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Robustness Testing of a Tablet Formulation Using Multivariate Design

Jon Gabrielsson and Michael Sjöström
Research Group for Chemometrics, Department of Chemistry, Umeå University, Umeå, Sweden

Nils-Olof Lindberg and Ann-Christin Pihl
Pharmacia AB, Consumer Healthcare, Helsingborg, Sweden

Torbjörn Lundstedt
Department of Medicinal Chemistry, Uppsala University, Uppsala, Sweden

ABSTRACT A total of 45 experiments were carried out to evaluate the robustness of two similar tablet formulations–a product of two strengths–with respect to normal batch-to-batch variation of the excipients and the active pharmaceutical ingredient. The formulations consist of 10 ingredients. Because of the differing amounts of active pharmaceutical ingredients, the two formulations also differ in the amounts of two of the diluents and one of the binders. The excipients and active pharmaceutical ingredient were characterized in terms of multiple variables, and principal properties were calculated with principal component analysis. A Plackett and Burman design was applied to the principal properties. The relationships between the design factors and two responses, mean disintegration time and mean crushing strength, were evaluated by using regression methods. Both formulations were found to be robust under controlled conditions.

KEYWORDS Robustness testing, Plackett-Burman design, multivariate design, PCA, PLS

INTRODUCTION

Webster's Online Dictionary defines robustness as "the property of strong in constitution" (2004). This is a desirable property in many situations and applications related to products and manufacturing.

Excipients are usually produced by a batch process, with inevitable possibilities for batch-to-batch variation (Armstrong, 1997). Hence, excipients from different batches, all within the specification limits, might not have identical properties.

The objective of robustness testing is normally to explore the sensitivity of the investigated system toward changes in critical factors (Eriksson et al., 2000). Robustness of a formulation is a measure of the reproducibility of the measured quality of produced tablet batches under the variations in conditions normally expected in a production environment, such as between-batch differences in raw materials, variations in air temperature and humidity, differences in elapsed production times, and different operators of the machinery. However, the influence of different operators was not included as a factor in this study.

The regression analysis phase in robustness testing is carried out in much the same manner as for screening and optimization studies. However, the focus is placed on acceptable limits of variation as well as model parameters such as R^2, Q^2, and ANOVA results (Eriksson et al., 2000). A system is indicated to be

Address correspondence to Torbjörn Lundstedt, Department of Medicinal Chemistry, Uppsala University, Uppsala, Sweden, Box 574 and 751 23. E-mail: torbjorn.lundstedt@acurepharma.com

robust when the pertinent quality measures vary within acceptable limits when the process conditions are changed over normal variation intervals, and a model of this quality variation is not significant, or the model shows that this quality variation is within the acceptable limits.

Suitable designs for robustness testing are fractional factorial designs of resolution III and Plackett and Burman (P-B) designs (Eriksson et al., 2000). These reduced designs allow for screening of many factors with few experiments without confounding of main effects. In a previously published study, multivariate design was used in the development of a tablet formulation (Gabrielsson et al., 2003). Models obtained in the study were later validated and the formulation was optimized.

In the study presented here, the robustness of two similar tablet formulations was evaluated by using a P-B design. The test only covered normal batch-to-batch variation of the excipients and active pharmaceutical ingredient (API). Normal batch-to-batch variation of excipients is usually small. Nevertheless, problems in production can occur because of inconsistent excipient properties, and there are many possible reasons for changes in excipient properties (e.g., changes in production site, the supplier of raw materials, or the manufacturing process).

Using qualitative variables in an experimental design for this kind of study limits the choice of excipients to an arbitrary selection of three of the available excipients of a certain type. The selection is arbitrary in the sense that prior to the investigation little or no information regarding the excipients is gathered, other than that provided by the manufacturer, to evaluate possible variation in their properties. Regardless of the size of the variation, the chances of obtaining a representative choice of excipient batches in this way are far from ideal.

