J. Kor. Pharm. Sci., Vol. 24, No. 3, S67-S77 (1994)

Application of Experimental Design to Optimize Vitamin C-90 Tabletting Performance

Kuei-Tu Chang

Hoffmann-La Roche Vlitamin Research & Development, Nutley, NJ. USA

(Received September 5, 1994)

The RMS statistical approach has demonstrated its potential in developing pharmaceutical dosage forms and in improving tabletting performance. Using an optimized formula, the tabletting performances of vitamin C-90 such as compressibility, disintegration time, lubrication and friability are significantly enhanced when compared with the performance of a traditional test formula. More important, this method also enables us to serve our customers better. Any customized modification of a suggested formula or any technical problem related performance etc. can be readily resolved by simple examination of the models.

Keywords—Experimental design, Vitamin C-90, Tabletting performance

Introduction

The use of response surface methodology (RSM),[1] has proven to a useful technique in the area of quantitative structure-activity relationships (QSAR) to develop quantitative methods for determining the activities of a series of compounds.[2-6] This method has also been successfully applied in analyzing the drug dynamic distribution[7] and in developing pharmaceutical dosage forms.[8-10] The conventional method in the development of dosage forms is tedious and inefficient where many combinations of ingredients may have to be tested before achieving an optimal formula. By using statistical methods, an optimal formulation can be effectively achieved with a proper design and with fewer experiments. The interaction between ingredients, which can't be seen in the traditional methods of evaluation, can also be revealed by this approach. Even if the resulting statistical models fail to define the optimal formulations at the first trial, the models can always serve as a tool to identify the right direction for further investigation.

The basic components of response surface method consist of 4 main steps:

1) Experimental design—develop the strategies for analyzing the response functions.

2) Data analysis—use regression to analyze the result of a specific design.

3) Building the empirical model—describe the

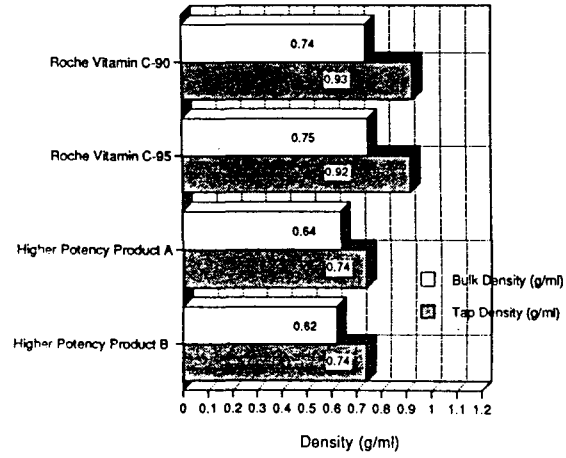

Figure 1—Bulk density and tap density profiles of various vitamin C products.

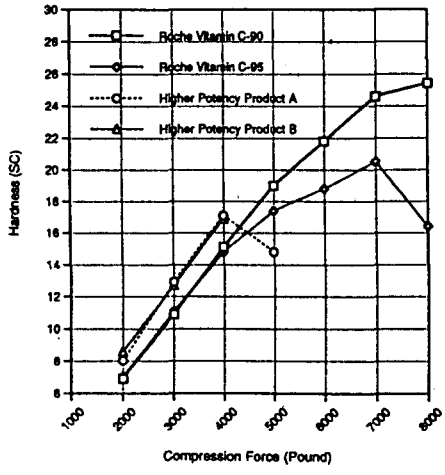

Figure 2—Compression profiles of various vitamin C products-tested in a standard test formula (95.0% vitamin C, 3.91% microcrystalline cellulose, 0.98% stearic acid and 0.16% magnesium stearate) containing 500 mg vitamin C.

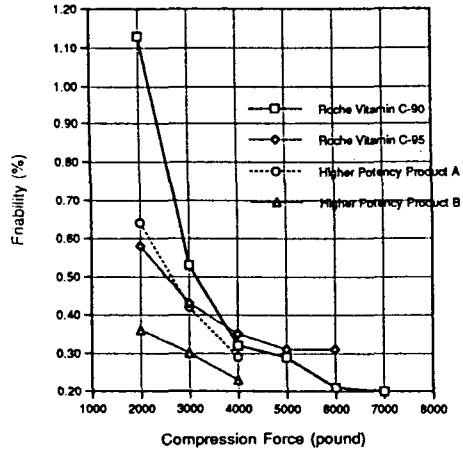

Figure 3—Friability profiles of various vitamin C tablets.

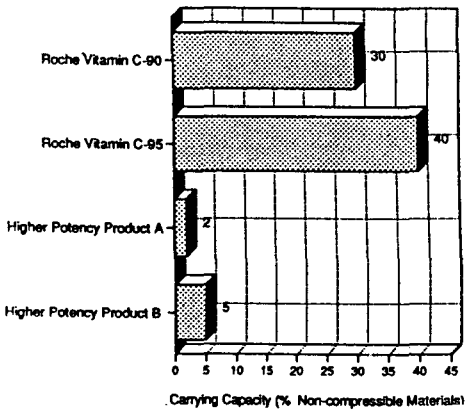

Figure 4—Carrying capacity of various vitamin C products tested in 500 mg vitamic C tablets and compressed at 4000 lbs & 45 rpm.

