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Multivariate Methods in the Development of a New Tablet Formulation: Optimization and Validation

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ABSTRACT

In a previous study of the development of a tablet formulation approximately 100 excipients were characterized in screening experiments using multivariate design. Acceptable values for important responses were obtained with some of the formulations. The relationships between the properties of the excipients and the responses were evaluated using PLS. In this study additional experiments were performed in order to validate models obtained from the screening study and to find a formulation of suitable composition with desired tablet properties. A formulation with the desired disintegration time was found with the additional experiments and the agreement between observed and predicted values was fair for the tablets that did disintegrate. A limitation of this study was that tablets from four experiments did not disintegrate within the set time limit. The lack of agreement between observed and predicted values of these four experiments was probably due to the nature of one of the factors in the design. Considering the reduced experimental design the results are still encouraging.

Key Words: Multivariate design; Validation; Disintegration time; PCA; PLS.

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INTRODUCTION

Multivariate design[1] was used in a previous study[2] when characterizing approximately 100 excipients in screening experiments. A fractional factorial design in 14 variables, 2^{14-9} design, and 35 experiments was used for the screening of the excipients.

The excipients were divided into different classes according to their potential use as fillers, binders, or disintegrants, see Appendix 1. Excipients can have dual functions.[3] Batches of active pharmaceutical ingredient (API) were also included in the study, see Appendix 1. All excipients and API were characterized by Fourier Transform Infrared (FT-IR) and Near-Infrared (NIR) spectroscopy, which should give information regarding properties that are important for tablet formulation.[4–7] The spectra were pretreated and combined to form the basis of the multivariate characterization. The PCA models were calculated, and the different classes were described by three principal components, except for API, which was described by one principal component.

The multivariate design included 10 factors that described the excipients and the API. The other four factors were part of or related to a mixture design. The mixture design consisted of only three constituents: buffer, disintegrant, and filler. Because the ratio between binder and filler was regarded as more interesting than the actual amount of each excipient, a separate factor described the ratio of binder and filler. The general formulation of the tablets is summarized in Table 1.

Formulations with acceptable values for disintegration time and crushing strength were obtained with some of the formulations. The results from the screening experiments were evaluated using partial least squares projections to latent structures (PLS). In the evaluation quantitative relationships between the formulations, described by principal properties (PP's) for the excipients, and the measured responses were established.

In the present study a formulation will be developed with the aid of a model obtained from the screening experiments. Additional experiments will be performed in order to validate the model and to find a formulation of suitable composition with desired tablet properties.

Table 1. The levels of filler, binder, disintegrant and buffer were varied in the screening study.

Component	Percentage (w/w)
API	13.7
Filler	21.0–59.0
Binder	21.0–59.0
Disintegrant	1.0–5.0
Buffer	0–10.6
Lubricant	1

OBJECTIVE

The objective of this second part of the study is dual; to obtain a formulation with suitable properties and to validate the PLS model for disintegration time.

In order to achieve the first objective the PLS model for disintegration time will be used to predict a formulation with a suitable composition as well as suitable tablet properties, i.e. a disintegration time of 15–30 min (with a target value of 20 min) and acceptable crushing strength and ejection force. The screening study included a diverse set of excipients of varying type and quality, more or less suitable for a commercial product. Undesirable excipients are e.g. those of natural origin where a large batch-to-batch variation may be expected and those that are not in the FDA inactive ingredient guide.[8] A region of interest for the formulation will be identified by the predictions made by the model. This region will then be further investigated with an experimental design.

The second objective is performed by validating the PLS model for disintegration time by comparing the results of the additional experiments of the 2^{5-2} design to the values predicted by the model. Also, the predictive ability of PLS models for friability and Hausner ratio will be evaluated.

METHODS

The methods used, except for simplex optimization, are described in some detail in the article for the screening study.[2]

In the Modde software (see Statistical Analysis) the Optimizer can be used once a response surface is determined. The Optimizer in Modde uses simplex optimization, which is a stepwise strategy.[9] A simplex is a geometric figure with $(k+1)$ vertices where k is equal to the number of variables in a k dimensional experimental domain.

Table 2. Work plan for the additional experiments.

Exp no	Filler t[1]	Filler used	Binder t[1]	Binder t[2]	Binder used	BFMF	Disint amount
1	5.0 (−1)	Xylitab 300	−43.9 (−1)	−32.8 (−1)	Pharmacoat 603	0.5	0.05
2	19.5 (1)	Xylitab DC	−43.9 (−1)	−32.8 (−1)	Pharmacoat 603	−1	0.01
3	5.0 (−1)	Xylitab 300	84.1 (1)	−19.8 (−1)	Pharmacoat 904	−1	0.05
4	19.5 (1)	Xylitab DC	84.1 (1)	−19.8 (−1)	Pharmacoat 904	0.5	0.01
5	5.0 (−1)	Xylitab 300	−37.7 (−1)	19.9 (1)	Methocel E4M	0.5	0.01
6	19.5 (1)	Xylitab DC	−37.7 (−1)	19.9 (1)	Methocel E4M	−1	0.05
7	5.0 (−1)	Xylitab 300	54.9 (1)	18.0 (1)	Metalose 90SH-400	−1	0.01
8	19.5 (1)	Xylitab DC	54.9 (1)	18.0 (1)	Metalose 90SH-400	0.5	0.05
9	9.6 (0)	Xylitab 100	2.1 (0)	7.0 (0)	Metalose 65SH-400	−0.25	0.03
10	9.6 (0)	Xylitab 100	2.1 (0)	7.0 (0)	Metalose 65SH-400	−0.25	0.03
11	9.6 (0)	Xylitab 100	2.1 (0)	7.0 (0)	Metalose 65SH-400	−0.25	0.03

The 2^{5-2} fractional factorial design in PP's for filler and binder, BFMF and amount of disintegrant is shown in this table. Next to the PP's the sign of the original fractional factorial design is given in brackets. The PP's that are given for the chosen fillers and binders are calculated from NIR and FT-IR. In the case of the binders the PP's are from the local model.