By applying principal component analysis (PCA) to a multivariate characterization of the excipients and API, principal properties (PPs) can be calculated (Wold et al., 1987). The choice of excipients for the robustness test is based on PPs, thus increasing the likelihood of obtaining excipient diversity within the presumed normal variation. Because no mechanical tests on the excipients and API are included in the characterization of the excipients, there are no guarantees that a representative set of excipients that display as much normal batch-to-batch variation as possible will be chosen, but the chances are increased dramatically.

OBJECTIVE

The objective of this study was to evaluate the robustness of two similar tablet formulations—a product of two strengths—with respect to normal batch-to-batch variation within the included excipients and API.

The robustness was studied with a P-B design applied to PPs to decrease the number of experiments and increase the diversity of the tested excipients compared with a fractional factorial design in qualitative variables.

METHODS

The P-B design is an example of a saturated design, (i.e., a design in which every performed experiment is associated with a model term) (Plackett & Burman, 1946; Box et al., 1978). The P-B design used here, with 12 experiments and 3 replicated center points (Table 1), was taken from the literature (Box et al., 1978).

Provided that all interactions are negligible, saturated designs allow unbiased estimation of all main effects of N-1 variables with the smallest possible variance. The fractional factorial designs are only available if N equals 2^k. Plackett and Burman have obtained arrangements with the same orthogonal property when N is a multiple of 4. The way two-factor interactions are confounded with main effects is complicated for most P-B designs. However, a fold-over design of any such orthogonal design will result in a design of resolution IV, in which main effects are not confounded with two-factor interactions (Box et al., 1978).

EXPERIMENTAL

Multivariate Characterization of Excipients and API

The investigated formulations contain 10 components (9 excipients and 1 API) (Table 2). The first multivariate characterization was performed on 50 batches, 3–7 batches for each of the 10 components (Table 3). Another multivariate characterization was performed on 30 batches, 3 from each of the 10 components (Table 4). Only one producer for each of the excipients was included in the study. Each excipient constitutes a separate class in contrast to the multivariate characterization in the screening design, where, for instance, all the binders were characterized in one binder class (Gabrielsson et al., 2003).

TABLE 1 P-B Design with Replicated Center Points for 11 Factors, as Given in Reference Wold et al. (1987)

	Variable										
Run	1	2	3	4	5	6	7	8	9	10	11
1	+1	−1	+1	−1	−1	−1	+1	+1	+1	−1	+1
2	+1	+1	−1	+1	−1	−1	−1	+1	+1	+1	−1
3	−1	+1	+1	−1	+1	−1	−1	−1	+1	+1	+1
4	+1	−1	+1	+1	−1	+1	−1	−1	−1	+1	+1
5	+1	+1	−1	+1	+1	−1	+1	−1	−1	−1	+1
6	+1	+1	+1	−1	+1	+1	−1	+1	−1	−1	−1
7	−1	+1	+1	+1	−1	+1	+1	−1	+1	−1	−1
8	−1	−1	+1	+1	+1	−1	+1	+1	−1	+1	−1
9	−1	−1	−1	+1	+1	+1	−1	+1	+1	−1	+1
10	+1	−1	−1	−1	+1	+1	+1	−1	+1	+1	−1
11	−1	+1	−1	−1	−1	+1	+1	+1	−1	+1	+1
12	−1	−1	−1	−1	−1	−1	−1	−1	−1	−1	−1
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0

TABLE 2 Factors in the Design with Abbreviations Used in Figures and Tables

Num	Components/ factors	Abbreviations for factors
1	Sweetener	swe
2	Binder1	bin1
3	Flavor1	fla1
4	Diluent1	dil1
5	Binder2	bin2
6	Diluent2	dil2
7	Lubricant	lubr
8	Active pharmaceutical ingredient	api
9	Flavor2	fla2
10	Diluent3	dil3
ucf	Air humidity, mixing	humbl
ucf	Air humidity, tableting	humtabl
ucf	Air humidity, testing of tablets	humipc
ucf	Compression force	force

Note that uncontrolled factors (ucf) that were not part of the P-B design are included in the table. The actual compression force (i.e., the small deviation from the intended compression force) was included as an "uncontrolled factor."