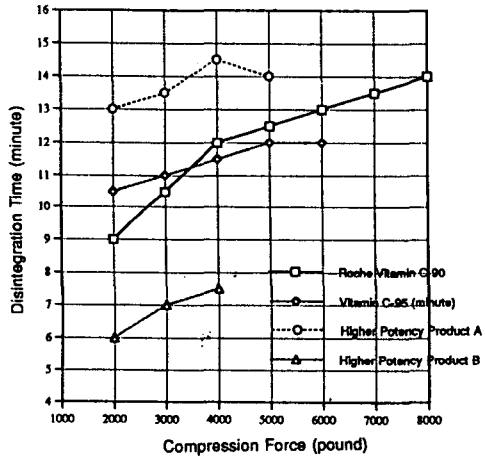

Figure 5—Disintegration profiles of various vitamin C products.

responses over the applicable ranges of factors of interest with the goal of obtaining an optimal solution.

4) Model validation-

a. Verify the significance of models based on coefficient of correlation (r), t test, residuals plots, and probability plots.[11]

b. Repeat experiments using optimized parameters to test the accuracy of actual performance vs. statistical prediction.

The application of RSM will be demonstrated using a vitamin C product of form as an example. Roche Vitamin C-90% has been on the market as a benchmark product for years. This product has higher density, superior compressibility/wider compression range, superior color stability and better carrying capacity (Figures 1-4). A new vitamin C-90% has evolved from the original product which has faster disintegration (Figure 5) while maintaining the same physical and tabletting per-

Table I—*Box-Behnken Designs*

No. of Factors	Code Factor Levels			Run No.
	Factor 1	Factor 2	Factor 3	
3	−	−	0	1
	−1	+1	0	2
	+1	−1	0	3
	+1	+1	0	4
	−1	0	−1	5
	−1	0	+1	6
	+1	0	−1	7
	+1	0	+1	8
	0	−1	−1	9
	0	−1	+1	10
	0	+1	−1	11
	0	−1	+1	12
	0	0	0	13
	0	0	0	14
	0	0	0	15

Table II—*Ingredients and Levels in Vitamin C-90 Tablets*

1. New Vitamin C-90 Granules	87.00%
2. Avicel PH102	3-5%
3. Corn Starch	2.5-7.0%
4. Stearic Acid	0.0-1.0%
5. Lactose	q.s.
6. Magnesium Stearate	0.5%

formance. In order to help our customers utilize Vitamin C-90 in developing an optimal, lower-cost formulation, an experimntal design (Box-Behken) was used to optimize customized formulas and provide information of ingredient effects (corn starch, microcrystalline cellulose and stearic acid) on the tabletting performance (DT, compressibility, lubrication, powder flow and friability).

Materials and Methods

Material

1) Vitamin C-90, Roche, Lot: 770073

2) Microcrystalline Cellulose, NF, (Avicel PH 102), FMC, Lot: 2239

3) Magnesium Stearate, NF, Mallinckrodt, Lot: 2256STP051

4) Starch, NF, National, Lot: KC5010

5) Stearic Acid, NF, Lot: HLR10

6) Lactose, NF, Foremost, Lot: 1RE214

Design of Experiments

There are many experimentl designs, such as Box-Behanken Designs, Central Composite Designs, Draper-Lin Designs and Factorial Designs that can be used for the optimization. The precision/efficiency (the number of experiments required in order to complete a test), availability of the statistical design, and the ease of operation were the criteria for the selection. In our study, a statistical package (statgraphics) was utilized to analyze the data and three-factor Box-Behnken design was selected to optimize Vitamin C-90 tabletting performance. This design is preferable not only because it requires fewer test runs but also because it is rotatable, and the replication of the design center point (0, 0, 0) also allows an estimate of the experimental error. Twelve runs plus three central replication runs as shown below were required for three factor at 3 level design.

The amount of three key ingredients (corn starch as disintegrant, stearic acid as lubricant and Avicel as filler) were used as variables. Each variable was tested at 3 levels. Vitamin C-90 granu-

Table III—Translation of Experimental Conditions into Physical Units

Coded Factor	Proposed Level	Variable 1 Microcrystalline Cellulose (%)	Variable 2 Corn Starch (%)	Variable 3 Stearic Acid (%)
−1	Low	3	2.50	0.0
0	Middle	4	4.75	0.5
+1	High	5	7.00	1.0

Table IV—*Box-Behnken #3-Factorial Design for the Optimization Vitamin C-90 Tablet Ingredients*