To maximize the response, e.g. the disintegration time, the first step is to generate $(k+1)$ starting points. The result in each vertex of the simplex is analyzed and the vertex showing the least desirable result is mirrored through the geometrical midpoint of the other vertices. In this way, a new simplex is obtained. The coordinates, i.e. the experimental settings, for the new vertex are calculated and when the disintegration time for this has been determined from the response surface model, the worst of the three vertices is again mirrored and another simplex is obtained. This procedure is repeated until the simplex has rotated and the optimum is encircled.

EXPERIMENTAL

Manufacturing and Characterization of Tablets

The experiments were carried out according to the work plan in Table 2. All experimental settings are generally the same as for the experiments in the screening study and the same properties have been determined for the tablets.[2] However, disintegrant type was constant (Grindsted PH 157), as well as buffer type (sodium carbonate), amount of buffer (5.8 mg/tabl) and batch of API (API S2 B1 with

Table 3. Results from the additional experiments for tablets compressed at 6 kN together with Hausner ratio.

Exp no	Exp name	Ejection force (N)	Crushing strength (kp)	Disintegration time (min)	Friability (%)	Hausner ratio (−)
1	Op1	32	8.1	35.9	0.3	1.46
2	Op2	80	4.1	10.1	0.7	1.45
3	Op3	62	5.3	7.7	0.7	1.43
4	Op4	44	8.0	18.3	0.2	1.42
5	Op5	46	2.6	3.7	1.3	1.41
6	Op6	59	1.9	7.7	1.4	1.44
7	Op7	59	5.4	9.7	0.5	1.42
8	Op8	47	8.0	>120	0.9	1.50
9	Op9	44	6.5	>120	0.4	1.44
10	Op10	54	6.3	>120	0.5	1.44
11	Op11	48	6.7	>120	0.3	1.44

PP=−75.7). The amount of binder and filler varied with BFMF and was 74.5–78.5 mg/tabl. The tablets were compressed at three different forces, 3, 6 and 9 kN. Responses for tablets compressed at 6 kN are given in Table 3 together with the Hausner ratio.

Statistical Analysis

For the data analysis the Modde 5.0 software for statistical experimental design was used. All principal component analysis (PCA) models were calculated in Simca-P 8.0. All software was supplied by Umetrics AB, Umeå, Sweden.

RESULTS AND DISCUSSION

Calculating the Optimal Formulation

Suitable properties for the formulation are a specified disintegration time of 15–30 min and acceptable values for ejection force (<100 N) and crushing strength (>6 kp). Many of the formulations in the screening design have acceptable values for ejection force and crushing strength.[2] The primary goal is thus to obtain a formulation with the required disintegration time of 15–30 min. Hence the PLS model for disintegration time, for tablets made at 6 kN compression force from the screening experiments, is the basis for all further calculations (Fig. 1). Compared to the default PLS model containing all factors, four factors that were not significant have been removed from this model. The removed factors are; Fill1, Dis1, Bind2 and DisM (see abbreviations in Table 4). Also, the response was log-transformed, which is a variance stabilizing transformation, in order to have an error distribution closer to the normal distribution. The model is based on 27 experiments, i.e. it does not contain formulations of tablets that did not disintegrate within 120 min.

There are formulations from the screening design with the required disintegration time. Alginic acid, the binder in two of the formulations with a disintegration time within the specified interval, was for instance not attractive to use in the formulation, due to its natural origin.

First of all a new formulation will be predicted by the PLS model for disintegration time. All excipients were characterized with FT-IR and NIR and the PP's were calculated as part of the screening study.[2] The composition of the predicted formulation, i.e. the predicted PP's for the different excipients, will be compared with available excipients of the screening study and adjusted when necessary. In this process a region of interest is identified. In the interesting region, around the predicted formulation, a new experimental design will be generated. This should ensure the identification of a potential formulation.

A disintegration time of 20 min was entered as target value for the response in the Optimizer in Modde 5.0.

Predicted formulations, given as PP's, with disintegration times close to the target value are listed in Table 4. These five alternative formulations are the result of several rounds of iterations. For the specified

