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SIMULTANEOUS OPTIMIZATION OF CAPSULE AND TABLET FORMULATION USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

The study described herein was undertaken to simultaneously optimize the composition of tablet and capsule formulation of an insoluble experimental drug, and to learn more about the effect of the interaction between the ingredients on the basic properties of the final dosage form. Four independent variables were varied in a set of statistically designed experiments, and a number of properties evaluated. A substantial saving in development time and quantity of drug was thereby achieved.

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] used a desk top computer for product optimization. Their method offered rapid access and

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versatility as an alternative to large-scale computing facilities which frequently are not readily accessible. Sequential Prediction Analysis[8] has been suggested for optimizing multiple potency systems coupled with invariant tablet weight. Schofield et al.[9] have discussed various statistical procedures to learn more about the relationships between tablet properties and formulation/process variables.

The drug considered in this study was supplied in a capsule dosage form for the initial clinical studies. Capsules are usually chosen for early phases of clinical testing because they are a convenient device for blinded studies. Additionally, smaller batch sizes can be easily handled. This is a particular advantage, since during early stages of development, quantities of active material may be limited. For eventual marketing, the tablet is the dosage form of choice, both for economical reasons and to guard against tampering. A surfactant and a super disintegrant were incorporated into the formulation to enhance drug bioavailability. The low bulk density of the drug necessitated utilizing a wet granulation technique, especially useful in this instance where the drug comprised 40 percent of the formulation. This densified product could then be easily accommodated into a manageable capsule. Additionally, this densification led to the formulation of a robust plug of the product, which for larger batches could easily be processed on the more efficient plug-type encapsulators. Therefore, this particular composition coupled with the wet granulation technique resulted in a formulation which could either be encapsulated in a plug type encapsulator or be compacted on a tablet press.

The objective was to optimize this single formulation for a capsule and tablet dosage form, in a single study. This 'simultaneous optimization' approach substantially shortened the development time and decreased the need for larger quantity of drug for development effort.

EXPERIMENTAL

A group of excipients was established to formulate an experimental drug in tablet and capsule dosage forms using the wet granulation process. The composition of both dosage forms includes the following identical ingredients, in the same concentration: (1) active drug, (2) lactose (carrier and bulking agent), (3) sodium lauryl sulfate (surfactant), (4) polyvinylpyrolidone (binder), (5)

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water/alcohol (granulating solution), (6) croscarmellose sodium (super disintegrant), and (7) magnesium stearate (lubricant).

An experimental statistical procedure was employed to determine the optimum quantities of four compositional factors, and to understand the effect of the interaction between these factors on the behavior of the final dosage forms. The experimental design was a 2^{4-1} factorial design. The design matrix involved 10 experiments that are shown in TABLE (1) below, along with the random order chosen for performing the experiments. The two experiments designated with zero represent the baseline formulation. The experimental range varied from -1 to +1 experimental units.

Polyvinylpyrolidone was used as a binder in the granulating process. The quantity of polyvinylpyrolidone might affect several properties such as dissolution, disintegration, and hardness (in case of tablets). Magnesium stearate served as a lubricant. This is an important variable in view of occasional machine problems encountered in early capsule batches during encapsulating, *viz.* indented capsules

TABLE (1)
The Statistical Design Matrix

Run Order	Run No.	x_1	x_2	x_3	x_4
2	1	1	1	1	1
7	2	1	1	-1	-1
5	3	1	-1	1	-1
3	4	1	-1	-1	1
1	5	-1	1	1	-1
6	6	-1	1	-1	1
8	7	-1	-1	1	1
10	8	-1	-1	-1	-1
4	9	0	0	0	0
9	10	0	0	0	0

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TABLE (2)
Independent Variables

x_1 - Quantity of Polyvinylpyrolidone
x_2 - Quantity of Magnesium Stearate
x_3 - Quantity of Granulating Solution
x_4 - Quantity of Croscarmellose Sodium

TABLE (3)
Dependent Variables

Y_1 - Dissolution profile of capsules expressed as % dissolved in 10 minutes.
Y_2 - Mean disintegration time of capsules expressed in minutes.
Y_3 - Dissolution profile of tablets expressed as % dissolved in 10 minutes.
Y_4 - Tablet Hardness expressed in KP.
Y_5 - Mean disintegration time of tablets expressed in minutes.
Y_6 - Lubricity of the formulation expressed as the ejection force of tablets compressed at 10 KN on the single-punch instrumented press.

and empty capsules. For tablets, it affects the ejection force. Croscarmellose sodium was used as a super disintegrant. Its quantity can have a direct effect on the disintegration of the capsule plug and the tablet and therefore dissolution. The proper amount of granulating solution is important in order to avoid under-wetting or over-wetting, which in turn may lead to lubrication or dissolution problems. For each experimental formulation studied, the tablet weight was fixed at 225 mg, while the amount (percentage) of active drug and sodium lauryl sulfate remained constant at 100 mg (44.44%) and 2 mg (0.88%) respectively. As a consequence, for any experimental formulation, lactose was adjusted to assure that the total tablet weight was 225 mg. The independent factors and dependent variables considered in this study are listed in TABLES (2) and (3) respectively.

