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FORMULA OPTIMIZATION FOR A MULTIPLE POTENCY SYSTEM WITH UNIFORM TABLET WEIGHT

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ABSTRACT

The study described herein was undertaken to develop formulations for a multiple potency system, in but a single optimization experiment. To achieve the objective, Sequential Prediction Analysis, a unique statistical procedure, where a computer is instructed to provide responses to predetermined levels of independent variables, was successfully utilized.

INTRODUCTION

The techniques of optimization in pharmaceutical dosage form design are well documented[1,2,3,4]. Schwartz et al[5,6] developed a technique whereby a formulation with optimum properties could be obtained through computer assisted data analysis. They used the results of a statistically designed series of experiments, based on five independent variables, as input into a computer. Down et al[7]

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used a desk top computer for product optimization. Their method offered rapid access and versatility as an alternative to large-scale computing facilities which frequently are not readily accessible.

Historically, optimization techniques have been applied to multiple potency tablet systems where the tablet weight varied proportionately with selected potencies. In a multiple potency system with invarient tablet weight, however, the ratio of active ingredient to excipient changes at each potency level. Formula optimization of such systems, as will be shown, became more complex, though may be simplified by undertaking optimization studies at each potency level. This, however, is costly with respect to time, materials and manpower. This paper discusses efforts to develop formulations for a multiple potency weight invariant system within a single optimization experiment. To achieve the objective Sequential Prediction Analysis, a unique statistical procedure where the computer was instructed to provide responses to predetermined levels of independent variables was successfully utilized.

In typical grid searches, a set of X-grid points are automatically generated and then used in a second order polynomial equation to yield Y-responses. A specific set of X-grids is accepted as a solution if its corresponding Y-value meets prespecified Y-constraints. X's of narrow ranges are introduced into the Y-equations for the purpose of prediction. The predictions are under no constraints. Thus one can sequentially predict the Y-values to determine if a particular set of Y-values meets the desirable conditions and, therefore, high resolution refinement in the

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prediction process becomes possible. One example,

Let X_{10}, X_{20} — X_{50} be the selected values

Let $\triangle X_{10}, \triangle X_{20} - \triangle X_{50}$ be the increments in the narrow range of X's; i.e., a window

$$Y = \sum_{i=0}^{k} b_i X_i + \sum_{i=2} b_{ii} X_{ii} + \sum_{i=j} b_{ij} X_i X_j$$

$$Y_o = \sum_{i=0}^{k} b_i X_{io} + \sum_{i=2} b_{ii} X_{iio} + \sum_{i=j} b_{ij} X_{io} X_{jo}$$

Where Y = the level of a given response

b = regression coefficient

X = level of independent variable

EXPERIMENTAL

In the system studied, it was known that the drug could undergo cyclization at a low pH while at higher pH's it could hydrolyze. Cyclization can be prevented through 'in-situ' deprotonation of the drug during wet granulation. A salt is obtained through equimolar reaction between the drug and sodium bicarbonate.

Initial optimization of the formulation employed a commonly used five factor, orthogonal, central, composite, second order design. The modified design of five independent variables which involves 27 experiments with zero as the base line and the experimental ranges varying from -1.547 to +1.547 experimental units, (e.u.) has been described in the literature[5]. The experiments were performed in random order. The translation of the statistical design into physical units for the five variables is shown in Table I. Each experiment

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TABLE I
Experimental Design

Factor	-1.547 eu	-1.0 eu	Base 0	+1.0 eu	+1.547 eu
X_1 = Drug 1 eu = 9.7 mg Drug	4.99 mg	10.3 mg	20 mg	29.7 mg	35.01 mg
X_2 = Starch Paste Conc. 1 eu = 1.94% w/w	4.99%	6.06%	8.0%	9.94%	11.00%
X_3 = Disintegrant Wgt 1 eu = 6.46 mg Wgt	10.006	13.54 mg	20 mg	26.46 mg	29.994 mg
X_4 = Lubricant Level 1 eu = 0.26 mg	0.698 mg	0.84 mg	1.1 mg	1.36 mg	1.502 mg
X_5 = Compression Press. 1 eu = 0.5 tons	1.2 tons	1.5 tons	2.0 tons	2.5 tons	2.8 tons

consisted of a batch of 5000 tablets. Granulation was tabletted on a rotary press. The responses (dependent variables) measured on the resulting tablets included: dissolution rate (Y_1), disintegration time (Y_2), tablet hardness (Y_3), tablet friability (Y_4), cyclized product level (Y_5), hydrolyzed product level (Y_6), pH of tablets in water (Y_7) and residual bicarbonate in a tablet (Y_8). The latter two response variables help determine the extent to which the deprotonation of the drug has taken place. Completeness of the reaction would be indicated by a neutral pH and absence of residual bicarbonate.

Dissolution rates were determined in 750 ml water with USP XX apparatus 2 at 50 rpm. Tablet disintegration time, breaking strength and friability were measured with commonly employed equipment.

