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PHARMACEUTICAL FORMULATION OPTIMIZATION USING SAS™

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ABSTRACT

Pharmaceutical formulation optimization consists of three distinct but interrelated analyses, optimization, selection of key parameters and selection of key factors, all accomplished from the same set of experimental data. However, the statistical formulas and their computational algorithms are complex. Development of an in-house software is a formidable task. Four short SAS programs are provided to accomplish the task effectively and speedily. Two optimization studies, a mobile phase composition study and a pharmaceutical formulation study are analyzed by using the programs. The contents of the output are explained clearly and interpreted appropriately.

INTRODUCTION

The primary purpose of this paper is to provide the development pharmacist with adequate computational and statistical means to accomplish in a most effective, convenient

and rapid manner the complex data analysis aspects of formulation optimization studies. Pharmaceutical formulation optimization analysis, as defined in (1,2), is composed of three distinct but interrelated component parts. The first part consists of the optimization analysis itself, generating the optimum levels of the factors (e.g. excipient, process) which simultaneously satisfy the goals associated with several response parameters (1,2). The second part analysis identifies the most important product property (e.g. dissolution, disintegration) from the same set of responses considered in the first part (3). The third part analysis selects the key factors which exert considerable influence on the outcome of the product properties (4). It should be noted here that the results of the last two analyses are primarily used for monitoring in a time-and-cost effective manner the future performance of the optimum formulation and for understanding the various mechanisms governing the pharmaceutical system (3-5). All three analyses are an absolute necessity for the development of a successful optimum formulation. However, the statistical formulas and their computational algorithms are enormously intricate involving iterative numerical methods. The development of an in-house software for these procedures is a formidable task. The in-house softwares, presently available, hardly meet the needs for even the first part analysis.

To mitigate the situation to a considerable extent this paper presents (a) the various statistical formulations for the analysis of optimization data, (b) a complete set of four SAS computer programs and (c) the salient results of the optimization analysis of a mobile phase composition study and a pharmaceutical formulation study, obtained by using the computer programs.

THEORY

The optimization theory pertaining to pharmaceutical formulation development is elaborated, in detail, in references (1-6). Only the salient features of the theory relevant to the objective of this paper are presented. Let X_1, X_2----X_k denote the k number of independent variables and let Y_1Y_2----Y_p denote the p number of dependent variables. In general, a second order polynomial regression function is fitted to each of the p dependent variables. The structure of the regression function is as follows: (without loss of generality consider k=3),

$$Y_i=B_0+B_1X_1+B_2X_2+B_3X_3+B_{11}X_1^2+B_{22}X_2^2+B_{33}X_3^2+B_{12}X_1X_2 +B_{13}X_1X_3+B_{23}X_2X_3$$

where i =1, 2, ---- p

Let W′ be the column vector of independent variables and their functions. Explicitly,

$$W' = [1\ X_1\ X_2\ X_3\ X_1^2\ X_2^2\ X_3^2\ X_1X_2\ X_1X_3\ X_2X_3]$$

$$= [W_0\ W_1\ W_2\ W_3\ \text{----------}\ W_9]$$

The number of terms in each regression function is $1/2(K+1)(K+2)$. The least squares estimates of the partial regression coefficients are $B=(W'W)^{-1}W'Y$ based on the normal equation, $W'WB = W'Y$. The expression for the R^2-value is $R^2=[B'W'Y-R(Bo)][Y'Y-R(Bo)]^{-1}$ where, $R(Bo)=N\bar{Y}^2$, N = number of formulations, $\bar{Y} = \sum Y/N$.

Canonical conversion of the regression function:

In vector notation, the regression function is expressed as,

$$Y = Bo + X'B + X'B^*X$$

where, $X = [X_1\ X_2\ X_3]$, $B = [B_1\ B_2\ B_3]$ and

$$B^* = 1/2 \begin{bmatrix} 2B_{11} & B_{12} & B_{13} \\ B_{21} & 2B_{22} & B_{23} \\ B_{31} & B_{32} & 2B_{33} \end{bmatrix}$$