The samples were characterized by FT-IR (649–4500 cm^{-1}; Mattson Fourier-transform 60AR instrument equipped with a Golden Gate Single Reflection Diamond ATR accessory) and NIR (400–2500 nm; NIR Systems 6500 Spectrophotometer, FOSS) spectroscopy. The variables of the multivariate characterization were the digitized NIR (1050 variables) and FT-IR (1997 variables) spectra.

The FT-IR and NIR spectra for the different kinds of excipient and API batches were pretreated separately with Standard Normal Variate transformation (SNV) and then combined to form the dataset for the multivariate characterization (Barnes et al., 1989). SNV transformation was used in a previous study and is performed to remove interference from variables such as sample packing (Gabrielsson et al., 2003). Variables were scaled to unit variance prior to analysis.

PCA models were calculated for the different excipients and API, and each class was described by one principal component; thus, 10 factors were used in the design (Table 2). The number of components was decided by the size of the eigenvalues (i.e., eigenvalue >2 for a significant component).

Plackett and Burman Design for Robustness Experiments

Eleven factors can be evaluated with a P-B design of 12 factors, but only 10 were studied here. The PPs of the 10 ingredients of the formulation were used as factors, and the most diverse set of excipients, with a few exceptions due to lack of availability, was chosen on the basis of the design (Tables 3 and 4).

The same design was used for both tablet strengths in the first part of the study (Table 3). The differences between the experiments with the two formulations lie in the amounts of API and some of the excipients (Table 5).

TABLE 3 **Identifiers and PPs of All Excipient and API Batches that were Included in the First Part of the Study**

Excipient no.	1	2	3	4	5	6	7
Sweetener t[1] swe	SWE B1 8.1	**SWE B2 12.3**	**SWE B3 –105.0**	**SWE B4 25.1**	SWE B5 19.8		
Binder1 t[1] bin1	BIN1 B1 –1.2	**BIN1 B2 –29.9**	**BIN1 B3 64.3**	BIN1 B4 1.9	**BIN1 B5 24.5**		
Flavor1 t[1] fla1	FLA1 B1 –19.2	**FLA1 B2 –10.6**	**FLA1 B3 69.1**	**FLA1 B4 –19.7**			
Diluent1 t[1] dil1	**DIL1 B1 –5.5**	**DIL1 B2 –12.5**	**DIL1 B3 75.4**	DIL1 B4 –19.1			
Binder2 t[1] bin2	BIN2 B1 8.9	**BIN2 B2 –32.4**	**BIN2 B3 –19.5**	**BIN2 B4 82.1**			
Diluent2 t[1] dil2	**DIL2 B1 –20.2**	**DIL2 B2 –85.7**	DIL2 B3 –72.6	DIL2 B4 17.9	DIL2 B5 36.4	**DIL2 B6 32.5**	DIL2 B7 18.7
Lubricant t[1] lubr	LUBR B1 –26.9	**LUBR B2 –61.4**	LUBR B3 –52.7	LUBR B4 –24.6	**LUBR B5 –12.5**	LUBR B6 36.8	**LUBR B7 47.1**
API t[1] api	**API S1B4 11.7**	API S1B5 –30.4	**API S1B6 –54.4**	**API S1B7 4.8**			
Flavor2 t[1] fla2	**FLA2 B1 40.2**	FLA2 B2 37.0	FLA2 B3 –14.6	**FLA2 B4 –58.9**	**FLA2 B5 –8.7**	FLA2 B6 –20.7	
Diluent3 t[1] dil3	**DIL3 B1 48.3**	DIL3 B2 –23.4	**DIL3 B3 –39.8**	**DIL3 B4 –2.3**			

The batches included in the design are shown in bold.

