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Multivariate Methods in the Development of a New Tablet Formulation: Excipient Mixtures and Principal Properties

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ABSTRACT A tablet formulation for direct compression has previously been studied using multivariate design. An optimization study of one of the most important tablet properties, disintegration time, revealed that excipients with Principal Properties (PP's) that were predicted as suitable by the model were not represented within the studied material.

The feasibility of using mixtures of excipients in the multivariate approach to tablet formulation to solve this problem has been investigated in the present study. By mixing different excipients of the same excipient class, it should be possible to obtain mixtures with the predicted PP's, which in turn should give a formulation with the desired properties. In order to investigate the utility of this approach, separate mixture designs were applied to both binders and fillers (diluents).

As reported here, the Partial Least Squares Projections to Latent Structures (PLS) model developed in the previously published screening study has been validated in the sense that the interesting region of the PP space identified in it has been shown to contain excipients, pure or mixed, that give the formulation suitable properties. Formulations with suitable properties were found with the mixture experiments. The local models also offer several alternatives for the composition of the formulation that yield the desired disintegration time.

KEYWORDS Mixture design, D-Optimal, Excipient, Tablet formulation, PCA, PLS

INTRODUCTION

In a previously published study a tablet formulation for direct compression was studied using multivariate design (Gabrielsson et al., 2003). Approximately 100 samples of excipients, with 21 different excipients of varying quality types and from different producers, were included in the screening study. The excipients were divided into different classes according to their potential use. For each of the excipient classes, separate Principal Component Analysis (PCA)

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models were calculated. By applying PCA to the descriptive data, the important information was extracted in a few principal components (PC). The PC's are often referred to as latent variables or the principal properties (PP) of the data set. Each excipient is assigned a value (score) in each PC and can thus be compared and related to other excipients on a continuous scale of PP's. The PP's are assumed to reflect real differences in excipient properties and larger distances between excipients along the PC's reflect bigger differences in behavior. Principal properties (PP) based on spectroscopic characterization of the excipients, as well as the active pharmaceutical ingredient (API), were used to describe the contents of the formulation in the screening study. The latent variables are continuous variables which allows for large numbers of excipients to be screened with relatively few experiments using statistical experimental design.

In the course of optimizing one of the most important tablet properties, disintegration time (dis. time), it was found that there were no excipients with PP's predicted by the model within the studied material (Gabrielsson et al., 2004). Despite this drawback, other excipients for which the important PP's were as similar as possible were used in the optimization study, resulting in a formulation with a disintegration time very close to the target. As a logical first step to investigate the possibilities of obtaining excipient mixtures with the predicted PP's, it was decided to test ternary mixtures of excipients. Would it be possible to obtain excipient mixtures with the predicted PP's? And if so, would these excipient mixtures yield tablets with the desired disintegration time?

Initial tests with mixtures of excipients were encouraging in the sense that the PP's reflected the contents of the mixtures, i.e., there was no dominant absorbance pattern for any of the included excipients.

If successful, the presented approach could potentially accelerate the development of new excipient mixtures to put on the market (Cook, 2003).

OBJECTIVE

The objective of the study was to investigate the feasibility of using mixtures of excipients in the multivariate approach applied to tablet formulation. By mixing different excipients of the same class, it should be possible to obtain mixtures with PP's that match those predicted by the model. This should, in turn, give a formulation with suitable properties, i.e., a disintegration time of 15–30 min with acceptable crushing strength and ejection force.

Separate mixture designs were applied to both binders and fillers in order to investigate the approach with mixtures. Including excipients of varying quality should result in mixtures with diverse characteristics. For the multivariate characterization to be successful, the PP's should reflect the characteristics of the excipient mixture as well as the contents of the mixture. Experiments were performed to assess the feasibility of this approach to tablet formulation.

METHODS

Mixture Design

Due to the nature of formulations, mixture designs are commonly used in pharmaceutical applications (Waaler et al., 1992; Bolhuis et al., 1995; Wells et al., 1996; Bodea & Leucuta, 1997; Geoffroy et al., 1998). In a mixture design, the sum of all components is 100%. Mixture factors are expressed as the fraction of the total amount and their experimental ranges lie between 0 and 1 (Fig. 1). This means that they cannot be changed completely independently of one another. The geometrical representation of a mixture design with two factors is a line, with three factors it is a triangle, and in the case of four factors a tetrahedron. Two examples are illustrated in the highlighted parts of the designs in Fig. 1: an axial design to the left and a simplex centroid design to the right.

A mixture factor can be a formulation factor or a filler factor. Only one mixture factor can be defined as filler. Formulation factors are the usual mixture factors used in formulations and have specifically defined experimental ranges. Eriksson et al. (1998) have published a comprehensive article on the topic of mixture design.

D-Optimal Design

D-Optimal designs are computer-generated designs that are particularly useful when a constrained region is studied and no classical design is available (Eriksson et al., 2000).

The D-Optimal design maximizes the determinant of the $X'X$ matrix, which is an overall measure of the information in X (Mitchell, 2000). Here, X is the

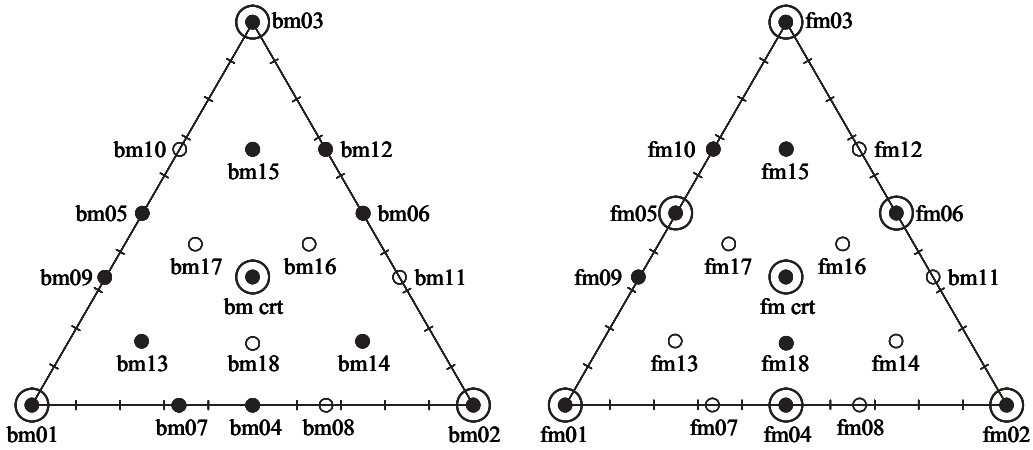

FIGURE 1 **Two examples of mixture designs for ternary excipient mixtures. The encircled filled circles represent mandatory experiments. Mixtures 13, 14, and 15 in the respective examples represent optional experiments. The design to the left supports a linear model and the design to the right a quadratic model. Figure 1 also provides an overview of the mixture designs, full cubic simplex centroid with additional interior check points, for the mixtures of binders (bm) and fillers (fm) that were prepared for this study. The multivariate characterization only includes the mixtures corresponding to the filled circles.**

model matrix in the regression $y = Xb + e$. Geometrically, this corresponds to maximizing the volume of X in a space of k dimensions.

