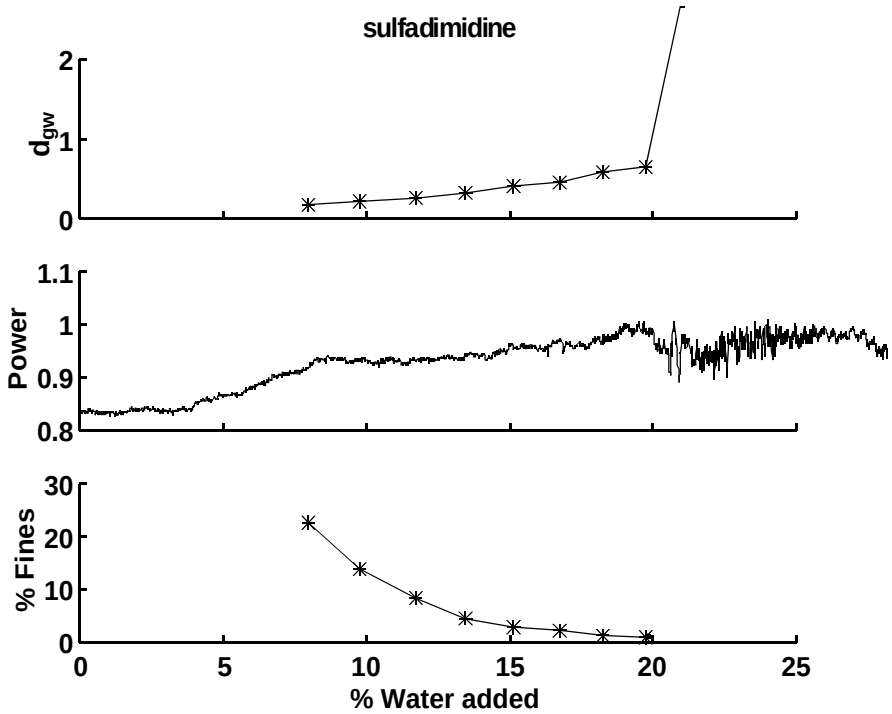
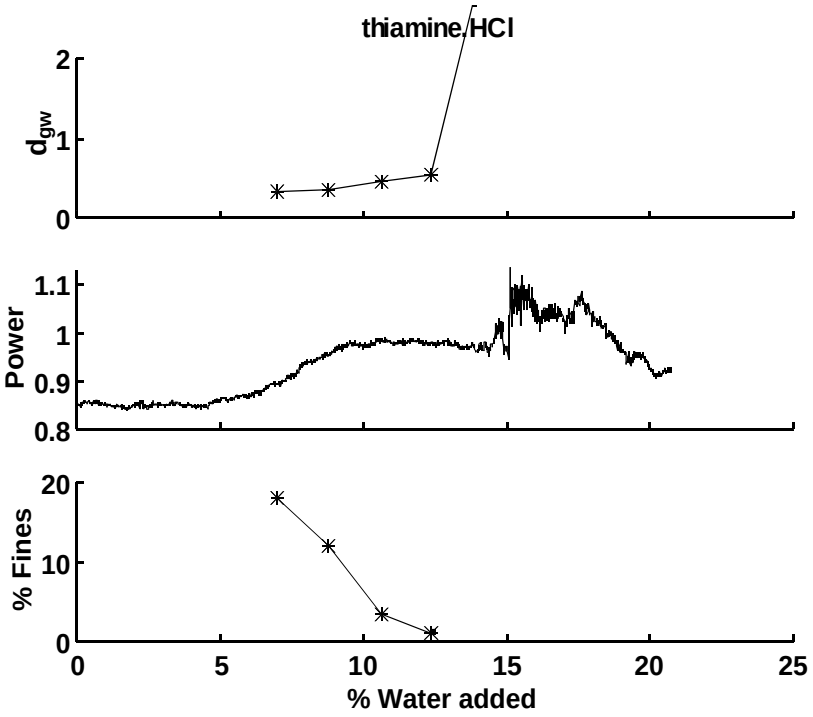


Figure E and F: Mean particle size, power consumption profile and percentage of fines (✳=<150µm, o=<600µm) for paracetamol and sulfadimidine.

G



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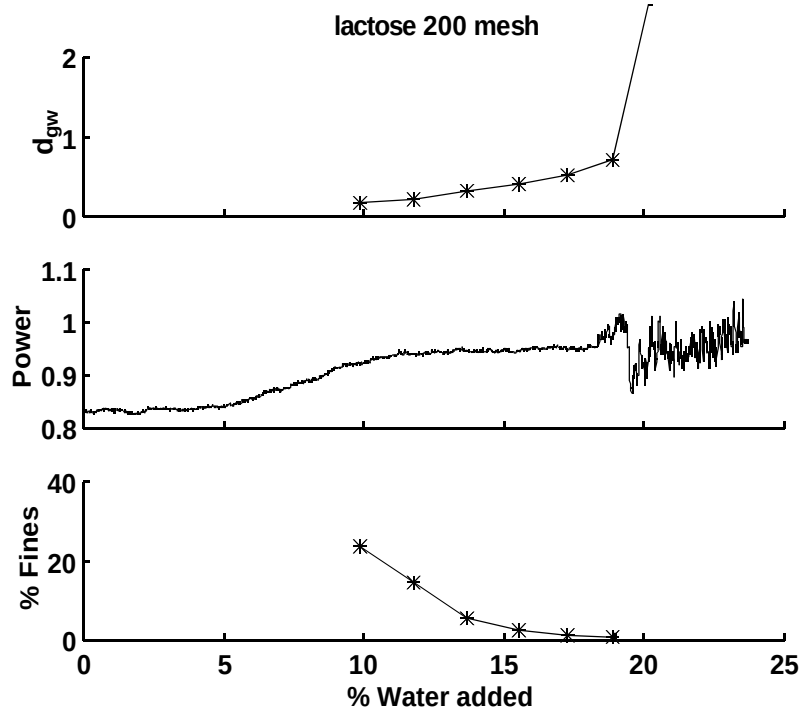

Figure G and H: Mean particle size, power consumption profile and percentage of fines (✳=<150µm) for thiamine.HCl and lactose 200 mesh.

I

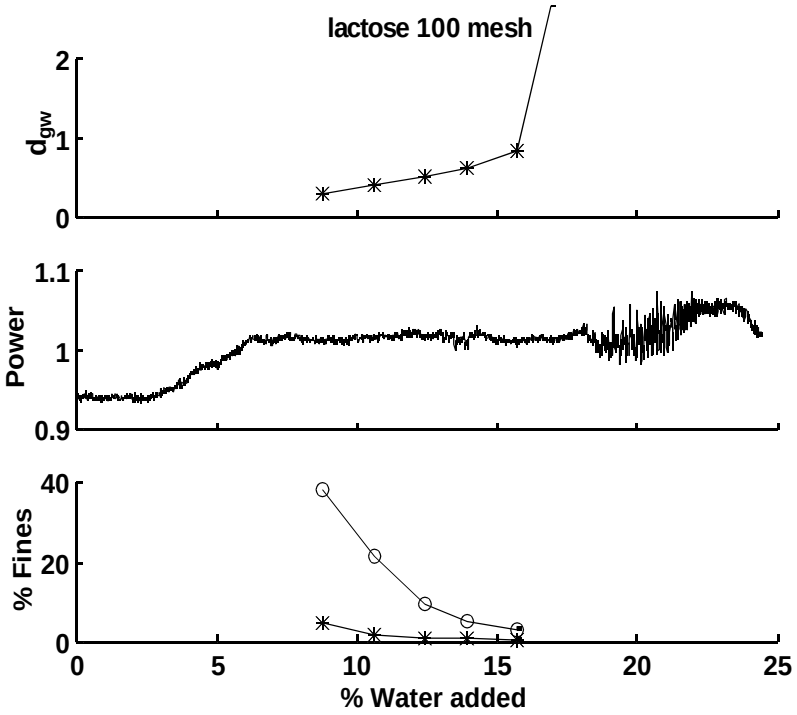

Figure I: Mean particle size, power consumption profile and percentage of fines (✳=<150µm, o=<300µm) for lactose 100 mesh.

Chapter 4

Multivariate calibration of the process of wet granulation and tableting

The pharmaceutical process of wet granulation and tableting is examined with different model drugs that were selected to have large spread in the most important physical properties for the wet granulation process (Chapter 2). Chapter 3 showed the influence of the physical descriptors of the drugs on the uncritical amount of granulation liquid that could be added to the powder mixture. The present chapter describes the granulation experiments, in a high-shear mixer, of powder mixtures of lactose 200 mesh, corn starch, polyvinylpyrrolidone (PVP) and a model drug with the uncritical amount of water added to the mixture. Furthermore, granulations were carried out with less water to reach the start of phase three in the power consumption profile as presented in Chapter 3. The tablet mixtures containing 0, 5 or 50% drug were wet granulated and further processed into pharmaceutical tablets. The addition of extra water during the granulation increased both the median particle size of the granulations and disintegration time of the tablets. Both the percentage of fines and the Hausner ratio of the granulations decreased. The influence of physical properties of the model drugs on the granule and tablet properties were also examined. The effect of the drug on the granule and tablet properties was only small when 5% drug was used. For the 50% drug mixtures, the solubility in the granulation liquid and the particle size of the pure drug were the most important descriptors of the drugs. High solubility and large particles of the drugs led to large median granule size and a small percentage of fines. A significant interaction between the amount of water added during granulation and the solubility of the drug was found. The difference in median granule size between soluble drugs and insoluble drugs increased when more water was added. Crushing strengths of the tablets were found dependent on the compactibility of the pure drugs. However, if a large amount of water was added during granulation, this effect diminished and the strength of the tablets shifted to the level of the tablet strengths of the standard mixture without drug. Disintegration times of the tablets were short for drugs with a high solubility and large surface area. No interactions between the amount of water and the drug descriptors were found to influence the tablet properties.

Introduction

Wet granulation in high-shear mixers is a process of particle size enlargement much used in the pharmaceutical industry to improve the tableting properties of powder mixtures, such as flowability and compactibility, necessary for the large scale production of tablets. High-shear mixers are used for their short process time and high densification. When a new drug has been developed, the process of wet granulation has to be optimised for this drug in an initial stage. However, often only a small amount of the new drug is available for experimentation. Therefore, some initial knowledge of the behaviour of the new drug in the wet granulation process is necessary. The effects of apparatus variables and process variables on the physical properties of granules and tablets have been investigated by many authors [1-11]. Studies on the influence of the components in the tablet mixture have not been very systematical. In most cases only two components were compared for their effect on granule properties and the process [12]. This cannot lead to general conclusions about the effects of drug descriptors, and predictions of granule and tablet properties for mixtures with a new drug are not possible. Kristensen *et al.* already mentioned that the knowledge of the effect of the starting material is rather unsystematical because it is difficult to make an experimental design for drugs where only one of the drug properties is varied [13]. The concept of multivariate design, for compounds that cannot be handled with standard experimental designs, described by Wold *et al.* and by Carlson [14,15], has been used in this investigation. For this approach, model drugs were selected with principal component analysis in Chapter 2 to have a large spread in important descriptors. In the present chapter the effect of physical drug descriptors on the granule and tablet properties is examined. Multivariate regression techniques will be used to develop regression models that can be used to study the effect of drug descriptors on granule and tablet properties, and to make predictions of physical granule and tablet properties for mixtures of lactose, corn starch, PVP and a new drug. Partial least squares regression (PLS) is used for the modelling of the physical granule and tablet properties. PLS is a biased regression method that searches for latent directions in the descriptor space with high covariance with the response variables. A biased regression method is used because multicollinearity exist between the descriptors. Furthermore, the descriptor variables may outnumber the objects. A mathematical description of the PLS method is given in Chapter 7 of this thesis. Tutorials on the PLS regression method have been given by Geladi and Kowalski [16] and by Höskuldsson [17].

Experimental

Granulations were carried out in a GRAL 10 high shear mixer (N.V. machines Colette, Wommelgem). The total amount of material for each experiment was maintained at 1.5

kg. Lactose 200 mesh, corn starch, polyvinylpyrrolidone (PVP) and one of the model drugs were dry mixed with an impeller speed of 300 rpm. The chopper speed was maintained at 1500 rpm. After two minutes of dry mixing, water was added continuously at a flow of 30 $cm^3.min^{-1}$. The total mixing time was set to 12 minutes (the dry mixing time included). Granulations were screened on a 2-mm screen on a Frewitt rotating granulator to remove large lumps. The granulations were dried in a fluid bed dryer (Aeromatic) for at least 25 minutes until constant temperature of the outlet air. After drying, another screening step was carried out on a 1.5 mm screen to remove the lumps that were formed during drying. Physical properties of the granulations were determined after one day of storage. Particle size distributions of the granulations were measured by sieving analysis (850, 600, 425, 300, 150 and 0 µm). Poured and tapped density of the granulations were measured. The moisture content in the granules was determined by Karl Fischer titration.

Prior to tableting, the granulations were lubricated with 0.5% magnesium stearate and mixed for two minutes in a Turbula mixer (Bachofen) at 90 rpm. Tablets (500 mg, 13 mm) were compressed from the granulations on a hydraulic tablet press (Hydro Mooi, 20 kN, $2kN.min^{-1}$). Tablet crushing strengths of ten tablets were determined (Schleuniger), and disintegration times of six tablets were measured without disks.

The composition of the mixtures was shown in Table 1 of Chapter 3. Mixture A and B contain 5 and 50% of drug, respectively and mixture C contains no drug. Experiments were carried out according to the experimental design shown in Figure 1. The circles indicate repeated experiments. Each model drug was granulated at two different concentrations, 5% and 50%. For powder mixture C, the drug was replaced by lactose, which is considered to be the model drug of the standard mixture for both 5% and 50% of drug concentration. The influence of the model drug was investigated at two levels, on a low dose (5%) and on a high dose level (50%). The mixture without a model drug was granulated three times. Each mixture was granulated with two different amounts of water. The levels of water were set according to the power consumption records given in Chapter 3. The high level was set to the uncritical liquid amount (ULA) which was defined as the middle of phase three of the power consumption record. The low level was set to the start of phase three of the record for the specific mixtures.

For the modelling of the granule and tablet properties, PLS computations were carried out with the PLS toolbox [18] and the H-principle toolbox [19] in MATLAB [20].

Results and discussion

The mixtures of lactose, corn starch, PVP and the model drug were wet granulated. The granulations were evaluated and compressed into tablets after one day of storage. Crushing strengths and disintegration times of the tablets were obtained one day after compression. Table 1 shows the physical granule and tablet properties of the powder mixtures for all model drugs granulated at the 5 or 50% drug level with a low or high

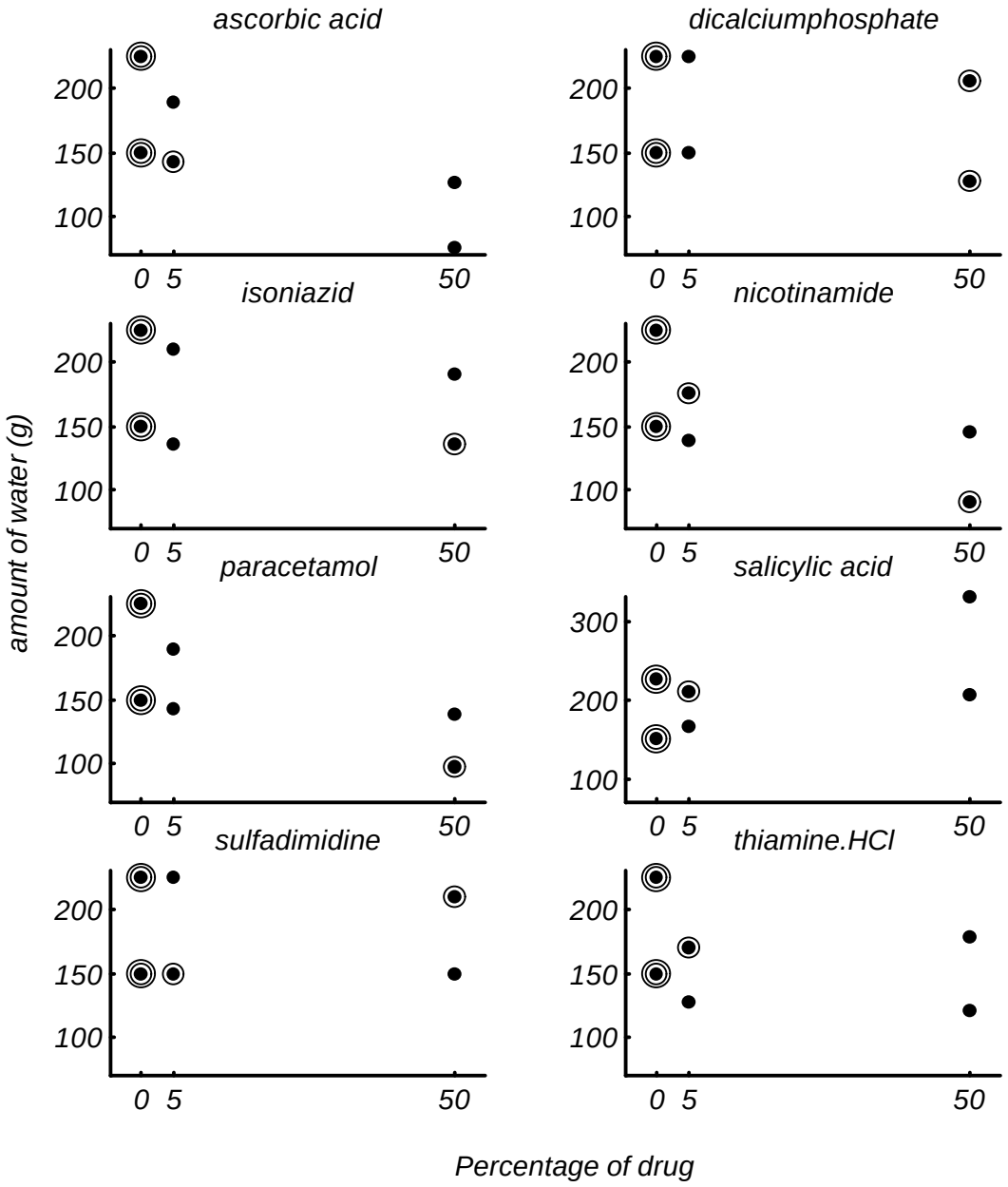

Figure 1: Experimental design of the granulation experiments. For each model drug granulations were caried out at three drug concentrations (0, 5, 50%) and two levels of granulation liquid. Each plot shows the amount of water (g) added to the powder mixture with a specific percentage of drug. Mixtures with 0% drug were repeated twice, whereas some other granulation experiments ⊙ were repeated once.

amount of water added during granulation. At the 5% drug level, deviations of the granule and tablet properties according to the mixture without drug were only small. The deviations are much larger when 50% of drug was used, which was already observed in the power consumption records of Chapter 3.

Table 1: For each tablet mixture the specific drug, the percentage of drug in the mixture and the amount of water (g) are given. Median granule size (d_{gw}, µm), fines < 300 µm (%) and the Hausner ratio of the granules are given as are the crushing strength (CS) and disintegration time (DT) of the tablets.

drug	% drug	water (g)	d_{gw} (µm)	%<300	Hausner	CS (N)	DT (s)
lactose 200 mesh	0	150	227	64	1.18	59.3	149
lactose 200 mesh	0	150	173	80	1.19	45.2	184
lactose 200 mesh	0	150	191	76	1.17	50.3	163
lactose 200 mesh	0	225	518	17	1.11	38.3	286
lactose 200 mesh	0	225	412	25	1.12	49.9	229
lactose 200 mesh	0	225	491	16	1.10	40.1	259
ascorbic acid	5	142.5	228	60	1.17	53.7	268
ascorbic acid	5	143	228	65	1.14	44.1	252
ascorbic acid	5	198.5	364	26	1.13	55.1	383
dicalciumphosphate	5	150	215	64	1.16	47.2	215
dicalciumphosphate	5	225	479	15	1.13	39.6	336
isoniazid	5	135	224	66	1.19	47.3	233
isoniazid	5	210	561	17	1.15	75.3	344
nicotinamide	5	138	294	37	1.16	67.4	669
nicotinamide	5	175	605	3	1.15	81.3	643
nicotinamide	5	175	660	3	1.11	85.4	662
paracetamol	5	142.5	188	69	1.11	45.4	206
paracetamol	5	189	305	42	1.18	45.9	233
salicylic acid	5	165	239	59	1.19	54.2	29
salicylic acid	5	210	350	27	1.15	52.4	54
salicylic acid	5	210	344	34	1.17	56.3	54
sulfadimidine	5	150	184	79	1.18	50.9	215
sulfadimidine	5	150	194	73	1.16	53.7	186
sulfadimidine	5	225	488	20	1.17	52.3	201
thiamine.HCl	5	127	229	65	1.16	44.5	349
thiamine.HCl	5	165	350	29	1.13	58.5	444
thiamine.HCl	5	170	421	16	1.11	48.3	473
ascorbic acid	50	75	278	43	1.16	25.0	114
ascorbic acid	50	126	626	2	1.09	57.2	324
dicalciumphosphate	50	127.5	260	49	1.13	38.0	463
dicalciumphosphate	50	127.5	203	76	1.17	43.9	138
dicalciumphosphate	50	205	331	32	1.15	46.8	404
dicalciumphosphate	50	205	301	41	1.14	47.8	244
isoniazid	50	135	328	41	1.22	77.7	351
isoniazid	50	135	314	43	1.19	74.4	378
isoniazid	50	190	494	25	1.14	63.1	418
nicotinamide	50	90	221	59	1.19	57.2	489
nicotinamide	50	90	213	74	1.18	62.1	489
nicotinamide	50	145	662	13	1.11	101.4	304
paracetamol	50	97.5	444	10	1.12	21.7	339
paracetamol	50	97.5	479	5	1.12	22.1	248
paracetamol	50	138	731	2	1.14	22.1	263
salicylic acid	50	203.5	158	75	1.18	160.8	156
salicylic acid	50	330	230	56	1.17	106.3	335
sulfadimidine	50	150	218	78	1.16	83.4	1000
sulfadimidine	50	210	427	11	1.15	72.6	1000
sulfadimidine	50	210	356	24	1.13	72.8	1000
thiamine.HCl	50	120	151	77	1.18	86.7	231
thiamine.HCl	50	178	621	13	1.14	85.8	241

The effect of the drug on the granule and tablet properties of the whole mixture was examined. Each drug will have its own interactions with the other components in the mixture. These interactions are affected by the physical descriptors of the drug such as the solubility, contact angle and particle size, and will influence the granules and tablets. The physical granule and tablet properties of the mixture with drug were compared to the standard mixture without a drug. The granule and tablet properties of the standard mixture were related to the descriptors of lactose, eventhough, the interaction between the same particles will differ from the interaction between different particles.

The settings of the water level and also the spread between the two levels are not constant. They are, however, constant in a relative way because the levels were set optimally for all drugs separately, according to additional information obtained from the power consumption records. Using the PLS method, regression models were developed that relate the physical granule and tablet properties of Table 1 to the drug descriptors in Table 2.

The effect of the physical descriptors of the drugs on the physical granule and tablet properties were studied for the 5% and 50% mixtures separately because the relation between the drug concentration and the granule and tablet properties were not expected to be linear. The information obtained will, therefore, be valid for a low or high dosage of drug, but not in between. Experiments of the two water levels were combined in a single model. Besides the influence of the drug descriptors, also the effect of the extra water will be studied. When this was done, fixed settings for the water levels (-1 and +1) were used instead of the actually added amounts, because the settings were chosen optimally for each drug separately. Interactions between the water level and some drug descriptors were also considered.

For each model the number of PLS factors used in the model, the percentage of the explained variance of the descriptors (%**X**) and of the response variable (%**y**) will be given. When only one water level is examined (+ or -), only 9 objects and 12 descriptors

Table 2: Physical drug properties of the model drugs used in the modelling of the granule and tablet properties. LAC=lactose 200 mesh, ASC=ascorbic acid, DIC=dicalciumphosphate, ISO=isoniazid, NIC=nicotinamide, PAR=paracetamol, SAL=salicylic acid, SUL=sulfadimidine, TIA=thiamine.HCl. The drug properties are explained in Chapter 3 and in the text of the present chapter.

drug descriptor	LAC	ASC	DIC	ISO	NIC	PAR	SAL	SUL	TIA
Solubility	0.70	0.54	3.70	0.90	0.00	1.85	2.70	3.70	0.00
10%	2.2	81	88	10	8.0	37	3.0	9.9	4.3
50%	26.6	216	242	39.5	25.9	360	12.0	54.5	20.7
90%	77.3	398	375	89.0	62.3	570	24	140	55.0
S_v	0.93	0.07	0.14	0.41	0.53	0.11	1.08	0.33	0.69
Poured	0.55	0.91	0.87	0.58	0.46	0.69	0.28	0.58	0.26
Tapped	0.85	1.00	1.00	0.78	0.68	0.77	0.43	0.78	0.43
Thickness	5.81	5.63	4.12	5.78	6.02	6.56	5.63	5.77	5.81
BET	0.50	0.06	0.32	0.19	0.18	0.03	0.41	0.07	0.39
Cos θ	0.80	0.78	1.00	0.66	0.70	0.50	-0.22	0.67	0.64
Hausner ratio	1.55	1.10	1.15	1.35	1.48	1.12	1.56	1.35	1.67
Compactibility	56	0	37	53	26	0	125	45	95

are used (Table 2). When both water levels are considered simultaneously (+ and -), the number of objects is 18 (9 drugs at two water levels). The descriptors in this case are the ones in Table 2 plus a column of -1 and +1 indicating the water level, and the interactions between the water level and the descriptors; a total of 25 descriptors. In each model only one response was modelled. When descriptors had no effect on the response they were removed from the model. The root mean squared error of the model (RMSE) will be given for the models. RMSE must be comparable to the experimental error of the response variables. For the validation of the models, leave one out cross validation was used. The square root of the mean PRESS values are given (RMPRESS). PRESS has been introduced in the introduction of this thesis. Furthermore, the predictive quality of the model is indicated with Q^2. The various training sets in the cross validation were not mean centred for the various models. This would lead to large extrapolations because only nine drugs are used which are quite different from each other. The predictive properties of the models (RMPRESS, Q^2) may, therefore, have been overestimated.

Granule properties

The amount of granulation liquid added to the powder mixture, influenced the physical properties of the granules. Granulations with the low water amount all had small median granule sizes and large percentages of fines < 300 µm. This resulted in higher Hausner ratios. The granules that were formed were still very brittle and disintegrated during the drying step in the fluid bed dryer. Furthermore, not all particles had already taken part in granule formation. When more liquid was added, the median granule diameter increased, and the percentage of fines decreased. The poured and tapped volumes both decreased. The Hausner ratio also decreased for most model drugs, which means that the flowability of the mixture improved when more water is added. The measure of change of the physical granule properties depends on the drug and its concentration used in the powder mixture.

Median granule diameter

The median granule diameter increased when more water is added during the granulation. The increase depends on the drug used in the mixture. Each subplot in Figure 2 shows the median granule size (µm) for a specific model drug at 0, 5 and 50% drug concentration for both levels of water added during granulation. The 0% drug lines represent mixture C in Table 1 of Chapter 3, where lactose was used as the model drug. The increase in median granule size is less for the drugs with low solubility in the granulation liquid (dicalciumphosphate, salicylic acid and sulfadimidine). These drugs did take part less in granule formation than the soluble drugs. For the very soluble drugs (thiamine.HCl and nicotinamide) the increase in median granule size was much larger than for the standard mixture. The soluble drugs with large particles (ascorbic acid and paracetamol) had much larger granule size in the 50% mixtures. The 5% mixtures of these drugs had quite deviating granule size at the high water level. Table 3 shows the results of the modelling of the median granule size for mixtures with 50%

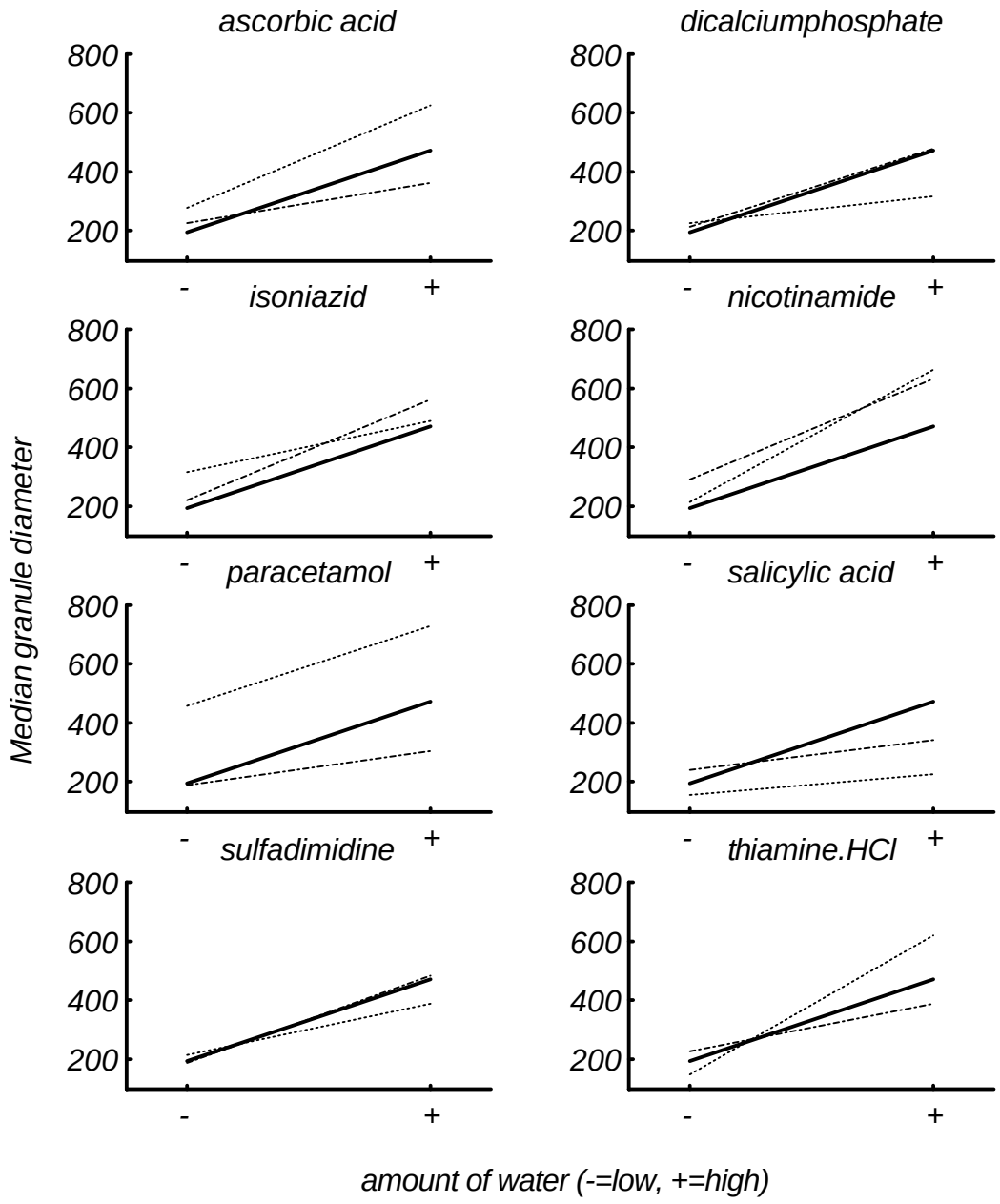

Figure 2: Median granule size (µm) of granulations from mixtures with 0% (bold lines), 5% (dotted lines) and 50% (thin lines) of drug for the low (**-**) and high (**+**) amount of water added to the mixture.

drug granulated with the high amount of water. The PLS model relates the median granule size to the drug properties of lactose 200 mesh and the other eight model drugs. The granule size was scaled logarithmically to diminish the heteroscedasticity of the variance. Two PLS factors gave an RMSE value of 0.09 which is comparable to the experimental error. The two PLS factors described 93% of the variance in the median granule size and 74% of the variance of the descriptors is used. The RMPRESS value of 0.19 is twice as high as the experimental error. Granulations will have a large

Table 3: Results of the modelling of the logarithmically scaled median granule size (ln d_{gw}), the percentage of fines < 300 µm for the mixtures with 50% drug on the high water level, and the median particle size at both water levels. The number of PLS factors, percentage explained variances of the descriptors (%**X**) and the response variable (%**y**), the reproducibility s, RMSE, RMPRESS and Q^2 are given for each model.

granule properties	water	# factors	%**X**	%**y**	s	RMSE	RMPRESS	Q^2
ln(d_{gw})	+	2	74	93	0.10	0.09	0.19	0.73
% fines < 300 µm	+	3	88	90	8	6	9	0.65
ln(d_{gw})	+ and -	4	82	92	0.10	0.14	0.21	0.82

median granule size if the drug used has high solubility in the granulation liquid and if the particle size of the pure drug is large. The poured and tapped density and the Hausner ratio were removed from the model.

