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RESEARCH PAPER

Optimization of a New Filler/Binder for Direct Compression Using Central Composite Design

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ABSTRACT

An experimental design, the Central Composite, was used for the optimization of a new filler/binder (Xylitab 200®) for direct compression, with aspirin as the model drug. The design consists of four independent variables (filler/binder, drug, disintegrant, and compression force) in varying amounts, and with crushing strength, friability, weight variation, disintegration time, and dissolution rate as response variables. Multiple regression in the form of a second-order polynomial was used to determine meaningful relationships. In this study, the amounts of compression force and disintegrant played an important role in controlling the response variables.

INTRODUCTION

The search for optimal formulations is costly and cannot provide a guarantee that an optimal formulation can be achieved. The adoption of experimental designs for use in pharmaceutical technology research (1–4) can help to ensure a reliable result. When optimizing tablet formulations, a number of criteria (such as adequate crushing strength, low disintegration time, and low friability) have to be considered. Frequently however, these requirements are conflicting in nature; a high crushing strength may result in an increase in disintegration time (1,4,5), thus the approach is not to optimize absolutely but to compromise under the given set of restrictions. Central Composite design (2,5,6) was used to determine the best possible formulation under these restrictions. The design developed consists of four independent variables (filler/binder, drug, disintegrant, and compression force) in five levels, each with the following response variables: crushing strength, friability, weight variation, disintegration time, and dissolution rate. With the aid of multiple regression, model coeffi-

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cients were calculated that illustrated the effect of variables on the response and a polynomial equation was derived that described the experimental system. Finally, graphs were used to assist in the selection of the ideal formulation. A filler/binder of interest, Xylitab 200®, was selected for optimization, with the rest of the formulation composed of ingredients found to withstand high humidity (7).

MATERIALS AND METHODS

Materials

Materials included Xylitab 200 (Pugh & Co., Belgium), composed of 98% Xylitol and 2% sodium carboxymethylcellulose, FCC (8); aspirin (Asagran®, Monsanto, Belgium); casein, cross-linked (Esma Spreng®, W. Schlüter, Germany); povidone, cross-linked (Kollidon CL®, BASF, Germany); lactose (HMS, The Netherlands); magnesium stearate, Ph.Belg. VI (Federa, Belgium); acetic acid p.a., DAB (E. Merck, Germany); sodium acetate trihydrate acid p.a., DAB (E. Merck, Germany); and milli-Q water (Millipore, USA).

Methods

Tablets were manufactured at random following a Central Composite design (Table 1). Ingredients were weighed (Mettler PC 4400, Switzerland) and mixed (Turbula Mixer, Switzerland) without lubricant for 5 min. Lubricant was always added separately and mixed for 1 min. Since the tablet ingredients are varied quantitatively from one formulation to another, in order to produce a uniform percentage of total tablet amount relative to 100%, lactose (filler) was added when necessary. As per preformulation results (7), cross-linked povidone was added at a fixed amount of 2% in all formulations. The tablets were compressed on a single-punch tableting machine fitted with flat punches 12 mm in diameter (Ateliers Ed Courtoy, Belgium). Compression force was measured with a piezoelectric cell (Kistler, Switzerland) attached to a recorder (Hitachi, Japan). For tablet average weight, standard deviation (SD), and coefficient of variation (CV%), data came from 20 tablets, individually weighed (Mettler PC 4400, Switzerland). Crushing strength was measured with a Schleuniger 2E hardness tester (Schleuniger, Switzerland). The data are the mean of 10 tablets. Friability was measured with an Erweka AR400 instrument (Erweka, Germany). The 10 tablets were first weighed then rotated at 20 rounds/min (rpm) for 5 min, then reweighed after careful dusting. The percentage of tablet weight loss was calculated. Tablet disintegration time was measured according to the pharmacopoeia (9) with Erweka ZT3 apparatus (Erweka, Germany) in milli-Q water at 37°C, without disks. The data are the mean of six tablets. Dissolution tests were performed according to the USP XXI monograph on aspirin tablets using the paddle method (10). Analyses were performed at 2-min intervals (Uvikon 860 Spectrophotometer, Switzerland) and stored (INS Computer Systems, Belgium). Dissolution data are mean of three tablets.

Table 1

Translation of Experimental Conditions into Physical Units

	Levels				
Factors	−2	−1	0	1	2
X_1 (mg)	38	42	46	50	54
X_2 (mg)	29	34	39	44	49
X_3 (mg)	1	2	3	4	5
X_4 (kN)	1.5	2	2.5	3	3.5

Legend: X_1 = amount of filler/binder; X_2 = amount of drug; X_3 = amount of disintegrant; X_4 = compression force applied.