No.	Run Order	Vitamin C-90	Variables X1 Avicel PH102	X2 Corn Starch	X3 Stearic Acid	Lactose	Magnesium Stearate
1.	13	87.00	4.00	4.75	0.50	3.25	0.50
2.	3	87.00	3.00	7.00	0.50	2.00	0.50
3.	9	87.00	4.00	2.50	0.00	6.00	0.50
4.	1	87.00	3.00	2.50	0.50	6.50	0.50
5.	7	87.00	3.00	4.75	1.00	3.75	0.50
6.	8	87.00	5.00	4.75	1.00	1.75	0.50
7.	4	87.00	5.00	7.00	0.50	0.00	0.50
8.	14	87.00	4.00	4.75	0.50	3.25	0.50
9.	12	87.00	4.00	7.00	1.00	0.50	0.50
10.	5	87.00	3.00	4.75	0.00	4.75	0.50
11.	10	87.00	4.00	7.00	0.00	1.50	0.50
12.	11	87.00	4.00	2.50	1.00	5.00	0.50
13.	2	87.00	5.00	2.50	0.50	4.50	0.50
14.	6	87.00	5.00	4.75	0.00	2.75	0.50
15.	15	87.00	4.00	4.75	0.50	3.25	0.50

les and magnesium stearate remained constant while lactose was to q.s. to maintain a constant tablet weight (1276 mg/tablet) as seen in the table below.

The translation of these concentration ranges into Box-Behnken Design is listed in the following table.

The equivalent design for the optimization new vitamin C-90 is given in the following table:

Preparation of Tablets

Care was taken to control all the process variables at constant, such as mixing times, tabletting press, compression speed, tablet weight, lot numbers of raw materials and test methods. All the tablets based on the experimental design were prepared according to the procedure listed below.

1) Mix Avicel PH102, stearic acid, corn starch and magnesium stearate in a suitable mixer (Twin-Shell blender) for 3 minutes.

2) Pass the mixture from above step through a #40 mesh screen.

3) Add the above mixture and Vitamin C-90 in a suitable mixer.

4) Mix for 3 minutes.

5) Measure powder flow (Agway method).

6) Compress the mixture on a rotary instrumented tablet press (B3B, strain gauge installed, from SMI) equipped with .3125″×0.75″ capsule shape punches at 4000 pounds and 42 rpm. Tablet weight was adjusted at 1271 mg/tablet to maintain the vitamin C potency at 1000 mg/tablet.

7) Record the compression force and ejection force.

8) Measure the hardness (10 tablets, in SC unit), disintegration time (6 tablets, minutes), and friability (20 tablets, %) as described in the standard testing document.

Data Analysis

The resulting responses (disintegration time, hardness, ejection force, powder flow and friability) were analyzed using the response surface analysis in Statgraphics statistical package. The significance of each variable was determined by analysis of variance (ANOVA) technique. Based

Table V—*Disintegration Time, Hardness, Ejection Force, Powder Flow and Friability of 15 Tablets Prepared according to Box-Behken Design*

No.	Run Order	Y1 Disintegration Time (Min)	Y2 Hardness (SC)	Y3 Ejection Force (P)	Y4 Powder Flow (Sec)	Y5 Friability (%)
1.	13	11.25	19.6	99.8	12.69	0.23
2.	3	8.4	17.5	84.3	12.95	0.39
3.	9	14.00	28.1	134.5	12.17	0.12
4.	1	13.80	23.2	95.5	11.71	0.11
5.	7	11.50	18.6	56.5	12.20	0.27
6.	8	11.00	19.3	71.2	11.86	0.19
7.	4	7.25	19.4	83.0	11.82	0.31
8.	14	10.50	20.0	84.7	11.91	0.23
9.	12	9.25	19.3	96.3	12.23	0.39
10.	5	10.70	23.2	110.5	12.48	0.11
11.	10	7.50	24.9	92.1	18.64	0.12
12.	11	14.50	19.8	66.5	13.76	0.23
13.	2	14.00	21.0	96.3	11.81	0.24
14.	6	11.40	25.0	113.0	12.82	0.16
15.	15	13.50	19.6	128.2	15.44	0.15

Table VI—*Values for Index of Determination from Regression Analysis*

Response	R^2, %	Significant Variables	Best Fitting Order	F Ratio	P Value	Actual t Value
Y1 DT	93.18	CS	1	65.05	0.0005	−8.07
Y2 Hardness	96.49	SA	2	84.60	0.0003	−9.20
		SA×SA		22.00	0.0054	4.69
		CS		17.48	0.0086	−4.18
Y3 Ejection	82.08	SA	2	13.72	0.0139	−3.70
		SA×CS		5.62	0.0640	2.37
Y4 Power Flow	78.34	SA×CS	2	7.76	0.0387	−2.79
Y5 Friability	88.50	SA	1	14.41	0.0127	3.80
		CS		11.54	0.0193	3.40

on the ANOVA, the statistical significant variables were then fitted in a second order model.

$$Y_i = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_{12}X_1X_2 + a_{23}X_2X_3 + a_{13}X_1X_3 + a_{11}X_1^2 + a_{22}X_2^2 + a_{33}X_3^2$$

where: Y_i = level of a given response (Vitamin C-90 tablet performance)

a = regression coefficients for second-order regression

X_j = level of independent variable (concentration of 3 ingredients)

The polynomial regression results were demonstrated on three dimensional graphs and contour plots. The significance of these models were further confirmed by diagnostic plots.

