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MANAGEMENT SCIENCE AIDS IN EXPEDITING PHARMACEUTICAL PRODUCT DESIGNS

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A new philosophy is proposed for obtaining improved product designs in shorter time periods using established concepts from engineering and management science. This philosophy is a simple systematic approach with sufficient flexibility to serve various product types, different time frames for action, and achieve a variety of conditions of acceptance. Four phases of effort make up the product design regimen. Each phase must be managed by selecting the appropriate techniques and allocating research and development efforts. Two case studies are presented to illustrate this philosophy.

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INTRODUCTION

Somewhere between the discovery of a new drug and the marketing of it lies an important and costly effort known generally as research and development. Management and other personnel in the research and development effort are primarily concerned about obtaining outstanding product designs in the most expeditious manner. Because different design attributes impact in various ways with purchasing, production, distribution, marketing, and government, some organized effort must be implemented which will assure the identification of all essential impacts and allow for tradeoff decision making during the product design process. Tradeoff decision making must be made between the often conflicting objectives of design quality and expeditious development. This situation is the context for the proposed philosophy which is described below.

Although the pharmaceutical industry shares many commonalities with other industries, pharmaceutical product designs differ in some important aspects from those in many industries. Pharmaceuticals are "life and death" consumer products. Also, drug products are among the most difficult to design because of the complexities of the drugs themselves and those of the biochemical and physiological functions of man. Minute differences in product purity, potency, and physical or chemical properties can have dramatic effects on product performance. Accordingly, there are stringent Federal

regulations on pharmaceutical products which in turn place further difficulties on the design of the products in this industry. In addition, a reformulation or improvement of already approved or marketed products require the undertaking of extensive and expensive retesting, possibly including clinical testing in man to reverify drug efficacy. Commitment is an important feature which distinguishes pharmaceutical product designs from those of many industries. Consequently, the initial product development of pharmaceutical products toward optimum is particularily important from the standpoints of safety, efficacy, and reliability.

All of the above factors mitigate for well designed experimental and management techniques in pharmaceutical research and development (R&D). High capital risks, corporate profits, and societal benefits demand the best that science and management can offer. Yet many developmental activities in the pharmaceutical industry proceed today on a general trial and error basis. At best, such methods leave both the investigator and management blind to the potential of further product improvements relative to an achievable optimum.

Any philosophy of design must be sufficiently robust to meet the needs specific to various types of products, different action time frames, and general conditions of acceptance by the firm. Acceptance conditions are particularly critical in the pharmaceutical industry because of the governmental regulations of the Federal Food and Drug Administration. In addition to robustness, this philosophy must be simplistic so that all impacted

concerns within the firm can interface with the design effort at the proper time. Simplicity is also needed in order to provide clearly stated inputs by interfacing personnel and so that the recommendations from the design team will be compatible with corporate level planning. We believe that our proposed philosophy not only possesses these features of robustness and simplicity but that it is powerful as well. After first describing the philosophy in somewhat general terms, we will illustrate the utility and functionability of this systematic management approach in two product design and analysis case studies typical to the pharmaceutical industry. One can also recognize the application of this philosophy to process design as well.

THE PROPOSED PHILOSOPHY

Four phases are suggested in this proposed philosophy: (1) a preliminary planning phase, (2) an experimental phase, (3) an analytical phase, and (4) a verification phase. Each phase plays an important role in the overall product design process. However, management of research and development must make decisions on the allocation of effort amongst these phases. An important aspect of this philosophy is the generation of information to assist in this decision making. --- Each of these phases are discussed individually below in terms of pharmaceutical products. Applications to other products and industries are apparent.

In the preliminary planning phase the principal activity ought to be a clear and concise description of the output properties desired by the product and the input variables available to achieve those properties. The term "output properties" is used here to mean those things the final product should be or do. A drug is a product which should carry some form of treatment to a patient in some prescribed manner. Accordingly, the drug must be in a form that is bioavailable to the appropriate human tissue or compartment and meet such characteristics as a proper rate of drug release, achievement of adequate but non-toxic tissue levels, uniformity and accuracy of dose, acheivement of high levels of purity, maintenance of physical and chemical stability, and other medical considerations. Also, the drug must get through production, distribution, and sales to the patient and maintain all the physical, chemical and biological characteristics designed into the product.

Output properties must therefore include all of the specifications needed for the design of a high quality drug delivery system (drug product), from raw materials purchasing down to the treatment effect within the patient. This process of identifying output properties requires the aid of interfacing personnel in the design team from various impacted areas of the firm. Various managerial techniques have been advocated for achieving this identification process more effectively and/or

efficiently (e.g. the "Ideal Concept" by Nadler (1970) "Brain Storming" by Clark (1958),etc.). Also different organizational approaches have been suggested in the past such as the committees approach, project managed teams, the matrix approach, etc., and any of these techniques and organizational approaches are compatible with the proposed philosophy. The ultimate objectives in this initial planning phase to (1) identify the output properties desired,(2) find some ranking of relative importance amongst them, and (3) determine a means for measuring how well any particular design meets the desired properties. Corporate management guidance and philosophy can assist in this effort.