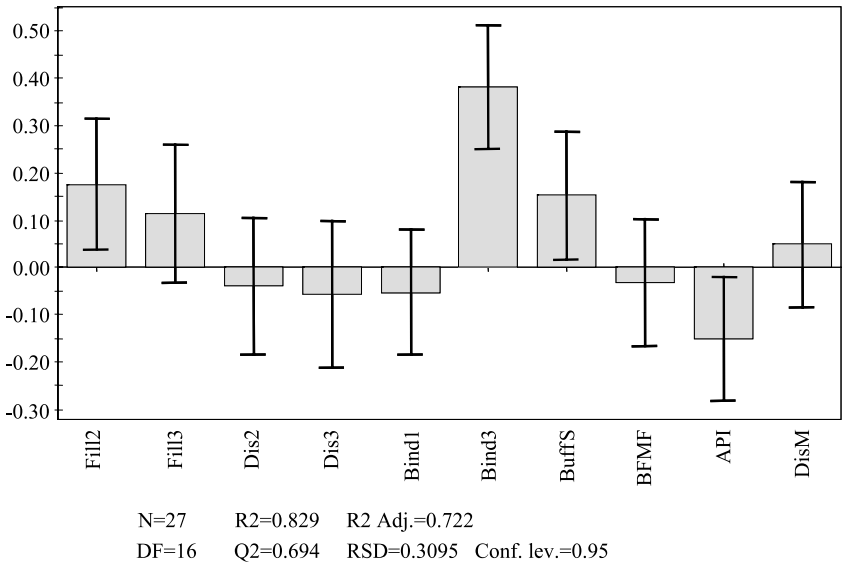

Figure 1. The regression coefficients plot for the PLS model for disintegration time.

Table 4. Formulations predicted by the optimizer together with the actual formulation, given in PP's and excipients.

Abbreviation	Factor name	Alt. 1	Alt. 2	Alt. 3	Alt. 4	Alt. 5	Actual formulation	Excipient
Fill1	First PP for the fillers	58.49	57.66	49.82	50.21	49.82	53.59	Xylitab DC
Fill2	Second PP for the fillers	24.66	−0.01	47.84	20.76	11.84	19.52	
Fill3	Third PP for the fillers	6.40	−12.87	−13.19	−15.87	−13.19	−9.50	
Dis1	First PP for the disintegrants	−0.03	−11.76	−3.05	−39.44	−3.05	−40.86	Grindsted PH 157
Dis2	Second PP for the disintegrants	55.76	55.76	45.28	59.59	57.28	3.40	
Dis3	Third PP for the disintegrants	−28.16	5.02	−27.13	46.29	−27.13	18.44	
Bind1	First PP for the binders	31.10	50.78	46.69	37.23	46.69	48.33	Pharmacoat 603
Bind2	Second PP for the binders	4.89	4.97	13.31	−59.07	13.31	−8.44	
Bind3	Third PP for the binders	−6.66	17.57	−6.06	14.24	5.94	5.08	
API	PP for the API	−78.41	−42.59	−75.72	−39.02	−75.72	−75.7	
BuffS	Buffer type, factor level	−0.64	−0.97	−1	−0.67	−1	−1	
BFMF	BFMF (ratio B/F), factor level	−0.91	−0.83	−1	−0.08	−1	0	
BuffM	Amount of buffer	0.058	0.058	0.058	0.058	0.058	0.058	
DisM	Amount of disintegrant	0.0132	0.0108	0.01	0.0204	0.01	0.0204	
No factor	Amount of binder and filler	0.7818	0.7842	0.785	0.7746	0.785	0.7746	
No factor	Amount of MgSt and API	0.147	0.147	0.147	0.147	0.147	0.147	
	Disintegration time (min)	20.1	19.6	19.3	19.9	19.4	18.5	

target time the Optimizer converged to these fairly similar solutions for the important factors. None of the excipients of these formulations, which are given in the form of PP values, actually exist. However, similar existing excipients can be found and reasonable alternatives can be identified. Alt. 4 was chosen as it is the most feasible option; it has predicted PP's that are similar to existing excipients.

The excipients that match the description are identified; they are given in PP's and as actual excipients in Table 4. Using the PP values of this formulation a disintegration time is predicted which is below the required value (Table 4). However, this formulation is just the basis for the design, thus it should not be a serious problem.

Excipients for Additional Experiments

Selection of Disintegrant

The disintegrant had little or no influence on the disintegration time, Fig. 1, but was still included. Based on the Optimizer sodium alginate (Grindsted PH 157) was selected as disintegrant, Table 4, see column Actual formulation.

Selection of Active Pharmaceutical Ingredient (API)

The predicted PP for the API, Table 4, was −39 and this corresponds rather well to batch API S2 B3 (−35). Due to practical reasons the batch API S2 B1, with the PP value of −75.7, was chosen, Table 4. As the API batch actually seems to influence the disintegration time, this should mean a longer disintegration time (Fig. 1). The range in PP's was caused by differences in particle size and water content.

Selection of Fillers

When selecting additional fillers, other than Xylitab DC which was suggested by the Optimizer, Table 4, for the new design the second PP is most important (Fig. 1).