The second row with results in Table 3 shows the results of the modelling of the median granule size for both water levels. Besides the drug descriptors, the relative water level (+ and -) and all interactions between the water level and the drug descriptors were used for the modelling. The median granule size was higher at the high water level. Besides the solubility and the mean particle size of the drugs, the linear factor of the water level was found to increase the median granule size. Only the interaction of the water level with the solubility, contact angle and tablet tickness were used in the final model. The effect of the solubility of the pure drugs is higher at the high water level than at the low water level. The difference in median granule size between

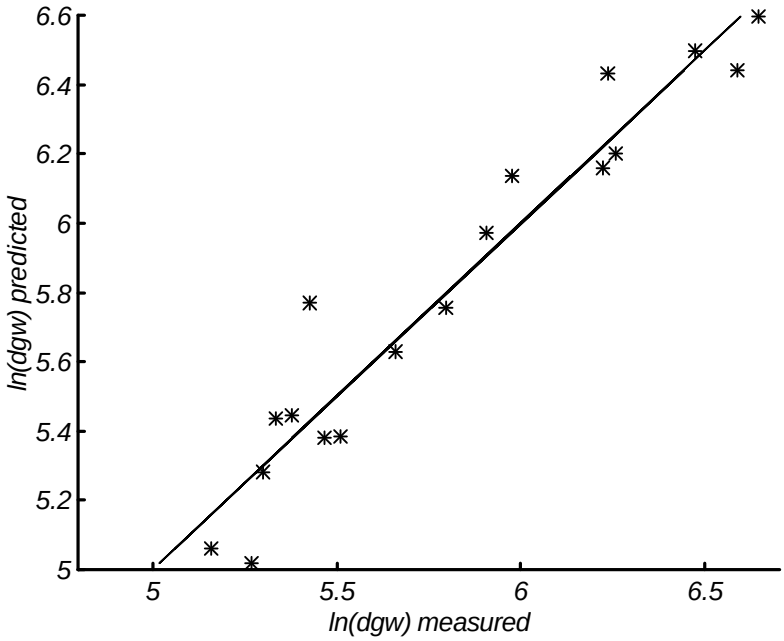

Figure 3: Predicted median granule diameter (dgw) *vs*. measured values for both low and high water levels. The median granule size was scaled logarithmically.

soluble drugs and non soluble drugs increased when more water is added during the granulation. Figure 3 shows the predicted *vs.* the measured values of the median granule size. Some non linearities in the modelling of the median granule size were found which could be described by a quadratic PLS model. This decreased the RMSE value, however the RMPRESS increased. Therefore, the linear model was maintained.

Percentage of fines

The results of the modelling of the percentage of fines < 300 µm are also shown in Table 3. Figure 4 shows the weight percentage of granules with diameter < 300 µm for the low and the high water level. This percentage for the standard tablet mixture without a model drug, decreased from 73% on the low water level to 19% when the high water amount was added. Sulfadimidine and thiamine.HCl showed only small changes when 5 or 50% drug was included in the mixture. Paracetamol and ascorbic acid, which are both drugs with large particle size and moderate solubility, had very small percentages of fines with 50% drug in the mixture. For both the median granule size and the percentage of fines, the same drug descriptors were important, with opposite PLS regression coefficients. Large median granule sizes were obtained with drugs that have large particle size and are soluble in the granulation liquid. Drugs with high contact angles are slightly wettable and do hardly take part in primary granule formation. Granule grow will be less and a small granule size will be obtained.

When only 5% drug is used in the powder mixtures, an obvious water effect was observed for the granule properties, median granule size increased and the percentage of fines and the Hausner ratio decreased when more water is added. The effect of the drug descriptors on the granule properties was only small. The mixture consists of 81% lactose and only 5% of the drug. Therefore, the mixture characteristics mostly come from the lactose. Considering all granule response variables in Table 1, median granule size, percentage of fines < 300 µm and the Hausner ratio, at both water levels, the properties of the granules had a smaller deviation of the standard mixture than two standard deviations. Nicotinamide had larger granules and smaller percentage of fines than the standard mixture, whereas paracetamol had smaller granules and more fines.

Tablet properties

Tablets were compressed from the granulations after lubrication with magnesium stearate (0.5%) for two minutes in a turbula mixer. The crushing strength and disintegration time of the tablets were measured one day after compression. Both tablet properties were logarithmically scaled because of the heteroscedastic variance structure.

Crushing strength

Figure 5 shows the crushing strengths of the tablets for the mixtures with the model drugs at 0, 5 and 50% dose. When only 5% drug was used in the powder mixtures, no large deviations in the tablet crushing strength from the standard mixture were observed. However, isoniazid and nicotinamide showed a large increase in crushing

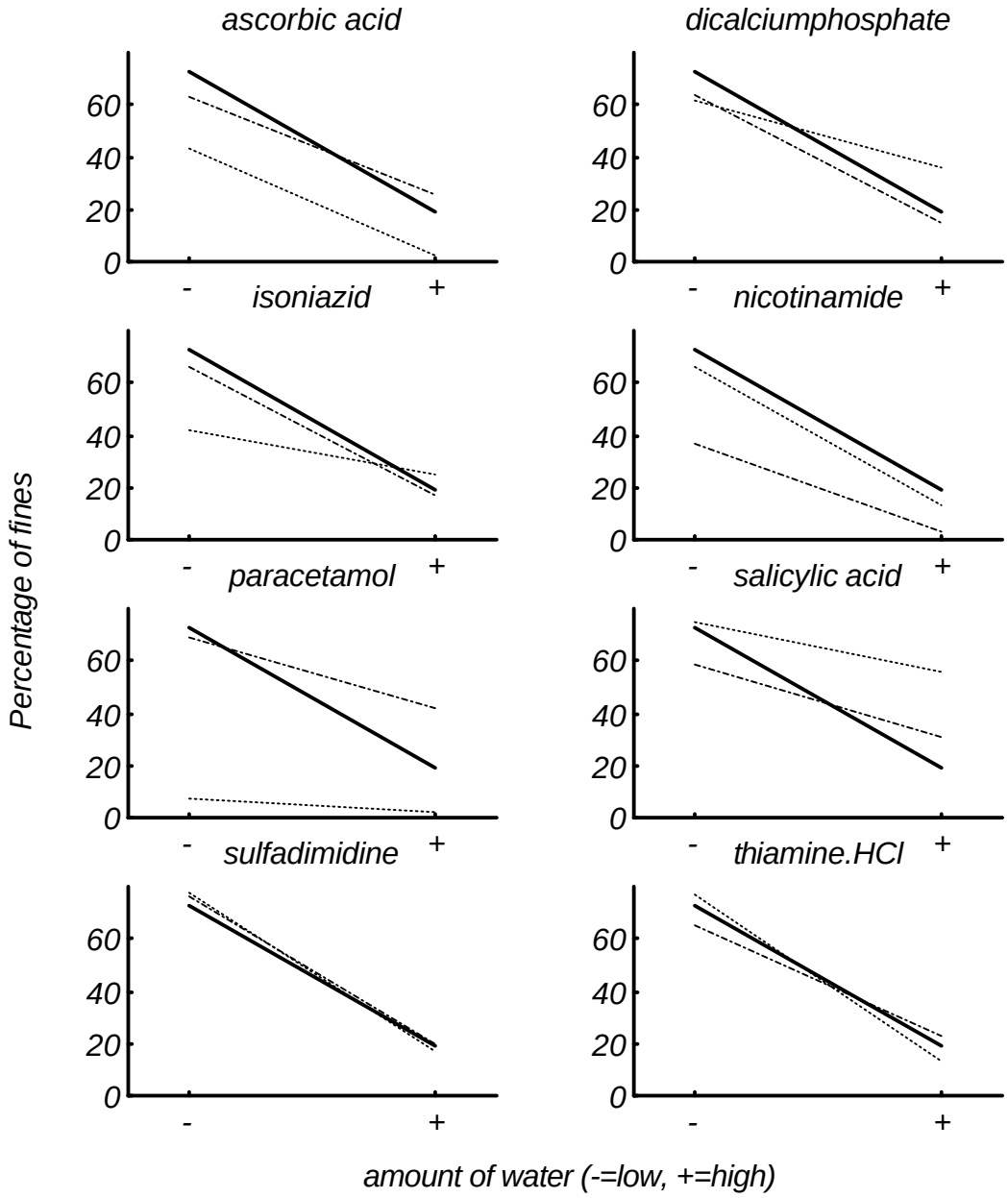

Figure 4: Percentage fines < 300 µm of granulations from mixtures with 0% (bold lines), 5% (dotted lines) and 50% (thin lines) of drug for the low (**-**) and high (**+**) amount of water added to the mixture.

strength at the high water level. Both drugs are rather soluble in the granulation liquid and have small particle sizes.

When 50% drug was used in the tablet mixture, compactibilities of the pure drugs influenced the crushing strength of the tablet mixture. On the low water level, the crushing strengths of the tablets could be described by the drug descriptors. Granulations with drugs that have high compactibilities and small particle size had high

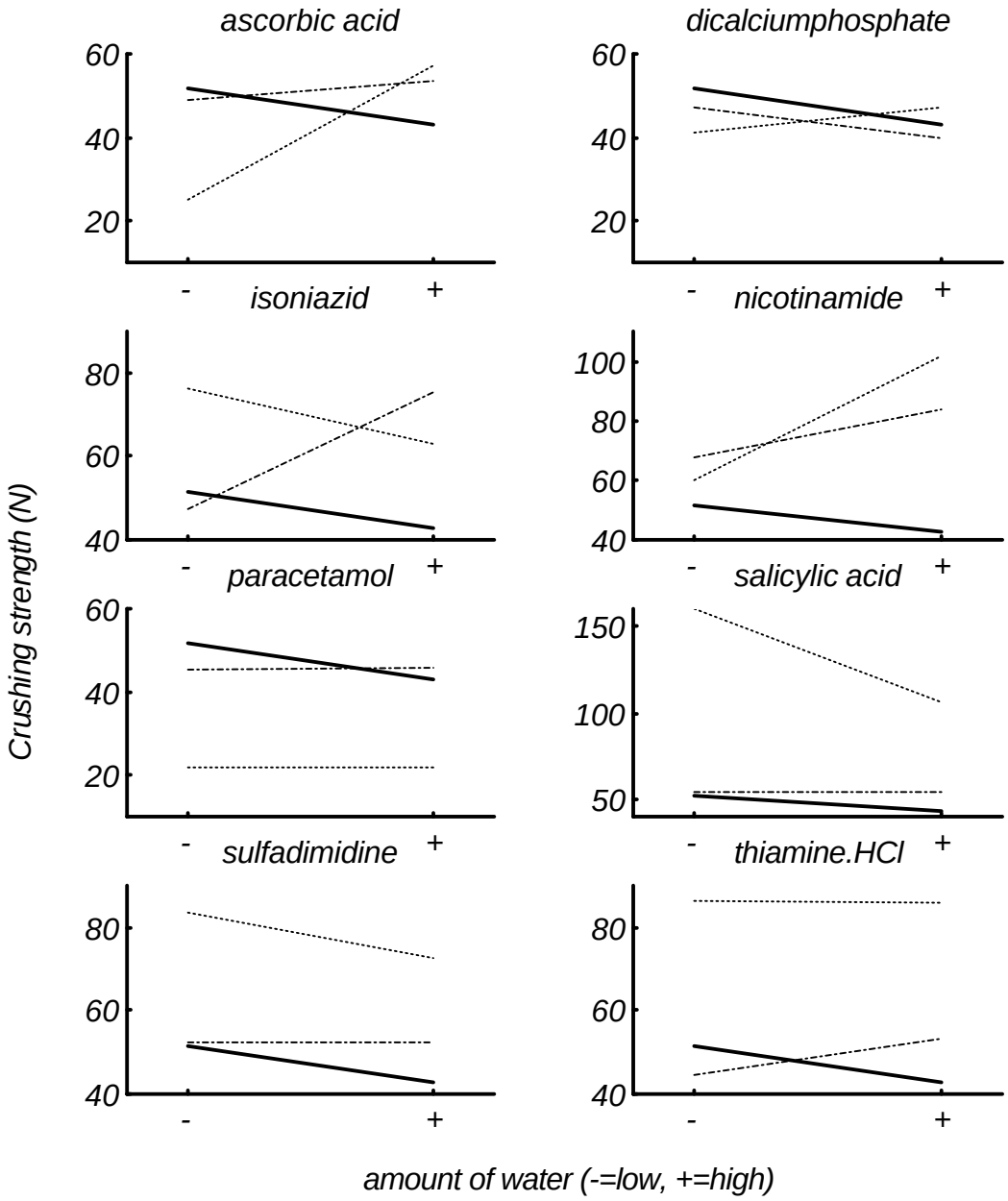

Figure 5: Crushing strength (N) of tablets from mixtures with 0% (bold lines), 5% (dotted lines) and 50% (thin lines) of drug for the low (**-**) and high (**+**) amount of water added to the mixture.

crushing strengths. Table 4 shows the results of the modelling of the crushing strength at the low water level. With only two PLS factors 95% of the response could be explained. A Q^2 of 0.80 is acceptable. Figure 6 shows the predictions of the crushing strength of the mixtures for the various model drugs against the measured values at the low water level. When the high amount of water was added to the mixture, crushing strengths of the tablets shifted towards the crushing strength of the standard mixture. The influence of the compactibility of the pure drug diminished when more water was

Table 4: Results of the modelling of the logarithmically scaled tablet properties: crushing strength (CS, 50%, low water level) and the disintegration time (DT, 50%, on the low and high water level). For each model, the number of PLS factors, percentage explained variance of **X** and **y**, reproducibility (s), RMSE, RMPRESS and Q^2 have been given.

	% drug	water	# factors	%**X**	%**y**	s	RMSE	RMPRESS	Q^2
ln CS	50	-	2	75	95	0.10	0.14	0.26	0.80
ln DT	50	+ and -	3	76	83	0.09	0.19	0.41	0.48

added to the tablet mixture during wet granulation. However, for nicotinamide and thiamine.HCl, both freely soluble drugs with small particle size, an opposite effect was observed. Paracetamol tablets still had low crushing strengths even at the high water level.

Disintegration time

The disintegration time of the tablets was measured without disks. When the tablets had not been disintegrated after 900 seconds, the disintegration time was set to 1000 seconds. This only occurred for 50% sulfadimidine tablets. The disintegration time of the dicalciumphosphate tablets with 50% of drug content was found to have extremely bad reproducibility on both water levels. It was decided to leave these disintegration times out of the modelling. The disintegration time of the tablets is shown in Figure 7.

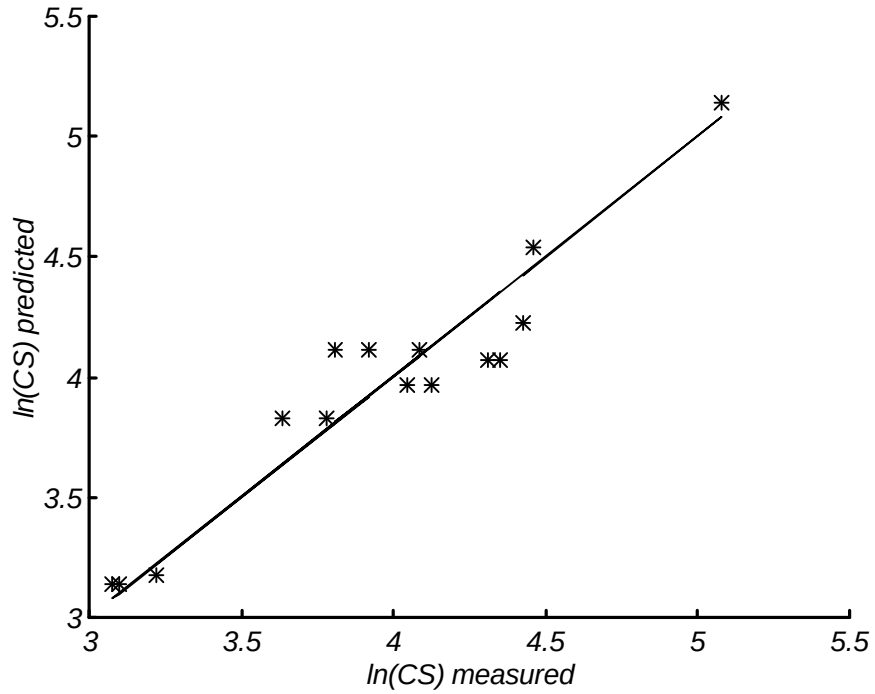

Figure 6: Predictions of the logarithmically scaled crushing strength (ln CS) *vs.* the measured values for tablets from mixtures with 50% drug on the low water level.

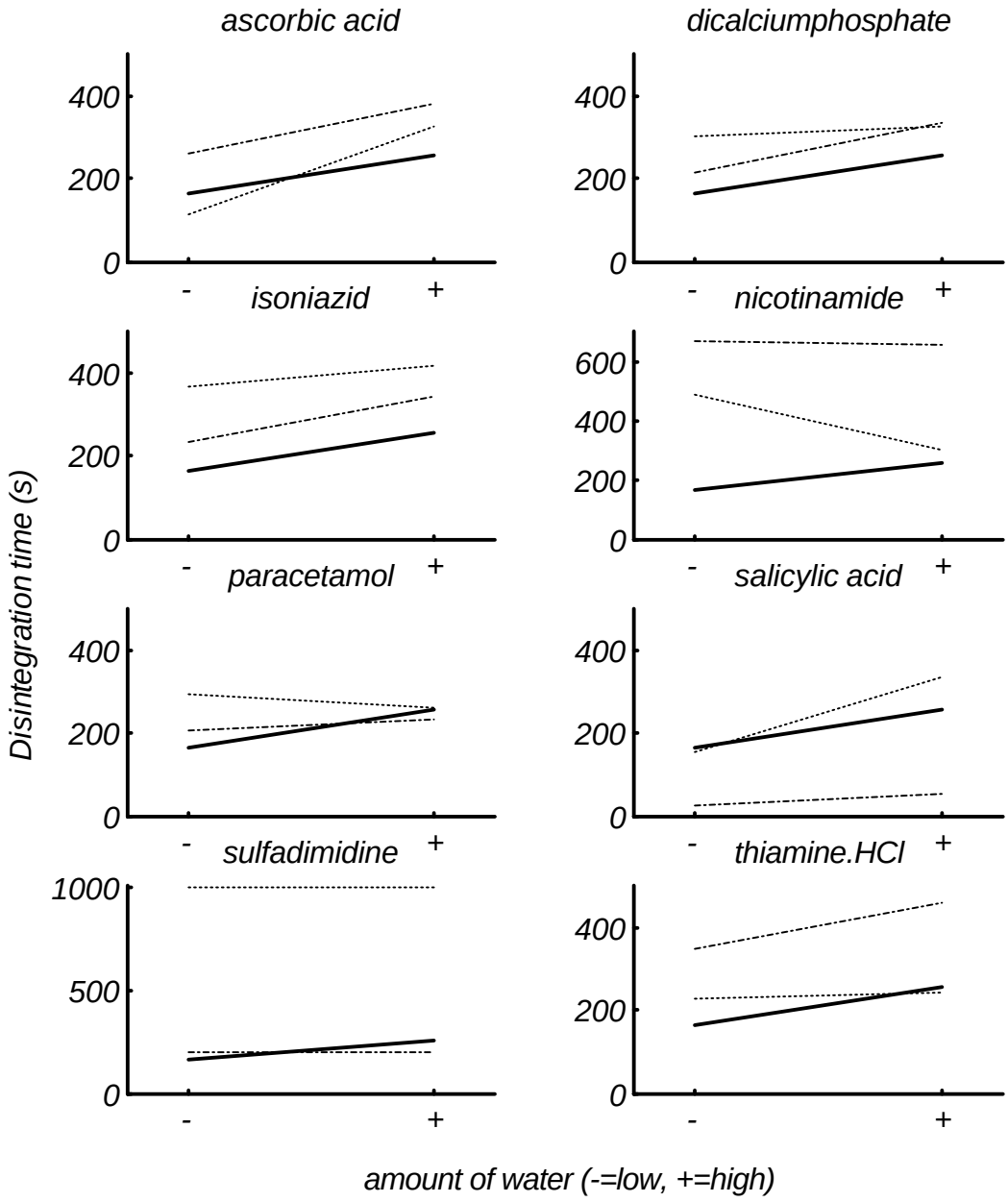

Figure 7: Disintegration time (s) of tablets from mixtures with 0% (bold lines), 5% (dotted lines) and 50% (thin lines) of drug for the low (**-**) and high (**+**) amount of water added to the mixture.

For most mixtures the disintegration time increased when 5% drug was added to the standard mixture. However, for salicylic acid the disintegration time became much shorter and for nicotinamide, the disintegration time got very long. For most tablet mixtures, disintegration time increased when more water was added during granulation.

Table 4 shows the results of the PLS modelling of the disintegration time for 50%

mixtures for both water levels. No interactions between the water level and a drug descriptor were found. 83% of the variance of the response variable could be described by the model with 3 PLS factors. Addition of extra water was found to increase the disintegration time, which was also found by Shiraishi [21]. Q^2 of 0.48 is very low, which indicates that prediction of the disintegration time from the physical properties of the drug is not good. However, a general trend is that nonsoluble drugs give longer disintegration times, and drugs with high surface area give short disintegration times. To control the disintegration time of the tablets, disintegrants have to be used.

The models of the granule and tablet properties were developed with only 9 or even 8 model drugs, which were more different from each other than expected. However, some trends about the influence of drug descriptors on granule and tablet properties have been indicated. When model drugs are more alike, as can be expected in industrial applications, the models are expected to be better than the ones presented in this chapter.

Conclusions

When a new drug is added to a mixture of lactose 200 mesh, corn starch and PVP, the process variables have to be adjusted to produce granulations suitable for tablet production. Physical properties of the granules and tablets are affected by the new drug. The effect of the drug depends on its concentration in the mixture. A concentration of 5% gives only minor changes as compared to the standard mixture.

At mixtures with 50% drug, median granule diameter increased and the percentage of fines decreased when drugs are soluble in the granulation liquid or have large median granule size. The solubility of the drugs shows a significant interaction with the amount of water. The difference in median granule size between soluble drugs and insoluble drugs increased when more water is added. When only 5% drug is used in mixtures, the effect of the drug descriptors on the granule properties is only small. The large amount of lactose dominates the properties of the mixture. The effect of adding extra water to the mixture during granulation was found significant for the granule properties for mixtures with 5% drug.

The tablet crushing strength of mixtures with 50% drug was found to be influenced by the compactibility of the pure drug when only a low amount of water was added during granulation. When more water was added, crushing strengths shift to the level of the standard mixture. For the disintegration time of the tablets no significant interaction between the amount of water and the drug descriptors was found. A high solubility and large surface area of the drugs seem to shorten the disintegration time.

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Chapter 5

Optimisation of the composition and production of mannitol/microcrystalline cellulose tablets

Mixtures of mannitol and microcrystalline cellulose (MCC) were investigated on small-production scale by granulation in a high-shear mixer and compression into tablets. For both excipients only a few cases of incompatibilities with active ingredients are known. Tablets with only MCC as the filler excipient have inferior strength as compared to pure mannitol tablets, whereas disintegration time of mannitol tablets is inferior to pure MCC tablets. However, combination of both excipients resulted in sufficiently rapid disintegrating tablets with acceptable strength. The composition of the tablet mixture and the process of tablet manufacturing were optimised using statistical techniques. Next to the effects of the amounts of MCC and hydroxypropylcellulose (HPC) in the composition, the effects of the amount of water and the granulation time were evaluated. For the production of tablets both the effects of moisture content in the granules and compression force were studied. Simultaneous optimisation of crushing strength, disintegration time and ejection force of the tablets was carried out to find optimal regions in the design space for these tablet properties.

In conclusion, mannitol/MCC mixtures can be considered as an interesting alternative in case classical excipients cannot be selected in formulation development, due to chemical incompatibilities with active ingredients or inferior physical characteristics.

Introduction

Wet granulation is a process of size enlargement and is generally applied in the pharmaceutical industry to prepare powdered materials for capsules and tablets.

Chapter 5 is a modified version of: Westerhuis JA, Haan de P, Zwinkels J, Jansen WT, Coenegracht PMJ and Lerk CF, *Int. J. Pharm*., 143, (1996), 151-162.

Several strategies have been used to optimise the process of granulation and tablet manufacturing [1-7]. Most of the research on granulation in high-shear mixers has been performed with lactose and calcium-hydrogen-phosphate as the major filler excipients in the blend. Both calciumphosphate and lactose formulations can give rise to physical and chemical problems, the latter particularly in formulations with drugs that give the Maillard decomposition reaction. Both MCC and mannitol are relatively inert and only a few cases of incompatibilities with active ingredients have been reported.

The aim of this study was to evaluate the applicability of mannitol/MCC mixtures and to optimise the composition and production of the tablets for their granulating and tableting properties using statistical optimisation techniques.

Methods

Design of experiments

The design of experiments in this study was divided into three steps: the screening of important process variables, the robustness of the process and the final experimental design. The final design was restricted to 40 granulation experiments aimed to give quantitative information about the effect of only six process or composition variables on the granule and tablet responses.

An extensive list of all variables that affect the process of wet granulation and tableting is based on everyday experience. From this list some variables were chosen for further research, others were kept constant at a specified level. The following criteria were used to come to a selection of important variables: known for its high influence, traditionally varied to solve technological problems, easy to control and vary, meets peoples interests, affects nearly all responses. Screening experiments finally resulted in the selection of six variables and their valid ranges.

An essential step in the optimisation process is to establish the robustness (reproducibility) of the manufacture of granules and tablets against disturbances in variables that are assumed to stay constant. If the process is not robust, effects of process variables are more difficult to detect.

The six chosen process and composition variables were set at specific levels for the final experimental design. Because of the expected curvature in the response surfaces, each variable was varied at three levels. A Box-Behnken design was selected, which only needed 55 experiments [8]. Figure 1 shows a three variable Box Behnken design. No experiments at the vertices of the cubic region are necessary. This can be advantageous because the corners of the cube represent extreme combinations of factors at the edge of the experimental region where physical-chemical problems may arise.

The six variable Box Behnken design used, is shown in Table 1. The ±1 stands for the high and low level of the specific variable, and 0 stands for the medium level.

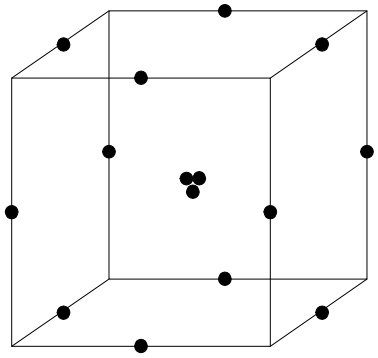

Figure 1: A three variable Box Behnken design. Each variable is varied on three levels. No experiments are selected at the corner points. The centre point is repeated several times.

The number of batches in each row that have to be granulated is given in the last column. Two of the four process variables, compression force and moisture in the granules, are not applied at the production of the granulation. These process variables can be varied using the same batch of granules. Therefore, the number of batches can be diminished from 55 to only 33 batches. Table 2 shows the variables and levels that were set. Two composition variables are varied, the amount of MCC and HPC in the blend. The other four variables: the amount of water added to the mixture, granulation time, moisture level of the granules and compression force (F_{up}), define the process. The moisture level of the granulation was set to a specific value using methods including drying in a Kocken vacuum stove. The binary mixture of MCC and mannitol can be represented by only one variable. The calculated effect of MCC, therefore, is not from the pure component. It points out the effect of the combination of MCC and mannitol.

Previous experiments showed that a high water level was incompatible with a low amount of MCC as was a low level of water with a high amount of MCC. For this reason the amount of water was set dependent on the amount of MCC according to a previous defined experimental relation given in Table 2.

Table 1: Box-Behnken design with four process: water, time, moisture and compression force (Fup), and two composition variables: MCC and HPC.

MCC	HPC	Water	Time	Moisture	Fup	# batches
±1	±1	0	±1	0	0	8
0	±1	±1	0	±1	0	4
0	0	±1	±1	0	±1	4
±1	0	0	±1	±1	0	4
0	±1	0	0	±1	±1	2
±1	0	±1	0	0	±1	4
0	0	0	0	0	0	7

Table 2 The levels of the variables in the Box-Behnken design.

Process variables	low level	medium level	high level
MCC (%)	65	75	90
Water (ml)	110+4.5*MCC	110+5.3*MCC	110+6.0*MCC
HPC (%)	2	3	5
Time (min.)	3	5	7
Moisture (%)	3	4	5
Fup (kN)	10	20	30

Statistical analysis of the results.
The use of regression analysis in this study has two main reasons, process investigation and optimisation of tablet properties. To obtain regression models that describe the data well and give good predictions, a well-defined strategy is followed. The strategy is divided into three steps.