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The Sequential Prediction Analysis program was written in the Fortran language which currently runs on a IBM 3084 computer.

RESULTS AND DISCUSSION

All stated responses from the 27 experiments were measured. A routine multivariate statistical optimization analysis was then carried out. Data reduction included calculation of means and correlation coefficients of the dependent variable measurements. Each response was examined as to fit in a second order polynomial equation as described before[5]. R-square values indicated that good linearity were obtained for all variables.

Traditional optimization analyses, i.e., feasibility and grid searches were performed. It was in the results of these analyses that the weakness of the traditional optimization became evident. In the feasibility search, for example, potencies ranging from 16 to 27 mg were suggested as optimum. These solutions, valid as they were, were of no practical significance since tablet potencies had been predetermined at 5 mg, 10 mg, 20 mg and 40 mg of drug per tablet. Likewise, the grid searches yielded optimum formulations which were considered improcessable. Recognizing these difficulties a newer analytical tool, termed Sequential Prediction Analysis, was developed. Herein the computer is instructed to provide responses to predetermined independent variables. For each potency, the level of X_2 was varied from 6% to 10% at 1% increments. Factors X_3, X_4 and X_5 deemed of less importance from preliminary probe experiments were kept constant at levels considered optimum. An example of the analysis for the 20 mg potency generated by the computer is presented in Table II.

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TABLE II

Sequential Prediction Analysis Output

	X_2=6	X_2=7	X_2=8	X_2=9	X_2=10
Y_1-Dissolution expressed as percent of initial assay dissolved in 30 mins.	101.32	102.54	103.07	102.89	102.03
Y_2-Disintegration time minutes	5.80	5.83	5.63	5.19	4.52
Y_3-Crushing strength in kiloponds	19.41	19.09	18.68	18.18	17.58
Y_4-Friability as percent weight loss	0.18	0.74	1.07	1.16	1.03
Y_5-Byproduct A as percent of drug	1.28	0.88	1.32	2.61	4.75
Y_6-Byproduct B as percent of drug	0.26	0.32	0.35	0.34	0.30
Y_7-pH	6.87	6.63	6.44	6.30	6.21
Y_8-Residual bicarbonate, mg/tablet	1.58	2.38	3.10	3.74	4.10

Optimum Formula - The solutions generated through sequential prediction analysis indicated decreasing levels of responses, Y_5 and Y_6, as the value of X_2 was decreased. This was expected since more solvent is available for the deportonation process. It was, however, mandatory to maximize the value of X_2 relative to that of X_1 to obtain a processable formulation. For instance, the reaction by-products may be minimized for the 20 mg formulation by employing a 7% instead of an 8% paste. However, the processability of the formulation would be sacrificed. Taking into consideration this limitation, an optimum formulation was selected for each potency.

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TABLE III
Optimum Formulations

X_1	X_2	X_3	X_4	X_5
5 mg	6%	20 mg	1.1 mg	2.0 tons
10 mg	7%	20 mg	1.1 mg	2.0 tons
20 mg	7.75%	20 mg	1.1 mg	2.0 tons
40 mg	9%	20 mg	1.1 mg	2.0 tons

These are presented in Table III. The optimum formulations, while not yielding the lowest levels of reaction by-product were the best compromise with regard to processability.

Verification Experiments - Based upon the output from Sequential Prediction Analysis, the optimum formulation was prepared for each potency. In general the values of the response variables parallel those predicted by the regression equation. This is commendable in

TABLE IV
Comparison of Tablet Properties

Property	5 mg		10 mg		20 mg		40 mg	
	Actual	Predicted	A.	P.	A.	P.	A.	P.
Dissolution, % - Y_1	106	94	104	99.6	101	103	96	85.5
Disintegration Time, Min - Y_2	-	1.8	4.75	3.5	6.5	5.6	6.5	5.8
Hardness, Kp - Y_3	-	7.6	14.3	12.1	18.8	18.7	27.4	20.2
Friability, % Y_4	-	5.9	4.0	3.9	0.32	1.1	0.26	6.2
Byproduct A Y_5	Trace	0.33	None	0.14	Trace	1.32	1.07	0.2
Byproduct B Y_6	0.072	0.0	None	0.19	Trace	0.35	Trace	0.0
pH - Y_7	6.36	7.43	6.65	6.92	6.32	6.4	6.18	6.4
Residual Bicarbonate Y_8	0.28	0.17	0.91	0.84	2.53	2.64	>10.0	5.5

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that there was only one 5 mg formulation (-1.547) in the design matr: and the 40 mg formulation was an extrapolation beyond the single extreme run, i.e., beyond +1.547 e.u. The best match between the actual and predicted values was for the 10 mg and 20 mg potencies where the number of experiments in the design matrix are 8 and 9 respectively. A comparison of the actual and predicted values of the response variables is presented in Table IV.

CONCLUSION

Based on this study, Sequential Prediction Analysis is suggested as a method for handling complicated situations in Formula Optimization where multiple potency systems are coupled with invariar tablet weight.

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