A second part in the sequence of the preliminary planning phase is to identify the input variables along with corresponding means for their measurement. Two classes of input variables should be found: (1) Controllable variables which affect one or more of the output properties, and (2) uncontrollable variables which also affect output properties. With both classes of variables it is useful to also know the practical range of values which these variables may assume. Once this identification is achieved, the response surface concept can be used. This concept, made famous in statistics and management science by Box (1957), is essentially the recognition that each output property is functionally related to the input variables in some manner. In the case of two input variables denoted

here as x_1 and x_2, an output property y can be described to functionally change with the different values of the input variables to form a response surface, such as the one shown in Figure 1. Although commonplace geometry is lost beyond two variables, this concept holds for many more.

Existing theory or data may be available to map out the response surface associated with each output property with sufficient accuracy for the analytical phase. In reformulation work and in process analysis of established products, a good deal of required data is often in hand for application of methods described herein. If so, this information can be held for the third phase

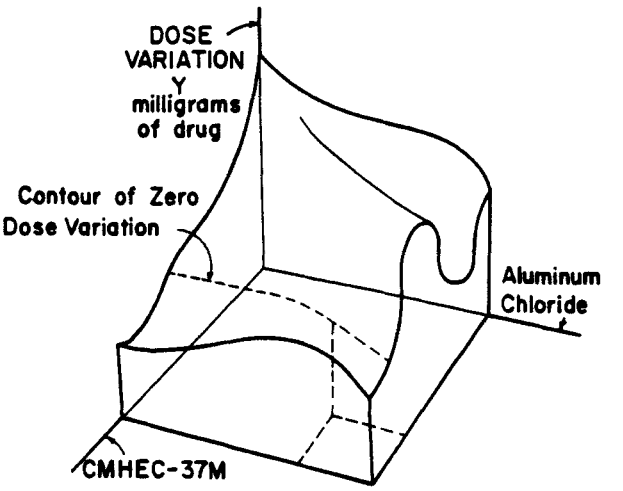

Figure 1. Response Surface Concept and Results of the Second Case Study.

and a complete experimental design will not be undertaken. Those response surfaces which cannot be sufficiently well described can be identified for efforts during the next phase of the product or process development.

Two principal activities comprise the experimental phase; planning and conducting those experiments which will describe the needed portion of each response surface with sufficient accuracy. Many drug companies through their preformulation programs have information at hand which describes probable drug compatability, bioavailability or stability problems which is of great use in designing the experimental phase. Of particular importance in the design of the experiments is the recognition that a surface map is needed for that portion of the input variables which likely will be needed in the analytical phase. The experimental design ought to be analogous to the plans of a surveyor on a construction site as differentiated from the plans of either a mountain climber or a cartographer. Some of the recent advances in the design of experiments, as described by Anderson and McLean (1974), provide added technical assistance toward the statistical part of the experimental design objectives. On the practical side of this experimental planning, the research and development personnel should account for the amount and types of testing required in order to describe the response surface as well as the means of data collection. The

amount of testing depends upon the initial degree of ignorance about the response surface and the relative significance of that particular output property. Concern should be given to the various types of testing required in order to obtain efficiency in conducting the experiments; such as collecting simultaneous test data and sequencing the nondestructive tests ahead of destructive tests. The methods of data collection are important for eliminating errors in data handling and getting the data in a form which is compatible with the techniques and procedures of analyses. When the experiments are conducted and the data are collected, then the experimental phase is complete.

Statistical forms of analyses classically constitute the first steps in the analytical phase. One of the most useful statistical techniques is the analyses of variance which serves to distinguish those input variables and variable combinations that significantly affect each output property. The purpose of this analysis is to collect only significant variables for the next analytical step. In the considerations of the kind of analyses of variance to use, the research and development personnel should be fully aware of four types of errors: (1) the error of excluding a significant variable, (2) the error of including an insignificant variable, (3) the error of setting improper levels of statistical significance, and (4) the error of using the wrong model for the analysis. Since there are costs

associated with each type of error, economic considerations must be included with statistical considerations in the analytical management. Once the significant input variables are identified, the response surface description can be completed by using regression and correlation analysis. In addition to the quantitative description of the response surfaces, these forms of analysis yield important information for managers of research and development. Goodness-of-fit information provides feedback to these managers on the need for further refinements in testing. Also the results of high correlations between output properties which vary considerably in their relative importance allows one to disregard or to significantly reduce efforts with the lesser important output property. Negative correlations amoungst output properties, especially important ones, signifies the likelihood of difficult tradeoff decisions and this feedback serves to show research and development managers where efforts should be intensified. Accordingly, the implementation of this product design philosophy provides a system to capture this important managerial information for properly allocating R&D resources.