- Outlier selection
- Model selection
- Model evaluation

The data measured are modelled to a linear model with linear, quadratic and interaction terms. The complete model is defined as follows:

$$\mathbf{y} = a + b_1\mathbf{X}_1 + ... + b_6\mathbf{X}_6 + c_1\mathbf{X}_1^2 + ... + c_6\mathbf{X}_6^2 + d_{12}\mathbf{X}_1\mathbf{X}_2 + ... + d_{56}\mathbf{X}_5\mathbf{X}_6$$

In this model the intercept *a* gives the response value **y** in the centre of the design where all variables $\mathbf{X}_1..\mathbf{X}_6$ are set to zero. The parameters *b*, *c* and *d* are regression coefficients for the linear, quadratic and two-factor interaction terms respectively.

Outlier selection
The residuals of the complete model are examined for outliers with an envelope plot of the Studentized residuals. Studentized residuals have mean zero and unit variance and they are corrected for the influence of the position in the design [9]. The residuals are plotted in an envelope plot [10]. When residuals fall outside the envelope, they are removed as outliers.

Model selection
Model selection starts with the determination of the complexity of the model. The successive addition of the linear, quadratic and interaction terms is evaluated with a F-test. The adjusted correlation coefficient ($R^2_{adj.}$) and Amemiya's prediction criterium (PRC) are calculated for these models [11]. $R^2_{adj.}$ gives the variance in the data accounted for by the regression model. The PRC compares mean squared errors of the models. Both are corrected for the number of observations and parameters in the model. For a good model, $R^2_{adj.}$ is close to 1 and PRC is as low as possible.

Variable selection is carried out to use only those variables that influence the

response. The models are stripped one group at the time. Groups of a specific variable are formed by its linear and quadratic term and all interaction terms. Groups are stripped until they all are significant at the 0.05 level. The p-value shows the significance for the F-test for the mean square of the type II sum of squares explained by the group and the mean square of the residuals [12]. In the evaluation of the models $R^2_{adj.}$ and PRC are included. The model with optimal $^2R_{adj.}$ and PRC values will be chosen as the final model. However, the figures may be ambiguous. They are not always both optimal for the same model. When this is the case, selection of the final model has to be made on additional arguments. The final model was tested for lack of fit [9].

Model evaluation

After estimation of all parameters in the model, several plots of responses against process variables can be drawn and evaluated. From these plots, optimal combinations of the process variables can be found for the tablet responses to meet given criteria. For prediction properties, the square root of the leave one out squared prediction errors (RMPRESS) is calculated. If the RMPRESS, the root mean squared error (RMSE) of the model and the experimental error (s) of the centre point are of comparable size, the model can predict new response values with the same precision as described by the data.

In the process of tablet making, a number of demands have to be satisfied. Usually, optimal values for different responses are not obtained at the same settings of the process and composition variables. Overlay contour plots can be drawn for several responses in the experimental space, to find regions in the experimental space that fulfil restrictions of tablet properties.

Experimental

Granulation and compression process

Granulations were prepared according to the formulation in Table 3. MCC (Avicel PH102; Roquette) and mannitol (FMC cooperation) were mixed for 1 minute in a Gral 10 high-shear granulator (Collette) at impeller speed 650 rpm. The HPC (Aqualon) solution was added in the middle of the powder bed with the necessary amount of water. The mass was granulated for 3, 5 or 7 minutes at impeller speed 650 rpm. and chopper speed 3000 rpm. After granulation, the mass was dried in a Kocken vacuum stove at 40 ^oC and -1000 mbar vacuum. The moisture content of the granules was determined with a Sartorius IR humidity analyser. The granules were sieved through a 710 µm sieve on an Erweka AMD oscillator. From the granules 400 g was taken and admixed with 1.5% colloidal silicon dioxide (Defussa) during 1 minute followed by admixing with 0.5% magnesium stearate (Otto Breyer b.v.) during 1 minute in an Erweka mixer. After admixing, the granules were compressed into flat

Table 3 The formulation of the tablets.

HPC	2-3-5%
magnesium stearate	0.5%
colloidal silicium dioxide	1.5%
MCC + mannitol	ad. 100%

faced tablets (9.0 mm; 250 mg) at a compression force of 10, 20 or 30 kN on a HOKO KJ excenter press.

Granule and tablet properties

Before admixing the granules with colloidal silicon dioxide and magnesium stearate, the particle size distribution was measured by sieve analysis (Retsch 50 Hz, 20 min. sieves 600, 500, 355, 212, 125, 75 µm), and the median diameter of the granules (D_{50}) was calculated. The flow rate of 100 g of granules through a funnel with an orifice of 4.5 mm was measured as were the poured and tapped specific volumes. During tableting, ejection forces of the tablets were registered with a Siemens Oscilloreg. Thirty minutes after preparation, crushing strengths of 10 tablets were measured on a Roche HT 300. Disintegration times of six tablets were measured with disks according to USP XXII.

The selected Box-Behnken design needed 55 experiments. Table 4 shows settings of the process and composition variables according to the BB design and the measured crushing strength (CS), disintegration time (DT) and ejection force (EF) of the tablets. Table 5 shows the measured granule properties. A-C=Flow through funnel with orifice 4.5, 6.0 and 9.0 mm respectively (s), D, E=poured and tapped volumes ($ml.g^{-1}$), F=Carr's index, G=median granule size (D_{50}; µm) and H-N=sieve fractions >600, 600-500, 500-355, 355-212, 212-125, 125-75, <75 (%). From experiment 14 and 15 no tablets could be obtained because of the bad compression characteristics of the granules.

Results and discussion

Robustness experiments showed that the process of wet granulation and tablet making is in control. The reproducibility of the tablet responses was considered good enough to continue the study.

Tablet properties

Tablets were compressed from the granules. One granulation experiment (90% MCC, 3% HPC, 585g H_2O, 4% moisture, granulation time 7 min.) turned out to have extremely poor compressibility properties. This batch was supposed to be tableted at two different compression forces. No tablet properties could be obtained for these experiments. Table 6 shows the results of the models for the tablet responses.

Table 4: Experimental design and measured tablet properties crushing strength (CS), disintegration time (DT) and ejection force (EF).

Nr	MCC(%)	HPC(%)	water(ml)	time(min.)	moist.(%)	comp. (kN)	CS(N)	DT(s)	EF(N)
1	75	3	500	5	3.9	20	23	11	138
2	75	3	500	5	4.3	20	48	42	110
3	75	3	510	5	4.0	20	33	24	91
4	75	3	510	5	4.3	20	38	23	91
5	75	3	510	5	3.8	20	25	11	111
6	75	3	510	5	3.8	20	35	30	92
7	75	3	510	5	3.8	20	38	34	100
8	65	3	450	7	3.8	30	55	104	126
9	65	3	450	7	3.8	10	15	2	101
10	90	3	585	3	4.0	30	11	10	50
11	90	3	585	3	4.0	10	4	2	59
12	65	3	450	3	4.2	10	23	10	235
13	65	3	450	3	4.2	30	66	291	274
14	90	3	585	7	3.7	10	*	*	*
15	90	3	585	7	3.7	30	*	*	*
16	75	5	450	5	4.0	10	14	2	99
17	75	5	450	5	4.0	30	51	138	120
18	75	5	560	5	3.8	10	17	5	74
19	75	5	560	5	3.8	30	53	400	83
20	75	2	450	5	4.2	30	75	215	358
21	75	2	450	5	4.2	10	30	2	214
22	75	2	560	5	4.0	30	51	84	99
23	75	2	560	5	4.0	10	20	6	86
24	90	3	510	5	3.3	20	22	16	81
25	90	3	510	5	4.8	20	22	15	72
26	65	3	500	5	4.8	20	61	149	117
27	65	3	500	5	3.2	20	48	65	132
28	65	3	400	5	3.1	20	44	28	141
29	65	3	400	5	4.9	20	58	72	134
30	90	3	650	5	3.4	20	6	8	53
31	90	3	650	5	5.4	20	8	15	41
32	65	2	450	7	4.0	20	49	26	153
33	65	2	450	3	4.0	20	52	42	142
34	90	2	585	7	4.4	20	9	2	68
35	90	2	585	3	4.3	20	13	4	62
36	65	5	450	3	4.0	20	37	55	138
37	65	5	450	7	4.0	20	31	32	115
38	90	5	585	7	4.2	20	6	10	44
39	90	5	585	3	4.3	20	8	16	51
40	75	3	560	7	4.5	20	65	118	79
41	75	3	560	7	3.1	20	55	54	86
42	75	3	560	3	4.6	20	57	90	88
43	75	3	560	3	3.0	20	51	33	134
44	75	3	450	3	3.0	20	51	51	134
45	75	3	450	3	4.6	20	51	38	110
46	75	3	450	7	3.1	20	43	21	127
47	75	3	450	7	4.6	20	48	47	120
48	75	2	510	5	4.8	10	22	6	92
49	75	2	510	5	4.8	30	60	125	102
50	75	2	510	5	2.8	10	11	4	91
51	75	2	510	5	2.8	30	61	48	124
52	75	5	510	5	3.1	30	57	156	110
53	75	5	510	5	3.1	10	13	6	92
54	75	5	510	5	4.5	10	23	9	85
55	75	5	510	5	4.5	30	68	421	91

Table 5: Measured physical granule properties of experiments given in Table 4. A-C=Flow through funnel with orifice 4.5, 6.0 and 9.0 mm (s), D-E=poured, tapped volumes ($ml.g^{-1}$), F=Carr's index, G=median granule size (D_{50}; µm), H-N=sieve fractions >600, 600-500, 500-355, 355-212, 212-125, 125-75, <75 (%).

Nr	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	1.15	2.54	7.28	1.55	1.46	6.2	344	3.9	11.6	31.4	43.2	7.9	1.2	1.0
2	1.14	2.51	6.76	1.71	1.54	11.0	257	6.2	6.5	11.3	37.2	35.2	2.0	1.2
3	1.13	2.55	7.25	1.57	1.45	8.3	378	7.3	16.7	30.9	36.4	6.3	1.2	1.2
4	1.05	2.36	6.45	1.71	1.59	7.5	325	5.0	10.0	25.6	46.2	8.6	1.6	3.0
5	1.05	2.44	6.90	1.56	1.38	13.0	429	10.6	21.0	37.5	25.8	3.5	0.8	0.7
6	1.05	2.23	6.45	1.65	1.53	7.8	444	10.2	21.8	39.2	21.2	4.3	1.4	1.8
7	1.02	2.34	6.37	1.78	1.58	12.7	280	1.2	4.0	16.2	53.4	19.6	2.8	2.2
8	1.22	2.72	7.37	1.52	1.45	4.8	337	2.9	11.0	30.1	44.9	8.2	1.4	1.2
9	1.22	2.72	7.37	1.52	1.45	4.8	337	2.9	11.0	30.1	44.9	8.2	1.4	1.2
10	1.16	2.70	7.53	1.47	1.32	11.4	304	6.0	9.6	21.0	38.5	19.1	3.5	2.7
11	1.16	2.70	7.53	1.47	1.32	11.4	304	6.0	9.6	21.0	38.5	19.1	3.5	2.7
12	1.13	2.54	6.90	1.66	1.57	5.7	285	5.3	7.2	16.2	42.5	26.4	1.3	0.5
13	1.13	2.54	6.90	1.66	1.57	5.7	285	5.3	7.2	16.2	42.5	26.4	1.3	0.5
14	1.23	2.68	7.82	1.35	1.27	6.3	478	20.6	24.3	39.1	14.4	2.1	0.5	0.2
15	1.23	2.68	7.82	1.35	1.27	6.3	478	20.6	24.3	39.1	14.4	2.1	0.5	0.2
16	1.01	2.25	6.41	1.69	1.54	9.7	273	5.9	7.8	16.4	34.3	31.1	3.6	0.6
17	1.01	2.25	6.41	1.69	1.54	9.7	273	5.9	7.8	16.4	34.3	31.1	3.6	0.6
18	0.95	2.15	6.26	1.60	1.50	6.7	507	26.1	25.6	24.5	13.8	5.2	1.8	2.9
19	0.95	2.15	6.26	1.60	1.50	6.7	507	26.1	25.6	24.5	13.8	5.2	1.8	2.9
20	1.20	2.56	6.41	1.75	1.56	12.2	151	3.3	3.4	4.7	10.0	41.5	30.7	6.8
21	1.20	2.56	6.41	1.75	1.56	12.2	151	3.3	3.4	4.7	10.0	41.5	30.7	6.8
22	0.95	2.14	6.24	1.63	1.52	7.2	533	27.5	32.8	27.7	9.0	1.6	0.3	0.7
23	0.95	2.14	6.24	1.63	1.52	7.2	533	27.5	32.8	27.7	9.0	1.6	0.3	0.7
24	1.27	2.75	7.18	1.63	1.45	12.4	196	4.2	9.8	12.2	17.8	34.6	18.0	3.6
25	1.29	2.82	7.35	1.59	1.42	12.0	189	4.0	8.0	10.6	17.0	40.8	17.0	3.2
26	0.95	2.18	6.26	1.66	1.48	12.2	510	22.2	30.4	25.6	13.8	4.6	1.4	1.6
27	0.98	2.23	6.41	1.64	1.47	11.6	507	22.8	29.8	26.2	14.0	4.6	1.4	1.6
28	1.26	2.62	6.67	1.70	1.49	14.1	177	1.6	4.6	8.8	17.0	45.2	18.8	4.2
29	1.18	2.56	6.66	1.74	1.55	12.2	184	1.4	5.2	9.8	18.0	47.2	14.2	3.8
30	1.11	2.54	7.30	1.37	1.30	5.4	563	41.8	21.0	19.4	11.0	4.0	1.2	1.2
31	1.18	2.62	7.69	1.36	1.26	7.9	539	36.0	22.6	21.6	12.6	4.4	1.2	1.4
32	1.15	2.47	6.42	1.80	1.62	11.1	174	1.3	4.5	7.0	11.8	58.9	13.4	3.2
33	1.15	2.47	6.17	1.82	1.64	11.0	177	0.8	3.4	5.8	15.4	57.9	11.2	4.2
34	1.38	3.07	8.27	1.50	1.33	12.8	204	1.7	3.9	8.8	29.7	49.7	3.7	1.0
35	1.25	2.75	7.42	1.59	1.44	10.4	212	1.9	5.4	11.8	30.6	44.3	4.4	1.3
36	1.12	2.54	7.13	1.50	1.38	8.7	380	7.5	18.3	28.8	32.9	10.0	1.4	0.8
37	1.05	2.44	7.12	1.52	1.35	12.6	475	18.7	25.5	31.1	17.6	5.1	1.1	0.5
38	1.13	2.61	7.58	1.40	1.27	9.3	502	22.8	27.7	23.3	14.9	7.6	2.2	1.5
39	0.99	2.31	6.82	1.52	1.40	8.6	520	25.3	30.4	27.9	13.9	1.8	0.2	0.2
40	0.82	1.90	5.56	1.74	1.63	6.7	518	25.2	29.6	22.8	12.8	5.4	2.0	1.8
41	0.85	1.94	5.59	1.74	1.62	7.4	529	26.4	32.6	22.0	11.0	4.2	1.4	1.8
42	0.86	1.96	5.71	1.75	1.63	7.4	511	22.6	30.8	24.2	12.8	5.4	2.2	2.0
43	0.88	2.05	5.88	1.75	1.60	9.4	509	23.6	29.2	25.6	13.0	4.8	1.8	2.2
44	1.09	2.30	5.88	1.86	1.66	12.0	164	1.2	4.8	8.2	16.2	38.4	25.6	7.0
45	1.09	2.31	6.10	1.79	1.59	12.6	181	1.6	6.0	10.2	17.2	40.2	18.6	5.4
46	1.07	2.24	5.85	1.87	1.65	12.7	183	1.4	4.8	8.8	16.8	49.6	15.0	2.0
47	1.04	2.25	5.75	1.91	1.70	12.4	183	1.4	5.4	9.2	17.4	51.6	11.6	4.2
48	1.02	2.32	6.37	1.80	1.63	10.4	290	1.8	5.8	18.0	53.0	16.4	2.4	2.2
49	1.02	2.32	6.37	1.80	1.63	10.4	290	1.8	5.8	18.0	53.0	16.4	2.4	2.2
50	1.03	2.31	6.39	1.83	1.61	13.7	282	1.2	4.4	16.8	55.0	17.8	2.6	1.6
51	1.03	2.31	6.39	1.83	1.61	13.7	282	1.2	4.4	16.8	55.0	17.8	2.6	1.6
52	0.91	2.11	6.17	1.67	1.56	7.1	501	21.8	28.6	26.8	14.4	5.2	1.6	1.8
53	0.91	2.11	6.17	1.67	1.56	7.1	501	21.8	28.6	26.8	14.4	5.2	1.6	1.8
54	0.88	2.04	5.82	1.72	1.60	7.5	516	23.2	31.8	24.8	12.6	4.4	1.4	1.8
55	0.88	2.04	5.82	1.72	1.60	7.5	516	23.2	31.8	24.8	12.6	4.4	1.4	1.8

Table 6: Final models for the ejection force, crushing strength and disintegration time of mannitol MCC tablets. Outliers, R^2, and lack of fit probability are given. Further model parameters are given with their significance (* p<0.05, ** p<0.01, *** p<0.001), and RMSE, error of reproduction (s) and RMPRESS values. t1 and t2 give indications of properties for the tablets with bad compression properties.

Response	Ejection force (N)		Crushing strength (N)		Disintegration time (s)	
Outliers	4		-		-	
R^2	0.85		0.93		0.91	
p(Lack of fit)	0.97		0.75		0.69	
Intercept	98.8		3.3794		3.22	
MCC	-28.0	***	-0.4785	***	-0.658	***
Fup	7.0	**	0.5741	***	1.687	***
moisture	-8.8	**	0.1555	**	0.489	***
HPC					0.231	***
water	-11.0	***	-0.0341		0.278	**
MCC^2			-0.3472	***	-0.241	**
Fup^2	-9.8	**	-0.2358	***	-0.315	*
$moisture^2$			0.1225		0.527	**
$water^2$			0.2002	***	0.315	**
MCC*Fup					-0.378	*
MCC*moisture					-0.357	*
MCC*HPC					0.158	*
MCC*water			-0.2660	***	-0.288	*
Fup*moisture			-0.1842	*		
RMSE	12		0.22		0.48	
s	17		0.26		0.53	
RMPRESS	12		0.25		0.55	
	t1: 43 N t2: 57 N		t1: 3 N t2: 10 N		t1: 1 s t2: 13 s	

Disintegration time

The analysis of the results of the disintegration time will be used to show the statistical route mentioned earlier in this chapter and is shown in detail. A logarithmic transformation was used to correct for the heteroscedastic measurement error of the disintegration time. No outliers were removed.

Scheme 1 shows the detailed results of the model building. A complete model with linear, quadratic and interaction terms was selected to fit the disintegration time data. A variable selection was carried out on this model. The granulation time variable group provides no significant addition to the model (p=0.3969). The whole variable group was removed. The new complete model shows no insignificant variable groups (p<0.05). The second model has an improved PRC, but $R^2_{adj.}$ decreased a little. Comparing both models the second was selected because it is simpler than the first model. Looking to the model in detail, only the MCC group of interactions is significant (p-values PROB>|T| below 0.05). The other interactions were removed from the model as was the quadratic HPC term (p=0.25). The final

Scheme 1: Detailed results of the modelling of the logarithmic scaled disintegration time.

```
ln disintegration time
-----------------------------------------------------
Regressors        R2         F          p     R2adj     PRC
linear        0.8026    66.302     0.0000    0.7768    0.5149
quadratic     0.0801     6.619     0.0003    0.8475    0.3870
cross         0.0669     2.209     0.0385    0.8951    0.3267
TOTAL         0.9496    17.432     0.0000
-----------------------------------------------------
full model
Factor     SSII        MS         F        p
MCC     25.4282    3.6326   16.9917   0.0000   R2    = 0.9496
water    5.3801    0.7686    3.5951   0.0082   PRC   = 0.3267
time     1.6371    0.2339    1.0939   0.3969   R2adj = 0.8951
Fup     67.3874    9.6268   45.0296   0.0000   LOF   = 0.7491
moisture 4.8328    0.6904    3.2294   0.0140
HPC      5.3739    0.7677    3.5909   0.0082
-----------------------------------------------------
full model (-time)
Factor     SSII        MS         F        p
MCC     25.3155    4.2192   19.3384   0.0000   R2    = 0.9341
water    4.8740    0.8123    3.7232   0.0064   PRC   = 0.3046
Fup     67.1179   11.1863   51.2711   0.0000   R2adj = 0.8929
moisture 4.9530    0.8255    3.7836   0.0058   LOF   = 0.7341
HPC      5.3972    0.8995    4.1229   0.0035
-----------------------------------------------------
                  ANALYSIS OF VARIANCE
SOURCE     DF        SS          MS     F-value    PROB>F
MODEL      20   98.9851     4.94925     22.6843    0.0000
ERROR      32   6.98175     0.21818
TOTAL      52   105.967
RMSE = 0.46710   PRESS = 21.33245

             PARAMETER   STANDARD    T FOR H0:
VARIABLE     ESTIMATE    ERROR       PARAMETER=0  PROB>|T|
intercept     3.2160     0.06416     50.12450     0.0000
MCC          -0.6482     0.09878     -6.56183     0.0000
water         0.2556     0.09386      2.72311     0.0052
Fup           1.6419     0.10439     15.72798     0.0000
moisture      0.4919     0.11846      4.15281     0.0001
HPC           0.2965     0.11008      2.69323     0.0056
MCC²         -0.2515     0.09320     -2.69855     0.0055
water²        0.3065     0.12420      2.46788     0.0096
Fup²         -0.2671     0.15280     -1.74833     0.0450
moisture²     0.4960     0.17399      2.85049     0.0038
HPC²         -0.0523     0.07685     -0.68069     0.2505
MCC*water    -0.2896     0.12113     -2.39099     0.0114
MCC*Fup      -0.3767     0.16076     -2.34306     0.0128
MCC*mois.    -0.3550     0.15626     -2.27170     0.0150
MCC*HPC       0.1493     0.08598      1.73599     0.0462
water*Fup    -0.2138     0.15835     -1.35010     0.0932
water*mois.   0.0977     0.13306      0.73414     0.2341
water*HPC     0.1594     0.10233      1.55816     0.0645
Fup*mois.     0.1670     0.18567      0.89956     0.1875
Fup*HPC       0.1450     0.07703      1.88236     0.0345
mois.*HPC     0.0439     0.13134      0.33459     0.3701
-----------------------------------------------------
New model
SOURCE     DF        SS         MS       F-value    PROB>F
MODEL      13   96.8979    7.45369     32.0539    0.0000
ERROR      39    9.069     0.23254
TOTAL      52  105.967

RMSE= 0.4822   R2 = 0.9144   PRESS = 16.38105
PRC = 0.2895   LOF= 0.69     R2adj =  0.8859
```

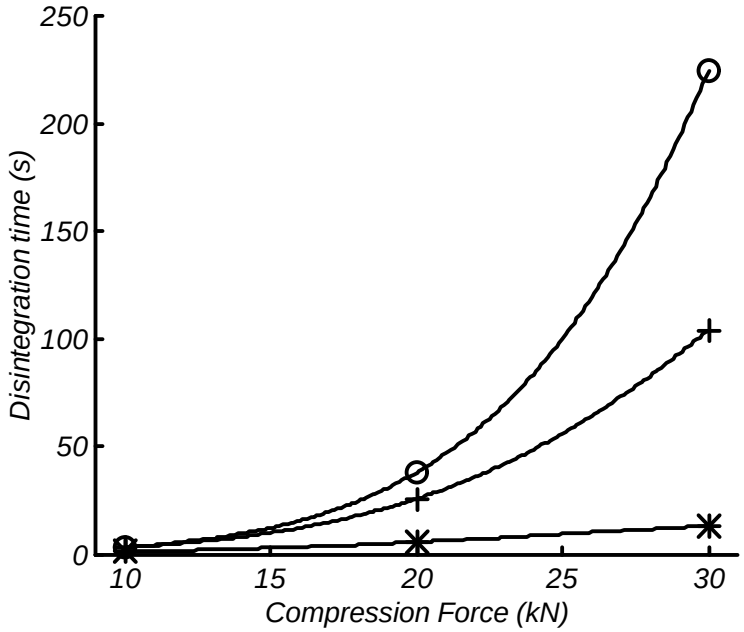

Figure 2: Prediction of the disintegration time of mannitol MCC tablets as a function of the amount of MCC and the compression force. (MCC: o=65%, +=75%, ✳=90%; HPC 3%, granulation time 5 min., moisture content in granulation 4%, water at its medium level).

model (Table 6) has a lower R^2_{adj}, but the PRC and PRESS values improved and it shows no lack of fit.

The amount of MCC has a reducing effect on the disintegration time. Higher compression forces give tablets with shorter disintegration time. The effect of the other variables depends on the level of MCC. Figure 2 shows the disintegration time as a function of compression force and amount of MCC. High levels of MCC give tablets that disintegrate fast as do tablets compressed at 10kN. At a low MCC amount, the effects of compression force, amount of water and moisture in the granules are higher than at high levels of MCC.

Other tablet properties

Table 6 shows models for the ejection force and crushing strength of mannitol MCC tablets. A logarithmic transformation was also used for the crushing strength of the tablets to correct for the heteroscedastic variance structure. MCC has to be below 80% and the compression force must exceed 15 kN to obtain tablets with crushing strengths of at least 40 N. Figure 3A shows the crushing strength as a function of MCC and compression force.For the ejection force of the tablets four observations (exp. 12, 13, 18 and 19; see Table 4) were selected as outliers. Figure 3B shows an obvious effect of the amount of MCC and compression force on the ejection force. When more water is added, the ejection force decreases. For all tablet properties the RMPRESS values are of comparable size to the RMSE and the experimental error (s). At the end of Table 6, indications are given for the tablet properties of the

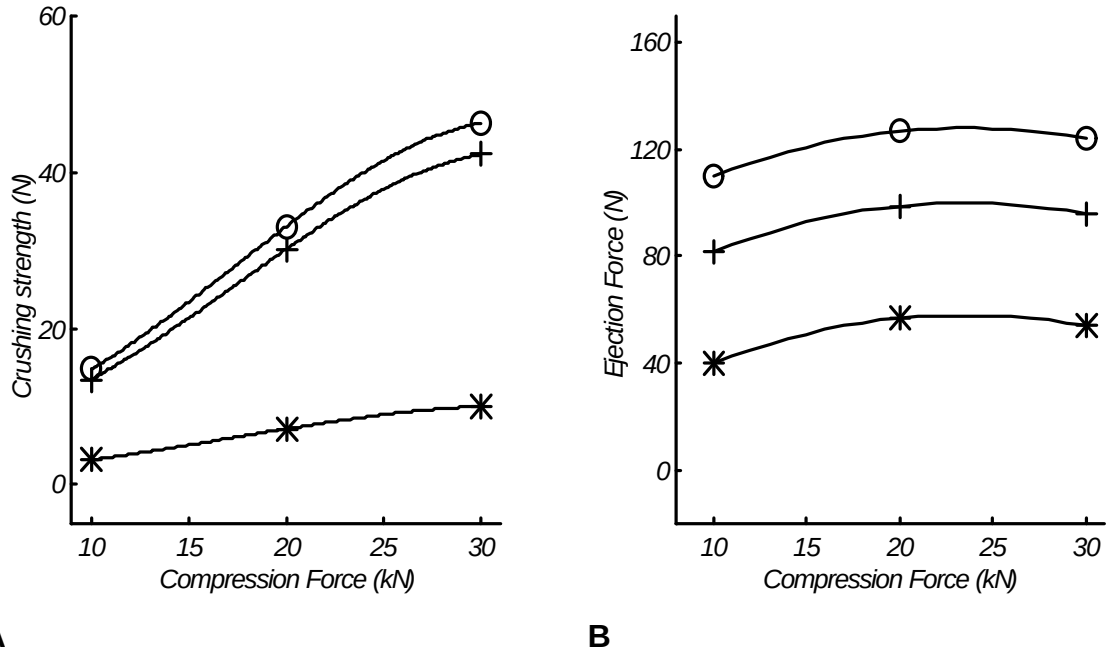

Figure 3: Prediction of the crushing strength (A) and the Ejection force (B) of mannitol MCC tablets as a function of the amount of MCC and the compression force. (MCC: o=65%, +=75%, ✳=90%; HPC 3%, granulation time 5 min., moisture content in granulation 4%, water at its medium level).

experiments with bad compressibilities (t1, 10kN; t2, 30kN). Although the models are extrapolating, they show that the tablets would be very weak and disintegrate fast.

Granule properties

The granule properties were also modelled on the process and composition variables. The compression force and the moisture content in the granules are process variables for the tableting step and are not taken into account for the modelling of the granule properties. Table 7 shows mathematical models constructed to describe the granule responses.

The median granule size is calculated from particle size distribution measurements. Only linear terms of the amount of water and concentration of the binder are used in this model. Both terms have a large positive effect on the response, so the median granule size increases with increasing amounts of water and concentration of binder. With this simple model the data is fitted well and predictions are also good. The percentage of fines indicates the material that has not been granulated or is segregated during handling. The highest percentage can be found at low levels of water and HPC. The number of fines decreases when more water or HPC is added. However when both are high, the percentage of fines increases again. For the specific volumes poured and tapped the same variables are important in the models. The highest specific volumes are obtained at a medium level of MCC and a low amount of water. The flow through a funnel with an orifice of 4.5 mm diameter is modelled with a full quadratic model. A strong curvature of the

Table 7: Final models for median granule diameter, % fines, specific volumes poured and tapped and flow of mannitol MCC granulations. Outliers, R^2, and lack of fit probability are given. Further model parameters are given with their significance (* p<0.05, ** p<0.01, *** p<0.001), and RMSE, error of reproduction (s) and RMPRESS values.

Response	Median granule size (µm)		Fines (%)		Vol. $_{Poured}$ ($ml.g^{-1}$)		Vol. $_{Tapped}$ ($ml.g^{-1}$)		Flow ($g.s^{-1}$)	
Outliers	-		-		-		-		-	
R^2	0.86		0.71		0.76		0.75		0.88	
p(Lack of fit)	0.88		0.37		0.77		0.76		0.73	
Intercept	353.58		2.18		1.65		1.50		1.079	
MCC					-0.0199		-0.013		-0.009	
time			-0.41	*	-0.018		-0.017		0.007	
HPC	64.2	***	-0.37	**	-0.070	**	-0.047	**	-0.043	***
water	156.8	***	-1.06	***	-0.051	**	-0.022		-0.103	***
MCC^2					-0.102	***	-0.097	***	0.094	***
$time^2$					0.056	*	0.054	**	-0.039	*
HPC^2					0.024	*	0.016			
$water^2$			1.02	***	0.057	**	0.042	*	-0.046	**
MCC*time									0.024	*
MCC*HPC									-0.025	**
time*water			0.66	*						
HPC*water			1.30	***					-0.031	*
RMSE	55		0.92		0.08		0.07		0.052	
s	71		0.66		0.09		0.08		0.053	
RMPRESS	57		1.02		0.09		0.075		0.062	

flow in the MCC direction is observed. The lowest flow is reached at medium levels of MCC with large amounts of HPC and water.