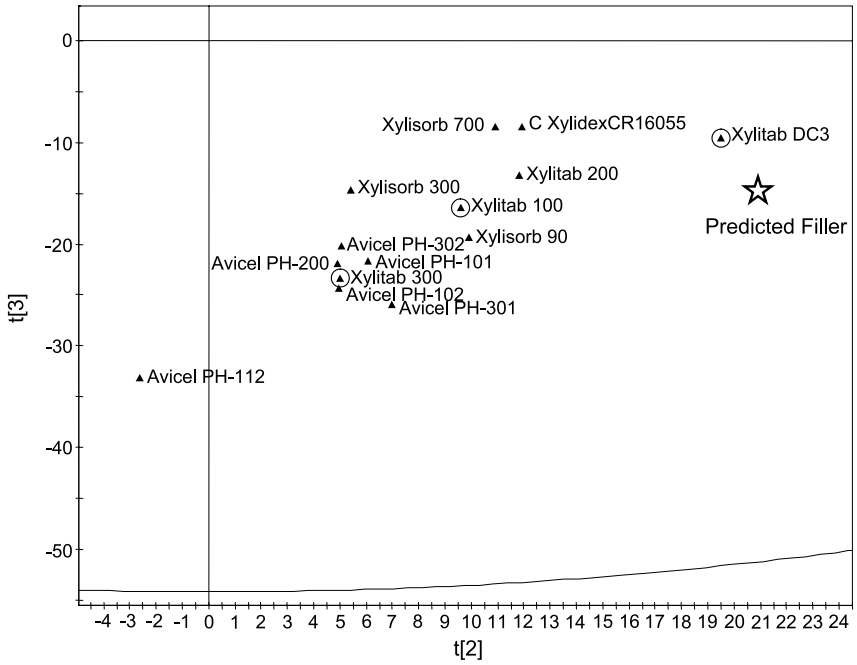

Figure 2. The region of interest for the fillers; a magnified section of the t[2]/t[3] score plot. The PP's that were predicted by the Optimizer are marked by a star in the plot. The fillers chosen for the additional experiments are encircled in the score plot.

The value in the second PP should be around 20 and there are a number of fillers in this area of the t[2]/t[3] score plot (Fig. 2). The value in the third PP offers some guidance and it should be negative.

The only filler to have a value close to 20 in the second PP is Xylitab DC. Instead of limiting the study to only one filler two additional fillers were chosen. Xylisorb 700 and C XylidexCR16055, which have values that are similar to Xylitab DC in the third principal component, are excipients with large particle sizes and were therefore not considered as interesting alternatives for the formulation. Instead of keeping the third PC fixed the values were varied somewhat and three excipients—Xylitab 300, Xylitab 100 and Xylitab DC—, encircled in Fig. 2, were chosen for the additional experiments.

Selection of Binders

The third PP for the binders has a dominating influence in the PLS model for disintegration time (Fig. 1). Naturally, the value in this PP to a large extent dictates the choice of binders for the additional experiments. According to Table 4 the value in the first PP should be positive.

There are mainly two types of excipients with positive values in the first PP; hydroxypropyl cellulose (HPC) and hypromellose (HPMC). Excipients of type HPMC were regarded as a more attractive alternative as binder in this formulation. It was decided to analyze these binders in a separate PCA model. This local model has two significant components according to eigenvalue and the model explains 75% of the variation in the spectral data.

The HPMC binders are well spread in the t[1]/t[2] scores plot (Fig. 3). Hence it was decided to implement the design in both PP's. This implied that Methocel E4M, Pharmacoat 603, Metolose 65SH-400, Metolose 90SH-400 and Pharmacoat 904 were used as binders.

Comparing the interesting area of the t[1]/t[3] score plot for all binders to the separate model the relative positions of the excipients in the respective models are the same (Figs. 3 and 4).

Experimental Design for the Additional Experiments

The basis for the multivariate design for additional experiments is a 2^{5-2} fractional factorial design with 11 experiments, see Table 2.

In the usual way the high and low values in the statistical experimental design are translated into excipients that best correspond to the description of the design, see Table 2. The bases for the choices of

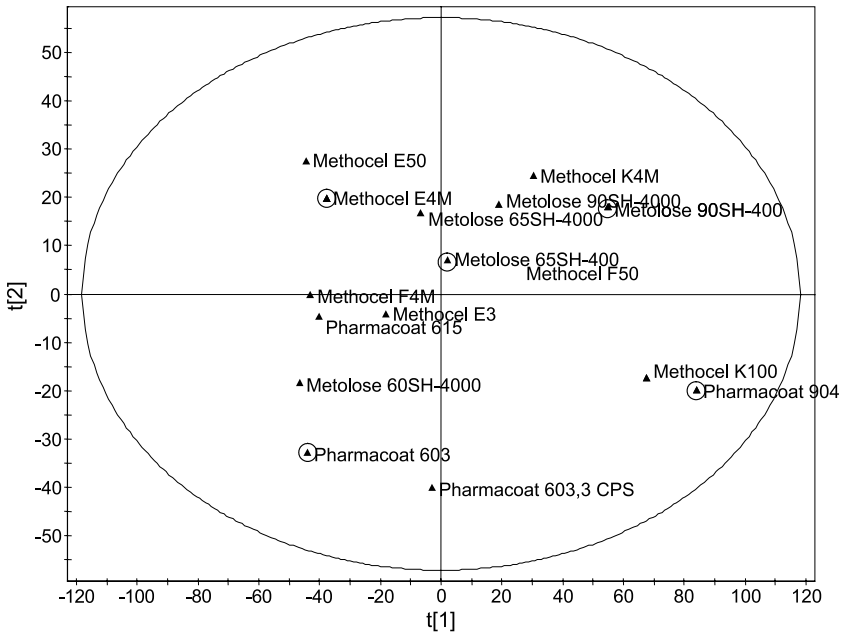

Figure 3. The t[1]/t[2] score plot from the local PCA model for HPMC. The binders chosen for the additional experiments are encircled.