The second part of the analytical phase consists of specificing acceptable limits on the output properties and searching for an optimum combination of the controlled input variables to meet these output-property limits. Determining the acceptable limits is a task which poses

managerial difficulties because different interfacing personnel will have varying concepts as to the tightness of these limits. Reference standards on degrees of limit tightness and soliciting opinions of multiple limits (at varying degrees) may be useful techniques for a design team. Some alternative procedures are illustrated both in the philosophy discussion below and in the case studies. As soon as these limits are identified, the personnel performing the analysis ought to first assure that there is some combination of controllable input variables which meets all the imposed limits. If there is not some combination satisfying all limits, then a reconsideration must be made either on the limits or on the rationale of the product design approach itself. Ultimately, the team must create a solution space of possible product designs which are distinguished uniquely by the input-variable combinations. The solution space concept is illustrated in Figure 2. When the bounderies are found for the solution space, the search can begin for the optimum design. However, the type of search which ought to be conducted depends upon a number of factors. If there is a single most important output property, then the search can be made on the solution space under a response surface corresponding to that most important output property. With several important output properties, it may be possible to find a weighting factor for each and then to simultaneously search all of the response surfaces.

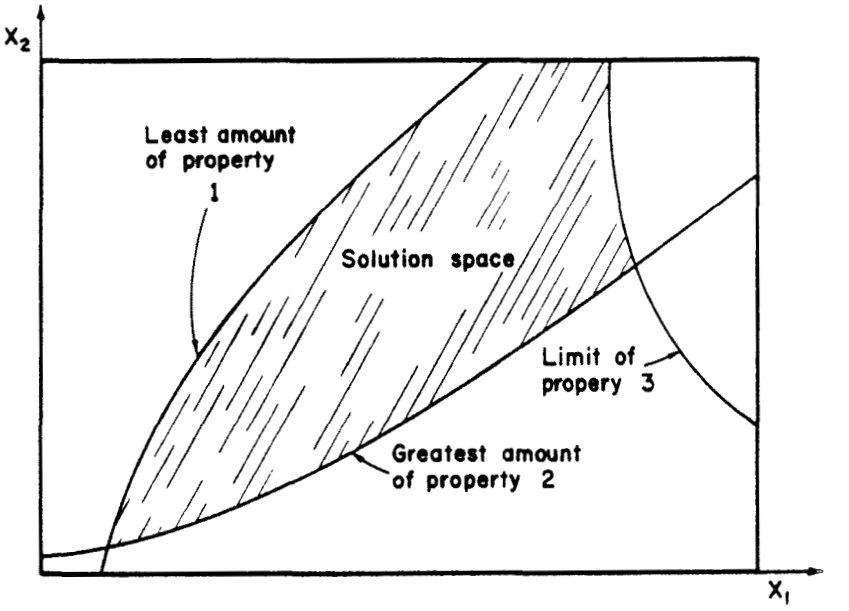

Figure 2. Solution Space Concept.

In this case one can use the weighted sum of each response as an objective function for the search. An alternative procedure of placing constraints on secondary objectives, then optimizing the pharmacy objective, is shown in the case studies.

The final part of the analytical phase consists of sensitivity analyses. There are at least two principal forms of sensitivity analyses: one form is used to determine appropriate tradeoffs between changes in various output properties and the other form entails an investigation of the changes in the output properties with changes in the uncontrolled input variables.

Typically, the first form of sensitivity analysis is performed by tentatively changing the acceptable limits of secondary output-properties and estimating the effects on the primary properties. Graphical plots of these effects provide information to the research and development team which will aid them in modifying their opinions of acceptable limits for the output properties. The second form of sensitivity analysis serves to provide guiding information to the team about the effects of uncontrollable input variables. Often a design of lower quality relative to the output properties is far more stable. Information from this second form of sensitivity analysis provides a vehicle for assisting in the tradeoff decisions between better output properties and product stability.

The verification stage provides the tests necessary to determine if the analytically-determined design is suitable or whether further revisions are needed. When further revisions are indicated, the verification procedure ought to indicate the directions of such changes. Such testing may be done by predicting the response surface values at and around the analytically-determined solution and then running laboratory tests at the same combinations of controllable input variables. With close agreement between predicted and obtained results, then the final product design is at hand. If there is not good agreement, then one ought to investigate for systematic prediction errors

and find the implications these predictive errors have on the product design solution. This information on prediction error and solution implication can serve the research and development managers to indicate the R&D resources needed on the second pass through these four R&D phases.

A CASE STUDY IN TABLET DESIGN

Tablets are the most common dosage form and, in a great many cases, the tablet serves primarily as a means of carrying small quantities of a drug into the patient. The problem faced by the development group is to arrive at a proper design (formulation) of this product. --- Although this design philosophy came out as a result of this experience[Fonner, Banker, and Buck (1970) and Fonner, Buck, and Banker (1970)], this case study is described as if it were developed following this philosophy.