Results and Discussion

Tabletting Performance

The tabletting performances of 15 Box-Behken

Design experiments are tabulated below:

The fit of the responses to a second order model are shown in the following table.

The results indicate that the vaues for DT and friability fit better with a linear model. The rest of the responses fitted best in second order polynomials. The goodness of fitting also can help predict the responses accurately. A high coefficient of determination (R^2) was obtained in the regression of tablet hardness, R2=96.49, which indicated that 96.49% of the total variation of the dependent variable is associated with or explained by

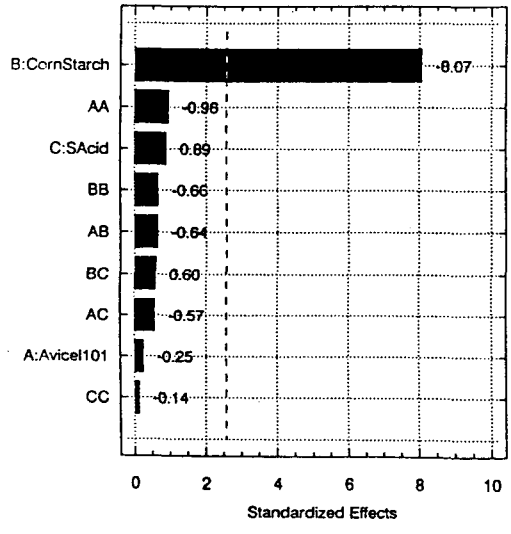

Figure 6—Pareto chart on the effect of ingredients on the disintegration time of a Vitamin C-90 tablet.

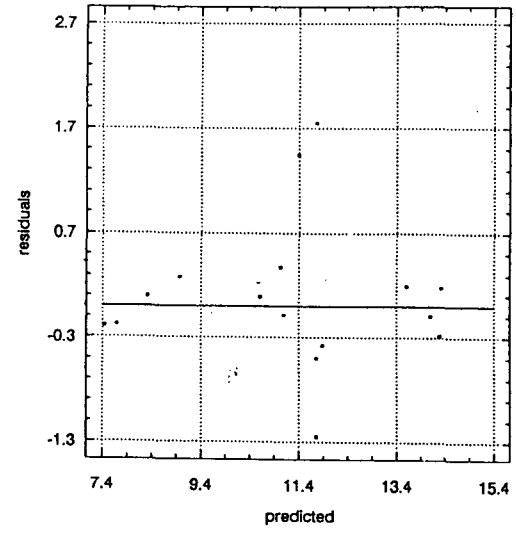

Figure 8—Residual plots-showing the deviation of actual DT from the predicted DT of Vitamin C-90 tablets.

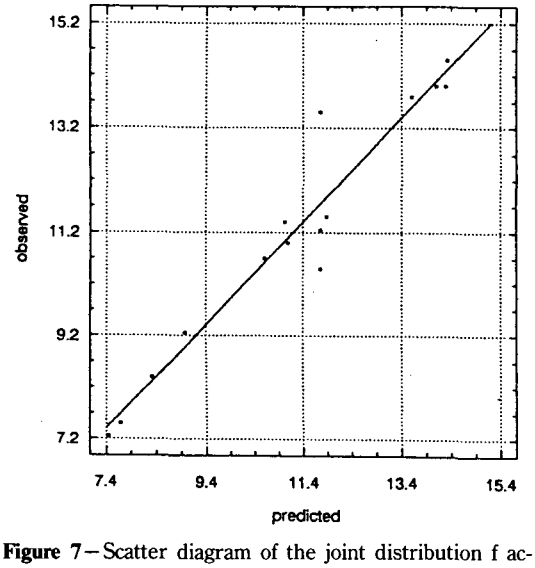

Figure 7—Scatter diagram of the joint distribution f actual and predicted disintegration time of Vitamin C-90 tablets.

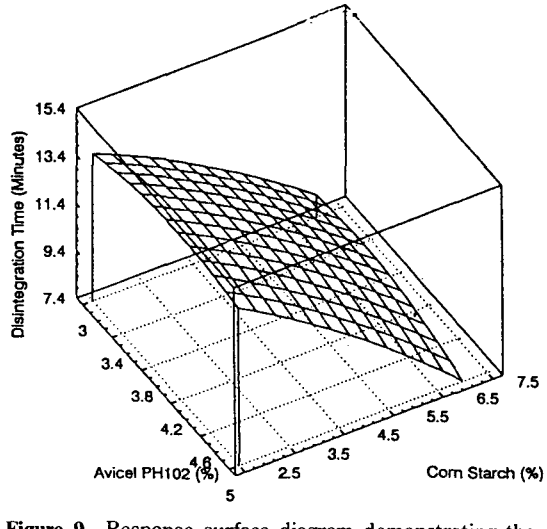

Figure 9—Response surface diagram demonstrating the effect of Avice PH102 and corn starch on Vitamin C-90 tablet disintegration performence.

the regression of Y, X1, X2 and X3. In addition to the coefficient of determination (R2), the significance of each variable was also determined by the F ratio, p values and T test. For Vitamin C-90 models at 5 degree of freedom (d.f.) and 95% confidence level, if F value was greater than 6.61, P value less than 0.05 or the absolute value of t greater than 2.57, reject the null hypothesis H_0 and accept alternate hypothesis Ha. This variable was coesidered statistically different from other variables.