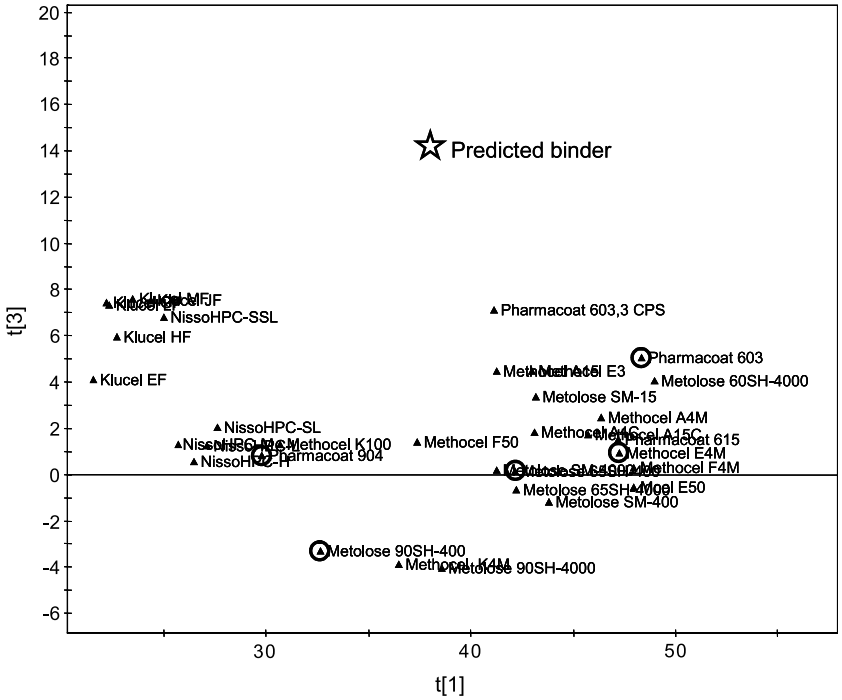

Figure 4. The region of interest in the t[1]/t[3] score plot from the PCA model for the binders. The PP's for the predicted binder are marked by a star in the plot. Excipients that were selected for the additional experiments are encircled.

excipients for this design are the original PCA model for the fillers and the local model for the binders. The fillers and binders are chosen according to the experimental design generated for the additional experiments (Table 2, Figs. 2 and 3).

The factor levels for the ratio between binder and filler (BFMF) are varied between −1 and 0.5 in the additional experiments compared to the screening design. This corresponds to varying the ratio between binder and filler between 30/70 and 60/40. Thus, the interval has been slightly narrowed compared to that of the screening design, which was considered too large. According to Table 3 less binder seems to increase the probability of obtaining the required disintegration time, thus the interval was not symmetrically narrowed. The factor BFMF only controls the ratio between binder and filler, not the actual amounts of the respective excipients, and is described in some detail in the previous publication.[2] It was decided to keep the same interval for the amount of disintegrant as used in the screening experiments.

In the usual way the high and low values in the statistical experimental design are translated into excipients that best correspond to the description of the design, see Table 1. The bases for the choices of excipients for this design are the original PCA model for the fillers and the local model for the binders. The fillers and binders are chosen according to the experimental design generated for the additional experiments (Table 2, Figs. 2 and 3).

Results of Additional Experiments Compressed at 6 kN

The results from the additional experiments compressed at 6 kN together with the Hausner ratio are presented in Table 3.

There is one formulation, Op4 that has a disintegration time close to the target as well as a good ejection force and crushing strength.

Except for Op1 the results compare quite well to the predicted ones (Fig. 5). The prediction error corresponds to 9.5% of the studied interval (1.1–111.9 min). In a study by Harcum et al. the root mean squared error of prediction (RMSEP) is 5.5 min, which is 11.7% of the studied interval (9.6–56.7 min).[10]

The content of binder is almost twice as large in Op1 compared to Op2, but the disintegration time is more than three times longer. In two other formulations, Op3 and Op4, the difference in disintegration time is comparatively short; only twice as long in Op4 compared to Op3. Even with other differences taken into account, e.g. different filler and a different amount of buffer, it is probably safe to say that the relationship between amount of binder and disintegration time is not linear. This is one of the reasons why the BFMF factor is not significant in the model; the differences between the excipients in the study are too large in the studied interval.

Tablets from four of the additional experiments, Op8 and all of the center points, did not disintegrate within the time limit for the disintegration time test. Possible

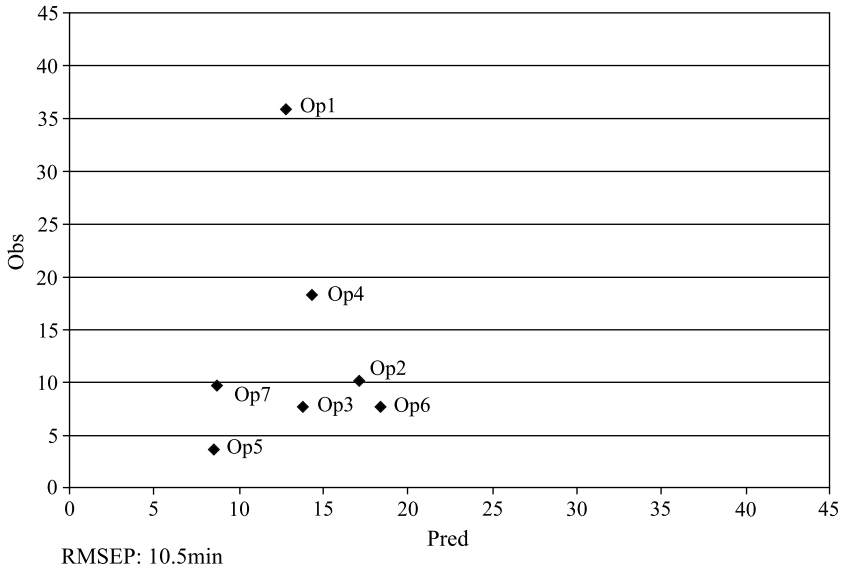

Figure 5. Additional experiments, observed vs. predicted values for disintegration time.

reasons for this are discussed below. These results are not included in the observed vs. predicted plot.