By choosing N experiments from a candidate set that consists of all potential experiments, the design can be tailor-made to meet specific demands regarding variables such as the number of experimental runs and experimental constraints. Full factorial and fractional factorial designs fulfill the D-Optimal criteria.

EXPERIMENTAL

In the first investigation (Study 1), a full cubic simplex centroid mixture design with additional interior check points was used to create two sets of 21 mixtures (Fig. 1) each weighing 2 g. Thus, a total 42 of excipient mixtures were prepared according to the mixture design. Only the mixtures corresponding to the filled circles were included in the multivariate characterization (Fig. 1). In order to select mixtures to test experimentally, a D-optimal design was generated from a candidate set containing all binder and filler mixtures described by PP's. The design contains many experiments with pure excipients since these will span the largest possible experimental domain. Including many experiments with pure excipients also makes it possible to evaluate the designs as ordinary mixture experiments, if necessary. The design in PP's corresponds to two separate mixture designs. All other constituents of the formulation were set according to Table 1.

In the second investigation (Study 2), only nine selected binder mixtures, each of 5 g, were included (Fig. 2). The mixtures were selected by generating two factorial designs, with one common center point, within the mixture domain spanned by the three excipients.

Spectroscopic Characterization

All excipients that were specifically included in this work, i.e., binders and fillers, are presented in Appendix I. All other constituents of the formulations were set according to Table 1 and were the same as those employed in previous studies (Gabrielsson et al., 2003, 2004). The constituents of the mixtures were weighed and put into small

TABLE 1 **Levels of the Constituents of the Investigated Formulation**

Ingredients	Percentage (w/w)
API	13.70
Filler in design	58.47
Binder in design	20.00
Additional filler	2.78
Flavor1	1.70
Flavor2	0.60
Sweetener	0.76
Lubricant	2.00

With the exception of the additional filler, the total amounts of filler and binder are fixed, and only the respective fillers and binders that make up these constituents are varied according to the mixture design.

APPENDIX I Materials Included in the Study

Excipient	Official name	Study	Manufacturer	Country
Pharmacoat 603	Hypromellose	1 and 2	Shin-Etsu Chemical Co. Ltd.	Japan
Kollidon K90	Povidone	1	BASF	Germany
Klucel EF	Hydroxypropyl cellulose	1	Hercules Incorporated	USA
Pearlitol SD200	Mannitol	1 and 2	Roquette Freres	France
Isomalt DC100	Isomalt	1	Palatinit GmbH	Germany
Xylisorb 700	Xylitol	1	Roquette Freres	France
Klucel HF	Hydroxypropyl cellulose	2	Hercules Incorporated	USA
Grindsted PH 157	Sodium alginate	2	Danisco Landerneau SA	France

glass containers. All glass containers were placed inside a box and were blended manually for 10 min with vertical and horizontal motions as a convective mixer. The samples were taken from the glass containers and placed on the sample holders using a spatula or spoon.

Due to problems, possibly associated with de-blending of the samples when placed on the sample holder accessories of the respective instruments, several replicate runs were required for each of the mixtures in order to obtain reliable results and to determine the variance. Hence, to save time, only selected mixtures from the mixture designs were characterized by NIR (400–2500 nm; NIR Systems 6500 Spectrophotometer, FOSS, Silver Spring, MD, USA) and FT-IR (649–4500 cm^{-1}; Mattson Fourier-transform Infinity 60AR, Madison, WI, USA, equipped with a Golden Gate Single Reflection Diamond ATR accessory, Graseby Specac, Orpington, Kent, UK) spectroscopy (Fig. 1). Because of a laser fault, the FT-IR characterization in Study 2 was performed using a different FT-IR system (a Mattson Fourier-transform Genesis I instrument, Madison, WI, USA) equipped with the sample holder accessory. The latter system gave noisier spectra, but this did not significantly affect the results of the multivariate characterization. The digitized NIR (1050 variables) and FT-IR (1997 variables) spectra were the variables used in the multivariate characterization.

Separate PCA models were calculated for the binders and filler (diluent) mixtures. The spectra of the different mixtures were also imported into existing PCA models and their principal properties were predicted by the models.

Manufacturing and Characterization of Tablets

The experiments were carried out according to the work plans shown in Tables 2 and 3. The tablets were compressed at 6 and 8 kN by a Korsch EKO (Germany) tabletting machine equipped with a computerized system (PuuMan, Portable Press Analyzer, Finland) for collecting compression data. About 80 tablets were made from each batch.

The disintegration time (ErwekaZT 3–4, Germany) was recorded for six tablets and the average was calculated. The crushing strength (crush. str.) (Schleuniger 2E/205, Switzerland) was recorded for ten tablets and the average was calculated.

Responses for tablets compressed at 6 kN are given in Tables 2 and 3.

Statistical Analysis

For the generation and analysis of experimental designs, Modde 6.0 software for statistical experimental design was used. Predictions of PP's were made in Simca-P 8.0. Separate PCA models of filler and binder mixtures were calculated in Simca-P 10.0. All software was supplied by Umetrics AB, Umeå, Sweden. The methods used, except for mixture design and D-Optimal design, are described in some detail in the article reporting the screening study (Gabrielsson et al., 2003).

RESULTS AND DISCUSSION

The binders in Study 1 were chosen to match the predictions made using a PLS model for disintegration time based on the screening experiments. The idea was to fill the void in the interesting area of the PP space and thus obtain an excipient mixture with a certain property that was lacking in the original material. This excipient mixture would then be expected to yield a formulation with the desired disintegration time. Binary mixtures would probably have sufficed for this objective, but ternary mixtures were chosen as they offer more alternatives.