Multi criteria optimisation

Crushing strength, disintegration time and ejection force of the tablets are examined simultaneously. Overlay contour plots of the tablet responses are given in Figure 4. Each subplot shows the crushing strength, disintegration time and ejection force of the tablets dependent on compression force and MCC.In the horizontal direction, water is varied from 450 to 550 ml and in the vertical direction the moisture in the granules is varied from 3 to 5%. The gray part of the plots have acceptable values for all tablet responses: crushing strength above 40 N, disintegration times below 300 seconds and ejection forces below 120 N. In each constrained plot (because of the MCC water relation) the upper left corner gives tablets that are too soft, the lower left corner gives ejection forces higher than 120 N and the lower right corner gives tablets with long disintegration times. HPC is set at 3% and the granulation time at 5 minutes.

To result in good mannitol/MCC tablets, MCC should be between 65 and 80%, water should be about 500 g or higher, dependent on the MCC amount and compression force must be about 25 kN. When the granulations contains more than

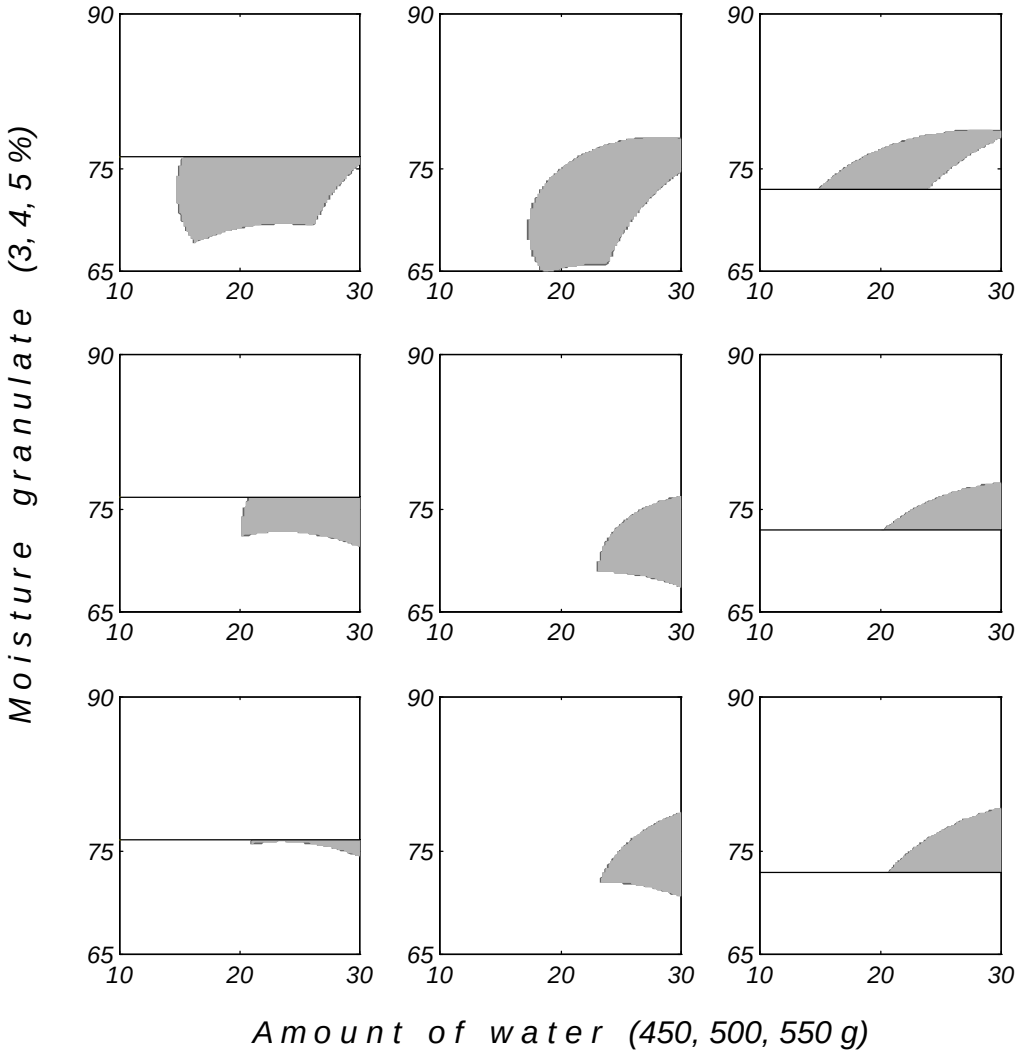

Figure 4: Overlay contour plots of crushing strength, disintegration time and ejection force. In each plot compression force (10, 20, 30kN) and MCC (65, 75, 90%) are varied. Horizontally water changes from 450 to 550 ml and vertically moisture in the granulation (3, 4, 5%). The dark area represents tablets with crushing strengths > 40N, disintegration times < 5 minutes and ejection force < 120N (HPC 3%, granulation time 5 min.).

5% moisture the tablets become stronger and a compression force of 20 kN satisfies. This also causes a lower ejection force, but the disintegration time increases. More compression force or less MCC gives stronger tablets. Table 8 shows predicted tablet properties for some settings of process variables. More HPC decreases the ejection force, but if enough water is added during granulation, HPC can be kept low.

Table 8: Predicted properties of mannitol MCC tablets at some settings of the composition and process variables

MCC (%)	HPC (%)	Moisture (%)	Water (g)	Fup (kN)	Time (min.)	Crushing strength(N)	Disintegr. time (s)	Ejection force (N)
75	3	5	450	20	5	51	74	102
75	3	5	450	25	5	59	160	103
70	3	5	500	20	5	48	134	100
75	3	5	500	25	5	45	144	93
75	3	5	550	20	5	43	106	81
70	3	4	500	25	5	46	95	110
75	3	4	550	25	5	41	83	91
75	3	3	550	25	5	43	86	100

Conclusion

Mixtures of MCC and mannitol in tablets can be used as a good alternative to classical filler excipients. The amounts of MCC, HPC and water strongly affect tablet properties as do compression force and moisture of the granulation. Granulation time hardly affects tablet properties. The amount of HPC does not influence the crushing strength and ejection force of the tablets. The combination of MCC and mannitol gives tablets with short disintegration times and sufficient strength. For tablets with crushing strengths more than 40 N, disintegration times less than 300 seconds and ejection forces less than 120 N, the amount of MCC should be between 65 and 80%, the compression force must be 25 kN and the amount of water should be at least 500 g, dependent on the MCC amount. When the moisture content in the granulation is 5%, a compression force of 20 kN appears adequate.

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Chapter 6

Multivariate modelling of the process of wet granulation and tableting for tablet optimisation and in-process control

The process of tablet manufacturing with wet granulation is described as a two-step process. The first step comprises the wet granulation of the powder mixture, and in the second step the granulations are compressed into tablets. For the modelling of the pharmaceutical process of wet granulation and tableting, two models are constructed and compared. The first model relates the crushing strength, disintegration time and ejection force of the tablets to the process variables from both wet granulation and tableting steps and the composition variables of the powder mixture. In addition to these predictor variables, the second model also uses physical properties of the intermediate granules to improve the predictive properties of the first model. Model 1 has to be used at the start of the process to find settings for the process variables and the composition of the tablet mixture that produce tablets with specific properties. Model 2 is used, in everyday production, for each new granulation batch. The granulation properties may differ from batch to batch due to uncontrolled external sources. With Model 2 these differences are taken into account, and the crushing strength and disintegration time of the tablets are predicted better than with Model 1. The advantage of incorporating the measured granule properties in the second model is not only an improvement of the predictive power, but the second model offers also the possibility to use a control scheme for the second step of the process. This control scheme adjusts the variables of the tableting step to produce tablets that better meet the specifications. Because the granule properties are highly collinear and also dependent on the process variables of the first step, a partial least squares regression method (PLS) has been used for the modelling.

Chapter 6 is a slightly modified version of:
Westerhuis JA, Coenegracht PMJ and Lerk CF, *Int. J. Pharm*., in press.

Introduction

In the last 15 years, the granulation process has been studied in a systematical way by experimental design and analysis of variance (ANOVA) [1-4] and by response surface methodology (RSM) [5-10]. In most studies, the effect of the process variables on granule properties such as the median granule diameter, percentage of fines, flow rate and porosity was investigated [1-4,7-9]. In some other papers, the effect of the process variables on the tablet properties was also investigated [10-12]. Alderborn gave a list of granule properties that are important to tableting [13]. Lindberg *et al.* studied the influence of the granule properties combined with the process variables for the tableting step on tablet properties as crushing strength, disintegration time and friability [5,6]. In the present chapter, physical granule properties are combined with the composition variables of the powder mixture and the process variables of both granulation and tableting steps to improve the modelling of the tablet properties. Therefore, the process of tablet manufacturing is described as a two-step process. In the first step, the powder mixture is wet granulated to improve the tableting properties of the mixture. Several process variables can be adjusted to change the physical properties of the granulations such as the granulation time and amount of granulation liquid. The granulations are described in terms of particle size distribution, flowability parameters and poured and tapped volumes. In the second step the granules are compressed into tablets. In the latter step other process variables such as the compression force and moisture content in the granules can be set to produce tablets with specific characteristics. The tablet characteristics include crushing strength, disintegration time and ejection force. Figure 1 shows the two-step process of tablet manufacturing with a wet granulation step. The powder mixture is described in three phases, as a powder mixture D, as granules G and finally as a tablet Z. The process variables PV1 and PV2 describe the transition from one phase to another.

The modelling of two-step or multi-step processes in pharmaceutical technology has not received much attention. Lundstedt and Thelin showed a multivariate strategy for the optimisation of a two-step process consisting of a synthesis and a purification step [14]. Their strategy requires that the measurements on the intermediate product contains all information from the starting materials and the

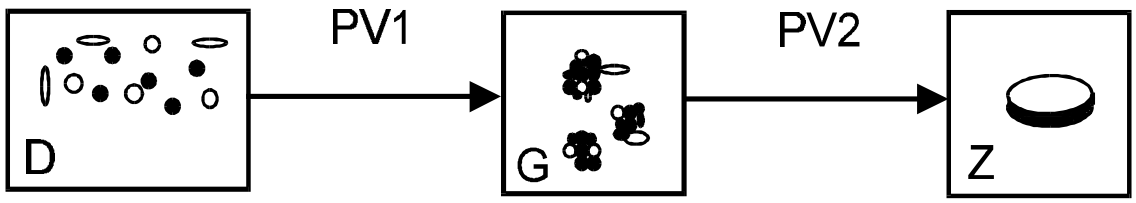

Figure 1: The two-step process of tablet manufacturing with wet granulation

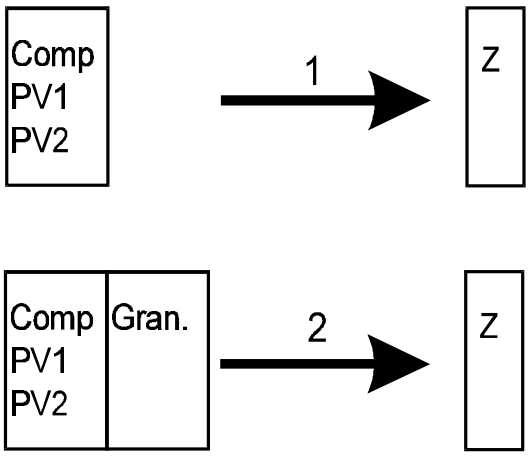

Figure 2: Two models for the modelling of tablet properties. In Model 1, the composition variables and the process variables of both steps are used. The granule properties are added in Model 2.

process variables of the first step that is necessary for modelling and prediction of properties of the final product. In the tablet manufacturing process, however, only few properties of the intermediate granules are measured, such as the particle size distribution and some flowability parameters. The granule properties do not have a strong relationship with the crushing strength and disintegration time of the tablets, and cannot be used solely for the modelling of the tablet properties.

The two-step process of wet granulation and tableting is modelled with two different models. Figure 2 shows the two models for the process. The first model describes the relationship between the composition of the powder mixture and process variables of both steps (PV1 and PV2) and the tablet properties. The first model can be used at the start of the process to find settings for the process variables and the composition of the tablet mixture that produce tablets with specific properties. E.g. if less binder has to be used in the formulation, Model 1 can be used to find settings for the other process and composition variables to produce tablets that still meet the specifications. After the granulation step, physical properties of the granules, important for the tableting properties, are added to the variables of Model 1. The granulation properties do not represent all the information from the first step and cannot be used solely for the modelling of the tablet properties. They do however influence the physical tablet properties and can be used to improve the first model. Model 2 has to be used, in everyday production, for each new batch of granulation. The granule properties will differ from batch to batch due to uncontrolled factors such as air humidity, temperature or other unknown features. With Model 2 these differences are taken into account, and tablet properties can be predicted better than with Model 1. Model 2 offers the possibility to use a control scheme for each new batch of granulation, to adjust the process variables for the tableting step, moisture content in the granulation and compression force, to produce tablets with specified properties.

The granule properties are highly collinear. Furthermore, the physical granule

properties are influenced by the composition of the mixture and the process variables of the first granulation step. Therefore, the descriptor variables of the second model are highly collinear. The partial least squares regression method (PLS) will be used for the modelling because ordinary least squares regression (OLS) suffers from collinearity in the descriptor variables. With PLS, the regression of the response **y** is carried out on a latent factor of **X**, which consists of the process and composition variables and, in Model 2, on the granulation properties. The latent factors, which are linear combinations of the process and composition variables in **X**, are selected to describe the variance in **X** as good as possible and also to optimise the correlation with **y**, *i.e.* the covariance between the latent variable of **X** and **y** is maximised. After the first factor is determined, a second can be calculated, orthogonal to the first that describes the variance of **y** that could not be described with the first latent factor. This can be repeated until most of the variance of **y** is described. PLS is much used in chemometrics and has already been introduced in pharmaceutical technology [15-18]. The PLS model may be evaluated with the root mean squared error (RMSE) which indicates the deviation between the measured and predicted values. For a real validation, each experiment is left out for the modelling once and predicted by the PLS model. The root mean of the predictive error sum of squares (RMPRESS) indicates how well the model predicts future response values. For a good model, RMSE and RMPRESS are comparable to the experimental error.

Experimental

The production of the granulations and tablets is carried out according to the experimental section of Chapter 5. The six descriptor variables consist of: two process variables for step one (amount of water and granulation time), two process variables for step two (moisture of granules and the compression force) and two composition variables (HPC and MCC). Previous experiments showed that a high water level was incompatible with a low amount of MCC as was a low level of water with a high amount of MCC. For this reason the amount of water was set dependent on the amount of MCC. The moisture of the granules was adjusted to a specific value by extra drying or moistening in a fluid bed humidiser of the granulation, and rechecked after one week of stabilisation in closed bags. Because of the expected curvature in the response surfaces, each variable was varied at three levels. Quadratic terms of all descriptor variables were also used for the modelling. The PLS models were calculated with use of the PLS toolbox in Matlab [19,20]. FIgure 3 shows the datasets for the two models. For the first model, D, PV1 and PV2 and their quadratic terms (53*12) are used to describe the tablet response **y** (53*1). For the second model, 14 granulation properties are added to the descriptor variables.

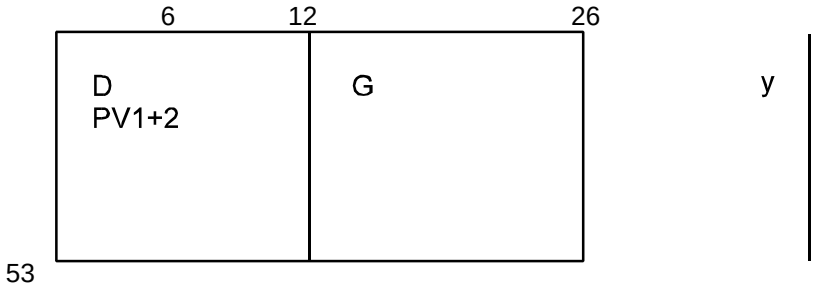

Figure 3: Dataset for the two regression models. The 2 composition variables (D) and 4 process variables for both steps (PV1+2) with the quadratic terms and the 14 granulation properties (G) are used to describe the tablet response **y**.

Results and discussion

According to the experimental design in Table 4 of Chapter 5, granulations were produced and compressed into tablets. The particle size distribution of the granules, the flow through funnels with orifices of 4.5, 6.0 and 9.0 mm and the poured and tapped volumes were measured and median granule size (D_{50}) and Carr's index were calculated (Table 5 of Chapter 5). The crushing strength (CS), disintegration time (DT) and ejection force (EF) of the tablets were measured. CS and DT of the tablets were logarithmic transformed because of the funnel shaped heteroscedastic variance structure. Four extreme large values of EF (exps. 12,13,18,19) were considered as outliers and were deleted before the modelling.

The first PLS model describes CS, DT and EF of the tablets dependent on the composition of the mixture and process variables. Previous calculations showed that quadratic terms were important to describe CS and DT, so they were included in the model for these tablet properties, but not for the modelling of EF [12]. Cross validation showed that three factors gave the best models for CS and DT, and only two PLS factors were needed for EF. Table 1 shows the results for the CS, DT and EF models. The percentage of explained variance of the descriptor variables and of

Table 1: Results of the modelling of the ejection force (EF), crushing strength (CS) and disintegration time (DT) with Model 1 and Model 2. For each model, the number of PLS factors, the amount of explained variance of the descriptors (**X**) and the response (**y**), the root meas squared error (RMSE), the root mean of the leave one out predictions (RMPRESS) and Q^2 for the models are given.

	Response	factors	%**X**	%**y**	RMSE	RMPRESS	Q^2
Model 1	ln CS	3	44	89	0.25	0.31	0.82
	ln DT	3	40	85	0.54	0.69	0.76
	EF	2	47	86	10.2	11.4	0.82
Model 2	ln CS	4	59	95	0.17	0.23	0.90
	ln DT	4	61	92	0.40	0.55	0.85

the response are given as are the RMSE, RMPRESS and the Q^2 values for the three tablet properties.

The linear and quadratic MCC term and the compression force are the most important variables for both CS and DT. Water is only important for CS and HPC influences only DT. For EF, both MCC and water had negative coefficients, *i.e.* high MCC and water levels give low ejection forces. The first model can be used for predictions at the start of the process, before a granulation step has been done.

In Model 2, the granulation properties are added to the first model. These properties improve the modelling of CS and DT, but the modelling of EF is not improved. For the second model, four PLS factors were found significant according to cross validation. Table 1 shows the results of Model 2 for CS and DT separately. The addition of the granulation properties requires one extra factor in the model. This factor is dominated by the flow times and poured and tapped volumes. Long flow times and low volumes give higher crushing strengths and disintegration times. The addition of the physical granule properties improves the modelling of the tablet properties CS and DT. The percentage explained variance increased from 89 to 95 for CS and from 85 to 92 for DT. Both RMSE and RMPRESS values decreased. The ejection force model was not improved by the addition of the granule properties. Figure 4 shows the observed CS and DT and the leave one out predictions by Model 1 and Model 2. The values predicted with Model 2 (closed circles) are closer to the observed ones than the predictions of Model 1 (open circles).

The physical properties of the granulations are also subject to the variation introduced by the composition variables and the process variables for the first granulation step. 60% of the variance in the granule properties could be explained by these design variables. The other 40% is, besides reproduction error, introduced by uncontrolled external sources and other unknown features. This causes the spread in granule properties when the settings of the process variables were kept the same. The extra variation in the granules, which is not introduced by the experimental design, is used to explain the variation in CS and DT that cannot be described by the variables in the experimental design.

The prediction of the physical properties of the tablets from Model 2 may differ from the ones of Model 1. Therefore, adjustment of the settings of the process variables for the second step may be necessary. This in-process control can lead to production of tablets that better meet the specified properties. A control scheme has been introduced to study the effect of the process variables of the second step on the compression of the granulations. Figure 5 shows the control scheme for two different granulations. For the granulations of experiment 5 and 7 (Tables 4 and 5 of Chapter 5), the ejection force, crushing strength and disintegration time are given in a contour plot respectively. CS and DT are predicted with Model 2 and EF is predicted with Model 1. In the control scheme, the compression force is varied from 10 to 30 kN and the moisture content in the granules is varied from 3 to 5%. The moisture content of the granulation is considered to be a process variable because it is set and rechecked to the predefined level by extra drying or humidising. For all

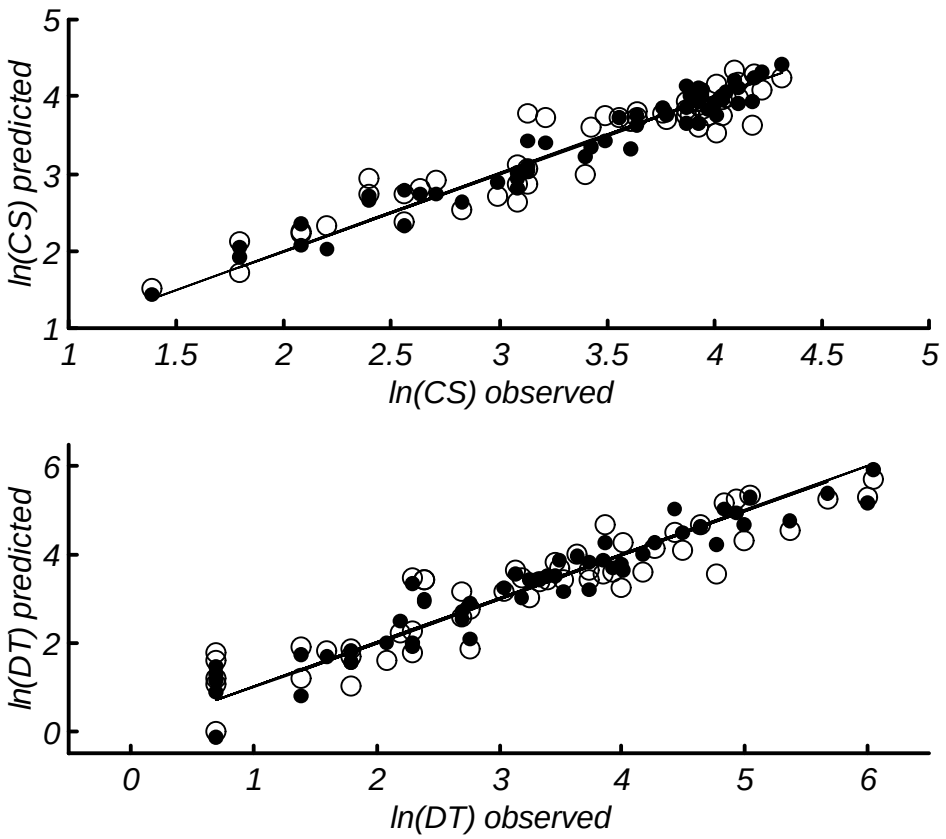

Figure 4: Leave one out predictions of the crushing strength (CS) and disintegration time (DT) with Model 1 (○) and Model 2 (●).

combinations of the compression force and moisture content, combined with the fixed settings the process variables of step 1, the composition variables of the mixture and the measured granulation properties, predictions of the tablet properties are given.

The predicted ejection force is shown with the small dots. It increases from left to right, when the compression force increases, and the ejection force decreases when more moisture is present in the granulations. The crushing strength and disintegration time increase when both process variables are increased. With the control scheme a specific setting of the process variables can be selected to obtain tablets with specific characteristics. Experiments 5 and 7 are both centre points of the experimental design. The settings of the composition variables and PV1 are equal. The difference between the plots is due to the difference in granule properties. The granule properties only affect CS and DT. Experiment 7 has higher predicted CS and DT for the same settings of the compression force and moisture content in the granulation. Experiment 7 has a lower median granule size, higher poured and tapped volumes and it has shorter flow times through the funnels. The combinations of these effects cause CS and DT of tablets from experiment 7 to be

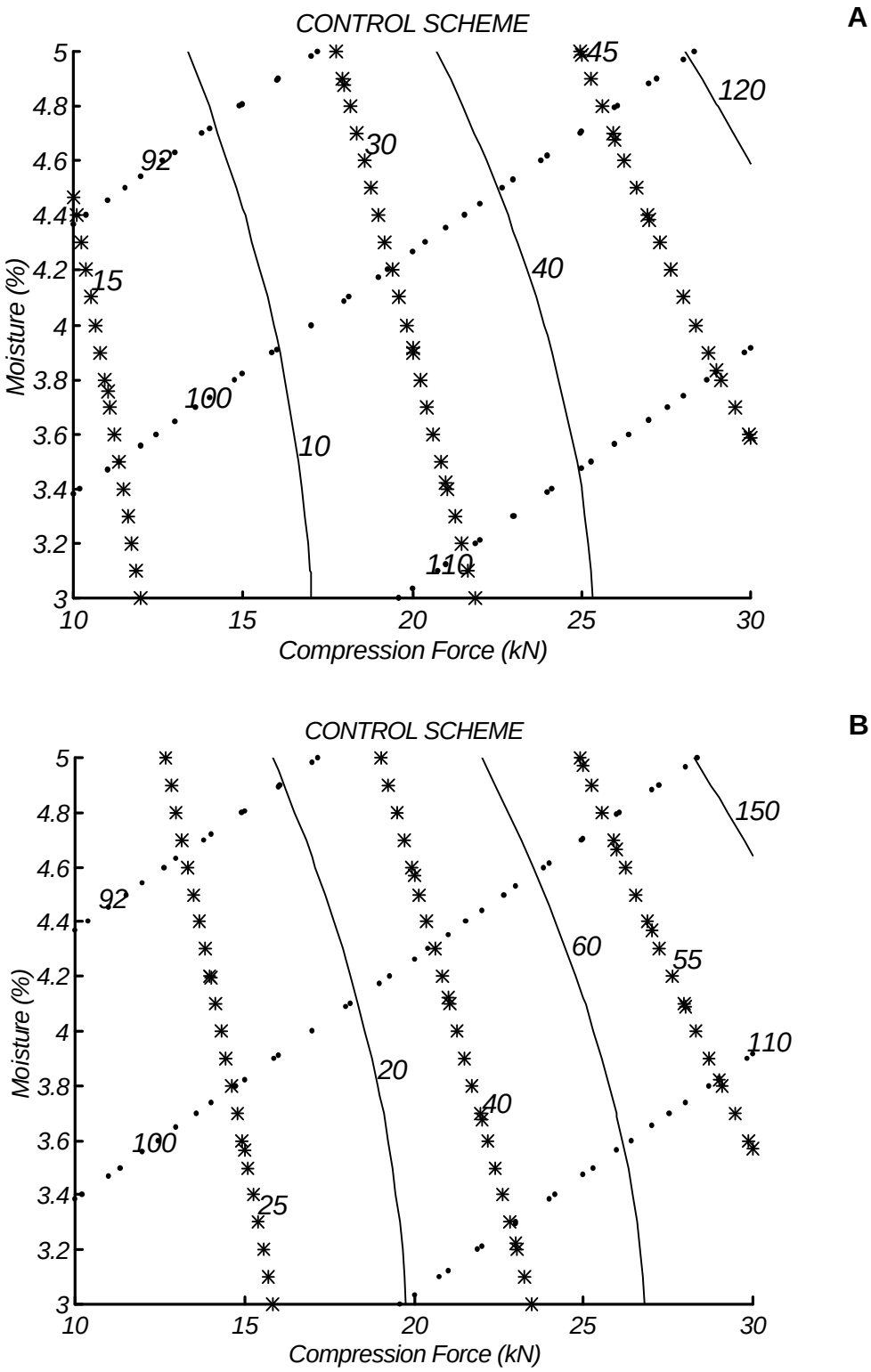

Figure 5: Control scheme for granulation 5(A) and 7(B). A) Predictions for the ejection force(●, 92, 100, 110 N), crushing strength(✳, 15, 30, 45 N) and the disintegration time(—, 10, 40, 120 sec) are given for different setting of compression force (kN) and moisture in the granulation (%). B) Predictions for the injection force(●, 92, 100, 110 N), crushing strength(✳, 25, 40, 55 N) and the disintegration time(—, 25, 60, 150 sec) are given.

higher than the tablets of experiment 5.

For the production of tablets with specific properties, Model 1 is used to define settings of the composition and of the process variables of both steps. When the first granulation step has been carried out and the granule properties have been measured, the control scheme can be used to adjust the settings of the step two process variables.

Conclusion

For modelling of the two-step tablet manufacturing process, two models are used. The first model relates the crushing strength, disintegration time and ejection force to the composition variables and process variables of both steps. In the second model the physical properties of the intermediate granules, are included. The first model can be used at the start of the process to find settings for the process variables and the composition of the tablet mixture that produce tablets with specific properties. Model 2 has to be used, in everyday production, for each new granulation batch. The granule properties may differ from batch to batch due to uncontrolled sources such as air humidity, temperature or other unknown features. With Model 2 these differences are taken into account, and the crushing strength and disintegration time are predicted better than with Model 1. Model 2 offers the possibility to use a control scheme for each new batch of granulation, to adjust the process variables for the tableting step, moisture in the granulation and compression force, to produce tablets with specified properties. Because of this adjustment, in-process control is possible and tablets can be produced that better meet the specifications. The control scheme gives predictions for all tablet properties at various settings of the process variables for the second tableting step for a specific granulation.

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Chapter 7

Multivariate modelling of the pharmaceutical two-step process of wet granulation and tableting with multiblock partial least squares

In Chapter 6, the pharmaceutical process of wet granulation and tableting was described as a two-step process. Besides the process variables of both steps and the composition variables of the powder mixture, the physical properties of the intermediate granules were also used to model the crushing strength and disintegration time of pharmaceutical tablets. In the present chapter, multiblock partial least squares regression (MBPLS) is used to model the two-step process. With MBPLS the highly collinear granulation properties can be segregated from the process and composition variables to study separately the influence of both groups of descriptor variables on the tablet properties. This improves the interpretability of a PLS model. The multiblock PLS model will be described after an introduction of the ordinary two-block PLS. Two different approaches of the MBPLS algorithm are compared for the modelling of the two-step process. One approach suffers severely from correlation between the two descriptor blocks, but when the correlation is removed the approach improves.

Introduction

Chapter 6 described the pharmaceutical two-step process of granulation and tableting with two models. The first model only uses the composition variables of the mixture and the process variables of both steps to describe the variation in the crushing strength, disintegration time and ejection force of tablets. In the second model, the physical granule properties are added to the first model to improve the predictive properties and to use a control scheme for the second step of the process.

Chapter 7 is a modified version of:
Westerhuis JA and Coenegracht PMJ, *J. Chemometrics*, in press.

In the present chapter a multiblock partial least squares method is used for the second model. Instead of combining the variables into a large descriptor block, the variables are segregated into two blocks to study separately the influence of different parts of the process. After an introduction of the ordinary PLS method and the multiblock PLS method, the modelling of the granulation and tableting process with MBPLS will be shown.