TABLE 4 Identifiers and PPs of all Excipient and API Batches that were Included in the Second Part of the Study

Excipient no.	1	2	3
Sweetener t[1] swe	SWE B6 –38.1	SWE B7 –33.4	SWE B8 17.4
Binder1 t[1] bin1	BIN1 B6 –11.8	BIN1 B7 6.5	BIN1 B8 54.3
Flavor1 t[1] fla1	FLA1 B5 41.9	FLA1 B6 –46.2	FLA1 B7 28.7
Diluent1 t[1] dil1	DIL1 B4 46.9	DIL1 B5 –32.0	DIL1 B6 –46.6
Binder2 t[1] bin2	BIN2 B5 –25.9	BIN2 B6 –38.0	BIN2 B7 54.6
Diluent2 t[1] dil2	DIL2 B4 30.6	DIL2 B8 40.0	DIL2 B9 –43.5
Lubricant t[1] lubr	LUBR B7 39.8	LUBR B5 –17.8	LUBR B8 –63.4
API t[1] api	API S1B5 29.4	API S1B6 –62.1	API S1B7 –15.3
Flavor2 t[1] fla2	FLA2 B7 –13.7	FLA2 B8 –24.3	FLA2 B9 35.1
Diluent3 t[1] dil3	DIL3 B4 44.1	DIL3 B5 18.2	DIL3 B6 –22.3

TABLE 5 The Levels of Excipients and API in Formulations 1 and 2

	Formulation 1	Formulation 2
Ingredients	amount/tablet (mg)	amount/tablet (mg)
API	6.17	12.33
Diluent1	48.87	47.62
Diluent2	15	5
Diluent3	2.5	2.5
Binder1	9	14
Binder2	4	4
Flavor1	1.53	1.53
Flavor2	0.45	0.54
Sweetener	0.68	0.68
Lubricant	1.8	1.8

In the second part of the study, only formulation 2 was investigated (Table 4).

Manufacturing and Characterization of Tablets

The excipients (except the lubricant) were mixed in a Turbula mixer, with a 0.5 l vessel, for 8 min at 46 rpm. The lubricant was then added and mixing continued for another 2 min. The batch size was 100 g.

Tablets were prepared from each powder mixture at a force of 8 kN in an instrumented single punch press (Korsch EK0) equipped with 6-mm diameter, flat-faced punches. Formulation 2 was also compressed at a force of 10 kN in the second study.

The studied tablet properties were disintegration time (minutes, 6 tablets) and crushing strength (kp, 10 tablets). Standard pharmacopoeial methods were used (Wade & Weller, 1994). For practical reasons, the study took almost 3 months to complete, from late spring to summer, so significant changes in air humidity occurred during the course of the experiments. This applied especially to Formulation 1 experiments, because most of Formulation 2 experiments took place during the summer. Therefore, the air humidity data during powder mixing, tabletting, and testing of tablets were included in the analysis as well as the actual compression force (see Table 7). From this data set, PLS models of crushing strength and disintegration time were calculated (Wold et al., 1986).

Statistical Analysis

For the data analysis, Modde 6.0 software for statistical experimental design was used.

All principal component analysis (PCA) and Partial Least Squares (PLS) models were calculated in Simca-P 10.0, and all software was supplied by Umetrics AB, Umeå, Sweden.

RESULTS AND DISCUSSION

Principal Properties of Excipients

To create an overview of patterns in the data, a PCA was made for the excipients included in the first part of the study (i.e., except for the API). Five components are significant according to the size of the eigenvalues, which together explain 96% of the variance in X.

As shown in Fig. 1, the first two components clearly separate the excipient batches, each of which forms a tight cluster. Diluent2 and Diluent3, which is a special quality of Diluent2, are almost overlapping in the t[1]/t[2] score plot, in accordance with

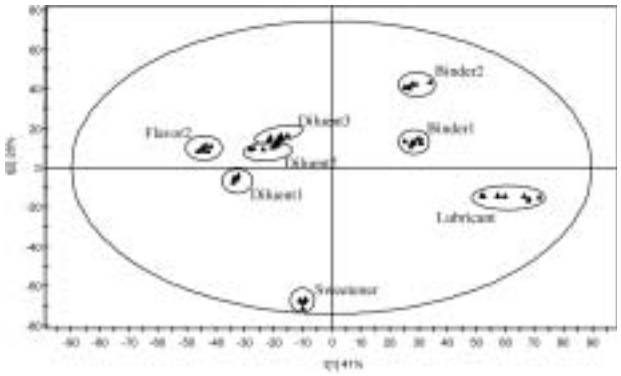

FIGURE 1 **Overview of the excipients included in the first part of the study. The contribution of each component to the explained variance is shown in the figure.**

expectations. Flavor1 and Flavor2 actually do overlap in the score plot, which again is consistent with expectations because the same carrier material is used for both flavors. The spread of the batches in the separate models is quite large (Tables 3 and 4). However, compared with the other types of shown excipients in Fig. 1, they are relatively homogenous. Constructing a separate model is very much like putting a magnifying glass to the overview model, because the relative positions of the excipients are retained (not shown here). Small differences are thus highlighted in the separate models.