The center points should be formulations with average qualities. Hence, the center point indicates curvature in the data.

The results of the additional experiments prompted the results from the screening design to once again be scrutinized. In the screening design the amounts of binder and filler were varied in the BFMF factor, i.e. not strictly according to an experimental design. It was decided that their ratio was more interesting than the actual amount of each excipient. In reality the amounts were between 21 and 59% of the total formulation.

Regarding the long disintegration times it seems there is a threshold interval for the amount of binder, individual for each excipient, which should not be exceeded in the formulation. Other factors, such as the amounts of the other excipients will influence the amount of binder that is manageable in a formulation. Six of the eight formulations of the screening design that yield non-dissolving tablets contain great percentages of binder, 52% (w/w) or more. The remaining two formulations contain Metolose 90SH-400 and Metolose 90SH-4000, 24% and 25% respectively, as binders. Only two of the formulations that contain either Metolose 90SH-400 or Metolose 90SH-4000, 22% and 21% respectively, disintegrate. These two formulations contain a high amount of glycinate buffer, 10.6%, and formulations with that buffer content all disintegrate within the set time limit. This suggests that for the two mentioned Metolose types the threshold value is in the region of 25% content.

The binder sodium alginate (Grindsted PH 157), also used as disintegrant in the study, is present in varying amounts in four experiments. In two of these the amount of binder is around 23% and the tablets disintegrate within 100 min. The formulation with 52% Grindsted PH 157 disintegrates in 107 min and the one containing 59% does not disintegrate within the time limit. Thus, the threshold value is higher than for the binders mentioned above and is not a problem unless Grindsted PH 157 is used in excessive amounts.

Combined Results of Screening and Additional Experiments

In the combined data sets the PP's calculated for the entire sets of fillers and binders will be used, i.e. the values from the models used for the screening design.

For the combined data sets consisting of both the screening and the additional experiments an account will be given for a limited number of models for the following interesting responses; disintegration time, friability and Hausner ratio. The model for the combined material for crushing strength is even poorer than the model fitted for the screening experiments. No account will be given of the model.

PLS Model for the Combined Data for Disintegration Time

In the analysis of the screening experiments, experiments with tablets that did not disintegrate within the time limit were excluded. In four of the

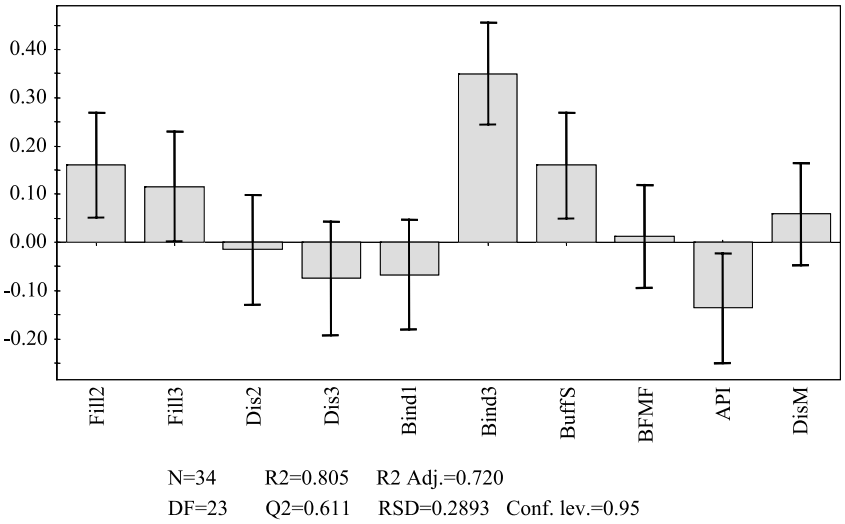

Figure 6. Regression coefficients plot from the PLS model for the combined data for disintegration time.

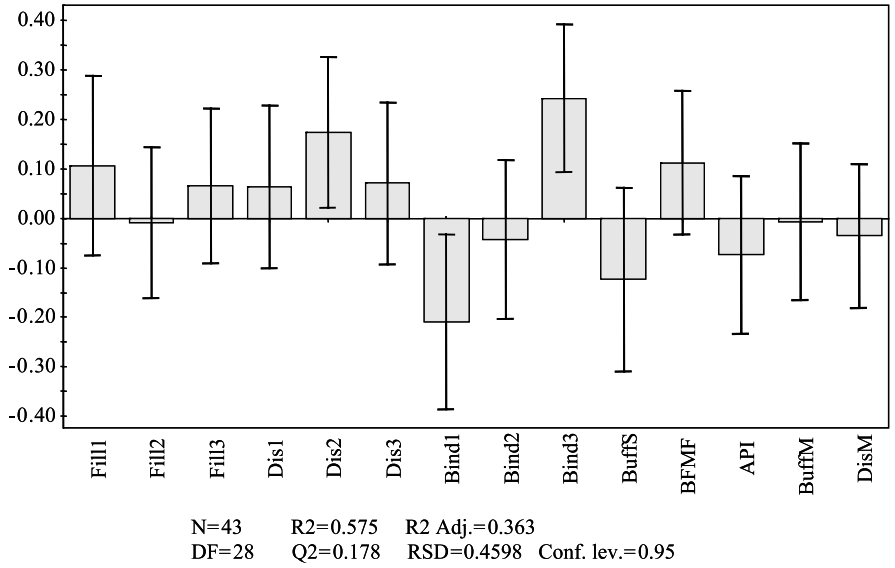

Figure 7. Regression coefficients plot from the PLS model for the combined data for friability.

additional experiments tablets never disintegrated within the test period, and were thus excluded (Table 2). The combined model contains 34 experiments. In order to achieve an error distribution closer to normal the response was log transformed.