Design and Calculation

Central Composite designs are not full factorial designs of the 3^n, where n is the number of factors (assigned variables). The design consists of a 2^n design plus extra points appropriately chosen to approach orthoganality (6). The technique involves performing a set of statistically designed experiments, wherein the first 16 runs is a full factorial (11) represented by −1 and +1; an additional eight extreme values are suitably selected (−2, +2) and seven centerpoints (0) midway between the above-mentioned levels. The design used in this study is a four-factor uniform precision rotatable Central Composite design and the type of predictor equation is a second-order polynomial (6),

$$Y = b_0 + b_1X_1 + \ldots + b_4X_4 + b_{11}X_1^2 + \ldots + b_{44}X_4^2 + b_{12}X_1X_2 + \ldots + b_{34}X_3X_4 \quad (1)$$

where Y = estimate of a response (i.e., dependent variable), X_i = level of independent variable, b_0 = intercept, and b_i = regression coefficient for the second-order polynomial. The independent variables (X) are: X_1 = amount (mg) of filler/binder, Xylitab 200; X_2 = amount (mg) of drug, aspirin; X_3 = amount (mg)

of disintegrant, casein, cross-linked; and X_4 = compression force applied (kN). The dependent variables (Y) are: Y_1 = crushing strength (N), Y_2 = friability (%), Y_3 = weight variation (%), Y_4 = disintegration time (sec), and Y_5 = dissolution rate (time in minutes at 80% release of the drug).

An equation is generated for each dependent variable relating to the set of four independent variables. Multiple regression was carried out using the SPSS program (12) to determine the fit to a second-order model [Eq. (1)] and generate polynomial models relating the response variables to the independent variables (6). For the theory and practice of Central Composite designs and regression analysis, Lieberman et al., (6) and Draper (13), respectively, provides a comprehensive discussion.

RESULTS AND DISCUSSION

Multiple Regression

The results obtained from the SPSS program (12) show that the R^2 value or the coefficient of determination (6) for weight variation and dissolution rate were less than desirable, probably due to some pharmaceutical responses that do not follow second-order polynomial, as similarly noted by Schwartz et al. (5). Since the ability of the system to accurately predict results is only as good as the regression fit of the predictor equation used (6), it was decided to restrict the model to the second-order polynomial, because predictions for several variables might be inaccurate (6). For the generation of polynomial models, only those coefficients found to be significant ($t < 0.05$) were used, hence only models for crushing strength, friability, and disintegration time were generated (Table 2).

Table 2

Significant Coefficients of Multiple Regression Carried Out Using SPPSS

	Coefficient			
Variable	b_0	b_3	b_4	b_{44}
Y_1	159.28		34.221	-8.207
sig. t			0	0.0168
			(+)	(-)
Y_2	0.4674		-0.072	0.0612
sig. t			0	0.0001
			(-)	(+)
Y_4	1258.9	-162.8	215.42	
sig. t		0.0003	0	
		(-)	(+)	

Legend: (+) = positive influence; (-) = negative influence. Dependent variables; Y_1 = crushing strength; Y_2 = friability; Y_4 = disintegration time.

Crushing Strength

Only coefficients b_4 and b_{44} were significant ($t < 0.05$), thus the model then becomes

$$Y = b_0 + b_4X_4 + b_{44}X_4^2 \quad (2)$$

wherein the compression force b_4 suggests a linear positive effect, and b_{44} suggests a negative quadratic effect on the response. Pharmaceutically, this means that up to a certain compression force applied, there is a corresponding increase in crushing strength.

Friability

Similar coefficients to those for crushing strength were found to be significant (b_4 and b_{44}), but their respective influences were opposite. Thus, the model becomes

$$Y = b_0 + b_4X_4 + b_{44}X_4^2 \quad (3)$$

As noted previously (7), the hardness of a tablet gives it the ability to resist abrasion and shock, as simulated by the friabilator machine. This suggests that to a certain extent, as the compression force is increased, the friability of a tablet proportionally decreases.