Preliminary planning on the development of a tablet needed for carrying a particular drug first must select a general type of formulation. In this case a decision was made that the tablet consist of starch as a disintegrant (facilities tablet breakup), stearic acid, as a binder (to produce a cohesive tablet compact), a diluent compound, and the drug. Output properties considered important for this product were: (1) the rate of drug release within the human body, (2) tablet volume, (3) the tendency for tablet breakup under handling or friability, and (4) tablet hardness. The first output property was based on medical reasons and was felt

to be the most important property. Tablet volume and friability were felt to be important for the maintenance of accurate packaging and dosing. These two properties, as well as tablet hardness are important marketing considerations as well as for a proper physical appearance. Production considerations were involved with both tablet volume and hardness. With the output properties identified, the design team moved on to determine means for measuring these properties. Since drug release rates in the human body were difficult to obtain, the rate of dissolution in water was initially substituted as an in-vitro test and a standard dissolution test was employed. Standard tests also existed for measurement of the other properties and these tests were selected. Next the controllable input variables of the percentages of starch and of stearic acid were identified. Practical chemical and production considerations allowed for the limiting of these two input variables as 1 to 41 percent and 5 to 45 percent respectively. Although no uncontrolled input variables were considered here, both average humidity and storage time might have been.

With this preliminary planning completed, the experimental phase was started. An experiment was designed whereby all combinations of three levels of each input variable were prepared and tested. At least ten tablets were made for each formulation because two of the standard tests were destructive. These standard tests were conducted and the results were recorded on computer data cards.

In the analytical phase a combination analysis of variance and regression analysis was run for each output property. A polynomial description was found for each property as descriptions of the response surfaces. Isoproperty lines were constructed for each property over the possible combinations of input variables and the results are shown in Figure 3. No correlation analysis was run. It was determined that practical upper limits for friability and tablet volume were 2.74 percent and 0.027 cubic inches respectively. With a single most important property (i.e., the release

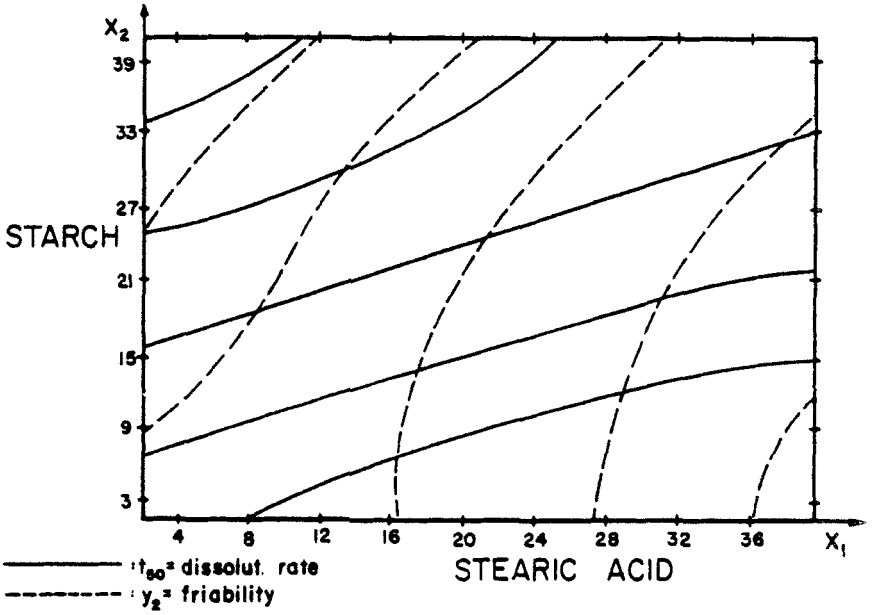

Figure 3a. Tablet Dissolution Rate and Friability as a Function of the Design Variables.