For this reason, instead of using the PPs obtained from this model, separate models were calculated for each type of excipient.

Results of Robustness Experiments

The responses—mean disintegration time (dis. time) and mean crushing strength (crush. str.)—were within the specified limits (>10 and <20 min and ≥4.5 kp, respectively) for both tablet strengths (Tables 6 and 7). The values for mean air relative humidity are given for both formulations and have been included where further analysis of possible reasons for observed variations has been performed. Additional experiments were performed for Formulation 2, but the results were inconclusive. Hence, the decision was made to run a new series of experiments for Formulation 2 in dehumidified conditions, thus limiting the influence of air humidity and more closely resembling the operating conditions of full-scale production. A compression force of 10 kN, again closer to normal operating conditions for this strength, was also tested in this part of the study.

The mean values of disintegration time and crushing strength were used in the calculations. Data were evaluated with each response separately. PLS was selected as the regression method.

Analysis of the Results for Formulation 1

With Formulation 1, the disintegration time was 14.0–18.7 min, and the crushing strength was 5.0–7.3 kp, with replicated center point disintegration times of 17.1–18.3 min and crushing strengths of 5.7–6.6 kp (Table 6). These results were deemed to be quite acceptable.

The PLS models for disintegration time and crushing strength are not significant according to ANOVA. The residuals are normally distributed. For disintegration time, the response was log-transformed to obtain a better approximation to a normal distribution. The PLS model for disintegration time has a R^2Y of 0.74, Q^2 of 0.14, and none of the regression coefficients are significant. The PLS model for crushing strength has a R^2Y of 0.76 and Q^2 of 0.0. Thus, Formulation 1 is robust with respect to normal batch-to-batch variation of the excipients and API.

Analysis of Results for the First Study of Formulation 2

For Formulation 2, the crushing strength was 4.6–6.6 kp, and the disintegration time was 13.2–16.5 min (Table 7), so the values of both of these responses were generally lower than Formulation 1. For two of the batches, the crushing strength was less than 5 kp. The values of the replicated center point for crushing strength were 6.2–6.5 kp, showing a very small variation.

According to ANOVA the PLS model for disintegration time is not significant (R^2Y, 0.76; Q^2, 0.0).

A two-component PLS model for crushing strength is significant according to ANOVA and has no lack of fit (R^2Y, 0.96; Q^2, 0.56). The residuals are normally distributed.

The regression coefficient plot for crushing strength indicates three significant factors: Binder1(Bin1), Diluent1(Dil1), and API (Fig. 2). One of the binders, Binder1, is hygroscopic, with an equilibrium moisture content of approximately 8% at 25°C and 30% RH,