Partial least squares regression

Partial least squares (PLS) is the name for a class of methods, used for relating blocks of independent and dependent variables measured on a system. The pioneering work of PLS was largely done by H. Wold. PLS was introduced mainly as a path modelling device [1]. It produced latent variables that contained the essentials of the original data and could be used in a simplified path model (PLS is also called 'Projections to Latent Structures'). The next quotation of H. Wold gives a good idea about the nature of PLS models: '*The model is designed in terms of blocks of directly observed variables; each block is approximately represented by a latent (indirectly observed) variable; The path of inner relations between the latent variables are the causal-predictive core of the model*'[2].

PLS is a method for biased regression, introduced in chemistry in the late 1970s. Multivariate instrumental methods as spectroscopy and chromatography were producing large numbers of related variables for only few objects that could not be handled by the ordinary least squares regression methods. Therefore, new calibration techniques were needed. Since then, many publications have shown the use of PLS not only in chemistry but also in pharmaceutic fields [3-5]. Frank and Friedman compared the PLS method with other biased regression techniques and studied the statistical properties of the regression method [6].

Partial least squares regression minimizes the sum of squared residuals between the response **y** and a model of **y** based on the descriptor variables **X**. The model of **y** is based on latent variables which are linear combinations of the variables in **X**. PLS can handle several responses at once, but often only one response variable is used

1: centre and scale **X** and **y**
2: **w** = **X'y**
3: scale **w** to ||**w**||=1
4: **t** = **Xw**
5: c = **y't/t't**
6: **p** = **X't/t't**
7: **X** = **X**-**tp**'
8: **y** = **y**-**t**c

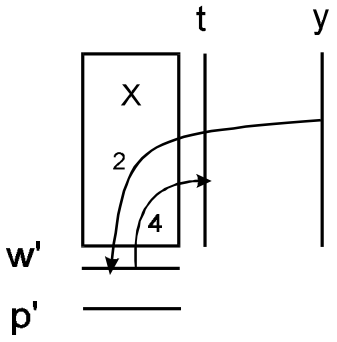


Figure 1: Algorithm and arrow scheme of the PLS1 method.

(PLS1). Several slightly different algorithms have been introduced during the last 20 years [7-11].

Figure 1 shows an arrow scheme for the algorithm. A model is estimated between the response **y** (*I**1) and the descriptors **X** (*I***J*). It is assumed that **y** and **X** are mean-centered and scaled. The **X**-variables can be weighted if additional information is known about the variables. PLS suggests to find a set of orthogonal latent score vectors **t** in the column space of **X** which is well suited to describe the response vector **y**. Any vector **t** in the column space of **X** can be written as **t**=**Xw** (**t**=$w_1\mathbf{x}_1$ + $w_2\mathbf{x}_2$ + ... + $w_J\mathbf{x}_J$). In PLS the **w** vector is chosen to be **w**=**X**'**y**, to maximise the covariance between **t** and **y**. In step 5, **y** is regressed on the vector **t** in a least squares sense, with c being the regression coefficient. Step 6 is to ensure that the score vectors **t** are mutual orthogonal, **p** being the loading of **X**. In step 7 and 8 residuals of **X** and **y** are calculated, and another score **t** can be determined by repeating step 2 to 8 of the algorithm. This can be continued until the prediction properties of the model become worse, which can be tested with a separate test set or by cross validation. The score and the loading vector together give an approximation of **X**. With each additional **t** and **p** vector, the approximation of **X** improves. When *K* is the number of PLS factors,

$$\hat{X} = \sum_{k=1}^{K} t_k * p_k'$$

For prediction of the response **y** for new objects, the **X** variables must be known and scaled just as the calibration **X** matrix was scaled. The **w**, c and **p** vectors from the model are used for prediction.

1: $\hat{\mathbf{y}}=0$;
2: for k=1 to K:
3: $t_k=\mathbf{x}_{new}\mathbf{w}_k/\mathbf{w}_k'\mathbf{w}_k$
4: $\hat{\mathbf{y}}=\hat{\mathbf{y}}+t_kc_k$
5: $\mathbf{x}_{new}=\mathbf{x}_{new}-t_k\mathbf{p}_k'$
6: end

The predicted value for $\hat{\mathbf{y}}$ is build up in a number of steps according to the number of scores in the model. The successive parts of $\hat{\mathbf{y}}$ (t_kc_k) are estimated independent from each other. This is possible because of the mutual orthogonality of the **t** scores.

The optimal number of scores that must be used for a model with minimal prediction error is determined with cross validation (CV). In CV, one observation is left out and predicted by the model constructed with all other observations. This is repeated until all observations have been left out once. The model with the lowest prediction error sum of squares (PRESS) is preferred.

$$PRESS = \sum_{i=1}^{I} (y_i - \hat{y}_{/i})^2$$

where $\mathbf{y}_i$ = the response value for object *i* and $\hat{\mathbf{y}}_i$ is the predicted response value for object *i*, predicted with a model made without object *i*. When the model has been estimated, we want to know how good it is. The fit of the model is usually measured by R^2. The R^2 value represents the proportion of variation in the response data that is explained by the model.

$$R^2 = \frac{\sum (y_i - \bar{y})^2 - \sum (y_i - \hat{y}_i)^2}{\sum (y_i - \bar{y})^2}$$

The R^2 criterion can vary form 0 to 1; the closer R^2 is to 1, the better the fit of the model. R^2 measures how well the model describes the variation in the response, it is also the squared correlation between $\hat{\mathbf{y}}$ and **y**. For the predictive properties of the model, Q^2 can be used. Q^2 is the squared correlation between the cross validated predictions ($\hat{\mathbf{y}}_{/i}$) and **y**. The model with lowest PRESS value will have the highest Q^2.

$$Q^2 = \frac{\sum (y_i - \bar{y})^2 - \sum (y_i - \hat{y}_{/i})^2}{\sum (y_i - \bar{y})^2}$$

For the interpretation of the model, regression coefficients $\mathbf{b}_{PLS}$ for each descriptor variable can be calculated:

$$b_{PLS} = \sum_{k=1}^{K} w_k * (w_k * p_k)^{-1} * c_k$$

The regression coefficients can be used to study the influence of the various variables.

Multiblock partial least squares regression

For the modelling of the two-step granulation process, a multiblock partial least squares (MBPLS) method is used. MBPLS is an extension of the PLS method. The ordinary two-block PLS method has been used intensively in chemometrics during the last decade. This method combines all the descriptor variables into one block that is used to fit the response data in the second block. Geladi [12] mentioned that for prediction purposes it is best to put all the variables in one block. However, to

improve the interpretation of the model, the variables can better be separated into meaningful blocks of variables as in MBPLS.

In the early days, PLS has been developed as a least squares path modelling technique to deal with several blocks of data [1]. Only few cases are known where PLS is used with more than two blocks [13-20]. However, the descriptor variables can often be divided into several blocks according to the nature of the data. In quantitative structure-activity relationships (QSARs) the steric and electronic descriptors of the molecules can be subdivided into two blocks. In comparative molecular field analysis (CoMFA) several probes are used at every grid point to give extra information about the molecules. The gridpoints of each probe can be divided into separate blocks. In continuous processes measurements are made at various points of the process and in different compartments of the reactors. In batch processes the starting material and the intermediates both give information about the end product. The information from these different sources has to be combined to improve fit of the model and predictions for the chemical systems.

Blocking of variables gives a better reflection of the process in the PLS method. MacGregor *et al.* showed the division of the descriptor variables of a low density polyethylene process in two blocks according to different parts of the process [18]. Because of this blocking approach, disturbances in the process can be detected earlier and it can be shown in which part of the process the disturbance occurs. Wold *et al.* showed the blocking of both predictor variables and response variables of a catalytic cracking process [20]. For interpretation purposes one can look at the overall information concerning all data at once, but it is also possible to zoom into a specific block to learn more of local phenomena.

Just as in Chapter 6, the present chapter combines the granulation properties with the process and composition variables to model the crushing strength and the disintegration time of pharmaceutical tablets. The MBPLS technique is used to segregate the highly collinear granule properties from process and composition variables to study separately the influence of both groups of descriptor variables on the tablet properties. Two different MBPLS approaches will be compared for their use in the modelling of a two-step process.

Theory

In the model, the total variation that influences the physical properties of the tablets is divided into two blocks. The process variables of both steps (PV1 and PV2) and the composition of the powder mixture are put in block **D**. The physical properties of the granulations are put in a second block **G**. The different sources of variation are used in two different blocks in the MBPLS method to improve the interpretation of the regression model. This specific separation of variables was chosen because then the effect of the granulation properties on the tablet properties can be studied

separately. The variables in block **D** are varied according to a Box-Behnken design, and are nearly orthogonal. The granulation properties are highly collinear. The process variables of the second step could also have been placed in a separate block, but for simplicity all process and composition variables were left in one block.

Multiblock PLS can be used for any number of blocks with any kind of relations between the blocks. Wangen and Kowalski presented a general algorithm that can be used in all possible cases. The model used in this article has been used by Wangen [17, (simulated test problem A)] and MacGregor *et al.* [18], *i.e.* two descriptor blocks **D** and **G** are used to model only one response block **Y**. Each block has the same number of observations (rows), but the number of variables (columns) may vary freely. Figure 2 shows an arrow scheme of the algorithm used.

The MBPLS algorithm:

1: take **u** = some column of **Y**
2: $\mathbf{w}_D$=**D'u**; $\mathbf{w}_G$=**G'u**
3: normalise $||\mathbf{w}_D||$ and $||\mathbf{w}_G||$ to 1
4: $\mathbf{t}_D$ =**D**$\mathbf{w}_D$; $\mathbf{t}_G$ =**G**$\mathbf{w}_G$
5: Combine $\mathbf{t}_D$ and $\mathbf{t}_G$ into block **T**
6: $\mathbf{w}_T$ = **T'u**
7: normalise $||\mathbf{w}_T||$ to 1
8: $\mathbf{t}_T$ = **T**$\mathbf{w}_T$
9: **c** = **Y'**$\mathbf{t}_T$/$\mathbf{t}_T$'$\mathbf{t}_T$
10: **u** = **Yc**/**c'c**

return to 2 until convergence of **u**

First some column of **Y** is selected as the response score vector **u**. This can be the column with the highest variance. When only one response variable is modelled, **u** equals **Y** and steps 9 and 10 are not used because **u** converges in the first cycle. For both blocks **D** and **G**, block scores $\mathbf{t}_D$ and $\mathbf{t}_G$ are calculated, which are linear combinations of the variables in the blocks with the highest covariance to **u**. The block weights $\mathbf{w}_D$ and $\mathbf{w}_G$ are the covariance vectors of the variables in **D** and **G** respectively and the **u** score. In step 5 $\mathbf{t}_D$ and $\mathbf{t}_G$ are combined in the super block **T**. Then **T** and the response **Y** are used in a two-block PLS step (6–10). The super weight $\mathbf{w}_T$ shows how much each block score participates in the super score $\mathbf{t}_T$. After convergence of **u**, loadings $\mathbf{p}_D$ and $\mathbf{p}_G$ can be calculated.
The residual of **Y** is calculated as:

11: **b** = **u'**$\mathbf{t}_T$/$\mathbf{t}_T$'$\mathbf{t}_T$; (**b** is the regression coefficient of the relation between $\mathbf{t}_T$ and **u**)
12: **Y** = **Y**-**b**$\mathbf{t}_T$**c'**;

Two different approaches have been used for the calculation of the residuals in **D** and **G**. The first approach, used by MacGregor *et al.* [18] and Wangen and Kowalski

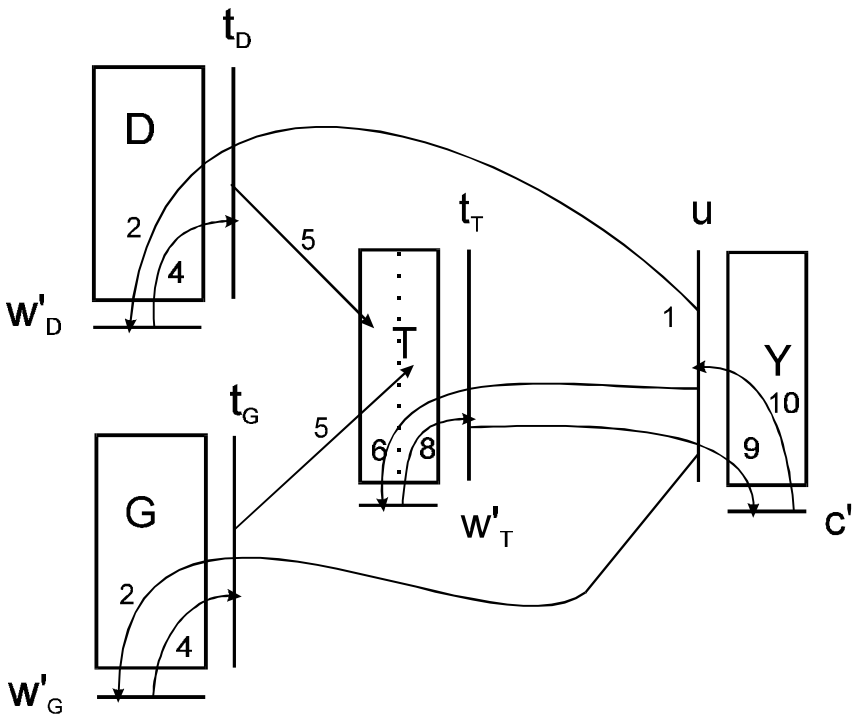


Figure 2: Arrow scheme of the MBPLS algorithm. See text for explanation.

[17], uses the block scores, $\mathbf{t}_D$ and $\mathbf{t}_G$, for the calculation of the loadings and residuals, and is in this paper referred to as the block score update method, or method *a*.

13a: $\mathbf{p}_D = \mathbf{D}'\mathbf{t}_D/\mathbf{t}_D'\mathbf{t}_D$; $\mathbf{p}_G = \mathbf{G}'\mathbf{t}_G/\mathbf{t}_G'\mathbf{t}_G$;
14a: $\mathbf{D} = \mathbf{D} - \mathbf{t}_D\mathbf{p}_D'$; $\mathbf{G} = \mathbf{G} - \mathbf{t}_G\mathbf{p}_G'$;

The block score update method *a* produces orthogonal block scores, but the $\mathbf{t}_T$ super scores are not orthogonal. One can also choose to obtain orthogonal super scores. Frank and Kowalski used this second method *b* to calculate residuals in their averaging algorithm [16]. This method is referred to as the super score update method or method *b*.

13b: $\mathbf{p}_{DT} = \mathbf{D}'\mathbf{t}_T/\mathbf{t}_T'\mathbf{t}_T$; $\mathbf{p}_{GT} = \mathbf{G}'\mathbf{t}_T/\mathbf{t}_T'\mathbf{t}_T$;
14b: $\mathbf{D} = \mathbf{D} - \mathbf{t}_T\mathbf{p}_{DT}'$; $\mathbf{G} = \mathbf{G} - \mathbf{t}_T\mathbf{p}_{GT}'$;

The residuals can be used to calculate the next factor, starting again at step 1. The block score update method *a* of Wangen and MacGregor produces correlated super scores which are used for the modelling and update of the response **Y**. The whole $\mathbf{t}_D$ direction is removed from **D**, but only $\mathbf{w}_{T(D)}*\mathbf{t}_T$ is used for the modelling of **u**, with $\mathbf{w}_{T(D)}$

being the super weight belonging to block score $\mathbf{t}_D$. Although $(1-\mathbf{w}_{T(D)})*\mathbf{t}_T$ is not used for modelling, it is nevertheless removed from block **D**. The explained amount of variance is therefore less than when the two blocks **D** and **G** were combined into one large descriptor block. The explained variance of the descriptor blocks becomes higher, which seems to give a more stable model. According to MacGregor *et al*. the loss of prediction power is only small if the blocks are hardly correlated. However, when a strong relation exists between the predictor blocks, the prediction can be worse. The super score update method *b* gives orthogonal $\mathbf{t}_T$ super scores, but the block scores are mutually correlated. This update method produces exactly the same results as the two-block PLS method when the variables are not blocked but are combined in one large **X**-block. The difference in explained variance of the blocks and the response between the two update methods appears after the first factor. The block and super scores of the first factor are the same for the two methods. The difference is introduced after subtraction of the first factor, because different **t**-scores are used in the update of the blocks.

For the prediction of new response values, the new values for all descriptor blocks **D** and **G** must be scaled and weighted in the same manner as the data used for calibration.

15: $\mathbf{t}_{D\,new} = \mathbf{D}_{new}\mathbf{w}_D$; $\mathbf{t}_{G\,new} = \mathbf{G}_{new}\mathbf{w}_G$
16: $\mathbf{t}_{T\,new} = \mathbf{w}_{T(D)}\mathbf{t}_{D\,new} + \mathbf{w}_{T(G)}\mathbf{t}_{G\,new}$
17: $\mathbf{u}_{new} = \mathbf{b}\mathbf{t}_{T\,new}$
18: $\mathbf{y}_{new} = \sum\mathbf{u}_{new}\mathbf{c}$

For each descriptor block, block scores are calculated. The super score $\mathbf{t}_T$ is a linear combination of all block scores. Finally a new **u** score is calculated, which gives the response value for properties of the new tablets. For the calculation of the residuals from the new data, the same update method as in the calibration must be used. For the block score update method *a* this is:

19a: $\mathbf{D}_{new} = \mathbf{D}_{new} - \mathbf{t}_D\mathbf{p}_D'$; $\mathbf{G}_{new} = \mathbf{G}_{new} - \mathbf{t}_G\mathbf{p}_G'$

and for the super score update method *b*:

19b: $\mathbf{D}_{new} = \mathbf{D}_{new} - \mathbf{t}_T\mathbf{p}_{DT}'$; $\mathbf{G}_{new} = \mathbf{G}_{new} - \mathbf{t}_T\mathbf{p}_{GT}'$

For a comparison with the PLS method, the block loadings are scaled to equal the loadings of the PLS method, when all blocks would have been combined into one large descriptor block. This causes the $\mathbf{t}_T$ super scores to be equal to the PLS score **t**. The block weights $\mathbf{w}_D$ and $\mathbf{w}_G$ times their corresponding super weight $\mathbf{w}_{T(D)}$ and $\mathbf{w}_{T(G)}$ equal the PLS weight **w**.

Weighting of blocks

Variable weighting can be important in all methods where least squares fitting is used to concentrate the information of many variables into a lower number of phenomena. Blocking of variables can lead to large differences between block sizes. When autoscaling of all blocks is used on all variables, the variance in each block equals the number of variables in the block. Therefore, larger blocks have larger weights. The information of a small block will be overwhelmed by that of the large blocks. One may choose to give each block the same weight. Then the weighting of a block is made dependent on the number of variables in the block. Weighting can also be made dependent on the rank of a block. E.g. when a block consists of spectra, the number of latent directions is important for the scaling, not the resolution used to measure the spectra.

Diagnostics

Just as in two-block PLS, plots of scores and loadings can be examined to learn from the process. The super level scores $\mathbf{t}_T$ and weights $\mathbf{w}_T$ give information about the whole descriptor data set. The plot of the super score $\mathbf{t}_T$ vs **u** shows the fit of the data set with all descriptors of all blocks considered to **Y**. Super weights $\mathbf{w}_T$ show the relative position of the several blocks. The block scores give information of the descriptor blocks only, $\mathbf{t}_D$ vs **u** shows the fit of the model to **Y** when only the descriptors of block **D** are considered. A score plot of the block scores $\mathbf{t}_G(1)$ vs $\mathbf{t}_G(2)$ shows for the variables in block **G** if there are outlying objects or groups in the data. Block loadings can be evaluated as well. The percentage of explained variance for each block shows how much the blocks participate in the final model. Just as in ordinary PLS, regression coefficients can be calculated for the variables.

$$b_{MB} = \sum_{k=1}^{K} w_{MB\,k} * (p_{MB\,k} * w_{MB\,k})^{-1} * b_{kk}$$

with: $\mathbf{w}_{MB\,k} = [\mathbf{w}_{D\,k} * \mathbf{w}_{T(D),k}, \mathbf{w}_{G\,k} * \mathbf{w}_{T(G),k}]$, $\mathbf{p}'_{MB} = [\mathbf{p}'_D, \mathbf{p}'_G]$

Experimental

The experimental details of the granulation and tableting experiments were shown in Chapters 5 and 6. Both approaches of the multiblock partial least squares method were programmed in MATLAB [21]. The super score update method was compared with the PLS function of the PLS Toolbox [22].

Results and discussion

Tablets were compressed from the granules with varying compression force. The crushing strength (CS) and disintegration time (DT) of the tablets were logarithmically transformed because of the funnel shaped heteroscedastic variance structure. Previous calculations showed that quadratic terms of the process and composition variables were important to describe both tablet responses, so they were included in the model. Both blocks of variables are necessary for the prediction. Block **D** describes 89% and 85% of the variance in CS and DT respectively, and block **G** describes only 53% and 20% of the responses. Block **G** together with the process variables of step two describe 79% and 83% for CS and DT respectively. All blocks together explain 95% and 92% of the crushing strength and the disintegration time.

The design and granule variables were divided into two blocks. The six design variables and their quadratic terms were placed in block **D** and fourteen granule properties in block **G**. The blocks were given equal weights, i.e. after autoscaling they were divided by the number of columns in the blocks. Four PLS factors were found significant according to cross validation for the super score update method *b*, where the block score update method *a* only needs three factors. Table 1 shows the results for both tablet response variables separately with both update methods. The explained variances are given for both blocks **D** and **G** for CS and DT of the tablets.

Table 1 shows that the block score update method *a* needs less latent variables to reach the minimal PRESS value, but the PRESS values are higher than with the super score method *b*. The amount of variance explained in the descriptor blocks cannot be compared because of the different number of PLS factors (f1-f4) used in the model. The super block weights $\mathbf{w}_T$ for both blocks are given in Table 2 for both update methods. Both methods have the same weight ($\mathbf{w}_T$) for the first factor. The block score update method *a* subtracts important information from the **G** block. In the next factors, **G** is hardly used by the block score method. In the super score update method, more of block **G** is used which leads to better prediction of the response. An extra factor is needed for this information.

The performance of the block score and super score update methods was also

Table 1: Percentage of explained variance for the descriptor blocks **D** and **G** and the response variable **y** for the block and super score update method for the crushing strength (CS) and disintegration time (DT). PRESS values are also given.

Method	# factors	Response	%**D**	%**G**	%**y**	PRESS
Block	3	CS	37	83	91	4.4
	3	DT	38	80	83	24
Super	4	CS	42	72	95	2.8
	4	DT	39	80	92	16

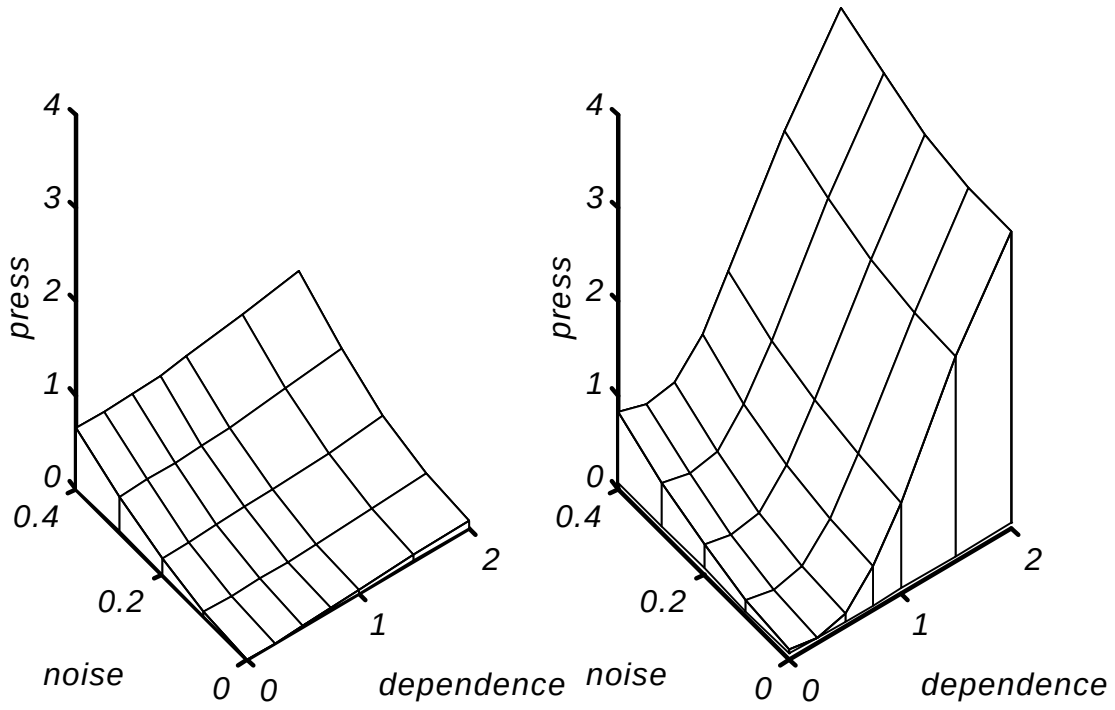
Table 2: The super score weights $\mathbf{w}_T$ of the first four PLS factors (f1-f4) given for each block **D** and **G** for both the disintegration time (DT) and crushing strength (CS) for the block score and super score update method.

Method	Response	Block	f1	f2	f3	f4
Block	DT	**D**	0.78	0.98	0.91	
		G	0.62	0.19	0.41	
	CS	**D**	0.74	0.92	0.89	
		G	0.68	0.38	0.45	
Super	DT	**D**	0.78	0.85	0.55	0.72
		G	0.62	0.52	0.84	0.69
	CS	**D**	0.74	0.85	0.46	0.93
		G	0.68	0.53	0.89	0.35

studied in a small simulation test. Two **X**-blocks (40*10) were created, with three and two different underlying latent variables respectively ($\mathbf{t}_0$, $\mathbf{t}_1$, $\mathbf{t}_2$ for $\mathbf{X}_1$ and $\mathbf{t}_3$, $\mathbf{t}_4$ for $\mathbf{X}_2$). All five latent variables were necessary to fit the single response variable ($\mathbf{y}=\mathbf{t}_0+\mathbf{t}_1+\mathbf{t}_2+\mathbf{t}_3+\mathbf{t}_4$). During the test the correlation between both **X**-blocks was increased by adding a certain amount of $\mathbf{t}_1$ and $\mathbf{t}_2$ to $\mathbf{t}_3$ and $\mathbf{t}_4$ respectively. This amount was varied from 0 to 2 times $\mathbf{t}_1$ and $\mathbf{t}_2$. This causes not only an increase in correlation but also dominance over the latent variables of block $\mathbf{X}_2$ by the latent variables of block $\mathbf{X}_1$. The noise level on both **X**-blocks and the response was simultaneously increased from 0 to 40%. Figure 3 shows the mean of the minimal PRESS values of 20 data sets for the super score update method (Figure 3A) and for the block score update method (Figure 3B). The increasing correlation of both **X**-blocks hardly affects the performance of the super score update method when only a limited amount of noise is added. The block score update method is severely influenced by an increased correlation of both **X**-blocks, even without any noise added. For a dependence above 0.5, the PRESS values increase rapidly.

The advantage of the multiblock approach becomes clear when the score plots of the various blocks are examined. The super score method is used. Figures 4 and 5 show the score plots of the first two scores of block **D** and **G** respectively for the disintegration time of the tablets. Here only the influence of the specific block is shown. Figure 6 shows the score plot of the PLS model when no blocking was used (i.e. block **D** and **G** are combined into one large descriptor block).

First the centre points of the experimental design are observed. There is some small spread between the centre points because the amount of moisture content in the granulation was not set precisely to the specific value. Figure 6, the combined score plot, shows some spread between the centre points, indicated by ✳. This has to be caused by a large spread in granule properties because the settings of the centre points in the experimental design are almost the same. This is exactly what we see in Figures 4 and 5. Figure 4, the score plot of the design **D** shows almost no



A **B**

Figure 3: Performance of the super score update method (A) and the block score update method (B) in a simulation test. The PRESS value is shown as a function of the dependence between the blocks and the additional noise added to the descriptors and the response. The block score update method suffers from correlation between the descriptor blocks.

spread, where the score plot of block **G** of the granule properties shows a large spread in the centre points. So the variation between the centre points is caused by the variation in granule properties. This unintended variation influences the tableting process. Therefore, by including it in the model, the tablet properties can be modelled better.

Furthermore some objects (11,18,28,29,32) have been marked in all score plots. The numbers correspond to the experiment numbers given in Table 4 and 5 of Chapter 5. In Figure 6, objects 11 and 32 are obvious extreme values and object 29 also lies at the border of the plot. Experiments 18 and 28 are not at the border. The plot gives no information why these experiments lie at the border of the plot. Looking at the **D** score plot, Figure 4, we see that objects 11, 28 and 29 lie at the outside. Their extreme values are caused by some event in the experimental design. If we look at the data, we see that for objects 28 and 29 the percentages of moisture in the granules was set at a too high level. The position of object 11 is merely caused by

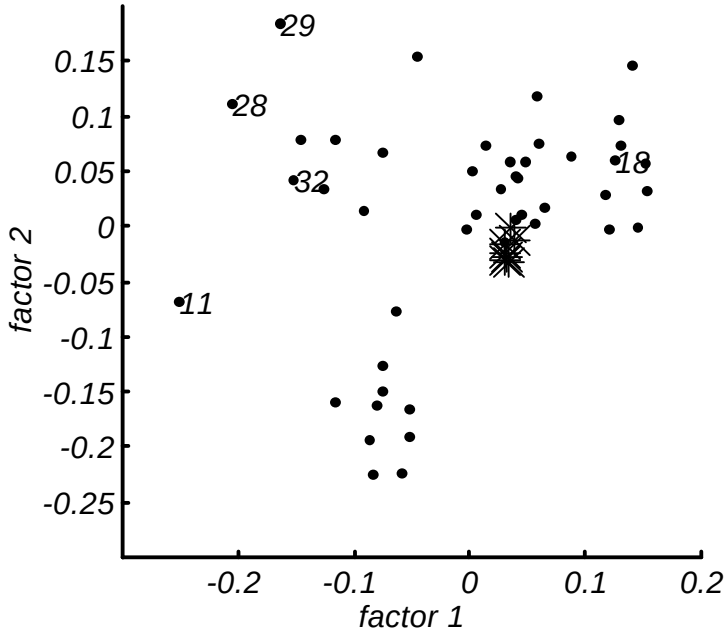


Figure 4: Score plot of block **D** from the MBPLS model for the disintegration time. Stars represent the centrepoints, the dots are the other experiments. The numbered objects are explained in the text.