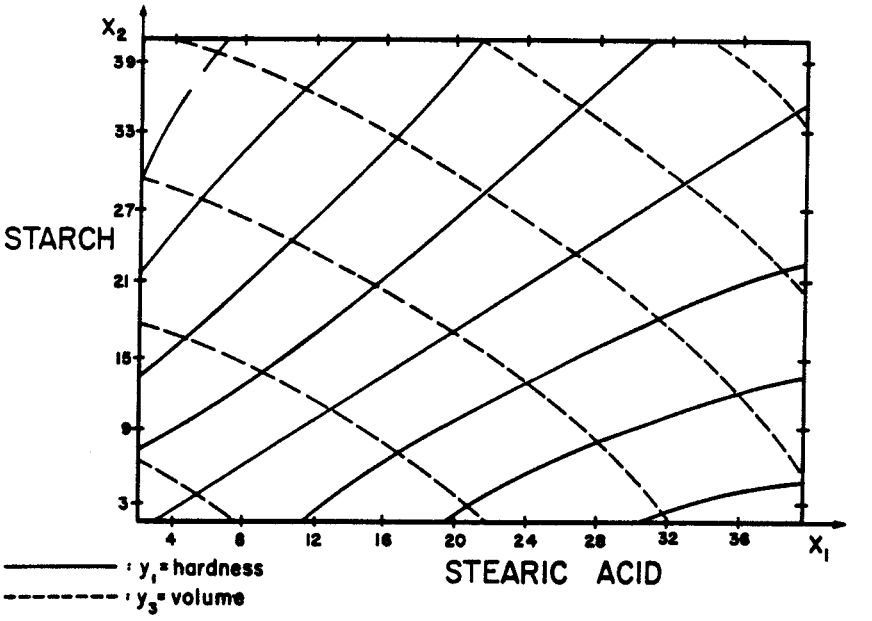

Figure 3b. Tablet Hardness and Volume as a Function of the Design Variables.

rate of the drug) and only two input variables, the Lagrange method of constrained optimization was employed for the search part of the analytical phase. Lagrange's method entails an expression consisting of the release rate response function, a multiplier times the friability response function less the upper acceptable limit for friability, and another multiplier times the total volume response function less the upper acceptable limit for tablet volume. These two multipliers designate the effect on the primary output property resulting from changes in the limits on friability and on volume. Differential calculus is employed with the

resulting expression for each variable and each resulting expression is set equal to zero. When the resulting equations are solved for the various variables, the analytical solution was found to consist of 22.5 percent starch and 26.8 percent stearic acid. Figure 4 shows the constraint contours for the release rate, and the analytical solution for this problem where the two constraint contours intersect. At this analytical solution the time for half of the drug to dissolve was found to be 17.9 minutes. Also, the multiplier of the friability constraint was found to be 0.5 whereas the volume constraint multiplier was 2.90. These two multipliers indicate the rate of improvement in the release rate for an increase in the upper acceptable

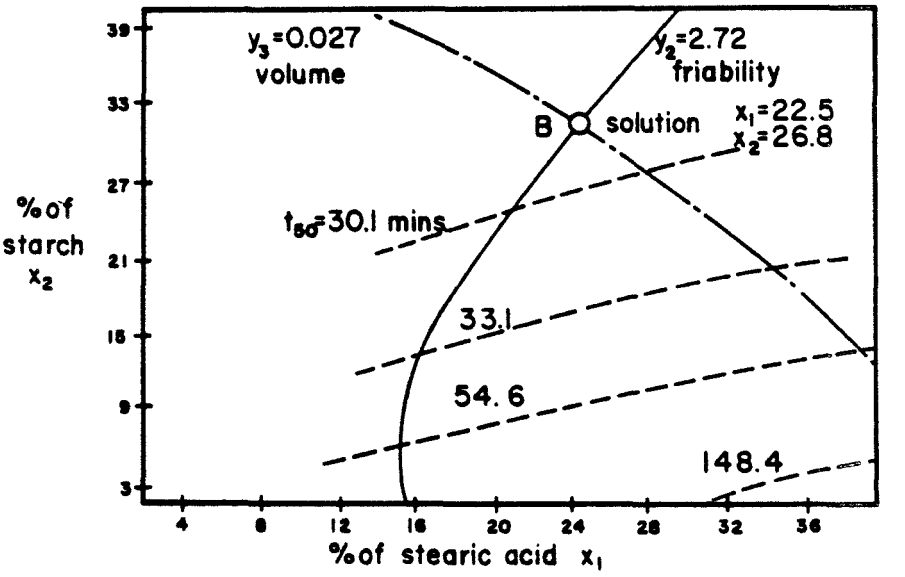

Figure 4. Constraint Contours and Objective Function Contours in Tablet Design Case Study.

limits on friability and tablet volume. Clearly, much greater improvement can be obtained by increasing the tablet volume limits than by increasing the upper friability limits.

Two sensitivity analyses were performed. In the first the upper acceptable limits of friability were changed in small steps from 0.3 percent up to 8.0 percent and the Lagrangian optimization was performed again at each step. The time for dissolving fifty percent of the drug was calculated and plotted in Figure 5 with the upper acceptable friability limit. It may be seen that the fifty percent dissolution time becomes extremely long unless an allowable friability limit is greater than about 1 1/2 percent. At greater friability limits the fifty percent dissolution time

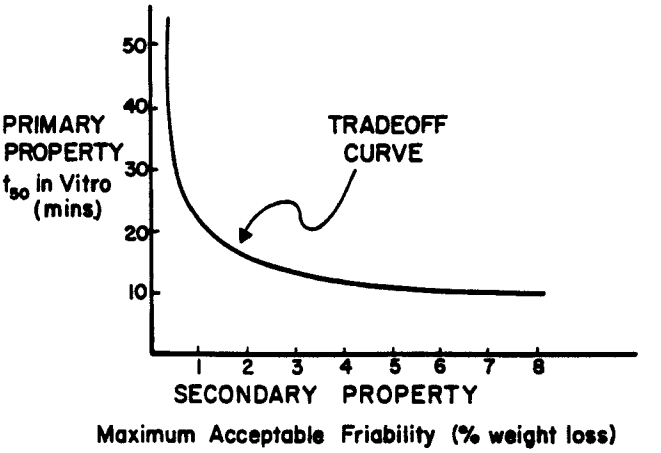

Figure 5. Dissolution Rate and Friability Tradeoff Curve in the Tablet Design Case Study.