TABLE 6 **Experimental Setup and Tablet Properties for Formulation 1**

Exp no.	swe	bin1	fla1	dil1	bin2	dil2	lubr	api	fla2	dil3	humbl	humtabl	humipc	force	dis. time	crush. str.
1	25.1	−29.9	69.1	−12.5	−32.4	−85.7	40.6	11.7	40.2	43.1	53	53	55	8.3	16.1	6.8
2	25.1	64.3	−21.7	75.4	−32.4	−85.7	−61.4	11.7	40.2	−37.5	23	24	26	8	14.5	6.3
3	−105	64.3	69.1	−12.5	82.1	−85.7	−61.4	−54.4	40.2	43.1	25	25	25	8.1	14.7	6.8
4	25.1	−29.9	69.1	75.4	−32.4	32.5	−61.4	−54.4	−53.9	43.1	25	25	25	8.3	14.5	6.4
5	25.1	64.3	−21.7	75.4	82.1	−85.7	40.6	−54.4	−53.9	43.1	53	55	55	8	17.5	6.3
6	25.1	64.3	69.1	−12.5	82.1	32.5	−61.4	11.7	−53.9	−37.5	25	25	25	8.2	15.3	7.3
7	−105	64.3	69.1	75.4	−32.4	32.5	40.6	−54.4	40.2	−37.5	53	53	55	8.5	15.5	5.1
8	−105	−29.9	69.1	75.4	82.1	−85.7	40.6	11.7	−53.9	−37.5	53	53	55	8	17.5	5
9	−105	−29.9	−21.7	75.4	82.1	32.5	−61.4	11.7	40.2	43.1	25	25	25	8.1	14	6.6
10	25.1	−29.9	−21.7	−12.5	82.1	32.5	40.6	−54.4	40.2	−37.5	53	55	55	8.3	17.8	6.8
11	−105	64.3	−21.7	−12.5	−32.4	32.5	40.6	11.7	−53.9	43.1	53	53	55	8.3	16.6	6.2
12	−105	−29.9	−21.7	−12.5	−32.4	−85.7	−61.4	−54.4	−53.9	−37.5	25	25	25	7.9	14.5	6.6
13	12.3	24.5	−10.6	−5.5	−12.2	−20.2	−12.5	4.8	−8.7	−2.3	53	55	55	8.4	18.3	6.4
14	12.3	24.5	−10.6	−5.5	−12.2	−20.2	−12.5	4.8	−8.7	−2.3	53	55	55	8.1	17.1	6.6
15	12.3	24.5	−10.6	−5.5	−12.2	−20.2	−12.5	4.8	−8.7	−2.3	53	53	55	8.4	18.7	5.7

Figures in columns swe-dil3 refer to PPs of excipients and API, whereas in columns humbl-humipc, the mean air relative humidity values for these steps are summarized. The compression force (force) is given in kN, the disintegration time (dis. time) in minutes, and the crushing strength (crush. str.) in kp.

TABLE 7 **Experimental Setup and Tablet Properties for Formulation 2**

Exp no.	swe	bin1	fla1	dil1	bin2	dil2	lubr	api	fla2	dil3	humbl	humtabl	humipc	force	dis. time	crush. str.
1	25.1	−29.9	69.1	−12.5	−32.4	−85.7	11.7	40.6	40.2	43.1	50	48	53	8.1	15.7	6.6
2	25.1	64.3	−21.7	75.4	−32.4	−85.7	11.7	−61.4	40.2	−37.5	39	37	43	8.2	13.4	5.9
3	−105	64.3	69.1	−12.5	82.1	−85.7	−54.4	−61.4	40.2	43.1	50	48	53	8.2	14.2	5.1
4	25.1	−29.9	69.1	75.4	−32.4	32.5	−54.4	−61.4	−53.9	43.1	50	50	55	7.8	13.7	5.2
5	25.1	64.3	−21.7	75.4	82.1	−85.7	−54.4	40.6	−53.9	43.1	48	48	45	8	16.5	4.6
6	25.1	64.3	69.1	−12.5	82.1	32.5	11.7	−61.4	−53.9	−37.5	51	48	55	7.9	13.5	5.5
7	−105	64.3	69.1	75.4	−32.4	32.5	−54.4	40.6	40.2	−37.5	48	48	45	8.4	15.7	4.7
8	−105	−29.9	69.1	75.4	82.1	−85.7	11.7	40.6	−53.9	−37.5	50	48	53	8.1	15	5.5
9	−105	−29.9	−21.7	75.4	82.1	32.5	11.7	−61.4	40.2	43.1	39	37	43	7.9	13.7	5.1
10	25.1	−29.9	−21.7	−12.5	82.1	32.5	−54.4	40.6	40.2	−37.5	50	48	53	8.3	14.7	6.4
11	−105	64.3	−21.7	−12.5	−32.4	32.5	11.7	40.6	−53.9	43.1	50	48	53	8	13.2	6
12	−105	−29.9	−21.7	−12.5	−32.4	−85.7	−54.4	−61.4	−53.9	−37.5	50	50	55	8	13.4	6
13	12.3	24.5	−10.6	−5.5	−12.2	−20.2	4.8	−12.5	−8.7	−2.3	55	50	45	8.1	15.2	6.5
14	12.3	24.5	−10.6	−5.5	−12.2	−20.2	4.8	−12.5	−8.7	−2.3	50	48	53	8.2	14.2	6.2
15	12.3	24.5	−10.6	−5.5	−12.2	−20.2	4.8	−12.5	−8.7	−2.3	48	48	53	8.4	14.5	6.5