The PLS model contains the same model terms as the PLS model for the screening experiments (Fig. 6). According to ANOVA the model is significant and has no lack if fit. The R^2 value is 0.81 and the Q^2 value is 0.61, which indicates a good model, however not as good as the model for the screening experiments. The significant regression coefficients are the same that were observed for the screening experiments. Bind3 is the main influence on the disintegration time. Notable is that the additional experiments verify the importance of the choice of supplier for API.

PLS Model for the Combined Data for Friability

A PLS model for friability has not been previously presented. The PLS model for the screening experiments

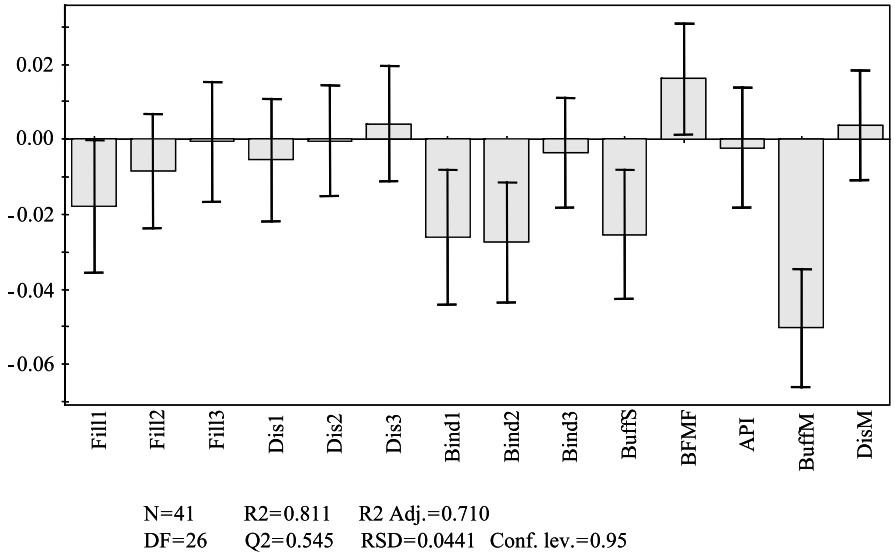

Figure 8. Regression coefficients plot from the PLS model for the combined data for Hausner ratio.

has an RMSEP of 0.6%. This corresponds to a prediction error of 16% of the response interval (0–3.8%) for the experiments in the PLS model.

For the combined data there are no missing values. However, the old center points were excluded due to the deviation in the replicate plot, not shown here. Lack of fit was calculated using the center points from the additional experiments. The response was log transformed in order to obtain an error distribution closer to the normal distribution.

The PLS model has an R2 of 0.58 and a Q2 value of 0.18, is significant according to ANOVA and has no lack of fit (Fig. 7). According to this model the choice of both disintegrant and binder affects the friability.

Appendix 1. All samples of fillers, binders, disintegrants and API that were included in experiments in the screening study.

ObsName	Type of filler	t[1] (52%)	t[2] (20%)	t[3] (14%)
Pearlitol SD200	Mannitol	−4.4	−42.8	17.3
Pearlitol 400DC	Mannitol	7.5	−36.8	17.0
Avicel PH-101	Microcrystalline cellulose	−53.6	6.1	−21.6
Avicel PH-112	Microcrystalline cellulose	−57.9	−2.6	−33.1
Xylitab 200	Xylitol	49.8	11.8	−13.2
C Sperse MD 01314	Maltodextrin	−23.4	25.3	22.4
Maltisorb P90	Maltitol	−16.0	−34.4	−11.2
Maltisorb P200	Maltitol	−10.9	−32.8	−5.8
Isomalt DC 100	Isomalt	7.1	21.1	32.4
ObsName	Type of binder	t[1] (51%)	t[2] (19%)	t[3] (9%)
Pharmacoat 603	Hydroxypropyl methylcellulose	48.3	−8.4	5.1
Metolose 90SH-400	Hydroxypropyl methylcellulose	32.7	4.6	−3.3
Metolose 90SH-4000	Hydroxypropyl methylcellulose	38.6	−1.5	−4.1
Klucel HF	Hydroxypropyl cellulose	22.7	13.3	5.9
Ac-Di-Sol	Sodium carboxymethylcellulose	−18.0	−0.1	−10.4
Avicel RC-581*	Sodium carboxymethylcellulose	−20.8	17.3	−21.8
Kelacid	Alginic acid	−37.3	−6.8	−22.4
Grindsted PH 157	Sodium alginate	−55.3	19.6	18.9
Manucol DMF	Sodium alginate	−49.3	−0.3	31.5
ObsName	Type of disintegrant	t[1] (46%)	t[2] (23%)	t[3] (19%)
Avicel PH-301	Microcrystalline cellullose	50.5	−16.9	13.5
Avicel PH-302	Microcrystalline cellullose	50.9	−5.5	4.7
C Pharm 01980	Maltodextrin	18.5	27.9	−17.4
Gum Guar Powder	Guar Gum	−8.7	5.4	2.6
Grindsted PH060	Alginic acid	−15.6	−56.7	−42.0
Alginic Acid H/FD	Alginic acid	−31.5	−45.7	−44.9
Grindsted PH 170	Sodium alginate	−33.4	−8.5	25.3
Manucol LD	Sodium alginate	−48.3	5.3	11.4
GGK 516	Potato starch	−3.0	57.3	−27.1
ObsName	Type of excipient	t[1] (74%)		
API S1 B3	API	47.7		
API S2 B1	API	−75.7		
API S3 B2	API	0.5		

*The excipient contains microcrystalline cellulose.