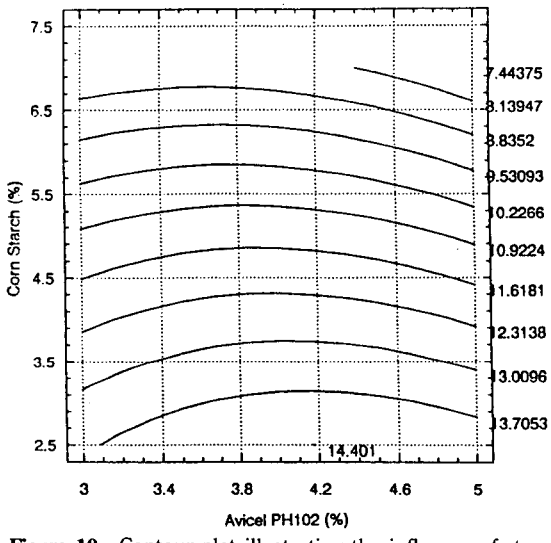

Figure 10—Contour plot illustrating the influence of starch and Avicel PH102 on Vitamin C-90 tablet disintegration time.

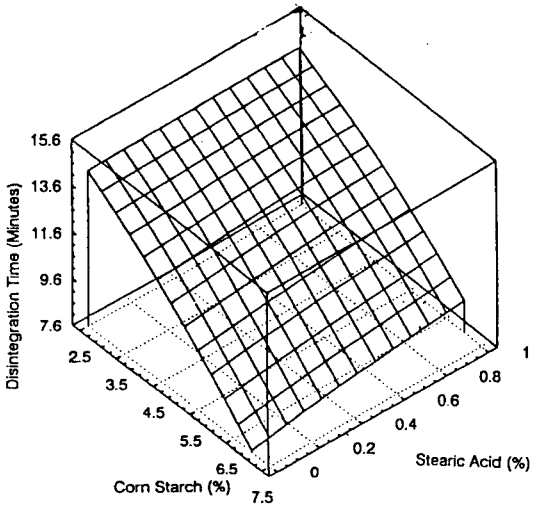

Figure 11—Response surface diagram showing the effect of corn starch and stearic acid on Vitamin C-90 tablet disintegration time.

Optimization of Tablet Disintegration Time (DT)

The ANOVA results shown in Table VI and Fig. 6 indicate that starch is the only ingredients among the three that significantly affects the disintegration of vitamin C-90 tablets (R2=93.18). The significance of this model is also revealed by the diagnosis plots, observed vs. predicted (Figure 7) and residuals vs. predicted (Figure 8). The actual T of all the experimental tablets closely match the predicted DT. Each DT was weighed the same and evenly contributed to the model. The deviations between actual and predicted DT (residuals) were well controlled between ± 0.4 minutes (Figure 8). This Vitamin C-90 disintegration model clearly demonstrates that if corn starch increases to 7%, the DT can be effectively reduced to less than 10 minutes (Figures 9-12) without using any superdisintegrants.

The DT gradient lines were parallel to the X

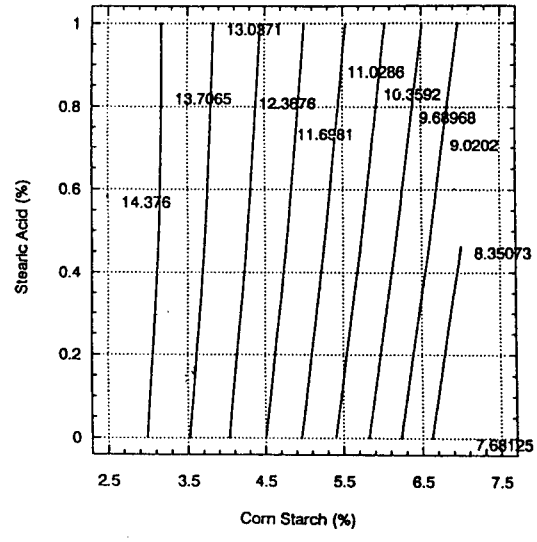

Figure 12—Contour plot of the effect of corn starch and stearic acid on Vitamin C-90 tablet disintegration performance.