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TABLE (4)
Actual Physical Amounts of Experimental Units

Factor	-1.0 e.u.	Base (0)	+1.0 e.u.
x_1 1 e.u. = 5 mg	3.00 mg	8.00 mg	13.00 mg
x_2 1 e.u. = 0.845 mg	0.85 mg	1.70 mg	2.50 mg
x_3 1 e.u. = 7.725 mg	23.20 mg	31.00 mg	38.60 mg
x_4 1 e.u. = 3 mg	2.00 mg	5.00 mg	8.00 mg

Due to the small amount of drug available to the formulator in the early stages of development, the ejection force from the tablet press and lubrication ratio were used as an indication of flowability of the granulation on the plug-type encapsulating equipment.

The actual values of the physical units at various level of experimental units are given in TABLE (4).

The experimental procedure involved granulating the drug, *per se.*, in a high intensity mixer with a solution of sodium lauryl sulfate in water-alcohol co-solvent system. After one minute, a blend of lactose and polyvinylpyrolidone was added to the mixer and the wet granulation continued for another minute. This granulation was then dried and screened. The disintegrant followed by the lubricant was blended into this granulation. A part of this granulation was filled into number 3 capsules and the reminder compressed into tablets on an instrumented tablet press using an applied force of 10 KN. All batches were prepared using the same manufacturing procedure.

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TABLE (5)

Experimental Results

x_1	x_2	x_3	x_4	Y_1 (%)	Y_2 (min)	Y_3 (%)	Y_4 (KP)	Y_5 (min)	Y_6 (N)
1	1	1	1	56	7.6	50	10.2	9.1	757
1	1	-1	-1	65	8.7	40	6.9	9.6	613
1	-1	1	-1	53	8.0	17	12.1	18.6	890
1	-1	-1	1	82	7.9	39	8.1	9.4	753
-1	1	1	-1	69	5.7	47	7.4	8.0	712
-1	1	-1	1	75	4.2	65	6.1	2.6	603
-1	-1	1	1	76	4.4	70	8.4	3.4	890
-1	-1	-1	-1	79	3.7	56	7.7	3.4	786
0	0	0	0	62	6.1	56	8.1	8.4	703
0	0	0	0	56	6.1	59	7.3	8.3	664

RESULTS AND DISCUSSION

The experimental data obtained are shown in TABLE (5). A linear 2-factor interaction mathematical model was used to approximate the relationship between the exipients and the responses. This model describes the main effect of each factor and the interaction effects between a particular factor with each other factor except croscarmellose sodium, on a measured response. The model has the following form:

$$Y = \mu + a_1 x_1 + a_2 x_2 + a_3 x_3 + a_4 x_4 + a_{12} x_1 x_2 + a_{13} x_1 x_3 + a_{23} x_2 x_3$$

Where: Y is the measured response, μ is the intercept which describes the response at the center of the design and the coefficients a's describe the change in response caused by a change of amount of ingredient in the formulation. Note that the equation does not include any of the interactions of the other three ingredients and the croscarmellose sodium or any of the 3 or 4-factor interactions under the assumption that they will have little effect on any response of interest when

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ingredients are changed over the proposed experimental ranges. These terms that are not in the model are 'aliased' with lower order terms included in the mathematical model. The reader is referred to (Box, Hunter, and Hunter)[10] for a description of the design rationale and analysis of data.

While four of the ingredients were varied in order to generate the 9 experimental conditions studied, in reality a fifth (lactose) was also varied in order to make up the slack between the tablet weight resulting from the prescribed factor settings of the four factor and 225 mg. This meant that that each experimental formulation had differing amounts of lactose from a low of (44%) to a high of (53%). It was assumed that any changes seen in the responses were results of changes in the level of the four experimental ingredients and not the results of the consequential changes in the slack variable. Each of the responses were fit to the above model. The estimated coefficients for each response are given in TABLE (6). The effect of a given factor on a response is estimated from the size of the coefficient for that factor. Factors with small coefficients are judged unimportant for the corresponding response. It simplifies the optimization process if the models are reduced by deleting such terms. The coefficients for the reduced models are underlined in TABLE (6).