The nature of the stationary point is obtained by examining the directions (signs) of the eigen values derived as a solution of the determinantal equation, $|B^*-\lambda I|=0$. If all the eigen values are positive, then the stationary point is a unique minimum. Whereas, if all the eigen values are negative, the stationary point is a unique maximum. The stationary point is given by $X_o=-B^{*-1}(1/2)B$. If the eigen values do not share the same sign, then the stationary point is a saddle point and there is no unique optimum. The exploration process is initiated by using the following canonical exploration function,

$$Y_i = Y_o + \lambda_1 Z_1^2 + \lambda_2 Z_2^2 + \lambda_3 Z_3^2$$

$$i = 1, 2, \text{---} p$$

where, Y_0 is the estimated response at the stationary point, λ_1, λ_2, and λ_3 are the eigen values of the Hessian Matrix B* and Z_1, Z_2 amd Z_3 are the new rigidly rotated coordinates. The relationship between the rigidly rotated coordinates and the original X-variables is established by the equation $Z = V'X$, where V is the eigen vector matrix derived from the Hessian Matrix. The construction of the grid-matrix of the X-variables is based on generating multidimensional grid-points by resorting to the following vector equation,

$$\dot{X}^{(\ell)} = \dot{\alpha} + \dot{\Upsilon}^{\ell}(\dot{\beta}-\dot{\alpha})$$

where, Υ is the grid search partition step parameter,

$0 \leq \Upsilon \leq 1$, and α and β are the grid search starting and end points respectively. A dot denotes a vector quantity.

The optimization procedure appropriate for pharmaceutical formulation is called "Multivariate Simultaneous Objective Optimization Procedure (M-SOOP), which is described, in detail, in references (1,2).

Selection of Key Response Parameters:

This is accomplished by resorting to Principal Component Analysis based on the variance-covariance matrix $\sum$. The relative magnitude of the square of the components of the eigen vector for the largest eigen value of the $\sum$ matrix provides a basis for selecting the key parameters, since the sum of the squares of the components is equal to one. The details of the method are provided in reference (3).

Selection of Key Formulation Factors:

This is accomplished by using the C-A-S technique (4) which provides a basis for combining the results of the all-possible-regression analysis and the results of the stepwise-regression analysis. Set-theoretic approach is used to extract parameters which are easily interpretable in the pharmaceutical context (4).

OPTIMIZATION COMPUTER PROGRAMS

The pharmaceutical formulation optimization analysis is accomplished by using four separate short SAS programs. Table-1 contains the main optimization program which is written in the SAS Statistical Comptuter language (7). The program has no restrictions with respect to the number of variables (independent or dependent) to be analyzed. Some of the statements in the program must be modified to suit the specifications of a particular study. It should be noted here that the program, as it appears in Table-1, is based on the specifications of the mobile phase composition study. As indicated by Statement-4, this study has 3 X-variables (independent) and 3 Y-variables (dependent) and the data for these six variables, arranged in columns of numbers, are in the data file named "ACET" (Statement-3) which is created separately and stored in the memory prior to the execution of the main optimization program (OPT•SAS). Should the user prefer another name for the file, that name must be inserted instead.

TABLE-1

SAS PROGRAM STATEMENTS FOR OPTIMIZATION

PROGRAM* STATEMENT NO.	PROGRAM STATEMENTS
1	XXXXXX XXXXXXXXXX XXXXXXX XXXXXX;
2	DATA A;
3	INFILE ACET;
4	INPUT X1 X2 X3 Y1 Y2 Y3;
5	PROC RSREG DATA=A OUT=C;
6	MODEL Y1 Y2 Y3 = X1 X2 X3 / PREDICT;
7	PROC PRINT DATA=A;
8	DATA B;
9	SET A END=EOF; OUTPUT;
10	IF EOF THEN DO; Y1=.; Y2=.; Y3=.;
11	DO X1=2.5 TO 7.0 BY .5;
12	DO X2=5 TO 50 BY 5 ;
13	DO X3=5.0 TO 50 BY 5;
14	OUTPUT;
15	END;
16	END;
17	END;
18	END;
19	/* PROC PRINT DATA=B; */
20	PROC RSREG DATA=B OUT=C;
21	MODEL Y1 Y2 Y3 = X1 X2 X3/ PREDICT;
22	/* PROC PRINT DATA=C; */
23	DATA D; SET C;
24	IF 3<Y1<7 AND Y2<1.1 and 0<Y3<0.5;
25	PROC PRINT DATA=D;

*The program statement numbers are not a part of the program.