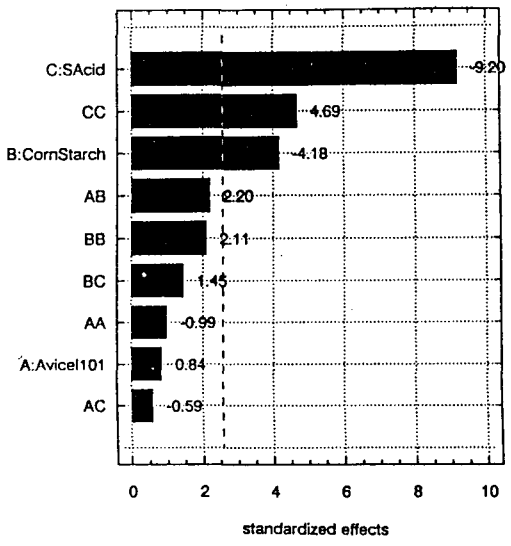

Figure 13—Pareto chart illustrating the significance of ingredients on the Vitamin C-90 compressibility.

or Y axis as seen in the contour plots (Graph 10 and 12). This indicates that the concentration of microcrystalline cellulose and SA within the test ranges have little or no influence on the disintegration time. A prolonged DT was observed when increasing the concentration of stearic acid as seen in the response surface plots. However, this effect on the DT is not statistical significant.

Optimization of New Vitamin C-90 Tablet Hardness

An excellent fit was obtained in the hardness model where coefficient of determination R2=96.49. Both stearic acid and corn starch showed a significant influence on vitamin C-90 compressibility (Figure 13). The hardness data can be explained by a second order polynomial equation. It is also noted that both ingredients had a negative effect on tablet hardness as seen in Figure 14 and 15. An increase in the concentration of stearic acid and/or starch reduced the Vitamin C-90 compressibility. In order to achieve an optimal compressibility and disintegration time, the concentration of corn starch has to be adjusted according to customers' needs while the concentration of stearic acid has to be kept at minimum.

Optimization of New Vitamin C-90 Tablet Lubrication

Table VII—*Comparing the Actual Performances of 3 Validation Tablets vs. Predicted Tabletting Performances*

Ingredient	Formulas		
	A	B	C
1. Roche Vitamin C-90	89.2	91.7	88.0
2. Microcrystalline Cellulose	3.3	3.3	4.6
3. Starch	6.0	3.5	6.5
4. Stearic Acid	0.8	0.8	0.2
5. Cab-O-Sil	0.2	0.2	0.2
6. Magnesium Stearate	0.5	0.5	0.5
Total	100.0	100.0	100.0
Tablet weight for			
1000 mg Ascorbic Acid Tablets	1246.0	1212.0	1263.0
500 mg Ascrobic Acid Tablets	623.0	606.0	631.0
Actual Hardness (SC) for 1000 mg tablets at 4000 pounds	20.8	21.1	23.5
Predicted Hardness	19-20	20-21	21-23
Actual DT (minute) for 1000 mg tablets at 4000 pounds	9-10	14	8-9
Predicted DT (minute)	9-11	13-15	8-9
Actual Ejection Force (pound) for 1000 mg tablets at 4000 pounds	94.0	75.0	90.0
Predicted Ejection Force (pound)	87-94	79-87	94-101

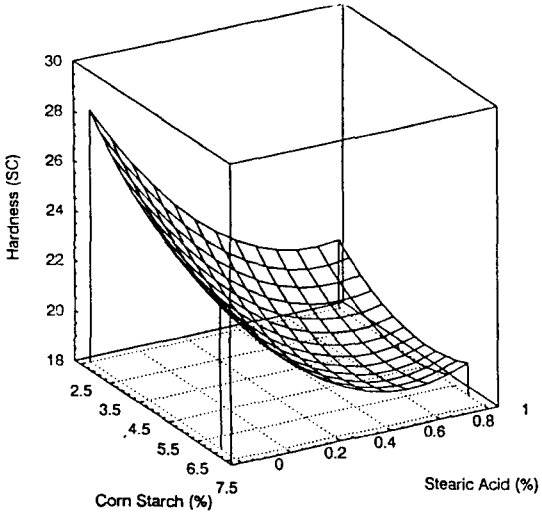

Figure 14—Response surface diagram showing the effect of starch and stearic acid on Vitamin C-90 compressibility.

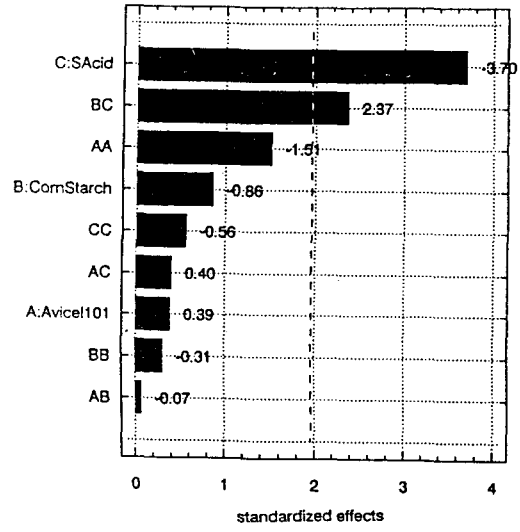

Figure 16—Pareto chart illustrating the significance of ingredients on the Vitamin C-90 lubrication.