decreases gradually. Accordingly the decision team can come to grips with the tradeoff decision very effectively with this backup analysis. The second sensitivity analysis was similarly performed on the upper volume limit. Results here, as reported in Figure 6, indicated dramatic improvements in the fifty percent dissolution time by as much as three minutes by simply raising the upper volume limit to 0.028 cubic inches. The tradeoff function in Figure 6 would greatly aid decision makers.

Verification testing was performed in two ways. First there were additional experiments conducted at and around the analytical optimum solution. Results

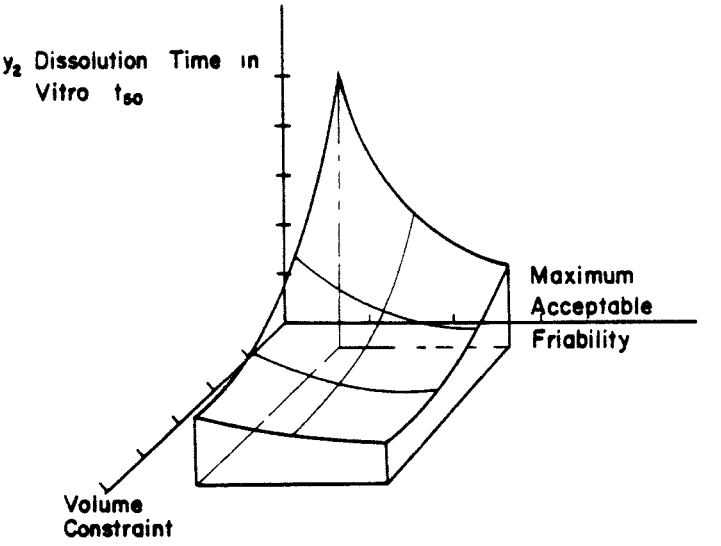

Figure 6. Tradeoff Surface Between Dissolution Rate, Friability, and Volume in the Tablet Design Case Study.

of these new tests were closely predicted by the previously obtained response surfaces. Table 1 shows the results of this first verification study where only a single experimental result fell outside the volume confidence interval. The second verification test was performed to see how well the fifty percent dissolution rate approximated the drug release rate in the human body. Results from this second verification testing showed that the fifty percent dissolution time predicted the drug release rate with extreme accuracy. These two verification tests provide a high degree of confidence in quality of the tablet formulation by the new product development team.

A CASE STUDY IN SUSPENSION DESIGN

Suspensions consist of liquids containing fine undissolved powders. This drug dosage form is particularly suitable for use with young children and in geriatric cases. However, the powders eventually settle to the bottom when the suspension is allowed to stand and shaking is required to remix the powders evenly in the liquid. Two recognized theories of suspension design lead to quite different designs. The case study shown below demonstrates the product design philosophy, it illustrates some variations on the management techniques which one might use, and it verifies that both theories of suspension design are right, depending upon the emphasis one gives to alternative output properties. Details of this case study are given in Hagmen, Peck, Banker, and Buck (1973).

Table 1. Verification Test Results of the First Case Study.

Response Variables	New Experimental Conditions		Predicted Values	95% Confidence Interval	New Experimental Results
	% Stearic Acid	% Starch			
Hardness	15.0	11.0	10.45Kg.	8.82 - 12.08	9.4 Kg.
	15.0	31.0	5.91Kg.	4.29 - 7.53	4.4 Kg.
	35.0	11.0	14.07Kg.	12.44 - 15.70	14.6 Kg.
	35.0	31.0	10.04Kg.	8.42 - 11.66	9.6 Kg.
Dissolution Time	15.0	11.0	37.3 Min.	31.7 - 43.8	34.4 Min.
	15.0	31.0	12.3 Min.	10.4 - 14.4	12.9 Min.
	35.0	11.0	68.0 Min.	57.9 - 80.2	72.8 Min.
	35.0	31.0	19.9 Min.	16.9 - 23.4	19.9 Min.
Friability	15.0	11.0	3.18%	2.32 - 4.36	4.14%
	15.0	31.0	7.04%	5.12 - 9.66	6.64%
	35.0	11.0	0.55%	0.40 - 0.78	0.51%
	35.0	31.0	1.21%	0.88 - 1.66	1.21%
Volume	15.0	11.0	0.02521 cu.in.	.02494-.02549	.02537 cu.in.
	15.0	31.0	0.02684 cu.in.	.02657-.02711	.02718 cu.in.
	35.0	11.0	0.02689 cu.in.	.02661-.02717	.02697 cu.in.
	35.0	31.0	0.02834 cu.in.	.02826-.02862	.02844 cu.in.