Figures in columns swe-dil3 refer to PPs of excipients and API, whereas in columns humbl-humipc, the mean air relative humidity values for these steps are summarized. The compression force (force) is given in kN, the disintegration time (dis. time) in minutes, and the crushing strength (crush. str.) in kp.

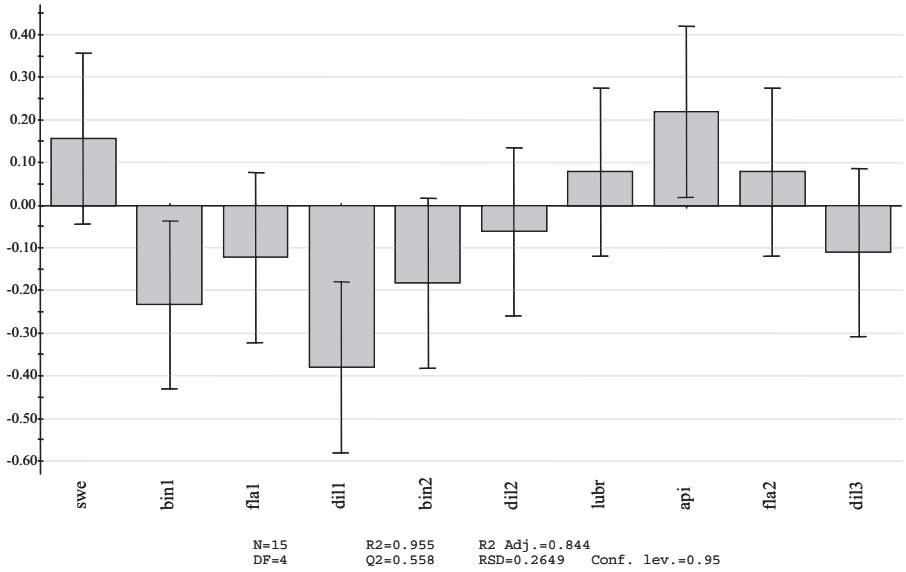

FIGURE 2 **Regression coefficients for crushing strength derived from the PLS model of the robustness experiments for Formulation 2.**

and about 16% at 50% RH, so the influence of air humidity was not unexpected (Walkling, 1994).

Because of the unexpectedly low values for crushing strength found in two of the experiments, the values were close to the acceptable limit. A further investigation of the humidity data did not provide any more information regarding Formulation 2.

Analysis of Results for the Second Study of Formulation 2

The second study of Formulation 2 yielded tablets with a crushing strength of 4.5–6.1 kp and a disintegration time of 10.6–13.9 min when compressed at 8 kN (Table 8). When compressed at 10 kN, the crushing strength values were 5.5–6.8 kp and disintegration times were 12.5–15.9 min. These results are similar to those obtained in the first study, where a compression force of 8 kN was used.

No significant model for this data set was obtained according to ANOVA, either for crushing strength or disintegration time, regardless of compression force. The residuals are normally distributed. For disintegration time, the response was log-transformed to obtain a better approximation to a normal distribution. The PLS model for disintegration time has a R^2Y of 0.63 and Q^2 of 0.0 for 8 kN compression, and R^2Y of 0.48 and Q^2 of 0.0 for 10 kN compression. The PLS model for crushing strength has a R^2Y of 0.86 and Q^2 of 0.24 (8 kN) and R^2Y of 0.86 and Q^2 of 0.41 (10 kN).

The results from the second study are within specifications and yield no significant model, which is the desired outcome.