Disintegration Time

Two coefficients, both linear, were found to be significant; b_3 indicating a negative effect, and b_4 indicating a positive effect. The model then becomes

$$Y = b_0 + b_3X_3 + b_4X_4 \quad (4)$$

In the breaking of a tablet or disintegration, the amount of disintegrant (b_3) is expected to play an important role; while for compression force, the harder the tablet, the longer it takes to disintegrate. The positive influence means that as the amount of independent variable increases, the corresponding response variable will likewise increase; the reverse happens in the case of a negative effect.

Calculation of the Pure Error and Lack of Fit

In a Central Composite design, the centerpoints are used to provide a mean response and an estimate of pure experimental uncertainty at the set of factor levels (6). Lieberman, et al. (6) gives an extensive discussion on

the calculation method of pure error and lack of fit. The significance adopted for F ratio is at the level of 5%. Residuals (data not shown) are the difference in the observed Y (Y_i) and the predicted Y ($\hat{Y}$) value, which is calculated from the model generated. It can be thought of as the amount of the response value Y_j that the regression model does not explain, or as the observed errors associated with the experimental data of the model (6). All generated models (Y_1, Y_2, Y_4) are good predictors for the response since the computed F values were respectively less than the critical F value, denoting no lack of fit (Table 3).

Optimization

Optimization means finding the best possible value of a dependent variable by varying certain independent variables (2). Mathematical explanations of optimization are found in Ref. 1. With weight variation and dissolution rate having undesirable R^2 values, only crushing strength, friability, and disintegration time will be used for optimization. The limits (tablet specifications) placed on the response variables were:

Crushing strength: ≥ 60 Newton (N)
Friability: < 1.0%
Weight variation: = 0.5–1.0%
Disintegration time: ≤ 750 sec
Dissolution rate: ≤ 80% of the drug should be dissolved within 30 min

The graphical procedure involves plotting a given response as a function of one of the independent variables. The responses are functions of the four independent variables and will be represented by:

$$Y_i = f(X_1, X_2, X_3, X_4) \quad (5)$$

where the full relationship is given in Eq. (1). The relationship between response and any one variable, e.g., X_1, may be viewed as a partial derivative Y_i with respect to X_1, while holding all of the other Xs constant (5).

Partial Derivative Plot

Using the regression models generated in Eqs. (2–4), partial derivative plots were created, respectively. In the case of crushing strength, Y_1 is plotted as a function of the X_1, where X_2, X_3, and X_4 were held constant at basal level or zero. Fig. 1 illustrates the derived plot for Y as a function of the Xs. Each line/curve represents one independent variable and the x axis represents the experimental field. The abscissa is kept in experimental units (–2, –1, 0, +1, +2) to allow superimposition since the illustration is a composite of each plot derived. In Figs. 1(a), as compression force increases from 1.5 kN (–2) to 3.5 (2), there is a corresponding rise in crushing strength of the tablet but in a nonlinear manner [presence of a quadratic coefficient in the model, Eq. (2)]. Fig. 1(b) on the other hand, indicates a decrease of friability as the compression force increases, except at experimental unit 2 where an opposite trend can be seen. This demonstrates that an increasing compression force generally diminishes friability, but as the tablet hardens, chipping of tablet edges occurs and as a consequence, an increase will then be noted. While Fig. 1(c) confirms that as the amount of disintegrant (X_3) increases (–2 to +2), there is a corresponding decrease of disintegration time (Y_4). Compression force (X_4) has a positive influence on disintegration time since it takes a longer time to break a harder tablet into pieces.

Table 3

Calculation for the F Value of the Response

	Response Value	*Df*	*SS*	*MS*	Calculated F Value
Pure error	Y_1	6	481.4485	80.24142	3.1266
	Y_2	6	0.0121	0.0020	2.3747
	Y_4	6	45942.85	7657.412	3.6136
Lack of fit	Y_1	22	5571.428	250.8851	
	Y_2	22	0.1054	0.0048	
	Y_4	22	611649.9	27669.88	

Note: F critical value at $p = 0.05$ with Df 22.6 = 3.8564.
Legend: Y_1 = crushing strength; Y_2 = friability; Y_4 = disintegration time.