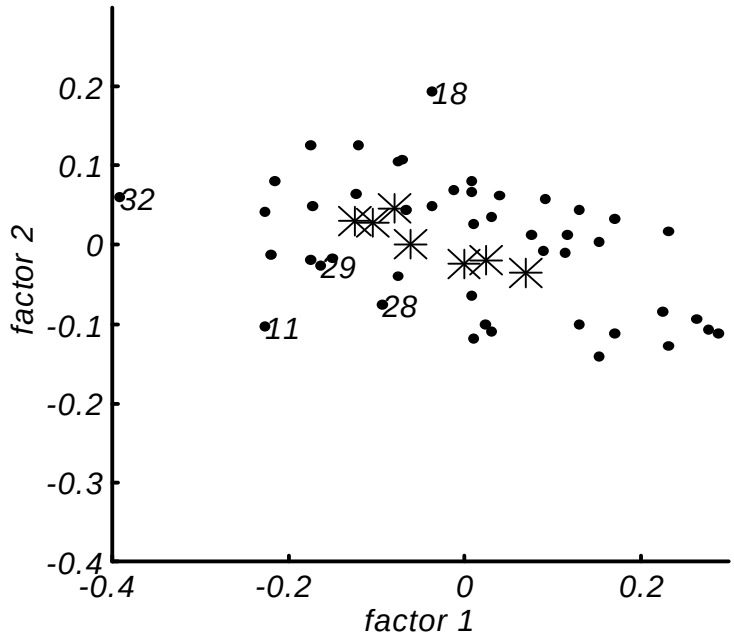


Figure 5: Score plot of block **G** from the MBPLS model for the disintegration time. Stars represent the centrepoints, the dots are the other experiments. The numbered objects are explained in the text.

an extreme low response value for the disintegration time (2 sec.). Score plot **G** shows that objects 18, 32 and 11 are at the outside of the plot. These are caused by a very low particle size for object 18 and a high flowability for object 32. The block **D**

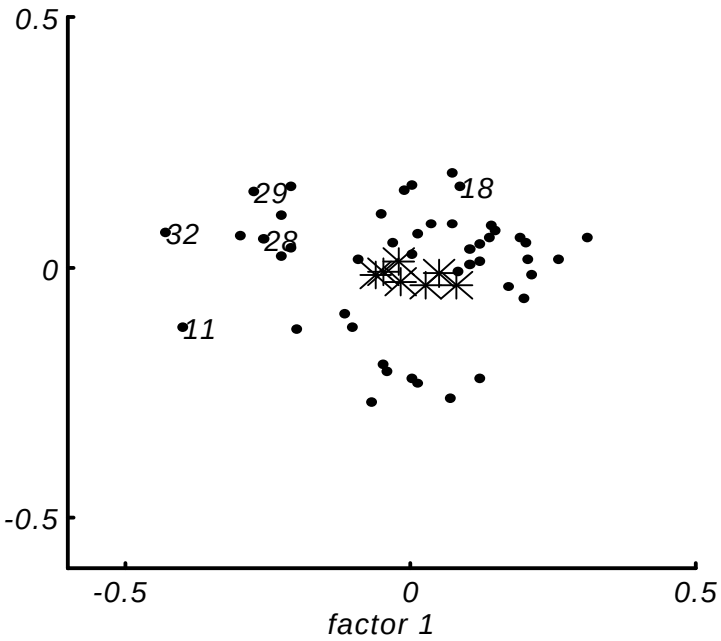


Figure 6: Score plot of the PLS model where block **D** and **G** are combined into one large descriptor block for the disintegration time. Stars represent the centrepoints, the dots are the other experiments. The numbered objects are explained in the text.

score plot shows three groups of objects with the centre points almost in the middle of the groups. The lowest group consists of experiments with high compression force and a low or mean amount of MCC. The group at the left side of the plot consists of experiments with high levels of MCC. These groups cannot be noticed in the **G** score plot. So, by dividing the descriptor data in several meaningful blocks, extra information can be obtained from specific parts of the process.

The blocking of the process variables could have been extended by also splitting up the process variables according to the step of the process. This could have given extra insight in the effect of the compression force and the moisture content in the granulations on the tablet properties, but the prediction of these responses would not have been improved.

Loading plots can become very messy when the number of variables increases rapidly.The block loading plots only show the loadings of the variables in the specific block. The contribution of important variables in blocks of minor importance would be missed in the large bulk of variables, but can be studied when blocking is used. In this study with only few variables, no loading plots were shown. The loadings were scaled to be equal to PLS loadings, so the MBPLS approach used here, gives no extra information on the loadings of the blocks compared with the ordinary PLS method.

In a two-step process such as the tablet manufacturing process with a granulation

Table 3: PRESS values for the disintegration time (DT) and crushing strength (CS) and for the block and super score update method when redundant information in **G** is removed. **G1**-**G4** present the PRESS values after removal of the predicted **G** with 1-4 PLS factors respectivily.

		G (0%)	**G**1 (17%)	**G**2 (39%)	**G**3 (52%)	**G**4 (58%)
Block	CS	4.4	4.0	2.8	2.5	2.5
	DT	24	30	19	17	17
Super	CS	2.8	2.6	2.7	2.6	2.7
	DT	16	16	17	18	19

step, correlation exists between the two blocks because the second block is influenced by the first. Some variation in the second block is redundant. When this redundant variance is removed from the second block, the correlation between both blocks diminishes and the block score update method *a* performs better.

For the removal of the redundant variance in the granule block, a PLS model between the granulation block and the process variables of the first step and the composition variables is developed. The part of the variance in **G** that can be explained by the model is subtracted from the **G** block in four steps. The residuals of the granule matrix, **G1** to **G4**, will be used in the multiblock PLS method. The **G**-block residual was not autoscaled because this would increase the noise in the block but the means of all variables were zero. Because most of the correlation between the two blocks is removed, the block score update method to calculate residuals can be used as well. Table 3 shows the PRESS values for the models with the redundant information removed from block **G** in steps for both response variables.

In Table 3, **G1** to **G4** represent the residuals of block **G** after removal of the predicted **G** with one to four PLS factors respectively. The cumulative amount of explained variance of the PLS factors are given. The super score and the block score update methods are compared. The PRESS values for the super score update method do not change much, because only redundant information has been removed from the data. The block score update method improves when the redundant information is removed, because the correlation between both blocks diminishes. When **G4** is used in the MBPLS method with the super score update method, the block scores become somewhat more correlated (r=0.4). The **G** block score is hardly used for the super score. Only little of the **G** block score direction is therefore subtracted from the **G** block, which causes the second direction to be correlated with the first. Figure 7 shows the score plot of the **G4** block calculated with the block score update method. Observation 32 is still at the outside in the plot. This observation and also the centre points are drawn in the direction of granulations with high flowability. Observations 11 and 18 have moved to the centre of the plot. Their extreme value in the **G** score plot of Figure 5 was mainly caused by the variation in **G** that was caused by block **D**.

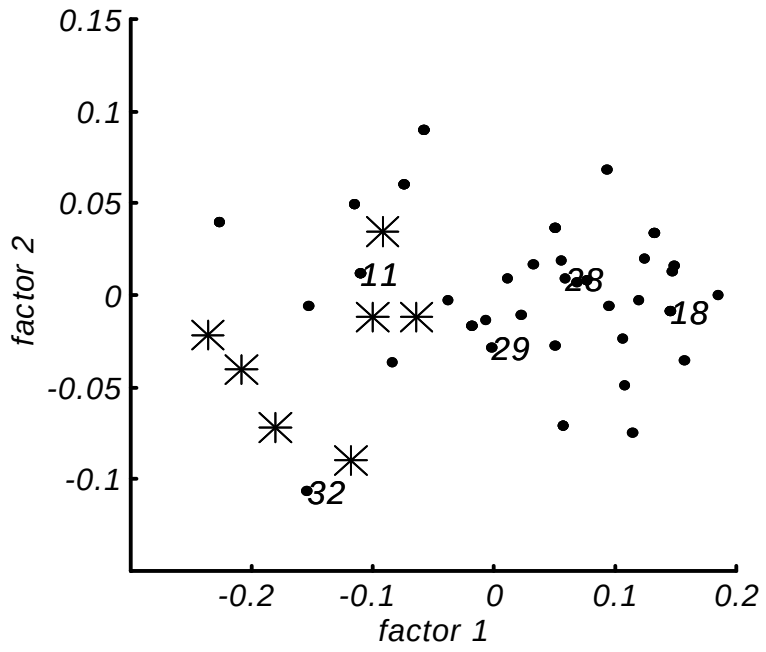


Figure 7: Score plot of block **G4** from the MBPLS model with the block score update method for the disintegration time. Stars represent the centrepoints, the dots are the other experiments. The numbered objects are explained in the text. No block weighting was used because some variance was already subtracted from block **G**.

With **G1** the PRESS value for the disintegration time increases a little, but thereafter the PRESS almost decreases to the same level as the super score method. If one wants to have orthogonal block scores, the block score update method has to be used. The correlation between both blocks has to be removed as much as possible to get good predictions by this method.

Conclusion

The prediction of the crushing strength and disintegration time of pharmaceutical tablets can be improved when physical properties of the intermediate granules are included in the model. When the highly collinear granulation properties are segregated from the process and composition variables multiblock PLS can be used. This regression method provides extra interpretation as compared to the common two-block PLS method, because one is able to see which block causes certain events in the response data. It is possible to zoom into a specific part of the process. The block score update method suffers from correlation between the descriptor blocks. However, when the redundant information is removed, the performance of the block score update method improves. The super block update method is equal to the PLS method with two blocks when all descriptor variables are put in one large **X**

block. The segregation of the variables into meaningful blocks gives extra interpretation because one can zoom into the separate blocks.

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Chapter 8

Multiblock partial least squares path modelling for multivariate processes

The process of tablet manufacturing with wet granulation has been described as a two-step process in the Chapters 6 and 7. The process variables can be divided into two groups, belonging to either step of the process. In Chapter 5 the physical granule properties were used as response variables. They were fit to the composition of the powder mixture and the process variables of the granulation step. In the Chapters 6 and 7, the granule properties were used as predictor variables to improve the modelling of the tablet properties. In the present chapter a multiblock partial least squares path model is constructed that incorporates the hierarchical structure of the process. The process variables of the wet granulation step affect both granule and tablet properties, where the process variables of the tableting step only affect the tablet properties. The same path model can be used for prediction of the tablet responses whether the granule properties are unknown (at the start of the process) or whether they have been measured (after the wet granulation step). The effect of introducing the granule properties in the model on the regression coefficients of the composition and process variables is smaller than when standard PLS or multiblock PLS models are used. The prediction of the tablet properties is comparable to the standard PLS models, but the granulation properties are predicted worse.

Introduction

Multiblock data analysis methods have their origin in path analysis and path modelling in the fields of sociology and econometrics. Path analysis was developed as a means for studying the direct and indirect effects of variables, where some variables are viewed as causes and other variables are viewed as effects. In the early days, PLS was described as a least squares path modelling technique to deal with several blocks of data [1]. Path modelling with PLS has been thoroughly described by Lohmöller [2]. The PLS model tries to incorporate the hierarchical structure of the process. In large processes a hierarchical structure exists between measurements at different parts of

the process. Intermediate materials in the middle of the process, are influenced by previous steps, and the physical properties of these intermediates also affect subsequent steps. For example, in a two-step process one can define starting materials, intermediates and the final product. At the start of the process materials are combined and several process variables are set to specific values. The intermediate, which is the product of the first step, has to meet certain specifications. Dependent on physical properties of the intermediate, one can set new process variables to specific values. The first set of process variables influences both the intermediates and the final product, whereas the second set of process variables only influences the final product.

Quality properties of the starting materials, intermediates and final products can be measured. The data sets can be placed in the hierarchical order according to the process. Between the data sets of properties the settings of the process variables, that work at a specific part of the process, can be varied to influence the product. In a two-step process, such as tablet manufacturing by wet granulation, process variables can affect either step. In the first step the starting materials are combined in the granulation bowl. The granulation time or amount of water can be varied to influence the wet granulation process. From a single tablet mixture several granulations are produced. In the second step, the different granulations can be tableted with varying compression force or compression speed. From each granulation several tablets are produced.

In monitoring the two-step wet granulation and tableting process, predictions are to be made for the granule and tablet properties at the start of the process. The influence of the composition and process variables of both steps on the properties has to be shown. When the granule properties have been obtained, they will be added to the model in order to improve the prediction of the tablet properties. In this chapter the multiblock PLS model will be extended to a path model to monitor the two-step process. The basic algorithm as presented by Wangen and Kowalski will be used to build the path model [3]. The performance and properties of the model will be investigated and compared to the standard PLS and multiblock PLS models presented in the Chapters 6 and 7.

The path model

The causal pathway of the model is assumed from left to right, where the left end blocks only predict (predictors) and the right end blocks are only predicted (predictees). Blocks in the middle of the process, interior blocks, are both predictors and predictees.

The whole process of tablet manufacturing with wet granulation is a hierarchical batch process that exists of two steps. Three blocks of physical properties can be distinguished. Figure 1 in Chapter 6 shows the three blocks in the granulation process. The left end block consist of the composition of the tablet mixture. The right end block contains the physical tablet properties and the granule properties are placed in the intermediate block. The two sets of process variables are placed at the stage where

they influence the process.

The main goal of the process is to produce tablets with specified physical properties. The granules must have specific properties necessary to perform the tableting step. The flowability and percentage of fines of the granulations have to meet certain specifications. The granule properties **G** are, therefore, response values of the granulation step. On the other hand, the tablet properties **Z** depend on the physical granule properties. The intermediate block has to be used as a predictee and as a predictor block. Two obvious relations exists, the first between the tablet mixture **D** and the granule properties, and the second between the granule and tablet properties. The third relation between the tablet mixture and the tablet properties is also important. The granule properties do not contain all the information from the first block that is necessary for the modelling of the tablet properties. The process variables of the first step influence both the granule and tablet properties and can be combined with the composition of the powder mixture. The process variables of the second step only influence the tablet properties. Therefore, they are placed in a separate block that only influences the tablet block **Z**. The data sets are placed in the hierarchical way with the causal relation from left to right. The connections are shown with straight arrows. Figure 1 shows the four blocks and their relations in this model.

In 1988, Wangen and Kowalski presented a base algorithm from which an algorithm for every model with any number of blocks and relations could be made [3]. The algorithm presented here is mainly based on theirs. The MBPLS path model for the granulation of mannitol microcrystalline cellulose granulations consists of the four data blocks. The step one process variables are placed within the first block of starting materials. They could also have been placed in a separated block parallel with the first block. The step two process variables have to be placed parallel to the granule

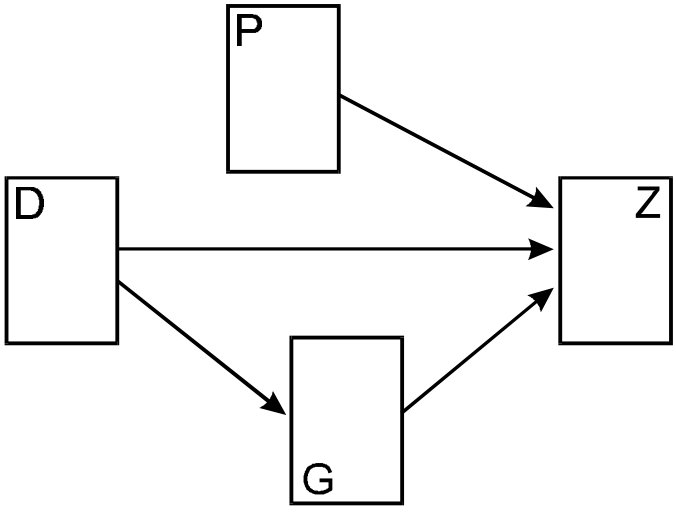

Figure 1: The placement of the various blocks in the MBPLS path model for the wet granulation and tableting process. Explanation of the blocks is given in the text. **D** consists of the composition of the tablet mixture and the process variables for step 1, **G** contains the granule properties, the process variables for the second step are in **P** and the tablet properties in **Z**.

properties block. The step two process variables block is also a left end block. It is only used to make predictions of the tablet properties.

The **D** block consists of the composition of the tablet mixture and the settings of two process variables that influence the first granulation step. The mixture of microcrystalline cellulose (MCC), mannitol and HPC is presented by two variables, the amount of HPC in the blend (2, 3 or 5%), and the percentage of MCC from the remaining (100–HPC)%. With only two variables the three components can be presented. The two process variables of the first step are the granulation time (3, 5 or 7 minutes) and the amount of water added during granulation. The amount of water is a process variable and not a composition variable because the water is removed from the granulations in a drying step. The quadratic terms of the variables are also included because they were found to influence the tablet responses (*e.g.* MCC^2).

The second left end block **P** consists of the process variables that affect only the second step of the process, the compression of granules into tablets. These process variables are the amount of moisture in the granulations (3, 4 or 5%), and the compression force (10, 20 or 30 kN). The moisture content of the granulation is in fact a response variable, but it was set to a specific value by additional drying or moistening. For block **P**, the quadratic effects of the process variables were also included, so for each process variables also the quadratic terms are used in the blocks. Block **D** has eight columns and block **P** has four columns.

The interior block **G** is filled with physical properties of the granulations. These physical properties consist of the particle size distribution (800, 550, 428, 284, 169, 100, 38 µm), the median granule diameter (D_{50}; µm), the flow of the granulation through funnels with orifices of 9, 6, and 4 mm ($g.s^{-1}$), the poured volume of the granulation ($ml.g^{-1}$), the tapped volume after 1000 taps ($ml.g^{-1}$). These granule properties more or less describe a latent variable that characterizes the flowability of the granules.

The right end block **Z** consists of the tablet properties. In all cases only one tablet property was handled at the time. The MBPLS path model is capable of handling more responses simultaneously, but then the interpretation becomes much more difficult. The crushing strength of the tablets and the disintegration time are the two tablet responses that will be handled separately with the model. The responses were logarithmically transformed because they both have heteroscedastic variance structures.

Block **G** of the granule properties needs to be weighted before calibration. This is necessary because block **D** has to predict both blocks **G** and **Z** simultaneously. The granule block however is much larger (14 columns) than the tablet block (1 column). When both blocks are autoscaled, the total variance of the blocks equals the number of columns. The granule block would, therefore, be favoured. The weigh factor of block **G** is defined to be the number by which **G** is divided. With a weight factor of 2 all granule properties are divided by 2 (after auto scaling). The weighing must not be too strong because the granule properties also are used in predicting the tablet properties. A too high weight factor would diminish this extra prediction power.

For all predictor blocks a **t** score vector will be calculated. This **t** vector is a linear

combination of all variables in the specific block. The vector **w** contains the weights for each variable of the block for the **t** score. The **t** score vector will be used as predictor for the next block or blocks. Furthermore, for each predictee block a **u** score vector is estimated. The **c** weights vector gives the weight for every variable in the block according to the **u** score.

Notation

Matrices are denoted by bold uppercase characters: **D**. Vectors are always column vectors and denoted with bold lowercase characters: $\mathbf{t}_D$, where the subscript indicates to which matrix the vector belongs. Vectors and matrices might be transposed if necessary: $\mathbf{p}_D$', **D**'. Scalars are denoted with normal lowercase characters: r_G . No multiplication signs are used, so $\mathbf{G}'\mathbf{u}_G$ means the transpose of matrix **G** times the $\mathbf{u}_G$ vector. Predictions of matrices of vectors are indicated with a hat: $\hat{\mathbf{n}}_Z$. Each block has the same number of objects, the number of variables may be different for each block. The size of each matrix or vector is given.

I	number of objects
J	number of variables
K	number of PLS factors
D	block with mixture composition and process variables of step 1 (I*J_D)
G	block with physical granule properties (I*J_G)
P	block with process variables for step 2 (I*J_P)
Z	block with tablet properties (I*J_Z)
T	temporary super block combining **t** scores of **D**, **G** and **P** (I*3)
U	temporary super block combining **u** scores of **G** and **Z** (I*2)
$\mathbf{t}_{D,G,P}$	predictor block score of block **D**, **G**, **P** (I)
$\mathbf{t}_T$	predictor super score (I)
$\mathbf{w}_{D,G,P}$	predictor block weight of block **D**, **G**, **P** (J_D, J_G, J_P)
$\mathbf{w}_T$	predictor super weight for variables in super block **T** (3)
$\mathbf{u}_{Z,G}$	predictee block score of block **Z**, **G** (I)
$\mathbf{u}_U$	predictee super score (I)
$\mathbf{c}_{G,Z}$	predictee block score of block **G**, **Z** (J_G, J_Z)
$\mathbf{c}_U$	predictee super weight for variables in super block **U** (2)
$\|\|\mathbf{w}_D\|\|$	norm of $\mathbf{w}_D$
$\mathbf{p}_{D,G,P}$	predictive block loading of **D**, **G**, **P** (J_D, J_G, J_P)
$\mathbf{q}_{Z,G}$	predictee block loading of **Z**, **G** (J_G, J_Z)
b_U	regression coefficient between $\mathbf{t}_D$ and $\mathbf{u}_U$
b_{UG}	partial regression coefficient of $\mathbf{t}_D$ to the column in **U** belonging to **G**
b_T	regression coefficient between $\mathbf{t}_T$ and $\mathbf{u}_Z$
b_{TP}	partial regression coefficient of the column in **T** belonging to **P** to $\mathbf{u}_Z$
$\mathbf{E}_{D,G,P,Z}$	residuals of **D**, **G**, **P**, **Z** after subtraction of explained variance (I*J_D, J_G, J_P, J_Z)
r_G	the fraction of **G** being a predictor
s_G	the fraction of **G** being a predictee
$\mathbf{n}_{D,G,P}$	block **D**, **G**, **P** data for a new object (J_D, J_G, J_P)
$t_{D,P,G}$	predictor score for block **D**, **P**, **G** for new object

$\mathbf{e}_{D,G,P}$	residual of $\mathbf{n}_D$, $\mathbf{n}_G$, $\mathbf{n}_P$ after subtraction of explained variance (J_D, J_G, J_P)
$\hat{u}_{G,Z}$	prediction of predictee score of block **G** for new object
$\hat{t}_G$	prediction of predictor score of block **G** for new object
$\hat{\mathbf{n}}_Z$	prediction of tablet responses for new object

The multiblock PLS path algorithm

The algorithm is divided into a backward phase, where the predictor vectors (**t**, **w**) are calculated, and a forward phase for the predictee vectors (**u**, **c**). The phases alternate until $\mathbf{u}_Z$ converges. The first step is to scale and mean centre each block. Furthermore, the blocks can be weighted according to additional information. For initialisation a **t** and **u** vector for each block are selected. These may be the column with maximal variance.

Backward phase

In the backward phase, the **t** scores of the predictor blocks are calculated. Figure 2A shows an arrow scheme for the backward phase. Block **P** and **G** predict only the tablet property and can be calculated directly:

$\mathbf{w}_G=\mathbf{G}'\mathbf{u}_Z$; scale $\mathbf{w}_G$ to $||\mathbf{w}_G||=1$
$\mathbf{t}_G=\mathbf{G}\mathbf{w}_G$
$\mathbf{w}_P=\mathbf{P}'\mathbf{u}_Z$; scale $\mathbf{w}_P$ to $||\mathbf{w}_P||=1$
$\mathbf{t}_P=\mathbf{P}\mathbf{w}_P$

Both block scores $\mathbf{t}_G$ and $\mathbf{t}_P$ have maximal covariance with $\mathbf{u}_Z$. Block **D** has to predict both **G** and **Z**. To come to a $\mathbf{t}_D$ score that predicts both blocks, a temporary **U** block is defined, that contains the **u** scores of all blocks that are predicted by the specific block.

$\mathbf{U}=[\mathbf{u}_G\ \mathbf{u}_Z]$

An ordinary PLS2 step is performed between **D** and **U** to calculate the $\mathbf{t}_D$ score.

$\mathbf{c}_U=\mathbf{U}'\mathbf{t}_D$; scale $\mathbf{c}_U$ to $||\mathbf{c}_U||=1$
$\mathbf{u}_U=\mathbf{U}\mathbf{c}_U$
$\mathbf{w}_D=\mathbf{D}'\mathbf{u}_U$; scale $\mathbf{w}_D$ to $||\mathbf{w}_D||=1$
$\mathbf{t}_D=\mathbf{D}\mathbf{w}_D$

Forward phase

In the forward phase, the **u** scores of the predictee blocks are determined. Figure 2 shows an arrow scheme of the forward phase. Only the blocks **G** and **Z** are predicted and need a **u** score. **G** is only predicted by **D**, so $\mathbf{u}_G$ can directly be calculated:

$\mathbf{c}_G=\mathbf{G}'\mathbf{t}_D$; scale $\mathbf{c}_G$ to $||\mathbf{c}_G||=1$
$\mathbf{u}_G=\mathbf{G}\mathbf{c}_G$

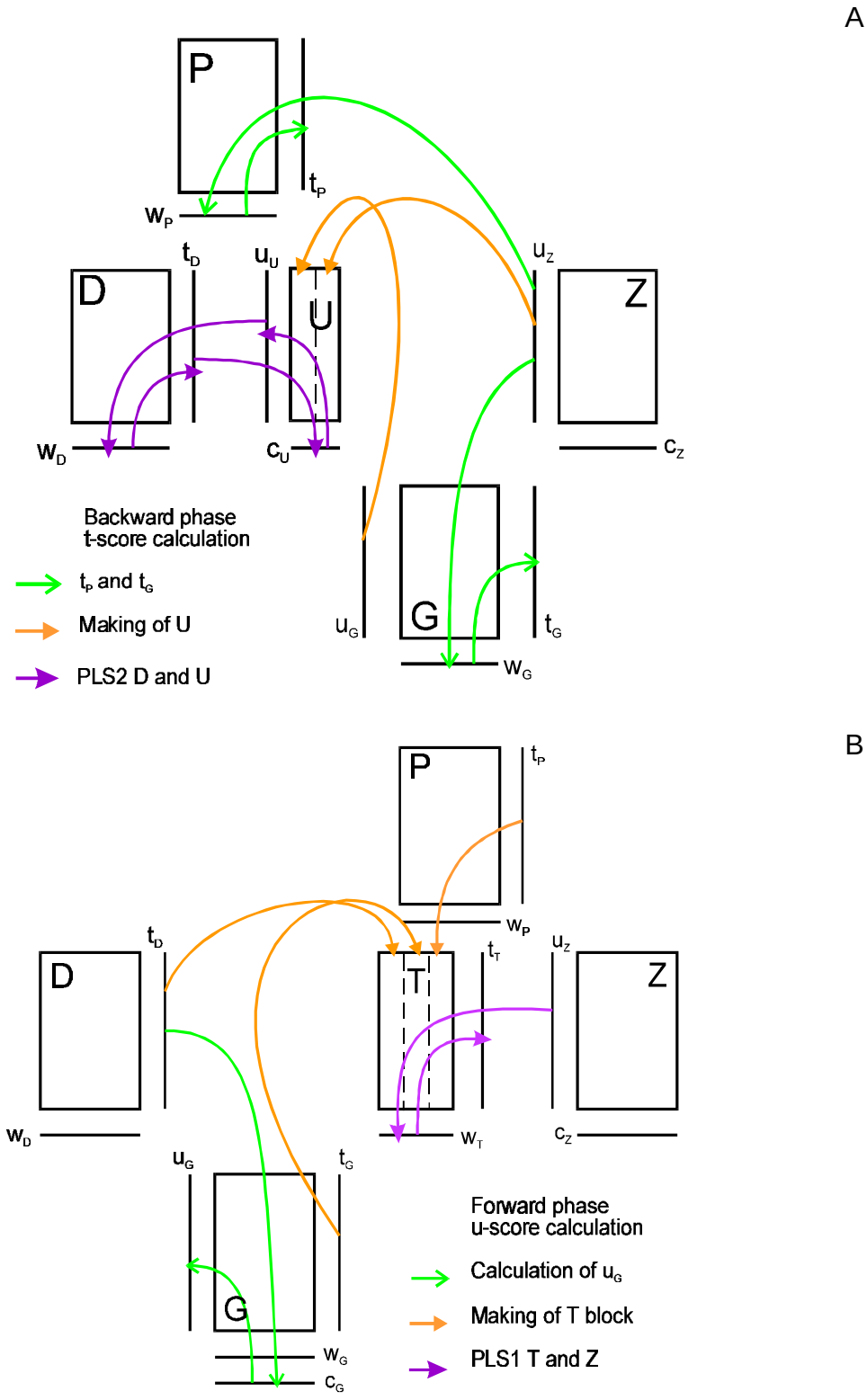

Figure 2: Arrow scheme of the backward (A) and forward phase (B) for the development of the MBPLS path model. In the backward phase **u** scores are combined in **U** to determine $\mathbf{t}_D$, and in the forward phase **t** scores are combined into **T** to calculate $\mathbf{u}_Z$.

Block **Z** is predicted by **D**, **G** and **P**. Now a temporary **T** block is introduced consisting of the **t** scores of these blocks.

$\mathbf{T}=[\mathbf{t}_D\ \mathbf{t}_G\ \mathbf{t}_P]$

An ordinary PLS2 step is performed between **Z** and **T** to calculate the $\mathbf{u}_Z$ score.

$\mathbf{w}_T=\mathbf{T}'\mathbf{u}_Z$; scale $\mathbf{w}_T$ to $||\mathbf{w}_T||=1$
$\mathbf{t}_T=\mathbf{T}\mathbf{w}_T$
$\mathbf{c}_Z=\mathbf{Z}'\mathbf{t}_T$; scale $\mathbf{c}_Z$ to $||\mathbf{c}_Z||=1$
$\mathbf{u}_Z=\mathbf{Z}\mathbf{c}_Z$

After completing one cycle of backward and forward phase, $\mathbf{u}_Z$ is tested for convergence within a desired precision (e.g. 10^{-8}).

Loadings
Loadings for predictor blocks (**p**) and predictee blocks (**q**) are calculated. Just as in the multiblock PLS algorithm introduced in Chapter 7, a distinction can be made between block scores and super scores. Super scores appear when two or more blocks are combined to do a prediction. The block scores $\mathbf{t}_D$, $\mathbf{t}_G$ and $\mathbf{t}_P$ are combined to give the super score $\mathbf{t}_T$. For the loadings of **G** and **P** the super score update method is used. Block **D** however, also predicts **G** directly. The block score $\mathbf{t}_D$ is used for calculation of the loading and residual of **D**, because the super score $\mathbf{t}_T$ is also partly dependent on $\mathbf{t}_G$. This part which may also be present in **D** would be subtracted of **D** without ever being used to estimate **G**.

$\mathbf{p}_D=\mathbf{D}'\mathbf{t}_D/(\mathbf{t}_D'\mathbf{t}_D)$
$\mathbf{p}_G=\mathbf{G}'\mathbf{t}_T/(\mathbf{t}_T'\mathbf{t}_T)$
$\mathbf{p}_P=\mathbf{P}'\mathbf{t}_T/(\mathbf{t}_T'\mathbf{t}_T)$
$\mathbf{q}_G=\mathbf{G}'\mathbf{u}_G/(\mathbf{u}_G'\mathbf{u}_G)$
$\mathbf{q}_Z=\mathbf{Z}'\mathbf{u}_Z/(\mathbf{u}_Z'\mathbf{u}_Z)$

Path regression coefficients
Path regression coefficients are calculated for each block involved in prediction.