TABLE 2 **The D-Optimal Design for the Mixture Experiments Has 13 Experiments and Three Replicates of the Center Point (N14-N16)**

Exp no	bindmix	Pharmacoat 603 (%)	Kollidon K90 (%)	Klucel EF (%)	bind1	bind2	bind3	fillmix	Pearlitol SD200 (%)	Isomalt DC 110 (%)	Xylisorb 100 (%)	fill1	fill2	fill3	Dis.time (min)	Crush. str. (kp)
N1	bm01	100	0	0	47.3	–8.8	4.4	fm01	100	0	0	–4.0	–37.2	19.1	10.2	6.7
N2	bm02	0	100	0	0.6	–0.4	45.0	fm01	100	0	0	–4.0	–37.2	19.1	12.5	3.2
N3	bm03	0	0	100	28.6	5.1	5.9	fm01	100	0	0	–4.0	–37.2	19.1	21.5	4.9
N4	bm01	100	0	0	47.3	–8.8	4.4	fm02	0	100	0	9.8	26.6	33.7	9.7	5.1
N5	bm02	0	100	0	0.6	–0.4	45.0	fm02	0	100	0	9.8	26.6	33.7	15.0	3.6
N6	bm03	0	0	100	28.6	5.1	5.9	fm02	0	100	0	9.8	26.6	33.7	27.4	6.3
N7	bm01	100	0	0	47.3	–8.8	4.4	fm03	0	0	100	62.3	7.9	–3.8	5.7	0.8
N8	bm02	0	100	0	0.6	–0.4	45.0	fm03	0	0	100	62.3	7.9	–3.8	5.7	0
N9	bm03	0	0	100	28.6	5.1	5.9	fm03	0	0	100	62.3	7.9	–3.8	7.7	1.9
N14	bmcrt	33	33	33	24.8	1.0	17.1	fmcrt	33	33	33	13.5	–1.5	29.1	12.7	3
N15	bmcrt	33	33	33	24.8	1.0	17.1	fmcrt	33	33	33	13.5	–1.5	29.1	13.0	3.1
N16	bmcrt	33	33	33	24.8	1.0	17.1	fmcrt	33	33	33	13.5	–1.5	29.1	13.0	3.2
T1 (N10)	bm06	0	50	50	1.0	7.3	32.4	fm01	100	0	0	–4.0	–37.2	19.1	14.7	4.1
T2 (N11)	bm05	50	0	50	40.6	–2.1	4.3	fm03	0	0	100	62.3	7.9	–3.8	6.1	1.4
T3 (N12)	bm07	67	33	0	33.0	–4.1	14.7	fm03	0	0	100	62.3	7.9	–3.8	10.4	4.9
T4 (N13)	bm04	50	50	0	21.3	–1.8	23.0	fm01	100	0	0	–4.0	–37.2	19.1	9.2	4

The binder and filler mixtures are given in the amounts (% is w/w of the respective mixtures) of the respective excipients as well as in PP's (bind1, bind2, bind3 for binders, and fill1, fill2, fill3 for fillers). The measured values for disintegration time and crushing strength are also presented. The last four experiments in the table were used as a test set in a separate analysis.

TABLE 3 **Experimental Settings for Study 2 with Contents of the Respective Binders (% Is W/W) and Predicted PP's (bind1, bind2, bind3) for the Binder Mixtures**

Exp no	bindmix	Klucel HF (%)	Pharmacoat 603 (%)	Grindsted PH 157 (%)	bind1	bind2	bind3	Dis. time (min)	Crush str. (kp)
N17	bm20	100	0	0	20.1	11.8	9.9	10.3	4.0
N18	bm21	45	5	50	–31.9	22.4	19.3	43.5	4.2
N19	bm22	5	45	50	–8.2	9.6	12.8	46.0	4.5
N20	bm23	30	70	0	31.6	–0.8	6.5	10.7	4.0
N21	bm24	56	5	39	–23.6	20.0	19.7	31.5	4.4
N22	bm25	15	25	60	–28.1	15.4	16.1	45.9	4.3
N23	bm26	15	60	25	8.8	6.1	10.7	8.4	4.0
N24	bm27	56	39	5	20.9	6.5	9.6	10.0	4.2
N25	bm28	35	35	30	–0.1	11.5	15.1	9.6	4.1

The responses are also shown.

Study 1 included a binder, Kollidon K90 (povidone), which was not part of the experimental domain of the screening study (Fig. 8). Kollidon K90 was included in order to obtain mixtures with PP's that match the first PP of the binders in the predictions reported in the optimization study (Gabrielsson et al., 2004). However, Kollidon K90 did not have the expected impact on the excipient properties, and for formulations containing this binder the agreement between observed and predicted values was poor. The results of Study 1 led to a second study (Study 2), which included only binders that were included in the experimental domain in the screening study. The new binder mixtures fill a void inside the previously explored experimental domain. This increases the probability of obtaining a good agreement between observed and predicted values. The results of Study 1 showed a good correlation between the PP's and the contents of the mixtures. Hence, the choice of binder mixtures in Study 2 was based on content, which meant that fewer mixtures were made.

The fillers were only varied in Study 1. Excipients for the filler mixtures were chosen out of general interest in testing this approach to tablet formulation, rather than a desire to meet specific principal properties. The fillers chosen span a wide range in properties, e.g., particle size.

Mixture Designs of Binders and Fillers

In Study 1, in which both binders and fillers were included, the excipients were mixed and blended according to a full cubic simplex centroid mixture design. Additional interior check points were also added to cover the mixture area as well as possible (Fig. 1).

A total of 13 binder mixtures were included in Study 1, see Fig. 1 and Table 2. Three of these were pure excipient samples and the other ten contained two or three binders. Eleven filler mixtures were included in the study (Fig. 1 and Table 2).

The strategy for selecting binder mixtures for Study 2 was somewhat different. Two factorial designs, with one common center point, were generated within the mixture domain spanned by the three excipients and the mixtures were characterized post selection (Fig. 2). Study 2 included only one pure excipient; the other experiments consisted of binary or ternary mixtures, see Table 3. One of the experiments contained only Klucel HF (hydroxypropyl cellulose) as binder. The reason for including this experiment was to compare it with a similar experiment in the screening design [N5 in (Gabrielsson et al., 2003)] in order to obtain an estimate of the influence of flavors and other additives.

Large variations between replicate runs in the spectral analysis of both binders and fillers was observed, especially in the FT-IR analyses, possibly due to problems associated with de-blending of the samples when placed on the sample holder accessory. For the multivariate characterization to be reliable, at least three replicate runs for each mixture were needed, necessitating a reduction in the number of mixtures that were characterized in the study. All spectra were then subjected to a PCA and deviating objects were excluded from the investigation. Averages of the remaining spectra were used in the subsequent analyses.