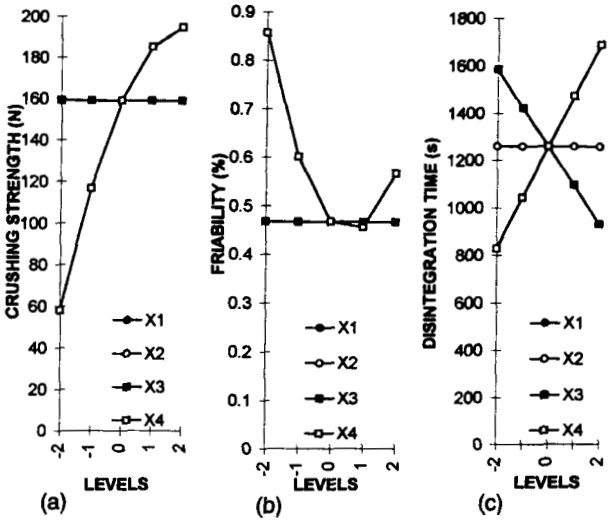

Figure 1. Composite Design for dependent variable as a function of each independent variable. (a) Crushing strength; (b) friability; (c) disintegration time; ● = X1, amount of filler/binder; ○ = X2, amount of drug; ■ = X3, amount of disintegrant; □ = X4, compression force applied.

Three-Dimensional Response Surface

This is another alternative method of illustrating influences of independent variables on the responses. To perform a three-dimensional representation, at least two independent variables are necessary. Hence only disintegration time (Y_4), which has two independent variables in its generated model, can be illustrated; whereas crushing strength (Y_1) and friability (Y_2) each has an independent variable in its respective model. Fig. 2 represents a more clear picture on the disintegrant (X_3) and compression force (X_4) on disintegration time. As the amount of disintegrant is increased and the compression force applied is reduced, there is a decreasing trend of disintegration time. As can be distinguished in the illustration, an optimal formulation met the technical specification of a maximum of 750 sec when the compression force is around 2 kN and the amount of disintegrant is 44%.

Although two of the responses were not included in the generation of models, pharmaceutically, responses obtained from weight variation and dissolution rate at the level at which the optimal formulation was located were within specification. Weight variation was 0.687%, while the dissolution rate was 28 min, well within the limits preselected (Fig. 3).

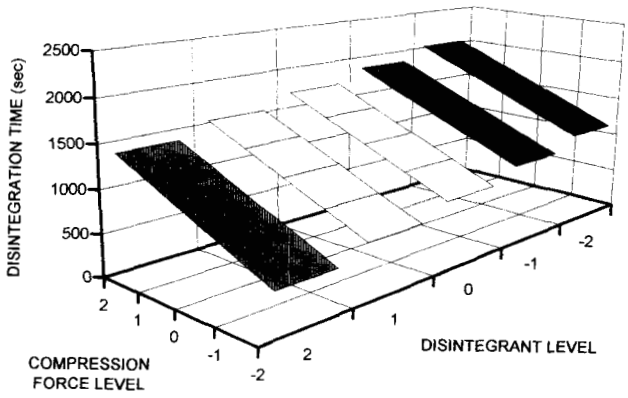

Figure 2. Three-dimensional response surface.

CONCLUSION

The regression models show that the compression force has a strong positive influence on crushing strength and disintegration time, but has a negative effect on friability. There were quadratic effects observed for crushing strength and friability, but disintegration time had linear effects. In addition to the location of an optimal formulation within the experimental area of the design selected, a trend is observed as to probable yield when the amount of an independent variable is either

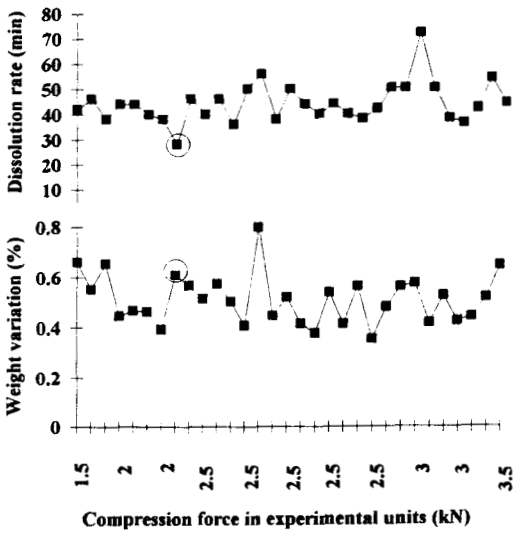

Figure 3. Pharmaceutical result of weight variation and dissolution rate.

increased or decreased. Using the filler/binder of interest (Xylitab 200), Central Composite design has been found to be a good tool in optimization. The location of an optimum area in this study can be done to the ranges preselected for the independent variables and the specification limits for the dependent variables. Pharmaceutically, the directly compressed tablet prepared with the optimum formulation exhibited good tableting properties with a high concentration of aspirin (model drug).

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