The usual criteria for model reduction is to compare each coefficient to its estimated standard error. If the absolute value of a coefficient is smaller than twice the standard error, then the coefficient is not statistically different from 0 and thus dropped from the model. Using this criteria, the only case in which factors whose coefficients are smaller than two standard errors are not deleted, is if the coefficient for an interaction term involving that factor is larger than two standard errors. This is known as the Hierarchy Principle; the rationale here is that if the factor is involved in a significant interaction, then it is probably important and should not be deleted from the model. An example of this can be seen in TABLE (6) with the response tablet dissolution at 10 minutes. There, the coefficient for magnesium stearate (a_2) is smaller than the standard error while the coefficient for the polyvinylpyrolidone by magnesium stearate interaction (a_{12}) is as large as two standard errors indicating an important polyvinylpyrolidone by magnesium stearate interaction; therefore the term involving the magnesium stearate is kept in the model.

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TABLE (6)

Estimated Model Parameters and Standard Errors

(The coefficients of the model having great influence for each response are underlined)

Term	Y_1 (%)	Y_2 (min)	Y_3 (%)	Y_4 (KP)	Y_5 (min)	Y_6 (N)
S.E.	3	0.05	3	0.3	0.11	22
μ	67	6.23	50	8.2	8.07	737
a_1	-5	1.77	-12	1.0	3.65	3
a_2	-3	0.27	2	-0.7	-0.69	79
a_3	-6	0.16	-2	1.2	1.77	62
a_4	3	-0.27	8	-0.2	-1.88	0
a_{12}	0	-0.18	6	-0.1	-1.63	11
a_{13}	-4	-0.38	-1	0.7	0.41	8
a_{23}	2	-0.05	0	0	-0.53	1

Applying the criteria above means that poor estimates of the standard error can lead to unrepresentive reduced models. Because the difference between the two repeat responses at the center point (the 0 levels) has a large impact on the estimation of the standard error, it is important to evaluate the repeat results at the center point in light of past performance of the procedure for measuring that response before applying the above criteria. After examining the two repeat results at the center point for the six responses of interest, it was determined that typical repeatability was demonstrated for the responses ejection force, tablet dissolution at 10 minutes, and hardness. The underlined coefficients listed in TABLE (6) were chosen according to this criteria for those three responses. For capsule dissolution at 10 minutes, all coefficients were less than standard error. We concluded that this was due to an inflated estimate of the standard error due to poor repeatability at the center points (56% and 62%). For tablet and capsule disintegration, all the coefficients were larger than two standard errors. It was concluded that this was due to much better than usual repeatability at the center points (8.42 and 8.26 for tablet disintegration and two 6.10's for capsule disintegration). For these three

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TABLE (7)
Predicted Optimal Formulation

Factor	Range	Initial Setting	Optimal Formula (coded)	Optimal Value (uncoded)
x_1	-1 to 1	-0.7	-1	3.0 mg
x_2	-1 to 1	0.8	0	1.7 mg
x_3	-1 to 1	-0.5	-1	23.2 mg
x_4	-1 to 1	0.0	1	8.0 mg
Response	**Range**			**Predicted Value**
Y_1	> 60 %			78.00 %
Y_2	---------			4.50 min
Y_3	< 680 N			679.00 N
Y_4	---------			6.80 KP
Y_5	MAX			69.00 %
Y_6	---------			0.81 min

responses, the relative size of the coefficients plus adherence to sound pharmaceutical principles was used to reduce the models.

Although six responses were measured, only three were used in the optimization. These were tablet dissolution at 10 minutes, capsule dissolution at 10 minutes, and ejection force. We maximized tablet dissolution at 10 minutes while keeping capsule dissolution at 10 minutes greater than 60% and ejection force less than 680 N using the optimization facility of the RS/1 MULREG object employing the Nelder-Mead search algorithm. Capsule disintegration time along with capsule dissolution time and hardness were monitored but neither optimized nor constrained.

The results of the optimization are listed in TABLE (7). Note that the optimal settings for the four exipient studied here differ from the base formulation (zero

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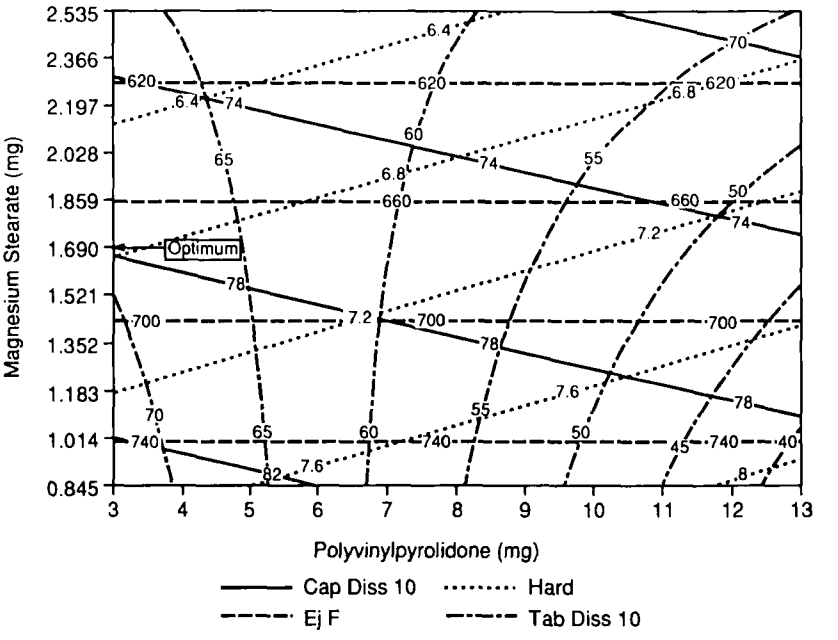