Three output properties were identified in the preliminary planning as: (1) drug dose variation, (2) ease of pouring, and (3) physical appearance. Each of these properties were measurable. Assays of the physical quantities provided a means for assessing the drug dose variation. Measurements on the ease of pouring required the development of a special apparatus and test procedure. Standard tests were available for two aspects of physical appearance: (1) the height of the sediment after setting occurs, and (2) measurement of the zeta potential, which describes the dispersion of the powders in the suspension.

Two ingredients, aluminum chloride and a celluose material, CMHEC-37H, were used in the suspension in addition to the drug. The quantities of these ingredients formed the controllable input variables and the range of the two respective inputs was set at 0 to 10^{-3} moles and 0 to 2 percent respectively. Also, two uncontrollable input variables were identified: (1) the undisturbed storage time since last used, and (2) the shaking time before use (a standard shaking intensity was employed). Experiments were performed at combinations of these variables.

In the analysis phase a form of regression analysis was used, known as orthogonal polynomials. The goodness-of-fit turned out to be unusually high at R^2=0.94. This analysis was employed with the uncontrollable variables as well as the controllable input variables. The particular case of 21 days of undisturbed storage

prior to 10 minutes shaking time was selected as the base condition for uncontrollable input factors. Using this base condition as fixed, combinations of the remaining input variables were searched to find those combinations which produced zero dose variation. An elementary technique of management science for seeking roots was used and the results are shown in Figure 1. Once this collection of combinations of controllable input variables that gave zero dose variation was found, the remaining efforts for determining an optimum product design consisted of searching around this collection. Since the combinations in this collection were equal with regards to the principal output property, the question was posed, "Which of these combinations was best with regard to each of the secondary output properties?" The search was then conducted from this collection to find those combinations which gave a zero zeta potential, the maximum sediment height, and the greatest ease of pourability. Representative formulations which provided near zero dose variations were plotted relative to the secondary properties of pourability, sediment height, and zeta potential. Results from these tests are shown in Figure 7. Two combinations were found that were optimum: (1) at 10^{-5} moles of aluminum chloride and 1.4 percent CMHEC-37M there was a zero zeta potential and the greatest ease of pourability, and (2) 10^{-3} moles of aluminum chloride and 1.75 percent CMHEC-37M

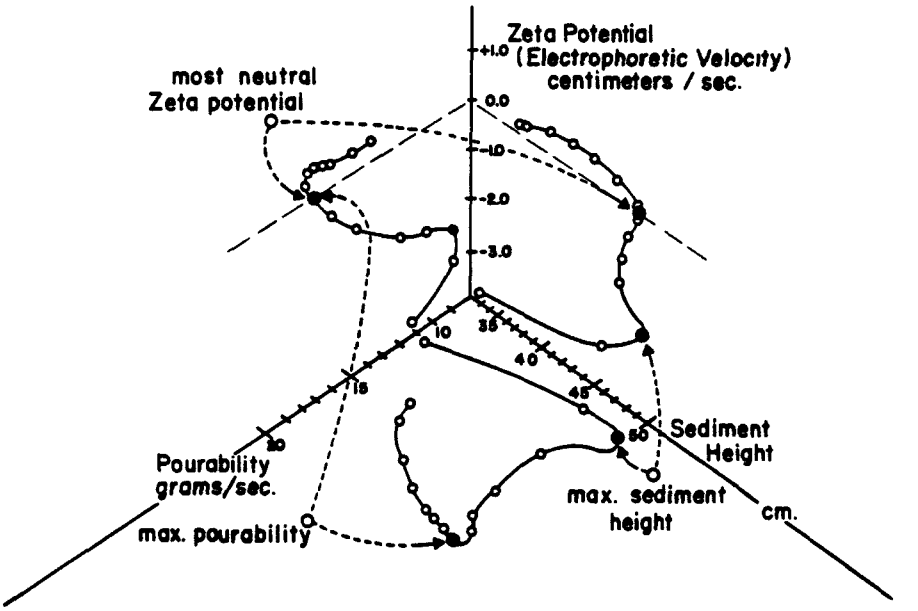

Figure 7. Secondary Properties of Various Suspension Yielding Zero Dose Variation.

gave the greatest sediment height. Combinations between these two analytical solutions were not as good in any of the secondary output properties as were these two solutions. Accordingly there was no tradeoff to be considered; simply a choice between these two solutions.

Sensitivity tests were employed to aid in the decision between these two alternative solutions. In these tests the rates of change in dose variation (i.e. partial derivatives) were found for changes in undisturbed storage times and in shaking durations; in both cases by ignoring complex terms in the regression

functions. These rates of change denote the sensitivity of each alternative solution to these uncontrollable input variables. Results of these tests generally indicated that increases in CMHEC-37M reduced the shaking time source of dose variation regardless of the amount of aluminum chloride present as indicated in Figure 8. This observation gave more weight toward the selection of the second analytical solution.