$b_U=\mathbf{u}_U'\mathbf{t}_D/(\mathbf{t}_D'\mathbf{t}_D)$
$b_{UG}=\mathbf{c}_{U(1)}\mathbf{b}_U/(\mathbf{c}_U'\mathbf{c}_U)$
$b_{UZ}=\mathbf{c}_{U(2)}\mathbf{b}_U/(\mathbf{c}_U'\mathbf{c}_U)$
$b_T=\mathbf{u}_Z'\mathbf{t}_T/(\mathbf{t}_T'\mathbf{t}_T)$
$b_{TD}=\mathbf{w}_{T(1)}\mathbf{b}_T/(\mathbf{w}_T'\mathbf{w}_T)$
$b_{TG}=\mathbf{w}_{T(2)}\mathbf{b}_T/(\mathbf{w}_T'\mathbf{w}_T)$
$b_{TP}=\mathbf{w}_{T(3)}\mathbf{b}_T/(\mathbf{w}_T'\mathbf{w}_T)$

The regression coefficients b_U and b_T are used for prediction of **G** and **Z** respectively. b_{UG} and b_{TG} are used to determine the predictor and predictee part of the block **G**.

Residuals
The calculation of residuals for each block depends on the role of the block. For block **D**, a left end block, the block score update method is used for reasons given earlier. For the second left end block **P**, the super block score will be used.

$\mathbf{E}_D=\mathbf{D}-\mathbf{t}_D\mathbf{p}_D'$
$\mathbf{E}_P=\mathbf{P}-\mathbf{t}_T\mathbf{p}_P'$

The residual of the right end block **Z**:

$\mathbf{E}_Z=\mathbf{Z}-\hat{\mathbf{u}}_Z\mathbf{c}_Z'$; where $\hat{\mathbf{u}}=b_T\mathbf{t}_T$

The residuals of interior blocks are calculated according to a weighted average of its role as predictor and predictee. Block **G** is the only interior block. The predictor and predictee roles of **G** are determined by the ratio of the regression coefficients that take part in predicting **Z** from **G** (b_{TG}) and in the prediction of **G** from **D** (b_{UG}).
The fractional role of **G** as a predictee block from **D**:

$r^2_G=b^2_{UG}/(b^2_{UG}+b^2_{TG})$

The fractional role of **G** as a predictor block to **Z**:

$s^2_G=b^2_{TG}/(b^2_{UG}+b^2_{TG})$; so $r^2_G+s^2_G=1$

The residual of the interior block **G**:

$\mathbf{E}_G=\mathbf{G}-(s_G\mathbf{t}_G\mathbf{p}_G'+r_G\hat{\mathbf{u}}_G\mathbf{c}_G')$; with $\hat{\mathbf{u}}=b_U\mathbf{t}_D$

In the next round for the calculation of the following scores and loadings, blocks **D**, **G**, **P**, and **Z** are replaced by $\mathbf{E}_D$, $\mathbf{E}_G$, $\mathbf{E}_P$ and $\mathbf{E}_Z$ respectively.

The number of factors that will be used in the model can be estimated by validation with a test set or by cross validation. The number of MBPLS factors that gives the lowest prediction error is selected for the final model. However, in the MBPLS model of the granulation process, two blocks are predicted. The user has to decide which prediction is the most important. It is also possible to combine both prediction errors in order to find a compromise for the final model.

Prediction

Prediction with the MBPLS path model depends on the calculation of the appropriate **t** scores for the various blocks of data. For prediction, data for all the left end blocks of the new objects have to be known. Right end blocks are always predicted by the model and are unknown. If data for the interior blocks are unknown, they can be predicted by blocks at the left of the specific block. If the data for these blocks are known, they can be used to improve prediction of the block at the right of the specific block. For prediction, weights of both predictor and predictee blocks and loadings of the predictor blocks have to be used. Furthermore, the regression coefficient b_{TZ}, and r_G and s_G are necessary for prediction.

In the tablet manufacturing process the granulation block is the only interior block. At the start of the process **G** is unknown. When a granulation step has been carried out, **G** can be measured. Let $\mathbf{n}_D$ and $\mathbf{n}_P$ be the values for **D** and **P** for the new object. First these new values have to be scaled according the scaling of the training set. For the new data for the left end blocks, new t scores can be calculated:

$$t_D=\mathbf{n}_D\mathbf{w}_D;\ \mathbf{e}_D=\mathbf{n}_D-t_D\mathbf{p}_D'$$
$$t_P=\mathbf{n}_P\mathbf{w}_P;\ \mathbf{e}_P=\mathbf{n}_P-t_P\mathbf{p}_P'$$

The parts explained by the first t_D and t_P scores are subtracted from the new data. In the next round $\mathbf{n}_D$ and $\mathbf{n}_P$ are replaced by $\mathbf{e}_D$ and $\mathbf{e}_P$ respectively. The granule properties of the new experiment $\hat{\mathbf{n}}_G$ can easily be predicted.

$$\hat{u}_G=b_{DG}t_D;\ \hat{\mathbf{n}}_G=\hat{u}_G\mathbf{c}_G$$

Besides the response for the first step, the granule block is also a predictor block for the tablet properties.

$$\hat{t}_G=\hat{\mathbf{n}}_G\mathbf{w}_G$$

If real data for $\mathbf{n}_G$ is known, a real t_G can be calculated, and this value can be used instead of the predicted $\hat{t}_G$. Prediction of the right end block of tablet properties $\hat{\mathbf{n}}_Z$ is performed by combining all t scores from the blocks that predict $\hat{\mathbf{n}}_Z$. These scores are combined in the temporary $\mathbf{n}_T$. Prediction of t_T is done by summation of all t values in $\mathbf{n}_T$ with their corresponding weight in $\mathbf{w}_T$.

$$\hat{t}_T=\sum_{l=1}^{NT} n_{T,l}w_{T,l}$$

where NT is the number of t scores in $\mathbf{n}_T$. The new tablet properties become:

$$\hat{u}_Z=b_{TZ}t_T;\ \hat{\mathbf{n}}_Z=\hat{u}_Z\mathbf{c}_Z$$

Results and discussion

Several variations can be implemented in the MBPLS path model. Most important ones are the use of the super score or block score update of the blocks, the calculation of the residual of the interior block and the construction of the super blocks **T** and **U**. As was indicated in Chapter 7, the block score update method subtracts information from the blocks that is never used for prediction purposes. Therefore, less variation of the response can be modelled. However, by using the super score update method, the block scores of the various factors become dependent of each other. The residual of the interior block can be determined in several manners. Wangen and Kowalski defined a predictor and a predictee part of the interior block, and the residual is calculated according to these parts. The construction of the super blocks **T** and **U** may also be changed. According to Wangen, the **T** block that is used to calculate the $\mathbf{u}_Z$ score must contain not only the **t** scores of the predicting blocks, but also the **u** scores of these blocks. In the present model the left end blocks, **D** and **P**, would have been favoured in the $\mathbf{t}_T$ super score estimation because for left end blocks the **u** scores equal the **t** scores, but $\mathbf{u}_G$ and $\mathbf{t}_G$ differ. In the present path model only the **t** scores were used in the **T** block.

The MBPLS path model has been developed with the data described above and given in Tables 4 and 5 of Chapter 5. The path model can be evaluated for prediction performance of the tablet property in two different manners. In case the granule properties have not yet been measured for the new experiment (at the start of the process) the model can be compared with a PLS1 model with the variables of **D** and **P** as the only descriptors. This PLS1 model is shown in Chapter 6 as Model 1. However, in case the granulation step has been carried out and the granule properties have been measured, the path model can be compared with a PLS1 model with variables of **D**, **P** and **G** as the descriptors, which has been shown in Chapter 6 as Model 2. For the development of the path model, the granule block **G** is always required.

For both response variables, the crushing strength (CS) and disintegration time (DT) of the tablets, an optimal weight factor was found for the granule block **G** in the model development. The optimal weight factor is influenced by the trade off between the amount to which **G** participates in the prediction of the tablet property, and the magnitude in which $\mathbf{t}_D$ is drawn away from the tablet response to the granule properties. When $\mathbf{t}_D$ is drawn in the granule direction, prediction of the tablet property gets worse.

Figure 3 shows the minimal PRESS values for both tablet response variables CS and DT for both cases, without and with block **G** used in prediction. When the granule properties are not used, the minimal PRESS goes to the same level as was earlier determined for the PLS1 model [4], and shown in Table 1, when the weight factor of **G** increases. For both tablet responses the minimal PRESS values were obtained at three PLS factors. When the weight of **G** is too high (the weight factor is low), $\mathbf{t}_D$ is trying to fit too much of **G**, and **Z** is somewhat neglected. This results in higher PRESS values

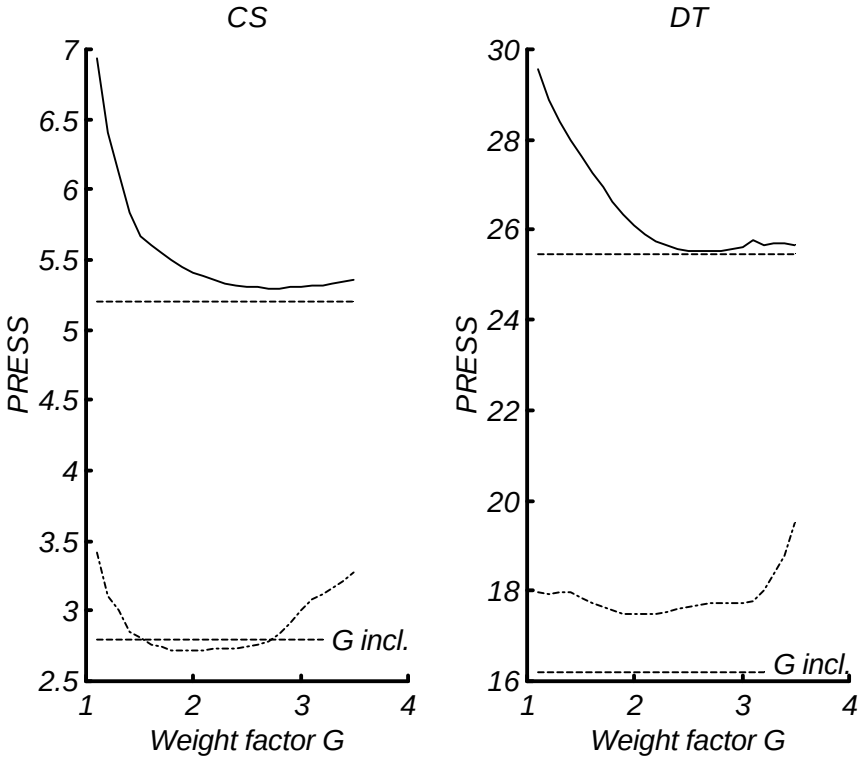

Figure 3: Minimal PRESS values for the crushing strength (CS) and the disintegration time (DT) without (black lines) and with (dotted lines) block **G** included in prediction when the weight factor of **G** is increased during development of the model. PRESS values of the PLS model with and without **G** included (straight dotted lines) are also given.

for the tablet property in **Z**. When the weight for **G** is low (a high weight factor), $\mathbf{t}_D$ is free to model only the tablet response, but the extra prediction power of **G** has disappeared because of the little information used from **G**, as a result of the high weight factor. A compromise between these two features gives the best prediction model for the tablet properties.

Predictions of the tablet properties with the MBPLS path model improve when the granule properties have been measured and can be used in the prediction. For both the crushing strength and the disintegration time, the minimal PRESS values have been reached when the weight factor for block **G** is about 2.5 when **G** was not included in prediction, and a weight factor of 2 when **G** was used in prediction. When the weight factor is above 3, PRESS increases again. The optimal weight factor is dependent on the use of **G** in prediction. A weight factor of 2.5 is used for the final models because this weight factor gives low PRESS values for both cases (**G** included and **G** not included).

Table 1 shows the minimal PRESS values for the PLS1 model and the MBPLS path model. The MBPLS path model gives almost equal prediction errors for both response variables as the PLS1 method when **G** is not included. When **G** is introduced, minimal PRESS values decrease for both methods.

Table 1 Minimal PRESS values for both the crushing strength (CS) and disintegration time (DT) for the PLS1 model and for the MBPLS path model without and with block **G** included in the model. The weight factor was set to 2 and 2.5.

Minimal PRESS	CS	DT	CS (**G** incl.)	DT (**G** incl.)
PLS1 model	5.2	25.5	2.8	16.2
MBPLS path model, weight factor 2.5	5.3	25.5	2.8	17.7
MBPLS path model, weight factor 2	5.4	25.9	2.7	17.5

In the MBPLS path model, the scores of block **D** have slightly been drawn towards the granule block. This has no negative influence on the prediction quality of the models for the tablet responses. As a bonus one gets a prediction for the granule properties with the same model. However, the prediction of the granule properties with the MBPLS path model are not as good as the use of a standard PLS2 model for the granule properties with block **D** as the single descriptors. Table 2 shows the modelling of the granule properties with the MBPLS path model and the standard PLS2 model.

The standard PLS2 model explains almost twice as much of the variance in block **G** as the MBPLS path model. The PRESS value is also much lower for the PLS model. The prediction of the MBPLS path model for block **G** is, as can be expected, not as good as a simple PLS2 model for this block because the scores are selected to give an optimal fit for the tablet response variables. Furthermore, the optimal number of latent variables for the model are selected according to the lowest PRESS for the tablet properties.

Table 3 shows the explained variances of all blocks for both response variables. The %**G** presented, includes both the amount used to predict **Z** and the amount **G** is predicted by **D**. The weight factor for block **G** is set to 2.5. The first factor describes 77 and 71% of the crushing strength and the disintegration time respectively. This variation is mainly described by block **D**, where block **P** is the main source of information in the second factor. This not only follows from the explained variation of the blocks in Table 3, but it can also be seen from the weight vector $\mathbf{w}_T$ in Table 4b.

To examine the model, the modelling of the crushing strength is studied in detail to study the properties of the MBPLS path model. The block **D** score $\mathbf{t}_D$ has to fit $\mathbf{u}_U$ as good as possible where $\mathbf{u}_U$ is a linear combination of the $\mathbf{u}_G$ and $\mathbf{u}_Z$ scores. The weight $\mathbf{c}_U$ gives the weights for block **G** and **Z** respectively for each factor (f1-f4) in the $\mathbf{u}_U$ score

Table 2: Prediction of **G** with PLS2 and MBPLS path model when the crushing strength (CS) or the disintegration time (DT) is modelled. The weight factor for **G** in the path model is set to 2.5.

model	% G explained	PRESS
PLS2	52.8	69
MBPLS path (CS, w=2.5)	29.5	93
MBPLS path (DT, w=2.5)	29.2	94

Table 3: Cumulative explained variances of the blocks **D**, **G**, **P** and the respons **Z** in the MBPLS path model for both the crushing strength (CS) and disintegration time (DT) of the tablets. The weight factor for **G** was set to 2.5.

% explained	%**D**		%**G**		%**P**		%**Z**	
# Factor	CS	DT	CS	DT	CS	DT	CS	DT
1	29	29	17	11	3	10	77	71
2	50	46	19	15	26	31	92	87
3	57	58	43	44	31	35	94	90
4	69	67	62	63	32	39	95	91

(Table 4a). In the first two factors **D** is mainly used to fit the $\mathbf{u}_Z$ score (−0.99 and −0.98) where only in the third and fourth factor $\mathbf{u}_G$ is fitted (0.83 and 0.92). Most of the variation in **D** is used to model **Z** instead of **G**.

The super score $\mathbf{t}_T$, the score to fit **Z**, is a linear combination of $\mathbf{t}_D$, $\mathbf{t}_G$ and $\mathbf{t}_P$. The super weight $\mathbf{w}_T$ gives the weights for the scores for all four factors respectively (Table 4b). The super weight $\mathbf{w}_T$ shows just as the percentage explained in Table 3 that the first factor mainly exists of **D** to fit **Z**. In the second factor, the information of **P** is used and in the last two factors the $\mathbf{t}_T$ scores are chiefly composed of the information from block **G**.

The interior block **G** is mainly used as a predictor, and only slightly as a predictee

Table 4a: The weights for the scores $\mathbf{u}_G$ and $\mathbf{u}_Z$ in $\mathbf{c}_U$ for the four PLS factors f1-f4 for the modelling of the crushing strength.

	f1	f2	f3	f4
$\mathbf{u}_G$	0.17	-0.21	0.83	0.92
$\mathbf{u}_Z$	-0.99	-0.98	-0.56	-0.39

Table 4b: The weights for the scores $\mathbf{t}_D$, $\mathbf{t}_G$ and $\mathbf{t}_P$ in $\mathbf{w}_T$ for the four PLS factors f1-f4 for the modelling of the crushing strength.

	f1	f2	f3	f4
$\mathbf{t}_D$	-0.84	-0.35	-0.28	0.33
$\mathbf{t}_G$	0.40	0.28	0.83	0.94
$\mathbf{t}_P$	0.38	0.90	0.48	0.11

Table 4c: The role of **G** as a predictor (s_G) and as predictee (r_G) in the modelling of the crushing strength.

	f1	f2	f3	f4
s_G	0.94	0.97	0.29	0.82
r_G	0.35	0.26	0.96	0.57

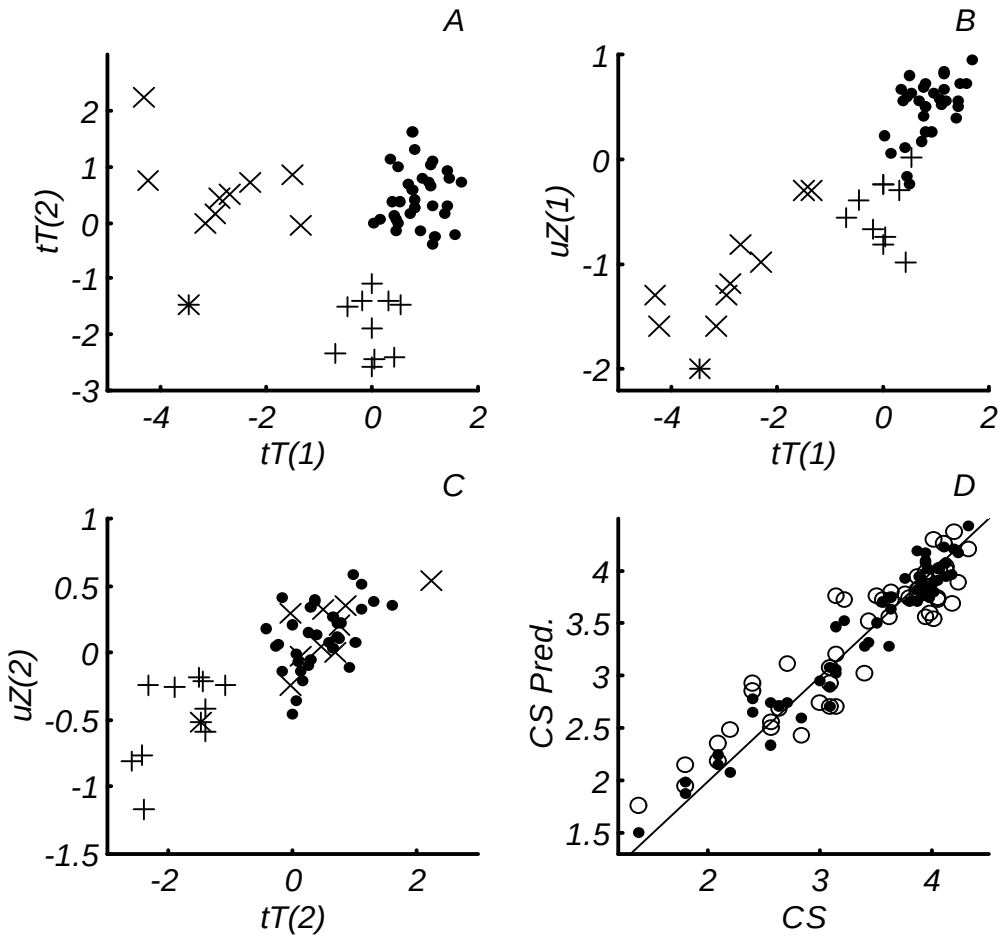

Figure 4: 4A) A scatter plot of the first two super scores $\mathbf{t}_{T(1)}$ and $\mathbf{t}_{T(2)}$ in the modelling of the crushing strength. Three groups can be distinguished (X, MCC=90%; +, Fup=10 kN; ●, other experiments; ✳ belongs to both the X and + groups). 4B and 4C show $\mathbf{u}_Z$ against the predicting super score for the first and the second factor. 4D shows the crushing strength predicted without (O) and with (●) use of the granule properties. The straight line represents the perfect fit.

block as indicated by $\mathbf{s}_G$ and $\mathbf{r}_G$ respectively (Table 4c). In the first two factors the predictor parts of **G** (0.94, 0.97) are much larger than the predictee parts (0.35, 0.26). Only in the third factor, the granule properties are described by the **D** block.

Figure 4A shows a scatterplot of the first two scores of the super block **T**. Three groups can be distinguished, a wide group at the left (X), a group at the bottom (+) and a third group (●). Object ✳ belongs to the first and the second group. The first group consists of experiments with a composition of 90% MCC. This information comes from block **D**. Experiments of the second group have compression forces of 10 kN. The compression force is placed in block **P**. The third group exists of the other experiments. Figures 4B and 4C show the $\mathbf{t}_T$ and $\mathbf{u}_Z$ scores of the first two factors. In 4B, the fit of the super score $\mathbf{t}_T$ against $\mathbf{u}_Z$ is mainly due to the MCC=90% group. Table 2 and $\mathbf{w}_T$ already

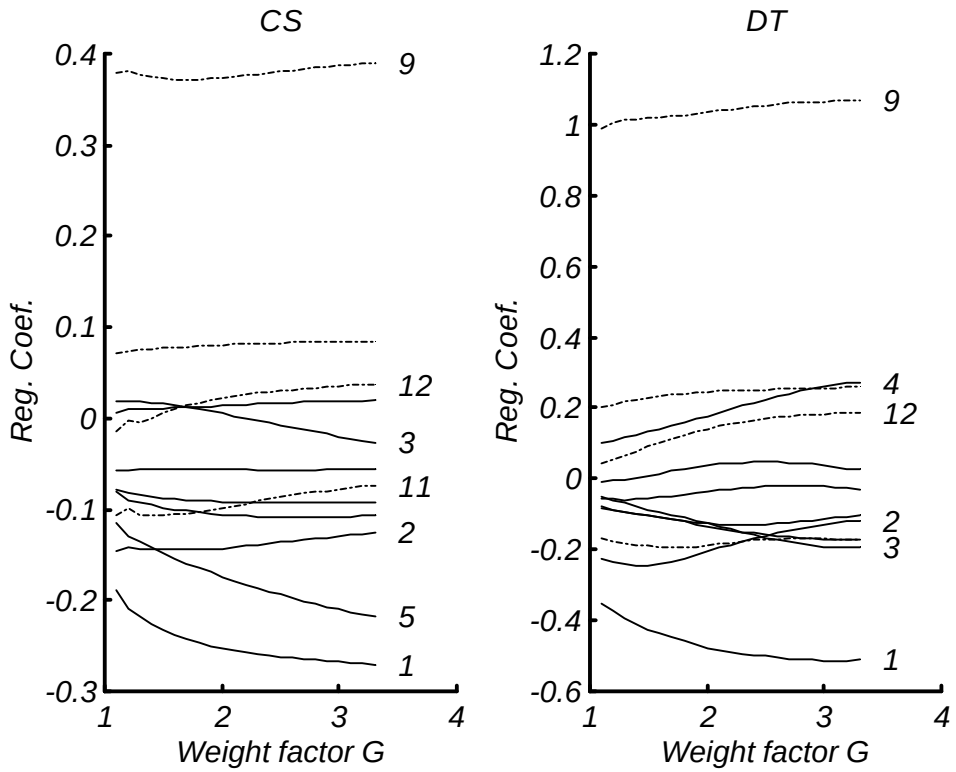

Figure 5: Regression coefficients for the variables of blocks **D**(**-**, 1-8) and **P**(⋯, 9-12) for the crushing strength (CS) and the disintegration time (DT) when the weight factor of block **G** during development of the path model has been increased. Some variables are indicated with their corresponding number: 1=MCC, 2=water, 3=time, 4=HPC, 5=MCC^2, 9=F_{up}, 11=$F_{up}{}^2$ and 12=moisture^2.

showed that the first super score $\mathbf{t}_T$ was built primarily of the $\mathbf{t}_D$ score, and the second super score on $\mathbf{t}_P$. The latter is shown in Figure 4C where the 10kN group is the main predictor of small crushing strengths.

Figure 4D shows the predictions of the crushing strength of the tablets with the MBPLS path model, without (O) and with (●) the granule properties used for prediction. The predictions are comparable to the predictions with the PLS and MBPLS model in Chapter 6 and 7. When **G** is used, the predicted values of the tablet responses are closer to the observed ones than without **G** used.

Regression coefficients

Figure 5 shows the regression coefficients of the variables in block **D** and **P** for the modelling of the crushing strength and disintegration time with the path model when the weight factor of block **G** increases. Some regression coefficients change when the weight factor increases, but they stabilize at a certain level. For the crushing strength, the coefficients of MCC and MCC^2 (1 and 5) show the largest change. These variables also have a large influence on the granule properties. When $\mathbf{t}_D$ is forced to fit mainly the tablet properties by increasing the weight factor for **G**, the regression coefficients of

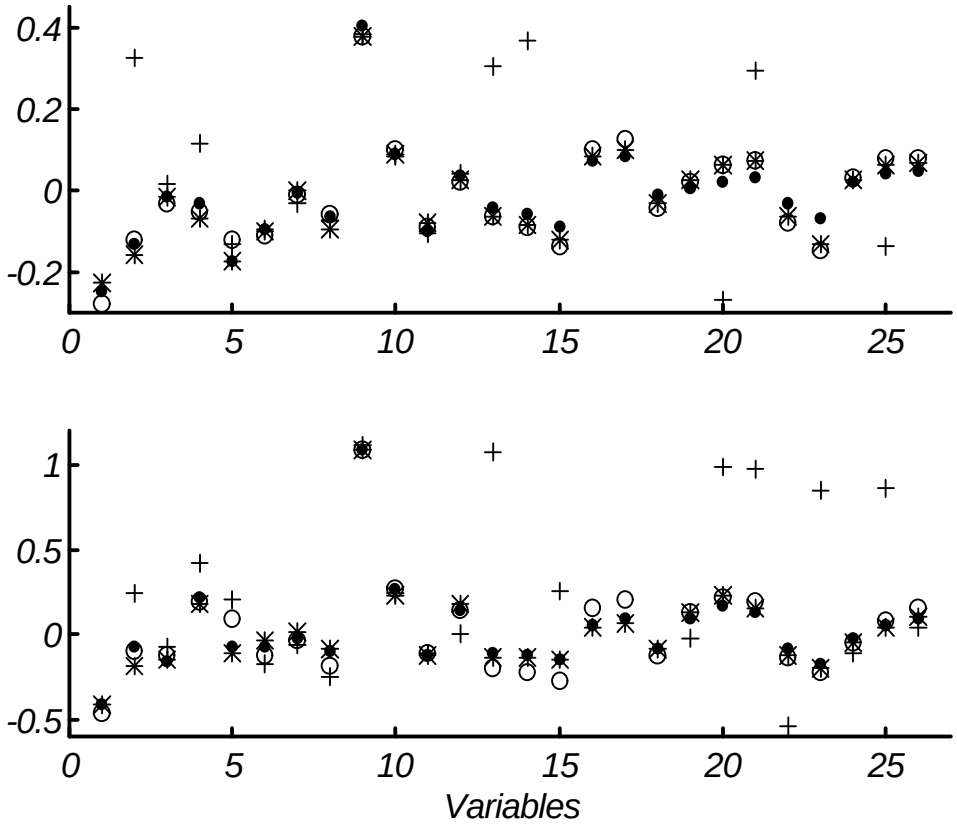

Figure 6: Regression coefficients for the variables in block **D**(1-8), **P**(9-12) and **G**(13-26) for the OLS(+), PLS(O), MBPLS_*a*(●) and MBPLS path(✳) models for the crushing strength (CS) and the disintegration time (DT). For some variables the OLS solution (+) is out of the range.

these variables change from the setting where both responses have to be fitted to the setting to fit just the tablet response.

Figure 6 shows the regression coefficients for the variables of blocks **D**, **P** and **G** for the modelling of crushing strength and disintegration time for four different regression methods: the MBPLS path model, the OLS regression method, the PLS method and the MBPLS_*a* method according to Wangen. The PLS1 method equals the MBPLS method with super score update of the residuals, and the MBPLS_*a* method uses the block score update method. The regression coefficients were determined by examining the change in predicted values when the values for the specific variable were increased by 1 (after autoscaling of the data). The effect of the variables of **D**(MCC, water, time, HPC, MCC^2, $water^2$, $time^2$, HPC^2), **P** (compression force F_{up}, moisture, $F_{up}{}^2$ and $moisture^2$) and **G** (granule properties) is found almost the same for all methods except for the OLS regression method. It is obvious that the OLS models are very different from the several PLS models. For the variables 13-27, which are the variables of the **G** block, the MBPLS_*a* method gives slightly deviating coefficients compared to the other two PLS

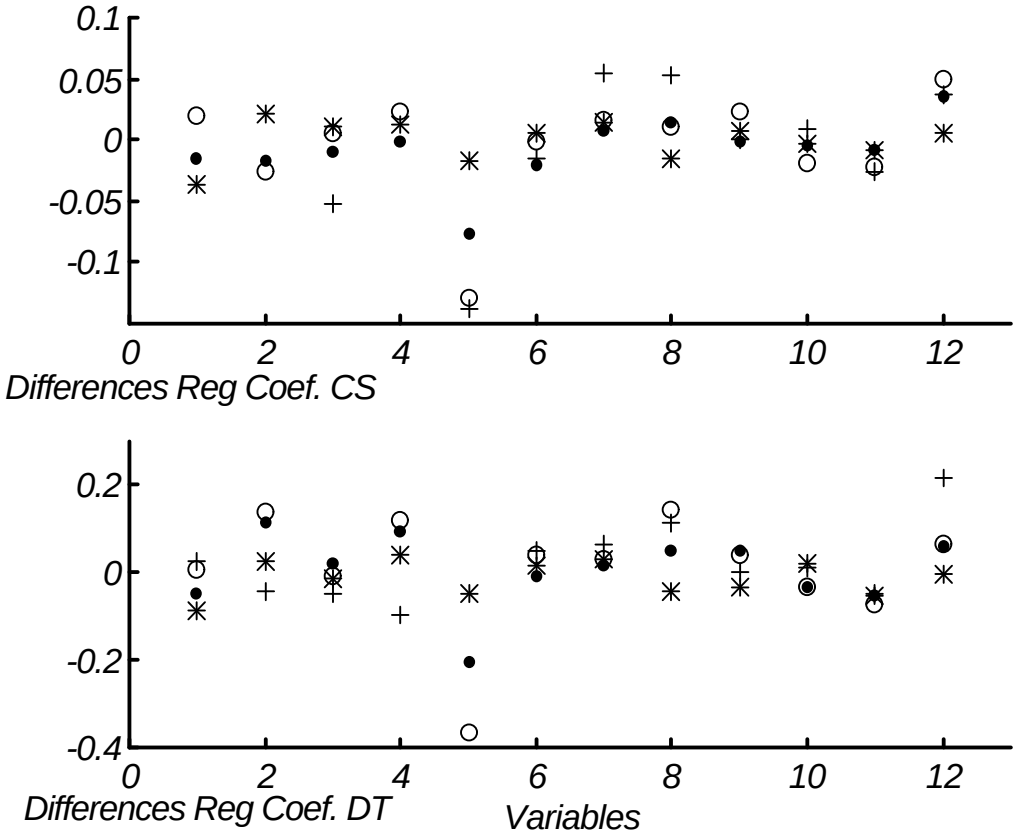

Figure 7: Differences of regression coefficients for the variables in **D**(1-8) and **P**(9-12) for the OLS (+), PLS(O), MBPLS_*a*(●) and MBPLS path(✳) models for the crushing strength (CS) and the disintegration time (DT).

methods. This is mainly caused by the fact that for the MBPLS_*a* method only three PLS factors were used (because three were optimal forthis method) and for the other two PLS methods, four factors were used.