FIGURE (1): tablet and capsule dissolution at 10 min, hardness and ejection force plotted as a function of changing polyvinylpyrolidone and magnesium stearate with granulating solution held constant at 23.175 mg (-1 e.u.) and croscarmellose sodium at 8 mg (1 e.u.).

levels). A decrease in polyvinylpyrolidone is recommended from the base line level of 8.0 mg to 5.5 mg, no change in the magnesium stearate from 1.69 mg is recommended while granulating solution should be decreased from its zero level of 30.9 mg to 23.18 mg and croscarmellose sodium is increased from the 5 mg to 8 mg.

From the underlined coefficients of the fitted models in TABLE (6) we would expect the optimum formulation to be at low levels of both polyvinylpyrolidone and granulating solution as indicated in TABLE (7). The selection of an appropriate level of magnesium stearate with low levels of polyvinylpyrolidone increased both tablet dissolution at 10 minutes and capsule dissolution at 10 minutes. There was a problem with the negative coefficients for magnesium stearate for both ejection force and hardness; decreasing magnesium stearate increased both, with ejection force affected the most. Low magnesium stearate, while mitigating some of the

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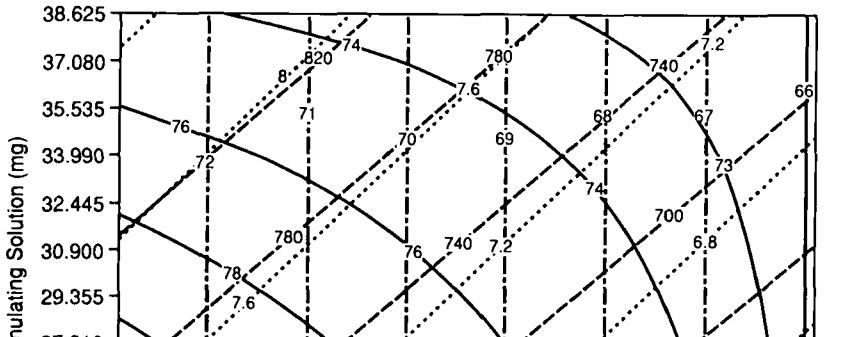

FIGURE (2): tablet and capsule dissolution at 10 min, hardness and ejection force plotted as a function of changing magnesium stearate and granulating solution with polyvinylpyrolidone held constant at 3 mg (-1 e.u.) and croscarmellose sodium at 8 mg (1 e.u.).

effect on hardness of what appears to be the required low polyvinylpyrolidone, increases the ejection force. The algorithm solves this problem by choosing the middle value of magnesium stearate. However, we note that any decrease in tablet dissolution at 10 minutes and capsule dissolution at 10 minutes caused by the effect of polyvinylpyrolidone, magnesium stearate or granulating solution can at least be partially offset by increasing the croscarmellose sodium. Consistent with this, the algorithm calls for increasing croscarmellose sodium to the highest level studied here.

FIGURE (1) is a contour plot of the four responses: tablet and capsule dissolution at 10 minutes, hardness and ejection force plotted as a function of changing polyvinylpyrolidone and magnesium stearate with granulating solution held constant at 23.175 mg (-1 e.u.) and croscarmellose sodium at 8 mg (1 e.u.). FIGURE (2) is a contour plot of the same four responses plotted as a function of

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changing magnesium stearate and granulating solution with polyvinylpyrolidone held constant at 3 mg (-1 e.u.) and croscarmellose sodium at 8 mg (1 e.u.). The symbol OPTIMUM corresponds to the predicted responses at the recommended optimum. We note from these plots that the effect of a decrease in magnesium stearate from this predicted optimum formulation increases ejection force while increases in magnesium stearate decreases hardness, tablet dissolution at 10 minutes and capsule dissolution at 10 minutes thus justifying the selection of the optimum formulation.

CONCLUSION

Factorial design was utilized to optimize the composition of a single formulation to serve as a tablet and capsule dosage form with acceptable properties. A substantial saving in development time and quantity of drug was thereby achieved. This technique was a valuable tool in order to identify and analyze the main and interactive effects on the physical properties of the final dosage form.

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