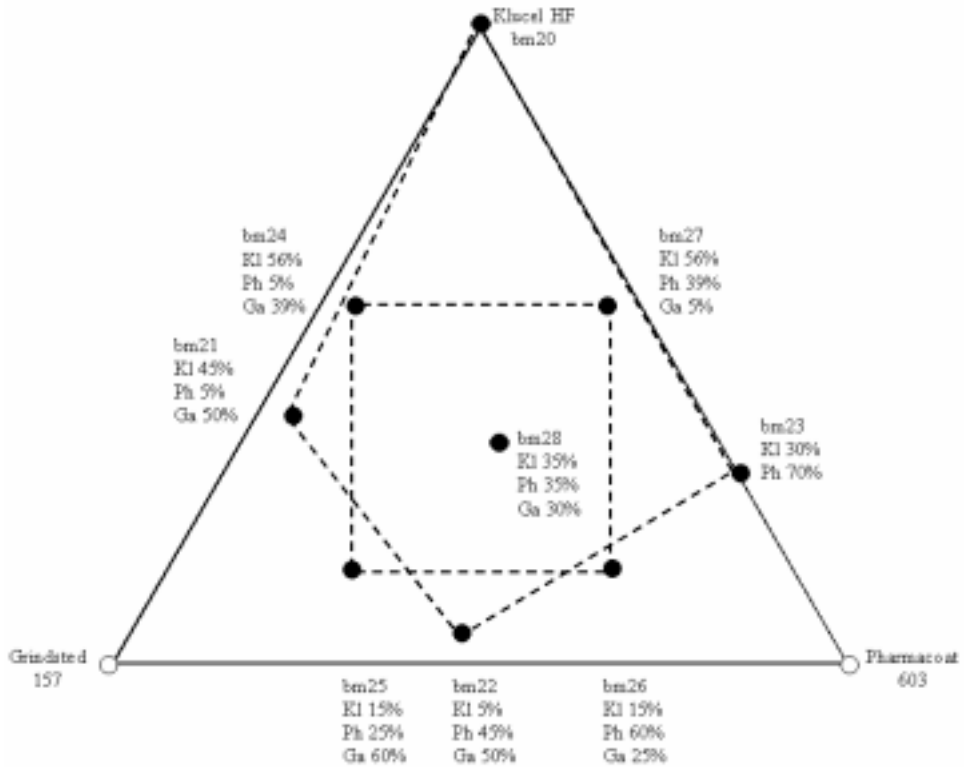

FIGURE 2 **Filled Circles Represent the Binder Mixtures Selected for Study 2. Binder Mixtures bm20–bm23 and bm24–bm27 Each Constitute Approximate Fractional Factorial Designs; the Former Somewhat Ill-conditioned, with bm28 As Center point.**

Multivariate Characterization of Binder and Filler Mixtures

PCA Models for Binder and Filler Mixtures

A separate PCA model was calculated for the 13 binder mixtures included in Study 1. The model has two significant components, according to the eigenvalues, and explains 95% of the variance in X with a Q^2 of 0.87.

With two components, the effects of varying the contents of the ternary binder mixture can be explained (Fig. 3).

In the PCA model for the filler mixtures of Study 1, there are 11 objects. The model has two significant components, according to the eigenvalues, and explains 86% of the variance in *X* with a Q^2 of 0.66. The filler mixtures are not as well explained as the binder mixtures.

In the PCA model for the filler mixtures, there is no linear relationship between the principal properties and the contents of the mixtures (Fig. 4). The reason for this is unclear, but de-blending due to a large difference in mean particle size between Pearlitol SD200 (mannitol, 200 μm) and Xylisorb 700 (xylitol, 800 μm) is a possible explanation.

A two-component PCA model of the binder mixtures of Study 2 explains 91% of the variance in X and has a Q^2 of 0.83.

The PCA model reflects the mixture character of the objects well (Fig. 5). The pure excipients that were part of the binder mixtures in Study 2 are included in the PCA model.

Prediction of Principal Properties for Mixtures of Study 1

The data sets for the binder and filler mixtures of the Study 1 set were imported into the respective PCA models and the PP's were predicted. Spectra are automatically subjected to Standard Normal Variate (SNV) transformation when imported into a project that has been SNV transformed (Barnes et al., 1989).

A number of objects, all of which have a large content of Kollidon K90, have a greater distance to the model in *X* (DModX) than the critical value (Fig. 6), being outside the 95% confidence interval for the model (Eriksson et al., 2001).

All binder mixtures are within the area covered by the model for the screening experiments (Fig. 7). The

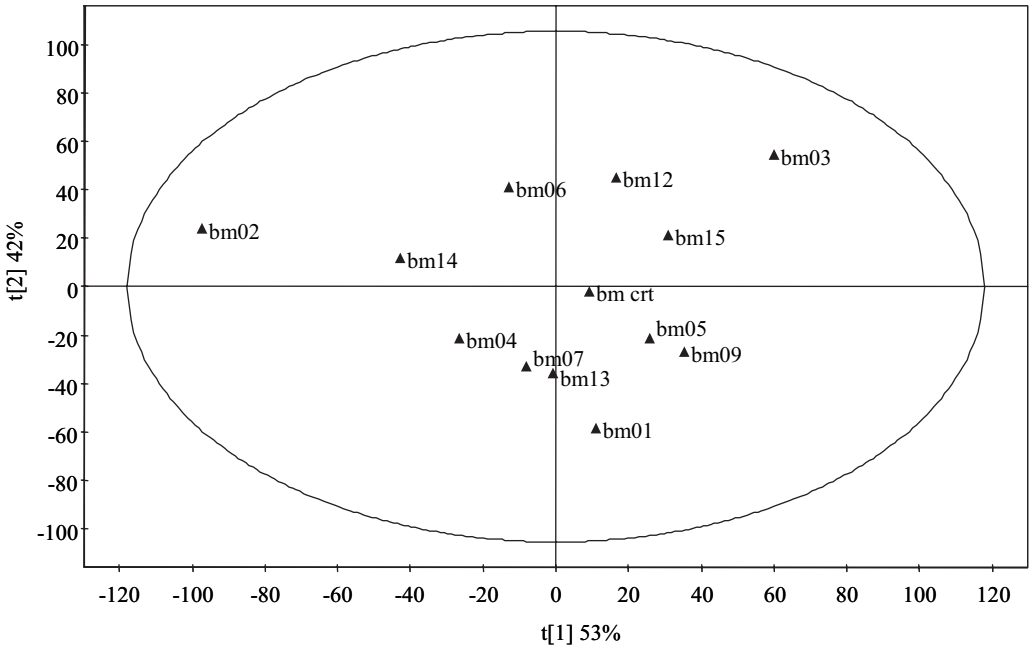

FIGURE 3 **A *t*[1]/*t*[2] Score Plot from a Separate PCA Model for the Binder Mixtures of Study 1.**