The contents of the following program statements must be modified. Statements 4, 6 and 21 are changed according to the number of X-variables and Y-variables being considered. Statements 10 and 24 are changed according to the number of Y-variables only. Statements 11, 12 and 13 are called the "DO" statements. There

TABLE-2

SAS PROGRAM STATEMENTS FOR SELECTION OF KEY PARAMETERS

PROGRAM* STATEMENT NO.	PROGRAM STATEMENTS
1	XXXXX XXXXX;
2	DATA A;
3	INFILE ACET;
4	INPUT X1 X2 X3 Y1 Y2 Y3;
5	PROC PRINCOMP COV OUT=PRIN;
6	VAR Y1 Y2 Y3;
7	PROC PLOT;
8	PLOT PRIN2 * PRIN1;

*The program statement numbers are not a part of the program.

must be as many "DO" statements as there are X-variables. The exploration range of each X-variable along with its increment value (supplied after the word "BY") are inserted into these "DO" statements. Small increment values lead to fine numerical resolution of the results. The numerical value of the goal associated with each Y-variable is inserted into Statement-24.

Tables 2, 3 and 4 contain the SAS programs for the selection of key parameters, selection of key factors (R^2) and selection of key factors (stepwise), respectively. Statement-3 of each table shows that the same data-file "ACET" is used in all three programs indicating that one does not have to create a new data-file for each program. Statement-4 in all three tables and statement-6 in Tables 3 and 4 are modified

TABLE-3

SAS PROGRAM STATEMENTS FOR SELECTION OF KEY FACTORS USING R^2 ONLY

PROGRAM* STATEMENT NO.	PROGRAM STATEMENTS
1	XXXXX XXXXX;
2	DATA A;
3	INFILE ACET;
4	INPUT X1 X2 X3 Y1 Y2 Y3;
5	PROC RSQUARE DATA=A;
6	MODEL Y_1 Y_2 Y_3 = X_1 X_2 X_3

*The program statement numbers are not a part of the program.

TABLE-4

SAS PROGRAM STATEMENTS FOR SELECTION OF KEY FACTORS USING STEPWISE PROCEDURE

PROGRAM* STATEMENT NO.	PROGRAM STATEMENTS
1	XXXXX XXXXX;
2	DATA A;
3	INFILE ACET;
4	INPUT X1 X2 X3 Y1 Y2 Y3;
5	PROC STEPWISE DATA=A;
6	MODEL Y_1 Y_2 Y_3 = X_1 X_2 X_3/STEPWISE;

*The program statement numbers are not a part of the program.

according to the number of X-variables and Y-variables considered. However, Statement-6 in Table-2 is modified according to the number of dependent variables considered. In all tables, 1, 2, 3 and 4, the contents of Statement-1 depend upon the specific computer system being used, and as such the computer department of the user's facility must provide this information as well as the appropriate instructions for proper implementation and execution.

Computer Printout

The output from the optimization program provides for each dependent variable, (1) R^2-value, (2) partial regression coefficients of the second order polynomial function, (3) eigen values and eigen vectors and (4) a statement indicating whether the stationary point is a maximum, minimum or saddle point. The last page of the output provides the final results, the optimum levels of the independent variables which satisfy, simultaneously, the goals associated with each dependent variable.

The output for the selection of key parameters program provides the variance-covariance matrix of the dependent variables and the eigen values and eigen vectors of the variance-covariance matrix. The output for the se ection of key factors (R^2) provides for each dependent variable all the R^2-values associated with (2^k-1) regression equations involving k independent variables (4). The output for the selection of key factors (stepwise) program provides for each

dependent variable the sequential significance tests for the partial regression coefficients in a stepwise manner (4).

OPTIMIZATION STUDIES: DESIGN, RESULTS AND DISCUSSION

The performance of the main optimization program is demonstrated by using it for the analysis of two optimization studies. a mobile phase composition study and a pharmaceutical formulation study. The description as well as the interpretation of the contents of the output are succinctly presented in this section.

Mobile Phase Composition Optimization:

The separation of pure drug substance from its degradation product is one of the primary functions of the Pre-formulation Section of the Pharmaceutics Department. Typically, the process involves the selection of a relevant set of solvents and modifiers and of their appropr ate concentrations for experimentally determining the optimum mobile phase composition which meets the goals associated with a prescribed set of quantitatively assessed column performance parameters. Table-5 presents the independent variables and their coded and actual concentrations.