Experiments were performed for verification purposes with product formulations at the two analytical solutions. Results of these tests are shown in Table 2 where the reader can verify that both solutions provided reasonable predictability. However,

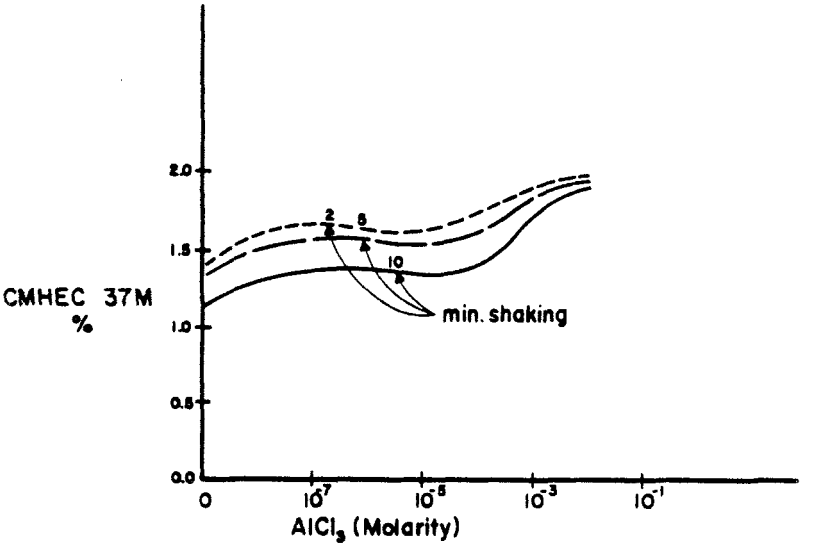

Figure 8. Shaking Duration Test Results for Sensitivity Analysis.

Table 2. Results of Validation Tests of Second Case Study.

	Candidate Formulations for Design			
	1.40% CMHEC-37M & 10^{-5} $AlCl_3$		1.75%CMHEC-37M&10^{-3} $AlCl_3$	
Property	Predicted	Actual	Predicted	Actual
Dose Variation	0	-25 mg	0	-33 mg
Zeta Potential	0	-0.005cm/sec	-0.22cm/sec	-0.18cm/sec
Viscosity	20.95 cps	26.40 cps	20.25 cps	25.54 cps
Sediment Height	48 cm	50 cm	49 cm	44 cm
Pourability	17.5gm/sec	19.5gm/sec	8.7gm/sec	7.84gm/sec

the results of this verification study indicates that a choice between these two solutions would be difficult but either would be superior to many other product designs. The scene fades on this case study while the R&D team makes the final decision, but what remains is the fact that this management science approach was able to pinpoint two optimal formulations, each advocated on theoretical grounds. This case study demonstrated some of the practical pros and cons on each side of this issue.

CONCLUDING REMARKS

The two case studies cited above demonstrate that the proposed product design philosophy provides both an effective and an efficient procedure. Effectiveness is demonstrated by the development of near optimum product designs. Efficiency is illustrated by the combining

of testing operations, by the use of response functions for compacting a great deal of information, and by the elimination of unneeded tests through analysis. Perhaps an even more important attribute of this philosophy is the information transfer and the management flexibility which is provided. Research and development management needs information input at the proper time in order to reduce unnecessary testing and to make hard tradeoff decisions before going into production. Thereby many down-stream production, distribution, and marketing problems can be avoided. Output information from the R&D process allows management the opportunity to make timely reallocations of research resources. The ability of the firm's R&D effort can, through this philosophy, be made more responsive to changing patterns in finance, marketing, production, or by the results they themselves generate.

Although the experimental and analytical techniques employed in these case studies proved to be effective, there are many alternative methodologies which might have been used with greater efficiency. Our choice of the more simplistic procedures allowed for a straight forward demonstration, uncluttered with sophistication which may have obscured the principal idea. In fact, Schwartz, Flamholz, and Press (1972) have correctly pointed out that the more typical product design situation entails a much greater number of input variables and therefore the situation demands more sophis-

tication in the choice of analytical techniques. There are also more efficient sequential forms of experimental designs which can and ought to be used. The bones of this philosophy needs the muscle which will insue when the philosophy is seriously accepted by management. Research and development needs aids for better management. These needs are particularly acute in the pharmaceutical industry, as Sherman (1973) points out in his observation of declining R&D output here. Although a major cause of this decline may be associated with regulatory difficulties, another cause may be in R&D management. Accordingly, this product design philosophy is offered here in hopes for the development of better drug products, greater productivity, and as a means of more effectively meeting the requirements of the Food and Drug Administration, while striving for optimal product safety, efficacy, and reliability.

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