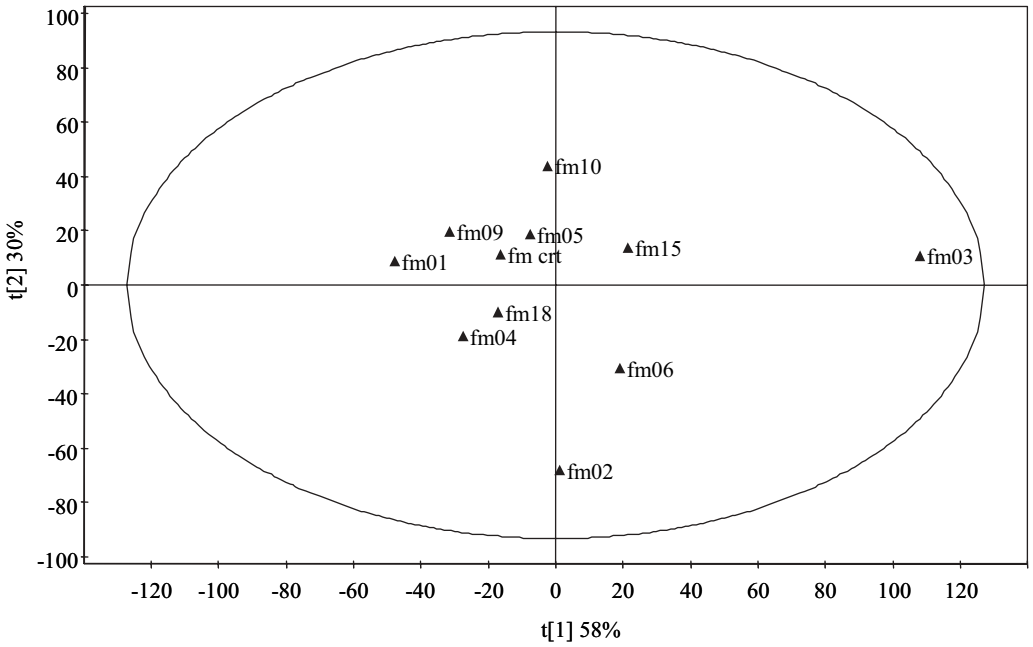

FIGURE 4 **The *t*[1]/*t*[2] Score Plot from a Separate PCA Model for Filler Mixtures.**

contours of a mixture design can be discerned in the score plot.

Only three of the binder mixtures are covered by the model for the screening experiments (Fig. 8). Kollidon is even outside Hotelling's T2 ellipse, a 95% confidence interval, and while this is expected it is not an ideal condition for predictions (Jackson, 1991).

Only a few of the filler mixtures are outside of the experimental domain of the screening study in the *t*[1]/*t*[2] plot (not shown here). More of the filler mixtures are outside the investigated area in the t[1]/t[3] scores plot (Fig. 9).

All binder mixtures of Study 2 belong to the model of the binders, in terms of both PP's and DModX.

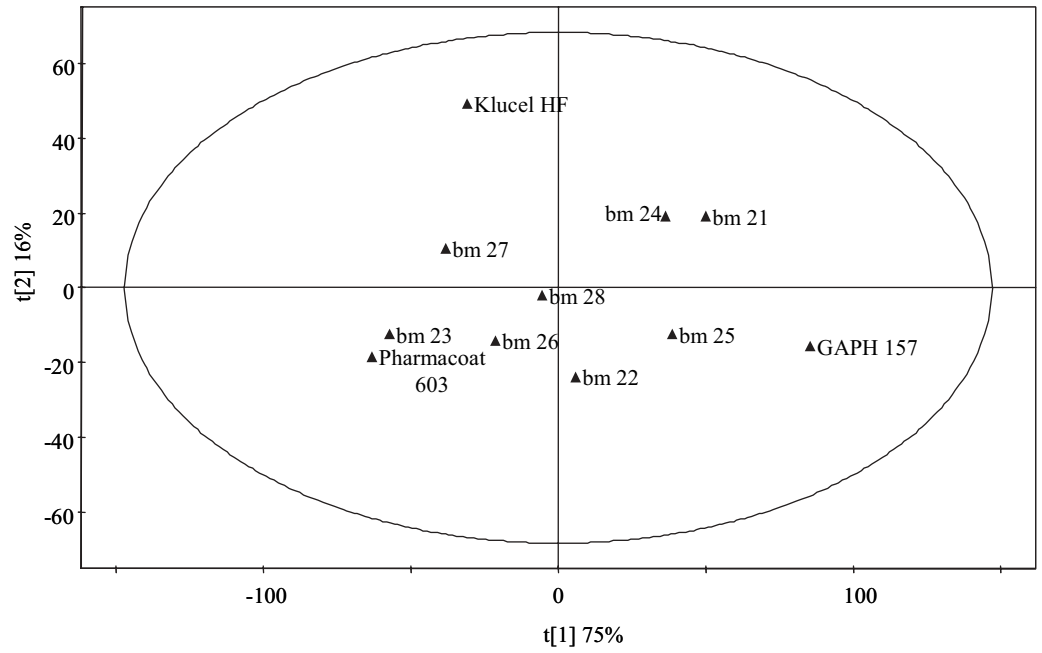

FIGURE 5 **The *t*[1]/*t*[2] Score Plot from the PCA Model for the Binder Mixtures of Study 2.**

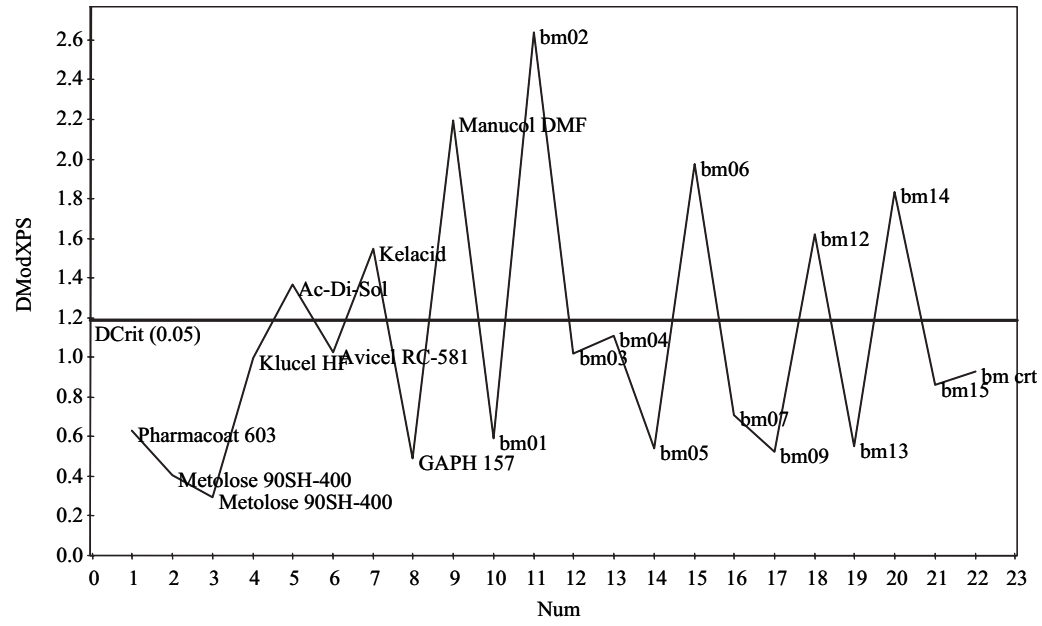

FIGURE 6 **DModX Plot for the Binders of the Screening Design and the Binder Mixtures of Study 1. Note That the Values for the Binder Mixtures Are Predicted.**