The dependent variables comprise of (i) capacity factor (k′) (ii) peak skew and (iii) HETP (Height equivalent theoretical plate). These column performance parameters are measured for the various combinations of the levels of the two

TABLE-5

CODED AND ACTUAL CONCENTRATIONS/LEVELS OF THE FACTORS

COMPOSITION STUDY

1.	Buffer pH	Coded*	-1.215	-1.0	0	+1.0	+1.215
		Actual	2.50	2.90	4.75	6.60	7.0
		Coded*	-1.215	-1.0	0	+1.0	+1.215
2.	Methanol %	Actual	5.0	9.0	27.5	46.0	50.0
3.	Acetonitrile %	Coded*	-1.215	-1.0	0	+1.0	+1.215
		Actual	5.0	9.0	27.5	46.0	50.0

FORMULATION STUDY

		Coded	-1.547	-1.0	0	+1.0	+1.547
1.	CAB-O-SIL (mg)	Actual	0.001	0.44	1.24	2.04	2.48
2.	Encompress/Lactose Ratio mg/mg	Coded	-1.547	-1.0	0	+1.0	+1.547
		Actual	0.98	1.26	2.15	4.19	6.68
3.	Starch Disintegrant (mg)	Coded	-1.547	-1.0	0	+1.0	+1.547
		Actual	0.001	2.25	6.44	10.6	12.88
4.	Stearic Acid (mg)	Coded	-1.547	-1.0	0	+1.0	+1.547
		Actual	0.001	1.22	3.44	4.66	6.80
5.	Magnesium Stearate (mg)	Coded	-1.547	-1.0	0	+1.0	+1.547
		Actual	0.35	0.60	1.05	1.50	1.75

*Coded conversion: C=(A-B)/E, where A=actual, B=base (=0) and E=experimental unit (factorial spacing)

TABLE-6

Second Order Polynomial Regression Functions

$$Y_1 = 33.77 - 1.16X_1 - 0.39X_2 - 074X_3 + 0.15X_1^2 - 0.003X_1X_2 - 0.001X_2^2 - 0.004X_1X_3 + 0.011X_2X_3 + 0.002X_3^2 \quad (R^2 = 98.3\%)$$

$$Y_2 = 3.96 - 0.90X_1 + 0.013X_2 - 0.01X_3 + 0.096X_1^2 + 0.001X_1X_2 - 0.00004X_2^2 - 0.002X_1X_3 - 0.00057X_2X_3 + 0.00015X_3^2 \quad (R^2 = 87.3\%)$$

$$Y_3 = 73.94 + 23.9X_1 - 0.56X_2 - 5.8X_3 - 2.63X_1^2 + 0.013X_1X_2 - 0.02X_2^2 + 0.024X_1X_3 + 0.028X_2X_3 + 0.069X_3^2 \quad (R^2 = 87.2\%)$$

Y_1 = Capacity Factor, Y_2 = Peak Skew, Y_3 = HETP,
X_1 = Buffer pH, X_2 = Methanol, X_3 = Acetonitrile

HESSIAN MATRIX FOR Y_3 = HETP =

$$\begin{bmatrix} -2.63 & 0.007 & 0.012 \\ 0.007 & -0.020 & 0.014 \\ 0.012 & 0.014 & 0.069 \end{bmatrix}$$

organic modifiers and buffer pH. Fifteen such combinations which constitute the mobile phase compositions are generated based on an orthogonal central composite (augmented) full three-factor factorial design with a center point. (The factorial structure of a three factor composite design can be derived by taking the first 8 rows and the last 7 rows of the table in page 159 in reference (1)). The second-order polynomial regression function and its R^2-value for each dependent variable are presented in Table-6. The Hessian matrices for the three response variables are constructed (only the Hessian matrix for Y_3 is shown in Table-6) and the eigen values for each matrix are extracted. Table-7 shows that the three eigen values of each response parameter do not share

TABLE-7

MAGNITUDES AND DIRECTIONS (SIGNS) OF EIGEN VALUES OF THE HESSIAN MATRIX (B*)

COMPOSITION STUDY

Dependent Variable	Eigen Values			Nature of the Stationary Point
	λ_1	λ_2	λ_3	
1 Capacity Factor	0.146	0.0059	-0.0053	Saddle Point
2 Peak Skew	0.096	0.0003	-0.00024	Saddle Point
3 HETP	0.0713	-0.0216	-2.628	Saddle Point