Different kinds of disintegrants with a negative value in the second PP decrease the friability. There are few binders with a positive value in the first and a negative value in the third PP, Metolose 90SH-400 and Metolose 90SH-4000 are two alternatives that will decrease the friability.

PLS Model for the Combined Data for Hausner Ratio

The PLS model from the screening experiments has an RMSEP of 0.03. In terms of the studied interval (1.21–1.56) the prediction error is 11%.

There are no missing values in the combined data for the Hausner ratio. The three center points of the additional experiments have identical values, which gave an unrealistically small pure error and lack of fit. For this reason two of the center points of the additional experiments were excluded (Op10 and Op11).

Three of the objects (N5, N9 and N15) in the model deviate from the others in the residuals plot for the PLS model for Hausner ratio (not shown here). Although the standardized residuals are only ±2, the objects were removed and the Q2 increased from 0.27 to 0.53.

The model for Hausner ratio has two PLS components with a R2 of 0.81 and a Q2 of 0.55 (Fig. 8). There is no lack of fit and the model is significant according to ANOVA. The model is similar to the one obtained for the screening experiments alone. Compared to the screening model the regression coefficients for the first PP for the fillers (Fill1), the ratio between binder and diluent in the filler (BFMF) and type of buffer are now significant. A high content of binder in the formulation increases the Hausner ratio.

Use of Sodium glycinate (coded +1 in the worksheet) decreases the Hausner ratio. In this model the influence of the amount of buffer on the flow properties of the powder mixture is more pronounced.

CONCLUSIONS

A formulation with the desired disintegration time was found with the additional experiments.

The agreement between observed and predicted values was fair for the tablets that did disintegrate. A drawback of this study was that tablets from four experiments did not disintegrate within the set time limit, although only two out of nine formulations were involved. The problem with poor agreement between observed and predicted values must in part be due to the BFMF factor. Changing this factor does not affect the predictions, since the factor is not significant in the model. However, the difference in disintegration time is of course quite different with 20% content of binder compared to 40%. This problem can probably be resolved, possibly by reworking the PP's. Another problem is that none of the excipients that were predicted by the Optimizer are commercially available. The possibilities of obtaining excipients of the predicted PP's will be investigated in a future study. Until these problems are resolved the PLS model for disintegration time can not be considered as fully validated.

Considering the reduced experimental design the results are encouraging.

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REFERENCES

1. Wold, S.; Sjöström, M.; Carlson, R.; Lundstedt, T.; Hellberg, S.; Skagerberg, B.; Wikström, C.; Öhman, J. Multivariate design. Anal. Chim. Acta **1986**, *191*, 17–32.
2. Gabrielsson, J.; Lindberg, N.-O.; Pålsson, M.; Nicklasson, F.; Sjöström, M.; Lundstedt, T. Multivariate methods in the development of a new tablet formulation. Drug Dev. Ind. Pharm. **2003**, *29* (10), 1053–1075.
3. Peck, G.E.; Baley, G.J.; McCurdy, V.E.; Banker, G.S. Tablet formulation and design. In *Pharmaceutical Dosage Forms*, 2nd Ed.; Lieberman, H.A., Lachman, L., Schwartz, J.B., Eds.; Marcel Dekker, Inc.: New York, 1989.
4. Pasikatan, M.C.; Steele, J.L.; Spillman, C.K.; Haque, E. Near infrared reflectance spectroscopy for online particle size analysis of powders and ground materials. J. Near Infrared Spectrosc. **2001**, *9* (3), 153–164.
5. Rhodes, C.T.; Morisseau, K. Tablet evaluation using near-infrared spectroscopy. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker, Inc.: New York, 2002; Vol. 3, 2689–2700.
6. Andre, M. Multivariate analysis and classification of the chemical quality of 7-aminocephalosporanic acid using near-infrared reflectance spectroscopy. Anal. Chem. **2003**, *75*, 3460–3467.
7. Gustafsson, C.; Nyström, C.; Lennholm, H.;

Bonferoni, M.C.; Caramella, C.M. Characteristics of hydroxypropyl methylcellulose influencing compactibility and prediction of particle and tablet properties by infrared spectroscopy. J. Pharm. Sci. **2003**, *92* (3), 460–470.

8. Website, F. http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.
9. Lundstedt, T.; Seifert, E.; Abramo, L.; Thelin, B.; Nyström, Å.; Pettersen, J.; Bergman, R. Experimental design and optimization. Chem. Intell. Lab. Sys. **1998**, *42*, 3–40.
10. Harcum, W.W.; Skinner, G.W.; Altekar, M.; Joneja, S.K.; Barnum, P.E.; Guo, J.-H. Modeling the effects of hydroxypropylcellulose in acetaminophen tablet formulation. Drug Dev. Ind. Pharm. **1998**, *24* (10), 911–918.