The effect of the variables of block **D** and **P** on the tablet responses changes when the **G** block variables are included in the model because of the correlations that exist between **D** and **G**. Figure 7 shows the differences of the OLS and PLS coefficients for the variables in blocks **D** and **P** for the modelling of CS and DT caused by the introduction of the granule properties in the model. The OLS method, as could be expected, gives the largest differences, because OLS suffers from correlations between the predictor variables. The PLS model, which equals the MBPLS model with super score update, suffers somewhat more of the introduction than the MBPLS_*a* model. The MBPLS path model shows the smallest differences in the coefficients. The path model is developed with the granule properties present, even if prediction is done without the granule properties. For the other two PLS methods, the model that predicts **Z** without **G** is developed without **G**. When the granule properties are included, another model is

used that was developed with **G** present. This may cause the effect of the **D** and **P** variables to change more than for the MBPLS path model.

Conclusion

The multiblock PLS path model can be used for the modelling of complex processes with two or more steps such as the wet granulation and tableting process. During development of the model, the granule properties have to be used. For prediction purposes, the granule properties may be used if they have been measured (after the first step), but prediction can also be done when they have not been obtained yet. The prediction properties of the path model for the tablet responses are comparable to the standard PLS methods where all data is combined in 1 block to model the tablet responses. The MBPLS path model is less influenced by introduction of the granule properties in the model than the standard PLS or MBPLS methods. The path model can be used to study the real effect of the process and composition variables and the granule properties on the tablet responses.

The prediction of the granule properties with the MBPLS path model is not as good as with a standard PLS2 model. The information of block **D** is mainly used to model the tablet responses. For monitoring of the whole wet granulation and tableting process, it seems better to use different models for the monitoring of the granule and tablet properties.

Multiblock pathway models may be used when interior blocks are present in the process, *i.e.* blocks in the middle of a process that are predicted by previous blocks, and predict subsequent blocks. Just as the standard PLS models, the MBPLS path model gives outlier detection and noise reduction for each block separately. All blocks can be predicted with the same model. Predictions of the right end blocks become better when the interior blocks can be filled with measured values. Furthermore, the path model may provide extra information on the way latent variables work through the process, which may lead to a better understanding of the process.

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Summary

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

Wet granulation in high-shear mixers is a process of particle size enlargement much used in the pharmaceutical industry to improve the tableting properties of powder mixtures, such as flowability and compactibility, necessary for the large scale production of pharmaceutical tablets. High-shear mixers are used for their short process time and high densification. When a new drug has been developed, the process of wet granulation has to be optimised for this drug in an initial stage. However, only a small amount of material is available for experimentation. Therefore, some initial knowledge of the behaviour of the new drug in the wet granulation process is necessary. The process has to be robust, and must give granules with specified characteristics that can be compressed into tablets with sufficient strength.

Once the wet granulation process has been optimised, it must be monitored and controlled in everyday production. The whole process of wet granulation and tableting is studied as a two-step process. The process variables of the first granulation step must be set according to the material that is granulated. Adjustments in the process variables may be necessary when the powder mixture changes. The process variables of the second step may be adjusted according to the physical properties of the granules. Therefore, mathematical models are used to describe the relation between the properties of the tablets and the process variables of both steps and the composition of the powder mixture. For the granule properties, the process variables of the tableting step are not used because they are applied after the granule properties have been obtained.

The thesis starts with a general introduction on wet granulation, the optimisation of this process, and on multivariate analysis in **Chapter 1**. Thereafter, two parts can be distinguished in this thesis. The first part deals with the multivariate calibration of the wet granulation process, aggravated on the effect of the powder mixture on the granulation process and on the granulation and tablet properties. The second part of this thesis deals with the multivariate modelling of the whole two-step process.

In the first part of the thesis (**Chapters 2-4**), a powder mixture of lactose 200 mesh, corn starch and polyvinylpyrrolidone is granulated with several model drugs at a concentration of 0, 5 or 50%. The multivariate design, analysis and calibration strategy is used to examine the effect of the physical properties of the drug on the granulation process and on the physical properties of granules and tablets. Studying the effect of a single drug descriptor on the granule and tablet properties is not possible because no group of drugs exists that only differ in one property, such as the solubility. Using standard experimental designs for drug descriptors is also not possible because not every combination of descriptors can be combined within a drug. Furthermore, high correlations exist between the several descriptors, which lead to designs that are not orthogonal.

From a set of potential model compounds, physical descriptors, important in the granulation process, were obtained. In **Chapter 2**, the multivariate principal component analysis is used to find latent directions in the drug space that are uncorrelated and describe a large amount of variance of the data in only a few factors. Eight model drugs that have a large spread in the latent directions and are representative for the whole set of drugs were selected as model drugs for use in the granulation experiments.

Because of the large spread in the physical properties of the selected model drugs, the amount of water added during granulation had to be adjusted for the several mixtures. **Chapter 3** describes the prediction of a certain amount of granulation liquid to carry out a robust granulation experiment. This uncritical amount is defined according to the power consumption profile of the granulation obtained during continuous addition of water. The typical profile can be divided in five phases that correspond to different states of the powder mixture. In the middle of phase three, the percentage of fines has decreased to a low level and overwetting of the powder mixture has not occurred. The uncritical liquid amount has been related to the physical descriptors of the drugs. A large surface area can take much water before overwetting occurs. When drugs dissolve in the granulation liquid, surface area decreases, and the amount of water has to be less. Predictions of the uncritical liquid amount for lactose 100 mesh as the new drug corresponded well with the measured values.

Chapter 4 describes the granulation and tableting experiments with the mixtures of the model drugs. Experiments were carried out with 0, 5 and 50% of drugs at two levels of granulation liquid, the start of phase three of the power consumption profile and at the uncritical liquid amount. The multivariate partial least squares regression (PLS) was used for the modelling of the granule and tablet properties. This method finds latent directions in the drug space that not only describe a large amount of the variance but also are highly correlated with the response variable. The addition of extra water to the powder mixture increased the median granule diameter and the disintegration time of the tablets. The percentage of fines and the Hausner ratio decreased. The influence of the drug was small when a concentration of 5% was used in the mixture. At a concentration of 50%, the influence of the drug was more obvious. High solubility and large particle size of the drugs lead to large median granule size and small percentage of fines. A significant interaction between the amount of water and the solubility of the

drug was found, meaning that the difference in median granule diameter between soluble and insoluble drugs increases when more water is added. The tablet crushing strength was found to be influenced by the compactibility of the pure drug when only a small amount of water was added. At the high water level, crushing strengths shift to the level of the standard mixture. The disintegration time of the tablets was shortened by high contact angles and large surface area of the drugs.

The second part of the thesis (**Chapters 5-8**) handles the multivariate modelling and control of the whole process. The process of wet granulation and tableting is described as a two-step process. The first step comprises the granulation of the powder mixture and in the second step, the granules are compressed into tablets. Process variables on either step of the process affect the physical properties of the tablets, where only the process variables of the first step influence the granule properties. The granules are the product of the first step that have to meet certain specifications such as a sufficient flowability and small amount of fines. On the other hand, the physical properties of the granules influence the strength and disintegration time of the tablets. The granule properties can be handled as responses in the first step but also as predictors in the second step.

The granulation of mixtures of mannitol and microcrystalline cellulose (MCC) was investigated on small production scale. The effect of the composition of the mixture and the process variables is studied with ordinary least squares regression in **Chapter 5**. The construction of the experimental design and the analysis of the results is handled in detail. The composition of the mixture and the process variables of the first step are used to describe the variation in the granule properties. Extra water seemed to increase the median granule diameter and decreased the percentage of fines. For the modelling of the tablet strength, disintegration time and ejection force also the step two process variables were used. Tablets were mainly influenced by the amount of MCC in the mixture and the compression force. The optimal tablet properties were not obtained at the same settings of the composition and process variables. In a multi criteria optimisation, settings were obtained that provided tablets with sufficient strength, that disintegrate in a short time and have low ejection force.

Chapter 6 uses the same experimental results as **Chapter 5**, however, the granule properties are now used to improve the modelling of the tablet properties. The two-step process is described with two models. The first model uses the process variables of both steps and the composition of the mixture. It can be used at the start of the process to find settings for the process variables and the composition for the granulation of a new mixture. When the procedure of the wet granulation step has to be changed, e.g. one wants to use less binder in the formulation, the first model can be used to find new settings of the other process or composition variables to produce tablets that still meet the specifications. The second model includes the granule properties as descriptors, and can be used in everyday production to improve the prediction of the tablet properties. For both models the multivariate PLS regression method has been used because the granulation properties are highly collinear. A control scheme is introduced

that gives predictions for all tablet properties at various settings of the process variables for the second tableting step for a specific granulation. From the scheme, settings for the moisture content in the granules and compression force can be selected that provide tablets with specified characteristics.

The two-step approach is extended in **Chapter 7**. A multi block partial least squares (MBPLS) method is used for the modelling of the second model. The granulation properties and the composition and process variables are placed in two different descriptor blocks to study separately the effect of the groups of variables on the tablet properties. This improves the interpretability of the PLS model because now it can be shown which block caused a specific variation in the response variable. Two different MBPLS algorithms have been compared, and one suffers from correlation between the descriptor blocks. When the correlation is removed, the method improves.

Chapter 8 describes the use of a multi block partial least squares path model for the modelling of the wet granulation and tableting process. The path model incorporates the hierarchical structure of the process. With the same model, the granule properties are used as responses and as descriptors. Prediction of the tablet properties can be carried out with the same model, whether or not the granule properties are available. The prediction properties of the path model are comparable to the standard PLS and MBPLS models for the tablet properties, however, the prediction of the granule properties is much less with the path model. The regression coefficients for the process and composition variables of the path model are more stable for the introduction of the granule properties than the other PLS models. The path model can be used to study the whole process, but for process control and monitoring, it seems better to use separate models for each response.

The combination of the techniques in the **Chapters 6 and 7** can directly be applied in pharmaceutical industry for control and monitoring of large processes. The two-step approach with two models and a control scheme for the last step can be extended to other two-step or multi-step processes. The multi block calibration method can then be applied for the detection of process failures. When the final product is out of specification limits, the part of the process that caused the problems can easily be detected.

Samenvatting

Multivariate statistische modellering van het farmaceutisch nat granuleer en tabletteer proces

Tabletten worden geproduceerd door poedermengsels, die bestaan uit een geneesmiddel en één of meerdere hulpstoffen zoals vulmiddelen en uiteenvalmiddelen, in een matrijs onder hoge druk samen te persen. Om een grote hoeveelheid tabletten in een keer te produceren worden rondloper tablettenpersen gebruikt, die een half miljoen tabletten per uur kunnen maken. Helaas kunnen de poedermengsels meestal niet direct in de tablettenpers worden verwerkt omdat ze slecht de matrijs in stromen en weinig binding geven zodat de tabletten na het persen meteen weer uit elkaar vallen. Verder kan er ontmenging optreden tussen grote en kleine deeltjes waardoor de verdeling over het gehele mengsel niet meer gelijk is. Daarom ondergaan de poedermengsels een voorbewerking: het granuleren. Bij het nat granuleren wordt in een grote mixer een opgelost bindmiddel aan het mengsel toegevoegd. Hierdoor plakken de poederdeeltjes aan elkaar waardoor er grotere deeltjes ontstaan (de granules) die van elke component in het mengsel de juiste hoeveelheid bevatten. De granules worden gedroogd en vervolgens tot tabletten geperst. Door het granuleren worden de stromings- en bindingseigenschappen van het poedermengsel verbeterd en kan er geen ontmenging meer optreden.

Wanneer in de farmaceutische industrie een tablet wordt ontwikkeld voor een nieuw geneesmiddel is het gedrag van het nieuwe tabletmengsel tijdens het granuleren niet bekend. In de ontwikkelingsfase is er vaak maar weinig van het nieuwe geneesmiddel beschikbaar om te experimenteren. Het is dus van belang dat er al enige kennis is over hoe het mengsel met het nieuwe geneesmiddel zich tijdens het granuleren zal gedragen.

Het onderzoek in dit proefschrift richt zich op het modelleren van het proces van nat granuleren en tabletteren (kalibratie). Het doel van een kalibratie is het maken van een wiskundige model tussen de instellingen van het proces (predictors) en de uitkomst van het proces (respons). De samenstelling en de eigenschappen van het mengsel behoren ook tot de instellingen van het proces. De predictors worden gebruikt om de respons te kunnen voorspellen. Bij multivariate kalibratie worden meerdere predictors gecombineerd om zo tot een beter model te komen. De onderlinge relatie tussen de

predictors wordt gebruikt om extra informatie over het proces te krijgen.

In dit proefschrift wordt getracht een model te maken dat de relatie beschrijft tussen de omstandigheden van het granuleerproces (predictors) en de kwaliteit van de tabletten (respons). De kwaliteit van de tabletten wordt hier uitgedrukt door een drietal eigenschappen: de breukvastheid (de kracht die nodig is om een tablet te breken), de uiteenvaltijd (de tijd nodig om tablet in water uiteen te laten vallen) en de uitwerpkracht (kracht nodig om tablet uit de matrijs de duwen). Het model geeft voorspellingen voor de respons op grond van de instellingen van het proces. Andersom kan het model worden gebruikt om instellingen van het proces te vinden waarbij een optimale (zo goed mogelijk) waarde voor de respons wordt verkregen. Dit laatste noemen we het optimaliseren van het proces.

Om een model te maken worden experimenten uitgevoerd volgens een bepaalde proefopzet. Deze proefopzet stelt de instellingen van het proces vast. Bij de verschillende instellingen van de procesvariabelen worden tabletten gemaakt, en de tableteigenschappen worden gerelateerd aan de instellingen van het proces. Om zoveel mogelijk informatie uit zo weinig mogelijk experimenten te halen is het belangrijk de proefopzet goed te kiezen.

Er zijn verschillende kalibratiemethoden die worden gebruikt om een model te maken. De standaard methoden geven problemen als de predictors van elkaar afhankelijk zijn, zoals de lengte en het volume van een poederdeeltje. Er zijn daarom nieuwe kalibratiemethoden gebruikt die geen problemen hebben met onderlinge afhankelijkheid van de predictors. De kwaliteit van een model wordt getest door de voorspellingen van de respons te vergelijken met de gemeten waarden. Het verschil tussen de gemeten tableteigenschap en de voorspelde waarde is een maat voor hoe goed het model is. Hoe kleiner dit verschil is, des te beter is het model.

In het eerste deel van het proefschrift wordt een poedermengsel van lactose, maiszetmeel en een bindmiddel gegranuleerd met 0, 5 of 50% van verschillende geneesmiddelen. Het doel is modellen te maken die de granulaat- en tableteigenschappen beschrijven afhankelijk van fysische eigenschappen van de nieuwe geneesmiddelen, zoals de oplosbaarheid of deeltjesgrootte. Omdat er geen reeks stoffen bestaat waarbij slechts één eigenschap verschilt, is een multivariate strategie gebruikt om het effect van fysische eigenschappen van de geneesmiddelen op het proces en op de granulaat- en tableteigenschappen te bestuderen.

De keuze van geneesmiddelen waarmee het model wordt gemaakt is belangrijk voor de kwaliteit van het model. Dit is gedaan door van een grote groep geneesmiddelen verschillende fysische eigenschappen te bepalen die belangrijk worden geacht in het proces. Een probleem is de grote hoeveelheid eigenschappen die ook nog van elkaar afhankelijk zijn zoals de gemiddelde deeltjesgrootte van de stoffen en de stromingseigenschappen. Met een wiskundige methode (principale componenten analyse) zijn enkele nieuwe eigenschappen berekend, die onafhankelijk zijn van elkaar, maar fysisch gezien niets voorstellen. Met slechts enkele van deze nieuwe eigenschappen worden de geneesmiddelen bijna net zo goed gekarakteriseerd als met

de grote groep afhankelijk eigenschappen. De geneesmiddelen voor het model zijn gekozen op grond van een grote spreiding in de nieuwe eigenschappen. De gekozen geneesmiddelen moeten representatief zijn voor de gehele groep van geneesmiddelen waarvoor het model moet gelden.

Omdat de gekozen modelgeneesmiddelen sterk van elkaar verschillen wat betreft de oplosbaarheid en deeltjesgrootte, is het niet mogelijk steeds dezelfde hoeveelheid water toe te voegen tijdens het granuleren. In het ene geval wordt het granulaat te nat waardoor er grote klonten ontstaan, en in het andere geval zijn de deeltjes nog nauwelijks aan elkaar gebonden. Er is een robuuste hoeveelheid water gedefinieerd waarbij er voldoende binding tussen de deeltjes heeft plaatsgevonden, maar nog geen overbevochtiging optreedt. Deze robuuste hoeveelheid is bepaald door het vermogen van de granulator te meten dat nodig is om de mengarm met dezelfde snelheid rond te laten gaan terwijl er continu water wordt toegevoegd aan het mengsel. De vermogensmeting levert een karakteristieke curve die uit vijf verschillende fasen bestaat, waarvan begin- en eindpunt per geneesmiddel verschillen. Veel onderzoeken gaven aan dat de hoeveelheid water die overeenkomt met de derde fase bruikbare granulaten oplevert. De hoeveelheid water die nodig is om het midden van de derde fase te bereiken is daarom genomen als de robuuste hoeveelheid water. Voor alle modelgeneesmiddelen geldt dat bij die hoeveelheid water nog geen overbevochtiging heeft plaatsgevonden, maar er al wel voldoende binding bestaat tussen de deeltjes. De robuuste hoeveelheid, die voor alle modelgeneesmiddelen verschilt, is gerelateerd aan de fysische eigenschappen van de stoffen. Een geneesmiddel dat een groot oppervlak heeft, wat kan komen doordat de deeltjes poreus of klein zijn, kan veel water opnemen voordat er overbevochtiging optreedt. Als een geneesmiddel gemakkelijk oplost in het water, verdwijnt een deel van het oppervlak, en kan er minder water worden toegevoegd.

De poedermengsels met 0, 5 of 50% geneesmiddel zijn gegranuleerd met twee verschillende hoeveelheden water, de robuuste hoeveelheid en de hoeveelheid die overeenkomt met het begin van de derde fase van de curve van de vermogensmeting. Op deze manier is bekeken wat het effect van het geneesmiddel is bij een lage dosering (5%) en bij een hoge dosering (50%). Er zijn modellen gemaakt om voorspellingen te doen over de granulaat- en tableteigenschappen wanneer er nieuwe geneesmiddelen gebruikt gaan worden in het lactosemengsel. De modellen zijn ook gebruikt om het effect van de fysische eigenschappen van de geneesmiddelen op de granulaat- en tableteigenschappen te bestuderen. Een multivariate kalibratiemethode is gebruikt om modellen te maken met de fysische eigenschappen van de geneesmiddelen als predictors en de granulaat- en tableteigenschappen als respons.

Bestudering van de modellen heeft geleid tot de volgende conclusies. Als er meer water aan het poedermengsel wordt toegevoegd, neemt de gemiddelde granulegrootte toe, wordt de stroming beter en de uiteenvaltijd van de tabletten langer. Als er 50% geneesmiddel in het mengsel zit is het effect van het geneesmiddel op de granulaat- en tableteigenschappen groot, terwijl bij slechts 5% geneesmiddel het effect maar klein is. De gemiddelde granulegrootte neemt toe als de geneesmiddelen goed in water

oplossen en grote deeltjes hebben. Er is tevens een belangrijke interactie gevonden tussen de oplosbaarheid van het geneesmiddel en de hoeveelheid toegevoegd water. Dit betekent dat het verschil in granulegrootte tussen oplosbare en onoplosbare stoffen toeneemt als er meer water wordt toegevoegd. Als er weinig water wordt toegevoegd is de breukvastheid afhankelijk van de tabletteerbaarheid van het pure geneesmiddel. Als er meer water wordt toegevoegd verschuift de breukvastheid naar het niveau van het standaard mengsel zonder geneesmiddel. De uiteenvaltijd van de tabletten wordt korter als het geneesmiddel een groot oppervlak heeft.

De conclusies uit dit onderzoek kunnen worden gebruikt in de praktijk om op een snelle manier het granuleerproces voor een nieuwe geneesmiddel in het mengsel van lactose en maiszetmeel te optimaliseren. De hoeveelheid water die moet worden toegevoegd, kan worden voorspeld, en ook de eigenschappen van het granulaat en de tabletten die met het nieuwe geneesmiddel gemaakt worden.

In het tweede deel van het onderzoek is aandacht besteed aan de manier waarop het gehele granuleer- en tabletteerproces gemodelleerd moet worden. Het gehele proces bestaat namelijk uit twee stappen, de granuleerstap en de tabletteerstap. De stappen zijn met verschillende modellen te beschrijven. Voor de eerste stap zijn de procesvariabelen zoals de granuleertijd, de hoeveelheid water die wordt toegevoegd en de samenstelling van het mengsel als predictors gebruikt. De granulaateigenschappen zijn als respons genomen. Er kan een model worden gemaakt tussen de predictors en de granulaateigenschappen. Van het granulaat worden vervolgens tabletten geslagen. Er zijn nu andere procesvariabelen van belang zoals de tabletteerkracht. Voor de tweede stap zijn de tableteigenschappen als respons genomen, en de predictors zijn de procesvariabelen van de tweede stap, maar ook de predictors voor de eerste stap hebben invloed op de tableteigenschappen. Als de eerste stap van het proces is uitgevoerd, kunnen de granulaateigenschappen ook als predictors worden gebruikt voor het beschrijven van de tabletten. In het tweede deel van dit proefschrift is uitgegaan van een tabletmengsel dat bestaat uit de vulmiddelen microkristallijne cellulose (MCC) en mannitol en een bindmiddel HPC. Bij deze experimenten zijn geen geneesmiddelen in het tabletmengsel gebruikt.

In eerste instantie zijn de granulaat- en tableteigenschappen van bovengenoemd mengsel beschreven met verschillende modellen waarbij de procesinstellingen en de mengselsamenstelling als predictors zijn gebruikt. De breukvastheid en de uiteenvaltijd nemen toe als er minder MCC in het mengsel zit. Als er met een grotere kracht geslagen wordt, nemen de breukvastheid en de uiteenvaltijd ook toe. De uitwerpkracht neemt af als er meer MCC en water wordt gebruikt. Helaas zijn niet alle tableteigenschappen optimaal bij dezelfde samenstelling van het mengsel of bij dezelfde procesomstandigheden. Er is daarom gezocht naar verschillende instellingen van het proces waarbij alle tableteigenschappen aan een bepaald criterium voldoen. Bij deze instellingen worden tabletten geproduceerd met voldoende breukvastheid, die snel uiteenvallen, en eenvoudig uit de matrijs te verwijderen zijn.

Vervolgens is het tweestaps proces met twee modellen beschreven. Het eerste

model gebruikt de procesvariabelen van beide processtappen en de samenstelling van het mengsel om de tableteigenschappen te beschrijven. Dit model moet worden gebruikt aan het begin van het proces om de juiste instelling voor de procesvariabelen en mengselsamenstelling te vinden. Als er veranderingen in de granuleerstap plaatsvinden, er moet bijvoorbeeld minder bindmiddel gebruikt worden, dan wordt het eerste model gebruikt om te bepalen hoe de andere mengselcomponenten en de procesinstellingen aangepast moeten worden zodat de tabletten de juiste eigenschappen behouden. Het tweede model gebruikt de granulaateigenschappen zoals de deeltjesgrootteverdeling, stromings- en volume eigenschappen om de voorspellingen van de tableteigenschappen te verbeteren. Het tweede model wordt gebruikt in de dagelijkse produktie. Als er twee maal op dezelfde manier een granulaat wordt gemaakt, zullen de granulaateigenschappen toch verschillen door niet bedoelde externe factoren. Dit verschil in granulaateigenschappen werkt door naar de tabletten. Met behulp van het tweede model is een controleschema ontwikkeld voor de tweede stap van het proces, het tabletteren. Dit schema geeft voorspellingen voor de tableteigenschappen bij verschillende instellingen van de procesvariabelen voor de tweede stap, zoals de tabletteerkracht. Met dit schema kan een bepaalde instelling voor de procesvariabelen van de tweede stap worden gekozen om tabletten te maken die voldoen aan gespecificeerde eisen.

Om de interpretatie van de modellen te verbeteren wordt voor het tweede model een multiblok kalibratiemethode gebruikt. De granulaateigenschappen worden apart van de procesinstellingen en mengselsamenstelling beschouwd. Als de tableteigenschappen een onverwachte afwijking vertonen, kan middels het multiblok model direct worden ontdekt of dit komt van verkeerde procesinstellingen of dat het granulaat afwijkende eigenschappen had. Twee verschillende methoden om een multiblok model te maken zijn met elkaar vergeleken. Eén methode leverde slechte resultaten als de predictors in de verschillende blokken van elkaar afhankelijk zijn. Deze methode kan daarom niet worden gebruikt voor het granuleerproces omdat de granulaateigenschappen afhankelijk zijn van de mengselsamenstelling en de procesinstellingen voor de eerste stap.

Tot slot is er nog gekeken naar een nieuw multiblok model waarin rekening wordt gehouden met de hiërarchische structuur van het proces. Het model bestaat uit vier blokken. In het eerste blok zitten de mengselsamenstelling en de procesinstellingen voor de eerste processtap die bekend zijn aan het begin van het proces. Het tweede blok bevat de granulaateigenschappen die afhankelijk zijn van het eerste blok. Het derde blok bevat de tableteigenschappen die van de eerste twee blokken afhankelijk zijn. Het vierde blok bevat de procesinstellingen voor de tweede stap die alleen van invloed zijn op de tableteigenschappen. De granulaat- en tableteigenschappen worden met dit model voorspeld. Indien de granulaateigenschappen na de eerste stap bekend zijn, hoeven ze niet meer voorspeld te worden maar kunnen ze gebruikt worden om de tableteigenschappen te voorspellen. Voorspellingen voor de tableteigenschappen met het model kunnen dus worden uitgevoerd indien de granulaateigenschappen bekend zijn, maar ook als ze nog niet bekend zijn (voor de granuleerstap). Voor het ontwikkelen

van het model zijn de granulaateigenschappen altijd nodig. De eigenschappen van dit multiblok model zijn bekeken. Het model levert vergelijkbare voorspellingen voor de tableteigenschappen als de vorige modellen, maar de voorspellingen voor de granulaateigenschappen zijn niet goed. Het hiërarchische multiblok model kan wel gebruikt worden om het gehele tweestaps proces in z'n geheel te bestuderen, maar voor controle van het gehele proces is het beter verschillende modellen voor de granulaateigenschappen en de tableteigenschappen te gebruiken.

Een combinatie van het controleschema en de multiblok kalibratiemethode voor het tweede model kan direct in de industriële praktijk worden toegepast. De tweestaps aanpak met een controle schema voor de laatste stap kan worden uitgebreid naar andere tweestaps of meerstaps processen. De multiblok modellen zouden dan gebruikt kunnen worden voor het opsporen van fouten in het proces. Als het uiteindelijke produkt onverwachte afwijkingen vertoont kan middels het multiblok model direct worden opgespoord waar in het proces de fout is opgetreden.

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Johan

Stellingen

behorende bij het proefschrift

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

1. Multivariate statistische modellen zijn een goed alternatief wanneer theoretische modellen te kort schieten.

2. Het meten van eigenschappen van tussenprodukten in een meerstapsproces geeft de mogelijkheid tot ‘in-process control’.

3. Als bij het modelleren van een proces de procesvariabelen in blokken worden verdeeld, kan de interpretatie van het model worden verbeterd.

4. Het feit dat MacGregor *et al*. verschillende waarden vinden voor het percentage ‘explained Y’ bij de eerste factor met PLS en multiblock PLS is onmogelijk tenzij verschillende wegingen zijn gebruikt, waardoor de vergelijking niet meer eerlijk is.
   J.F. MacGregor et al., AIChE Journal, 40(5), (1994), 826-838.

5. Zonder een gedegen kennis van experimental design technieken bij de analytisch chemicus leidt het gebruik van de in analytische apparatuur ingebouwde modeleringstechnieken tot ‘Garbage in, garbage out’.

6. Een farmaceutisch technoloog moet handig zijn.
   “A rough way of determing the granulation end-point is to press a portion of the mass in the palm of a hand ... if the ball crumbles under moderate pressure, the mixture is ready for the next stage of processing.” *Lachman et al., The theory and practice of industrial pharmacy, Lea & Febiger, Philadelphia, 1986*.

7. Leren programmeren vergroot het analytisch denkvermogen.

8. Strafvermindering bij gevangenisstraffen zou slechts als uitzondering toegepast moeten worden, niet als regel.

9. Volgens de uitvoeringsinstelling sociale zekerheid voor overheid en onderwijs (USZO) is het solliciteren belangrijker dan het vinden van een baan.

10. Voor een eerlijk verloop van het rallypointsysteem in de vijfde set van een volleybalwedstrijd zou er om en om geserveerd moeten worden tot er een verschil van twee punten is ontstaan.

11. Veel rugklachten worden eerder veroorzaakt door onderbelasting dan door overbelasting.

12. Om de macht van een onderdrukkend regime te verkleinen is het beter de positie van de burgers te verbeteren door middel van economische impulsen dan het land te straffen met een economische boycot.

Johan Westerhuis 22 september 1997