FORMULATION STUDY

	λ_1	λ_2	λ_3	λ_4	λ_5	
1 Content Uniformity:	0.303	0.065	-0.016	-1.442	-4.992	Saddle Point
2 Tablet Strength:	0.863	0.024	0.007	-0.056	-0.710	Saddle Point
3 Relative Dissolution:	1.118	-0.010	-0.400	-2.333	-8.154	Saddle point

The number of optimum compositions thus generated by the program for Y_1, Y_2 and Y_3 are 9, 5 and 8 respectively. A cursory examination of these optimum compositions reveals that the level of acetonitrile remains consistently at 40% or above

the same sign, indicating that the nature of the stationary point is a saddle point in each case. This finding leads to the construction of the canonical form of the second-order polynomial regression function (See Table-8) for implementing systematic exploration of the solution space for the optimum which is equally likely to occur in the experimental region (MSOOP procedure). Transformation matrices are necessary at this point to convert the X-variables into Z-variables (rigidly rotated coordinates) to enter the canonical functions. Table-9 presents the exploration ranges and the grid-step parameters for the independent variables and the prespecified goals for the dependent variables. Based on 1015 iterations, two optimum mobile phase compositions that achieved the prespecified goals associated with the three response parameters are found and listed in Table-10. The results of the regression analysis, as shown in the output, indicate that acetonitrile has a significant ($p<0.02$) effect on HETP and peak skew. It is decided to examine this result, in detail, because of the computer speed and the program's versitility and capability. The main optimization program is run for each dependent variable, separately, imposing the most ideal goal for each variable. The goals set for Y_1, Y_2 and Y_3 are, respectively, 4.0-4.9, less than 0.8 and less than 0.5. for all dependent variables. This consistency is maintained, irrespective of the magnitude of the levels of the other two independent variables.

TABLE-8

CANONICAL FORM OF THE SECOND-ORDER POLYNOMIAL REGRESSION FUNCTION

COMPOSITION STUDY

$$Y_1 = 2.25 + 0.146Z_1^2 + 0.0059Z_2^2 - 0.0053Z_3^2$$
$$Y_2 = 1.37 + 0.096Z_1^2 + 0.00034Z_2^2 - 0.00024Z_3^2$$
$$Y_3 = 16.02 + 0.071Z_1^2 - 0.0216Z_2^2 - 2.628Z_3^2$$

TRANSFORMATION MATRIX FOR Y_1: (COLUMN 1 FOR λ_1, COLUMN 2 FOR λ_2, COLUMN 3 FOR λ_3)

$$\begin{bmatrix} 0.99986 & 0.0167 & 0.000415 \\ -0.01039 & 0.6025 & 0.79808 \\ -0.01308 & 0.79797 & -0.6026 \end{bmatrix}$$

Y_1 = Capacity Factor, Y_2 = Peak Skew, Y_3 = HETP
Z_1 = RRC(X_1 = Buffer pH), Z_2 = RRC (X_2 = Methanol,
Z_3 = RRC (X_3 = Acetonitrile)
RRC = Rigidly Rotated Coordinate

FORMULATION STUDY

$$Y_1 = 100.64 + 0.304Z_1^2 + 0.065Z_2^2 - 0.016Z_3^2 - 1.44Z_4^2 - 4.99Z_5^2$$
$$Y_2 = 4.46 + 0.863Z_1^2 + 0.024Z_2^2 + 0.007Z_3^2 - 0.055Z_4^2 - 0.710Z_5^2$$
$$Y_3 = 164.81 + 1.119Z_1^2 - 0.010Z_2^2 - 0.400Z_3^2 - 2.33Z_4^2 - 8.154Z_5^2$$

TRANSFORMATION MATRIX FOR Y_1:

$$\begin{bmatrix} .32 & .09 & -.12 & .93 & -.10 \\ .68 & .18 & -.61 & -.34 & -.08 \\ .00 & .95 & .31 & -.06 & -.03 \\ .65 & -.24 & .71 & -.11 & -.02 \\ .11 & .05 & -.04 & .06 & .99 \end{bmatrix}$$

Y_1=Content Uniformity, Y_2=Tablet Strength, Y_3=Relative Dissolution (15 min)
Z_1=RRC(X_1), Z_2=RRC(X_2), Z_3=RRC(X_3), Z_4=RRC(X_4), Z_5=RRC(X_5)
RRC=Rigidly Rotated Coordinate