Experimental Design for Mixture Experiments

Based on the predicted PP's of the excipient mixtures, a D-Optimal design with 16 experiments was generated for Study 1 (see Table 2). The condition number for the D-Optimal design in Table 2 is high (58), showing that factors in the design are correlated. This is due to the mixture designs on which it is based. In Study 2, fractional factorial designs were applied in the mixture region (Fig. 2). The condition number for the design in Table 3 is 26. Again,

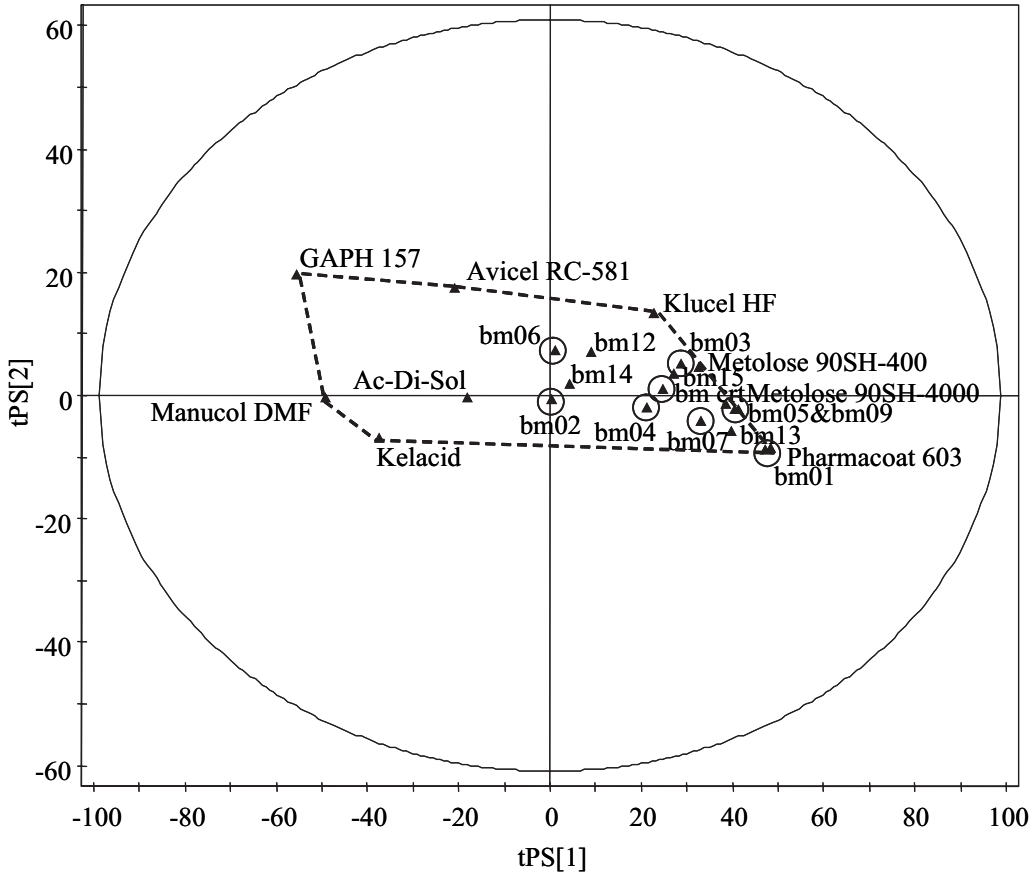

FIGURE 7 **The *t*[1]/*t*[2] Score Plot for the Binders of the Screening Design and the Binder Mixtures. The Highlighted Area Is the Part of the Score Space That Was Investigated in the Screening Design. The Binder Mixtures Chosen for the Experiments of Study 1 Are Encircled. Note That the Values for the Binder Mixtures Are Predicted.**

the high condition number is due to the constraints associated with mixture designs. The resources did not permit replicates of the center point to be applied (see Table 3).

Results of Mixture Experiments

During the course of this project the composition of the basic formulation has changed. All experiments in this study lack a disintegrant but contain flavors as well as other additives that were not included in the screening experiments, making these experiments unsuitable for model validation. Instead, separate local models were calculated for the mixture experiments (see below).

Evaluation of Results from Study 1

The results from Study 1 of mixtures compressed at 6 kN are presented in Table 2. There are a couple of formulations that have a disintegration time close to the target as well as an acceptable crushing strength, i.e., N3 and T1.

A separate Multiple Linear Regression (MLR) model was calculated for Study 1. The model has four factors (bind1, bind3, fill2, and fill3) (see Table 2). The binder and filler mixtures are adequately described using only two components (see, for example, Figs. 8 and 9) and, using only four factors instead of six, the condition number is considerably improved.

The design has a condition number of 6.1 and the model is significant according to analysis of variance (ANOVA), but has significant lack of fit, due to a very small replicate error. The model has a R^2Y of 0.88 and a Q^2 of 0.63 (Fig. 10). Using four of the experiments as a test set, the Root Mean Squared Error of Prediction (RMSEP) is 3.7 min, which is about 17% of the investigated interval (int.) (see Table 4). The RMSEP value is comparable to that obtained with an MLR model using the amounts as factors (not shown here).