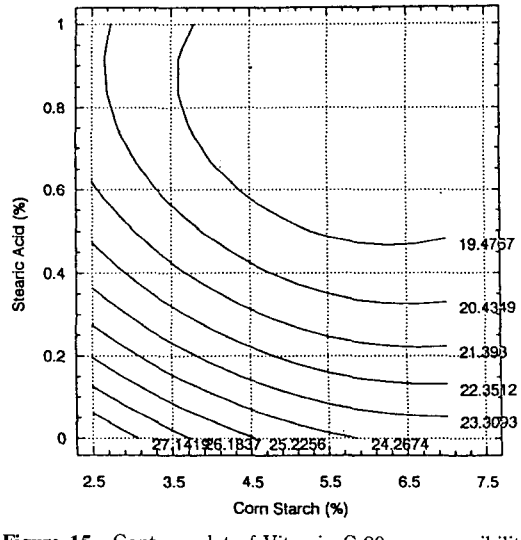

Figure 15—Contour plot of Vitamin C-90 compressibility model.

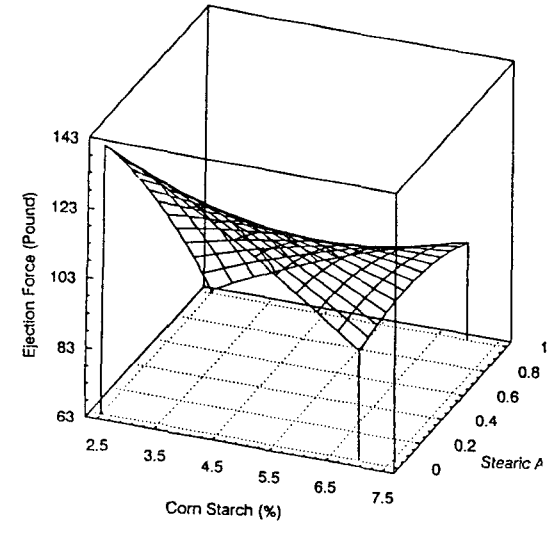

Figure 17—Influence of starch and stearic acid on Vitamin C-90 lubrication.

Magnesium stearate and stearic acid, are commonly used in the tablet formulation as a lubricant due to their excellent lubrication efficiency and low cost. In developing Vitamin C-90 lubrication model, stearic acid was found to be an important lubricant in addition to magnesium stearate while corn starch interacting with stearic acid also provided a certain degree of lubrication (Figure 16). The response surface analysis (Figure 17-18) show that at lower concentrations of corn starch, the ejection force was reduced significantly by the addition of stearic acid. However, at higher levels of corn starch in the formulation, stearic acid showed little influence on lubrication where as the lubrication from starch became significant. It also

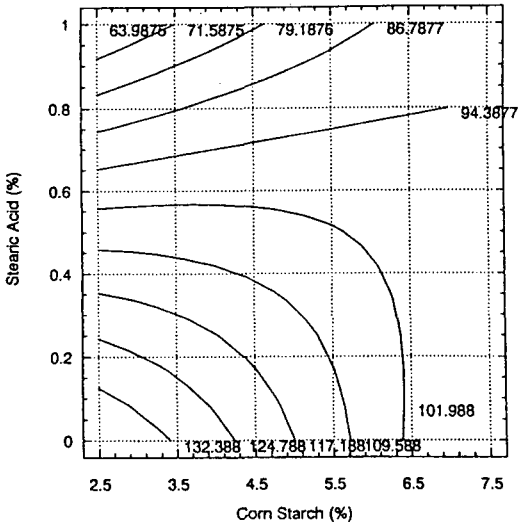

Figure 18—Contour plot on the effect of stearic acid and starch on Vitamin C-90 lubrication.

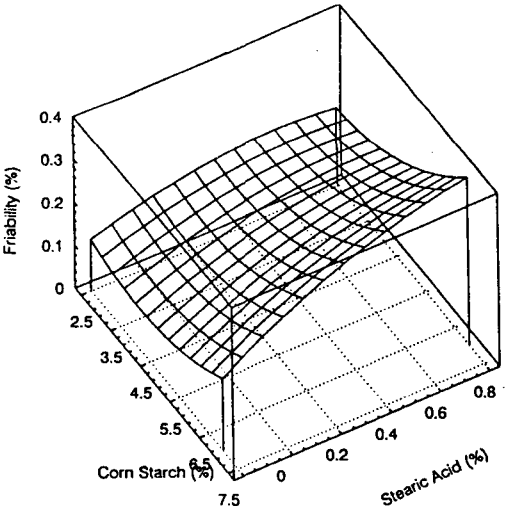

Figure 19—Response surface diagram showing the effect of stearic acid and starch on Vitamin C-90 tablet friability.