CONCLUSIONS

The robustness of the formulations has been evaluated with relatively few experiments, and at the same time the most diverse excipients have been tested. Both formulations are robust with respect to normal batch variation of excipients and API when produced under controlled conditions.

In the first part of the study, the crushing strength of Formulation 2 was not found to be robust with respect to normal batch-to-batch variation of excipients and API in the investigated environment. Without going into detail for the reasons for the observed fluctuations in crushing strength, the fact that they were discovered should probably be credited to the applied methodology. If the excipients had been randomly chosen, the chances are high that the sensitivity of the tested formulation toward uncontrolled factors in the production environment would have passed unnoticed. Even if this sensitivity had caused no problems later in production, in a controlled environment, the finding shows the potential and usefulness of the applied approach.

The second part of the study shows that Formulation 2 is robust when prepared under controlled conditions. The responses are rather low for some of the experiments, but this can be remedied by increasing

TABLE 8 **Experimental Setup and Results for the Second Study of Formulation 2**

Exp no	swe	bin1	fla1	dil1	bin2	dil2	lubr	api	fla2	dil3	8 kN dis. time	8 kN crush. str.	10 kN dis. time	10 kN crush. str.
1	17.4	−11.8	41.9	−46.6	−38.0	−43.5	39.8	29.4	35.1	44.1	13	5	14.5	5.7
2	17.4	54.3	−46.2	46.9	−38.0	−43.5	−63.4	29.4	35.1	−22.3	13.4	5.8	13.7	6.6
3	−38.1	54.3	41.9	−46.6	54.6	−43.5	−63.4	−62.1	35.1	44.1	10.9	5.3	12.5	6.5
4	17.4	−11.8	41.9	46.9	−38.0	40.0	−63.4	−62.1	−24.3	44.1	13.5	5.9	14.7	6.8
5	17.4	54.3	−46.2	46.9	54.6	−43.5	39.8	−62.1	−24.3	44.1	13.1	5.9	15.9	6.5
6	17.4	54.3	41.9	−46.6	54.6	40.0	−63.4	29.4	−24.3	−22.3	13	5.4	14.6	6
7	−38.1	54.3	41.9	46.9	−38.0	40.0	39.8	−62.1	35.1	−22.3	13.6	6.1	14.5	6.6
8	−38.1	−11.8	41.9	46.9	54.6	−43.5	39.8	29.4	−24.3	−22.3	11.6	5.1	14.5	6.3
9	−38.1	−11.8	−46.2	46.9	54.6	40.0	−63.4	29.4	35.1	44.1	13.9	5.1	15.2	6.1
10	17.4	−11.8	−46.2	−46.6	54.6	40.0	39.8	−62.1	35.1	−22.3	12.7	4.9	14.4	5.9
11	−38.1	54.3	−46.2	−46.6	−38.0	40.0	39.8	29.4	−24.3	44.1	10.8	4.5	13.8	5.6
12	−38.1	−11.8	−46.2	−46.6	−38.0	−43.5	−63.4	−62.1	−24.3	−22.3	12	5.5	14.6	6.5
13	−33.4	6.5	28.7	−32.0	−25.9	30.6	−17.8	−15.3	−13.7	18.2	12.9	5.2	15.3	5.7
14	−33.4	6.5	28.7	−32.0	−25.9	30.6	−17.8	−15.3	−13.7	18.2	12.5	4.8	13.1	5.5
15	−33.4	6.5	28.7	−32.0	−25.9	30.6	−17.8	−15.3	−13.7	18.2	10.6	4.6	13.2	5.6

The compression force (in kN) is given above the responses, disintegration time (dis. time) in minutes, and crushing strength (crush. str.) in kp.

the compression force. This does not affect the robustness of the formulation.

The models obtained from the multivariate characterization could serve as the basis for quality control measures (e.g., measures to check the suitability of new excipient and API batches on arrival at the plant). By predicting the principal properties of new batches, a simple classification procedure for determining each batch as normal or abnormal could be implemented, and possibly reduce the risk of production disturbances. In the future, the models could be continuously updated as more tablet batches are produced with new excipient and API batches. This would further increase the reliability of the models over time.

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