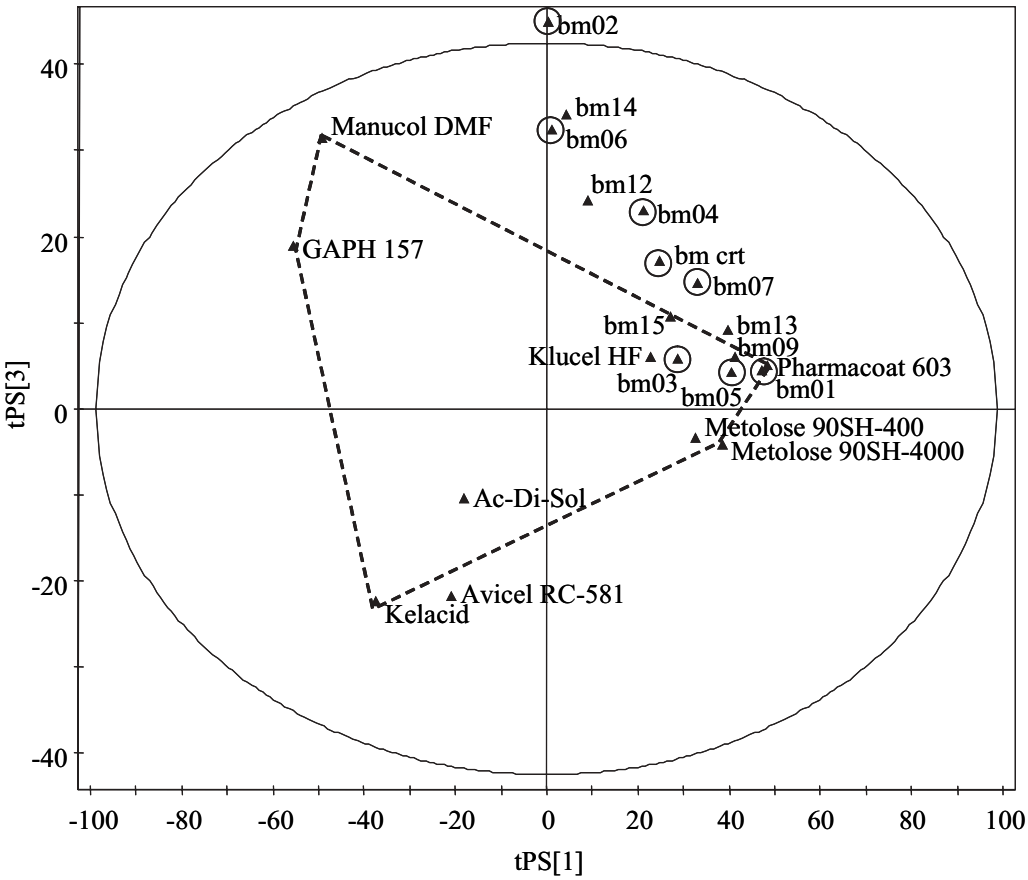

FIGURE 8 **The *t*[1]/*t*[3] Score Plot for the Binders of the Screening Design and the Binder Mixtures. The Highlighted Area Is the Part of the Score Space That Was Investigated in the Screening Design. The Binder Mixtures That Were Tested in Study 1 Are Encircled. Note That the Values for the Binder Mixtures Are Predicted.**

Evaluation of Results from Study 2

The results from Study 2, shown in Table 3, do not include a formulation with the required disintegration time. However, the experimental domain should contain formulations of suitable disintegration time.

Study 2, with only binder mixtures, included too few experiments to select a test set. The design, evaluated with PLS, has a condition number of 3.9. The PLS model has two components, a R^2Y of 0.76 and a Q^2 of 0.62. The model is significant according to ANOVA; the lack of fit could not be estimated since there are no replicated runs. By creating a contour plot of the mixture region, the results can be interpreted in terms of the original score plot (Fig. 11). The experiments containing binder mixtures bm26 and bm28 are not well explained by the model since both experiments actually have disintegration times of around 10 min.

As is evident from Fig. 11–compared to Fig. 2–a relatively small amount of Grindsted PH 157 (sodium alginate) has a very strong effect on the disintegration time. The contents of Klucel HF and Pharmacoat 603 (hypromellose) are less important, offering scope for modifying other aspects of the formulation, e.g., flow properties.

CONCLUSIONS

The Partial Least Squares Projections to Latent Structure (PLS) model of the screening study has been validated in the sense that the interesting region of the PP space identified in it has been shown to contain excipients, pure or mixed, that give the formulation desired properties.

Predicting the mixture experiments would not necessarily aid in determining the predictive ability of the screening model in terms of RMSEP. Should the agreement between observed and predicted values be good this could also be interpreted as a sign that the formulation is not sensitive to these changes, or that the additives somehow cancel out each other. A poor

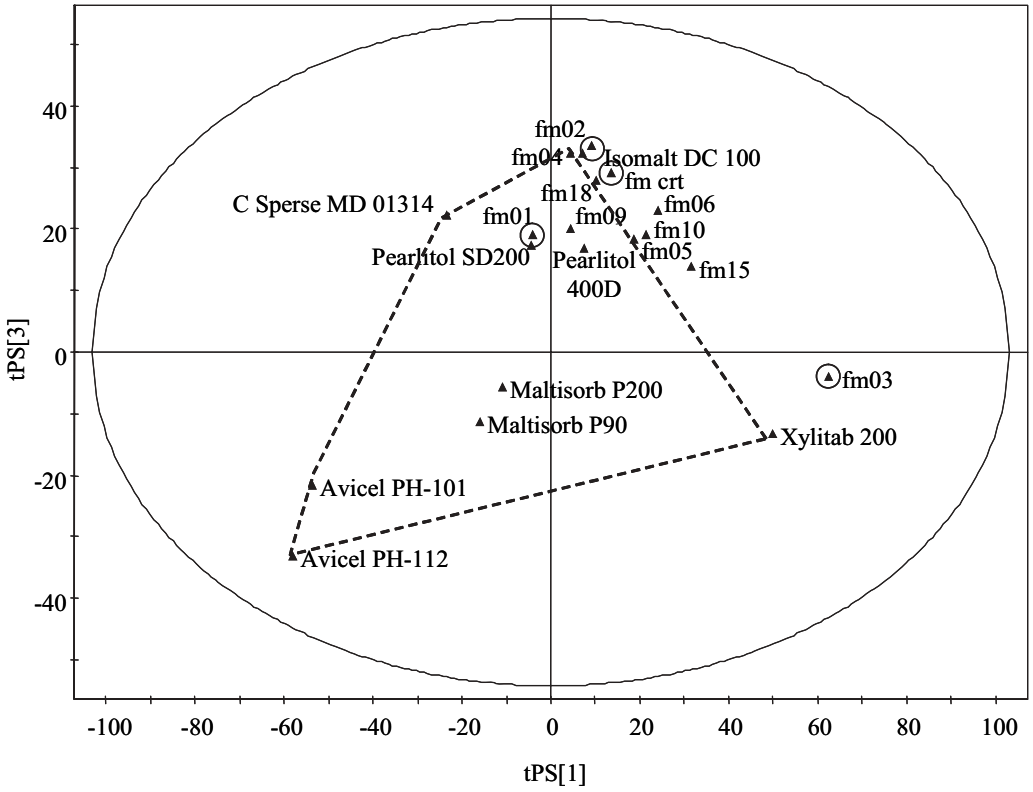

FIGURE 9 **The *t*[1]/*t*[3] Score Plot for the Fillers of the Screening Design and the Filler Mixtures. The Highlighted Area Is the Part of the Score Space That Was Investigated in the Screening Design. The Filler Mixtures Chosen for the Experiments Are Encircled. Note That the Values for the Mixtures Are Predicted.**