Pharmaceutical Formulation Optimization Study

Formulation optimization commands the major function of the Pharmaceutics Department. The experiment typically involves the selection of a relevant set of excipients and process variables and of their appropriate levels for experimentally

TABLE-9
EXPLORATION RANGES AND GOALS FOR THE OPTIMIZATION STUDIES

NO.	EXPLORATION RANGES	GRID-STEP PARAMETER*	PRESPECIFIED GOALS
	COMPOSITION STUDY		
1.	$2.5 \leq X_1 \leq 7.0$	$\gamma = 0.11$	$3.0 \leq Y_1 \leq 7.0$
2.	$5.0 \leq X_2 \leq 50.0$	$\gamma = 0.11$	$Y_2 < 1.1$
3.	$5.0 \leq X_3 \leq 50.0$	$\gamma = 0.11$	$Y_3 < 0.5$
	FORMULATION STUDY		
1.	$0.0 \leq X_1 \leq 2.48$	$\gamma = 0.20$	$Y_1 > 100$
2.	$0.98 \leq X_2 \leq 6.68$	$\gamma = 0.14$	$Y_2 > 5$
3.	$0.0 \leq X_3 \leq 12.88$	$\gamma = 0.08$	$Y_3 > 80$
4.	$0.0 \leq X_4 \leq 6.80$	$\gamma = 0.07$	
5.	$0.35 \leq X_5 \leq 1.75$	$\gamma = 0.21$	

*γ is the grid-step parameter, calculated by the reciprocal of the ratio (Range/Increment)

TABLE-10

FINAL RESULTS
OPTIMUM CONCENTRATIONS FOR MOBILE PHASE COMPOSITIONS AND OPTIMUM LEVELS FOR PHARMACEUTICAL FORMULATIONS

COMPOSITION STUDY

NO.	OPTIMUM CONCENTRATIONS			PREDICTED RESPONSE		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
1.	4.5	45.0	40.0	3.38	1.09	0.24
2.	5.0	45.0	40.0	3.35	1.08	0.49

FORMULATION STUDY

NO.	OPTIMUM LEVELS					PREDICTED RESPONSE		
	X_1	X_2	X_3	X_4	X_5	Y_1	Y_2	Y_3
1.	2.1	1.98	12.0	5.0	1.35	100.35	5.2	80.1
2.	2.1	1.98	12.0	6.0	1.35	100.52	5.2	81.2

determining the optimum formulation which meets, simultaneously, the prespecified goals set for the product properties considered. The experimental specifications of this study are described, in detail, in reference (1) in pages 168-173, in which the drug product is referred to as Product-T. Table-5 shows the actual and coded levels of the independent variables. Amont the six response variables measured originally, only three variables are considered for this paper. Twenty seven formulations are generated based on an orthogonal central composite (augmented) half fractional 5-factor factorial design with a center point. Table-7 depicts the directions of the eigen values for each dependent variable. Since the eigen values do not share the same sign, it would be surmised that the nature of the stationary point is a saddle point for each case. Table-8 shows the canonical form of the regression function and the transformation matrix for Y_1. Table-9 presents the exploration ranges and the grid-step parameter for each independent variable and the goals set for the three dependent variables. The final results consisting of two optimum formulations are presented in Table-10.

It is interesting to note that the optimum levels of the independent variables presented in Table-10 fall within the respective ranges of the optimum levels of the independent variables of the three optimum formulations obtained for Product-T, (presented in reference (1)), with the exception of

Cab-O-Sil (X_1) and stearic acid (X_4)(See table below).

	X_1	X_2	X_3	X_4	X_5
Range (Ref. 1)	0.83-1.39	1.67-3.0	12.5-13.0	2.29-3.44	1.0-1.4
Present Study	2.1	1.98	12.0	5.0-6.0	1.35

The optimum levels of these two excipients are essentially doubled in this study. This is because disintegration is not included in the optimization analysis of the present study. These two excipients seem to impede rapid disintegration (1).

SELECTION OF KEY RESPONSE PARAMETERS AND KEY FACTORS IN OPTIMIZATION SYSTEMS

For selecting the key response parameters and the key factors, the computer programs in Tables 2-4 generate all the statistics presented in reference (3) and (4). The interpretation of the statistical results in the output is also provided, in detail, in the same two references.

NOTE: The user may contact the author (Dr. N. R. Bohidar, 1530 Bridal Path Road, Lansdale, PA 19446) for any clarification of the contents of Tables 1-4.

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