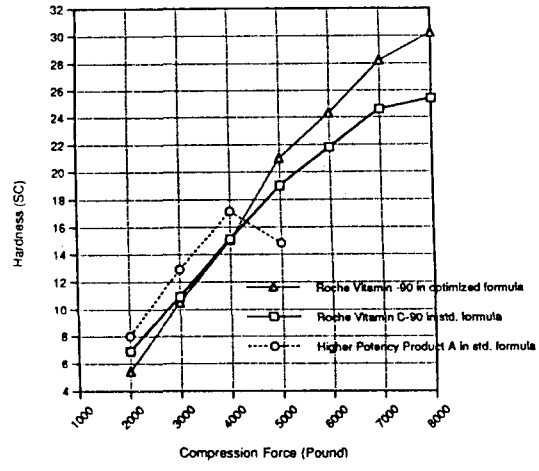

Figure 20—Compression profiles of Vitamin C-90 in an optimized formula vs. a standard test formula.

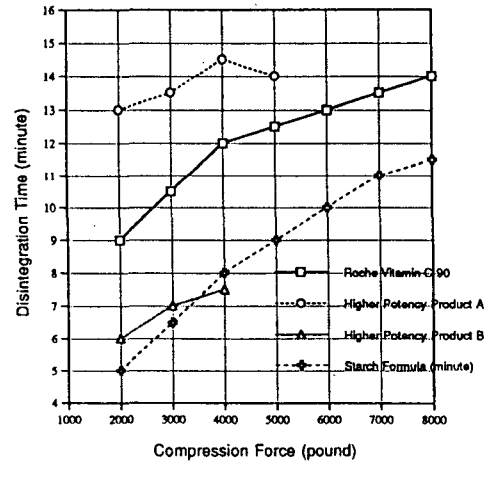

Figure 21—Disintegration profiles of Vitamin C-90 in an optimized formula vs. vitamin C tablets in a standard test formula.

indicates that in order to maintain proper lubrication (ejection force<100 lbs), either the concentration of stearic acid has to be kept higher than 0.6% or cornstarch level has to be maintained higher than 6.3%. Thus, in considering the influence of starch and stearic acid on DT, compressibility and lubrication, the concentration of corn starch should be above 6.3% and stearic acid kept at a minimum level.

Optimization of Global Vitamin C-90 Tablet-Friability

Both corn starch and stearic acid showed a negative effect on the tablet friability. Due to the excellent compressibility from Vitamin C-90, all the formulations consistently showed low friability (<0.4%) as seen in Figure 19. Because of the abi-

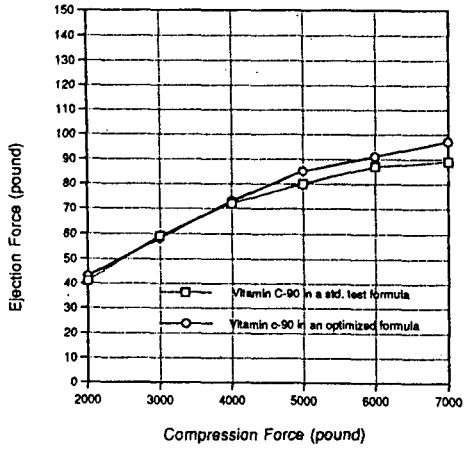

Figure 22—Comparing the ejection force of Vitamin C-90 tablets formulated in an optimized formula (Formula C) vs in a standard test formula.

lity of the Vitamin C-90 tablets to withstand mechanical shock, friability will not be an issue.

Model Validation

Based on the models, three formulas listed below were selected and retested to validate the predictability of these models.

An excellent predictability was achieved by utilizing the models as shwon in the above table. The actual performances successfully matched what was predicted in the models.

References

1) R.L. Mason, R.F. Gunst, J.L. Hess, Statistcal Design and Analysis of Experiments, John Wiley & Sons, p.538, 1989.
2) A. Camarata and G.K. Menon, *J. Med. Chem.*, **19**(6), 739 (1976).
3) K.C. Chu, R.J. Feldmann, M.B. Shapiro, C.F. Harzard and R.I. Geran, *J. Med. Chem.*, **18**(6) 539 (1975).
4) A.J. Stuper and P.C. Jurs, *J. Pharm. Sci.*, **67**(6) 745 (1978).
5) K.C. Chu, *Anal. Chem.*, **46**(9), 1181 (1974).
6) W.J. Dunn III, *Am. Chem. Soc.*, **23**, 595 (1980).
7) K.T. Chang, dissertation, chapter 4, University of Texas at Austin, 1986.
8) D.E. Fonner, Jr., J.R. Buck, and G.S. Banker, *J. Pharm. Sci.*, **59**(11), 1587 (1970).
9) J.B. Scheartz, J.R. Flamholz, and R.H. Press, *J. Pharm. Sci.*, **62**(7), 1165 (1973).
10) R.L. Garrote, V.R. Coutaz, J.A. Luna, E.R. Silva, and R.A. Bertone, **58**(4), 821 (1993).
11) N.R. Draper and H. Smith, Applied Regression Analysis, John Wiley & Sons Inc. 1966.