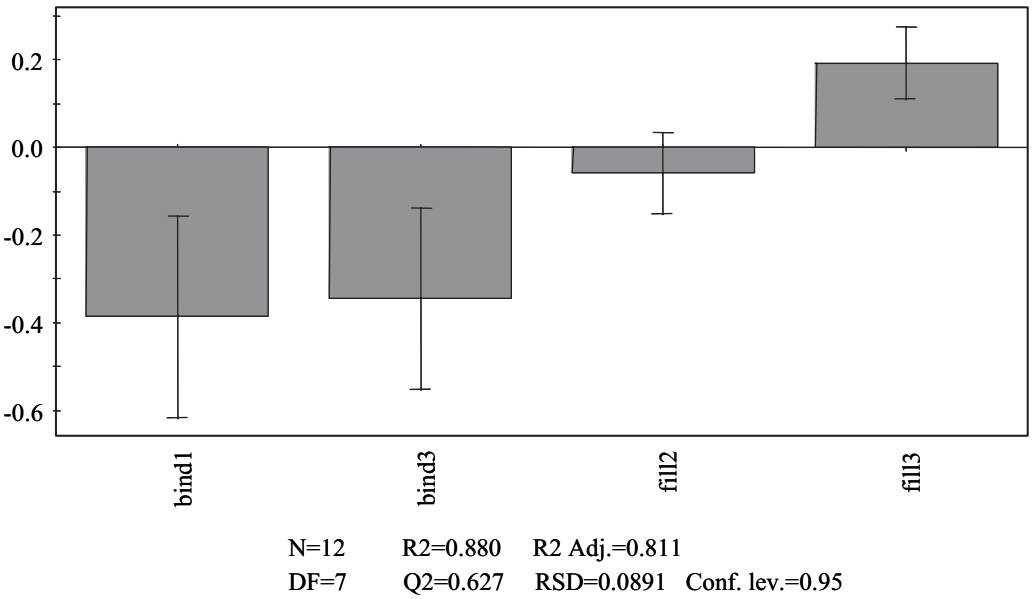

FIGURE 10 **Regression Coefficients Plot for the MLR Model for Disintegration Time.**

agreement is also indicative of a system that responds to these additions, and since a diverse set of excipients has been studied they likely respond differently to these additives. Whichever of these interpretations is true, comparing observed disintegration times to those predicted by the screening model is bound to be misleading.

The spread between replicate runs of the mixtures in the spectral analysis suggests that a different method for

TABLE 4 **Observed and Predicted Disintegration Times for the Test Set of Study 1**

Exp no	bind1	bind3	fill2	fill3	Pred dis. time	Obs dis. time
T1 (N10)	1.0	32.4	–37.2	19.1	19.0	14.7
T2 (N11)	40.6	4.3	7.9	–3.8	6.2	6.1
T3 (N12)	33.0	14.7	7.9	–3.8	5.5	10.4
T4 (N13)	21.3	23.0	–37.2	19.1	12.7	9.2
					RMSEP	3.7
					% of int. (5.7–27.4)	17.1

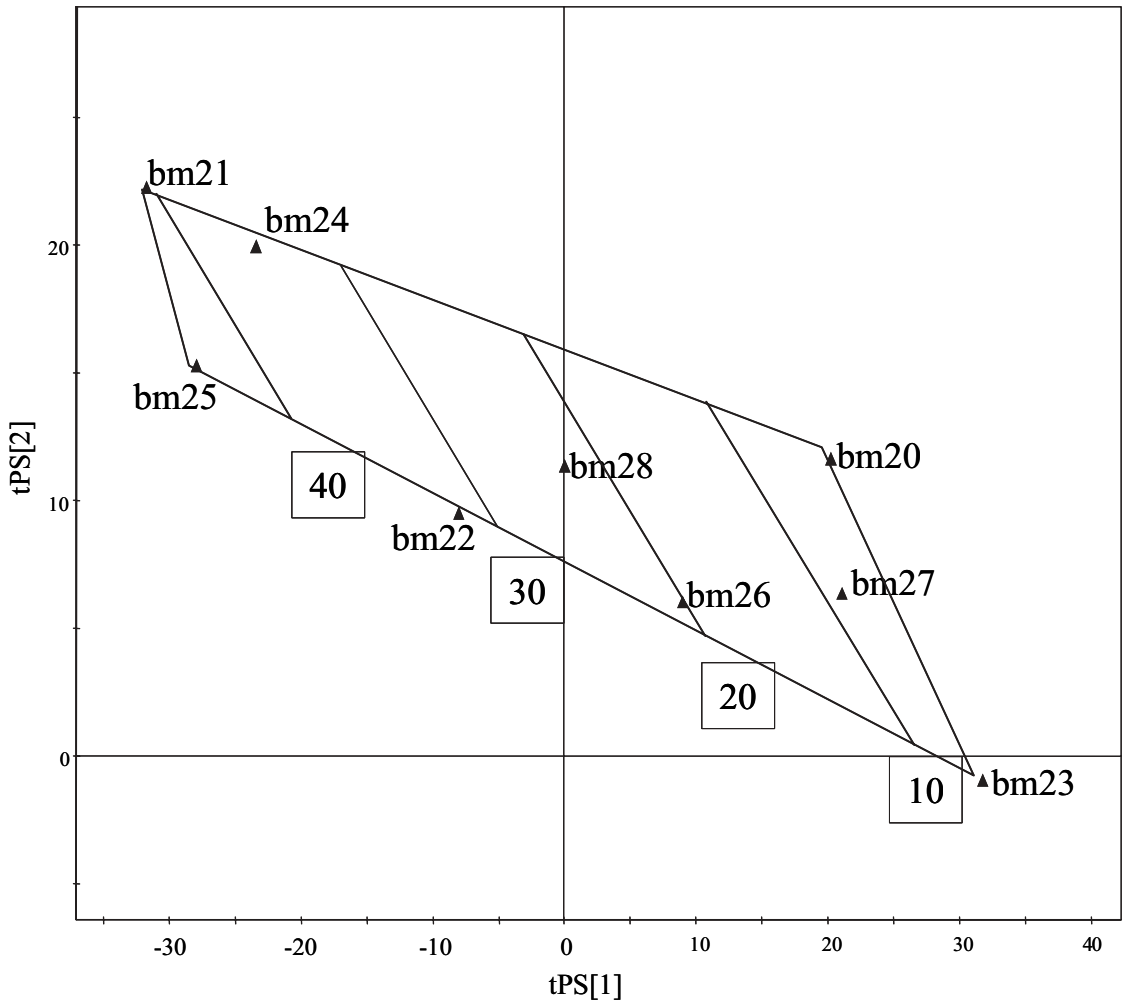

FIGURE 11 **The Contour Plot from the PLS Model for the Second Study of Excipient Mixtures (Study 2), Superimposed on a *t*[1]/*t*[2] Score Plot. The Boxed Numbers Correspond to the Predicted Disintegration Time (Min).**

sample presentation should be used. Diffuse reflectance measurements on the excipient mixtures could be a viable option for coming to terms with these problems.

Formulations with suitable properties were found with the mixture experiments. The calculated models also offer several alternatives for the composition of the formulation. The presented approach could possibly aid in the continuous development of new grades of materials and co-processed excipient combinations.

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