Construction and analysis of mixture-process variables designs as applied to tablet formulations
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Summary

This thesis is concerned with methods for the systematic optimization of pharmaceutical formulations. Such methods are of interest for pharmaceutical industries. In order to limit the problem only one kind of formulation is examined. This is the direct compressed tablet. Several techniques which can be used for the optimization of a direct compressed tablet are described. This kind of tablet is made by mixing the ingredients (among which the pharmacon) for some time, addition of a lubricant and again mixing. From the resulting powder fixed portions are taken which are compressed in a die.

The tablet has a number of physical chemical properties. Of these the crushing strength and the disintegration time of the tablet and the dissolution rate of the pharmacon are used in this dissertation. These properties can be measured relatively quickly. Other tablet properties, such as absorption speed of the pharmacon in the body are also of importance, but need more measurement time. Since this thesis is directed at the methodology of optimization it is not of importance than only the easy measurable properties are used.

There are minimum required values before a tablet can be accepted for use. The search for a combination of mixture and process settings where these or even higher demands are satisfied is called the optimisation of a formulation.

In chapter 1 a differentiation is made between several techniques which can be used for the optimisation of a formulation. One of the methods uses pharmaceutical preknowledge. An example of such a method is to increase of the compression load to obtain a harder tablet, without any measurements at different compression load levels.

In this thesis systematical methods are examined and developed. For these methods it is assumed that based on a number of observations on combinations of settings of the process variables and compositions of the powder the effect of change of these variables on the tablet properties can be quantified. It can most easily be visualized as linear interpolation. The variables which can be adjusted (process variables and mixture composition) are called the independent variables. Tablet properties are dependent on these variables and are therefore called the dependent variables.

The selection of the mixture composition and the settings of the process variables is called the experimental design. The design consists of design points. A design point is therefore one combination of settings of the independent variables. An experimental design has to satisfy certain demands before it is acceptable. A very basic demand is that the independent variables are used at several levels. More specifically, there are design points at one level of the independent variables and design points at another level of the independent variables. This demand follows from the objective of description of the effect of the independent variable on the response. When the independent variable is used on only one level this information is absent. Chapter 1 contains some information about design choice. Experimental design is the main topic in chapters 4 to 6.

The quantification of the effects of the independent variables on the dependent variables is called modelling. The mathematical form is called the model. With the aid
of the model responses can be predicted at settings where no observations are made. With such predictions it is possible to select combinations of settings which result in an optimal combination of responses. Modelling involves several problems. The first concerns use of both variables which describe the composition of a mixture and process variables. Process variables can be varied independently of each other. This is not true for mixture variables. A mixture can most naturally be described by fractions (percentage of the whole). These are the mixture variables which are used. Since these fractions add to 100% (a mixture restriction) it is mathematically difficult to quantify the effect of the components. The following question illustrates this: When the taste of a vodka-orange juice is better after use of less vodka, is this caused by addition of orange juice or by the presence of less vodka? This problem is even more complex when the effects of mixture variables and process variables must be determined at the same time. In chapter 2 problems and approaches for the modelling of mixture variables are described. Chapter 3 is also concerned with the selection of models, but now the problem involves both mixture and process variables.

As stated, chapter 2 is concerned with modelling responses dependent of mixture variables. The purpose of the chapter is twofold. On the one hand these techniques are used in the other chapters, on the other hand they are not yet compounded in pharmaceutical context.

A model consists of several model terms which each describe part of the effects of the independent variables. The problem of model selection is the selection between a too simple model and a too complex model. A too simple model can not approximate the complexity of nature. In case of a too complex an abundance of model terms will cause large error in estimation of each of the model terms. Therefore there are methods for determination of good models and model terms. With mixture variables all techniques which are used for process variables can be used. Some criteria and methods for a model selection are given.

The next part of chapter 2 concerns case deletion diagnostics. With such statistics it can be determined whether individual observations satisfy the model as calculated by the remainder of the model terms. The purpose of such diagnostics is detection of influential observations or outliers. Such observations can influence the model in a great extend and may not be neglected.

In order to demonstrate the model selection three examples of the construction of a model are given.

Chapter 3 is concerned with the selection of model terms for a model with both mixture and process variables. Several methods to do this are known but each method has its disadvantages. A new method is developed to avoid these disadvantages. In the second part of chapter 3 the methods are compared to each other.

The subject of chapter 4 is the construction of designs for combinations of mixture and process variables. For this purpose several methods are available from the literature. Since these methods are reasonably complex and sometimes result in designs with very much design points a method is sought which is not difficult and which results in a sparse design. An adaption of the projection design is developed for this purpose. The result is a method which is mathematically difficult, but this is of no concern for the user when a computer is used.
The designs of chapter 4 are compared with each other in chapter 5. The preferred properties of a design are examined for this purpose. The designs are compared on the size of the prediction intervals of predicted responses and estimated model terms.

A logical continuation of chapter 5 is chapter 6. The designs are compared again, but now with the aid of real data. Therefore a number of observations are made. The data contains design points which are necessary for the designs of chapter 4 but there are also extra design points. The data belonging to a design is used to estimate models. After that the extra observations can be used to examine the prediction capabilities of the models.

One of the conclusions of chapter 6 is that it is difficult to select good models with the designs of chapter 4. This should be more easy when more design points are available. Therefore a method is developed to add design points to a design. Two steps are essentially here. The first is selection of the additional design points, the second is a stop criterion. Several methods are known to do this, but neither of the methods is both simple and suitable for more than two responses. Therefore a new method is developed. This method can be found in chapter 7. After presentation of the method the capabilities of the method are examined.

Chapters 3 to 7 contain aspects of the construction of a model with both mixture and process variables as independent variables. In all these chapters it is assumed that it is possible to construct models which are feasible for the entire design space. However, when the relation between the dependent and the independent variables is very complex it is not feasible to use this approach.

When there is one response then this problem can be avoided by use of local designs and models (steepest ascent). The local model is then used to find a direction in the independent variable space where the dependent variable obtains a preferred value.

With optimization of a tablet formulation several responses are of interest. In general every response results in another direction. In chapter 8 a method is developed with which a direction can be selection which is favourable for several responses.

In chapter 9 this method is demonstrated with two problems. The first of these is simple, the second concerns a design space which consists of both mixture and process variables.