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NON CLASSICAL EXPERIMENTAL DESIGNS IN PHARMACEUTICAL FORMULATION

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Classical experimental designs suitable for studying the effect of the proportions of the components on the properties of a mixture are readily developed and are of optimum efficiency. Their applicability depends however on the experimental factor space having a very simple form, and because of the many limits imposed on the levels of pharmaceutical excipients in pharmaceutical dosage forms their practical use in formulation is restricted.

Methods are available for defining the experimental factor space where it is not a simplex and the number of components is too large for the space to be defined graphically. A relatively easy method of obtaining good experimental designs is to use the D-optimum criterion, where a given number of experiments is selected out of the many possible mixtures, to give a statistically optimized design.

An example of the use of this method in formulating a modified release matrix tablet, containing 5 variable components is described. One of the advantages of the method is the possibility of a step-wise approach, and this is demonstated in the present case where the formulation was carried out in two stages. The results enabled the formulation of tablets with the desired dissolution characteristics together with a fairly complete characterisation of the system.

INTRODUCTION

Formulations are by definition mixtures, and once the excipients have been selected in the early stages of the development of a product we would usually investigate the effects of different proportions of these excipients on the formulation characteristics. We may wish to study factors other than the composition, such as processing variables, at the same time.

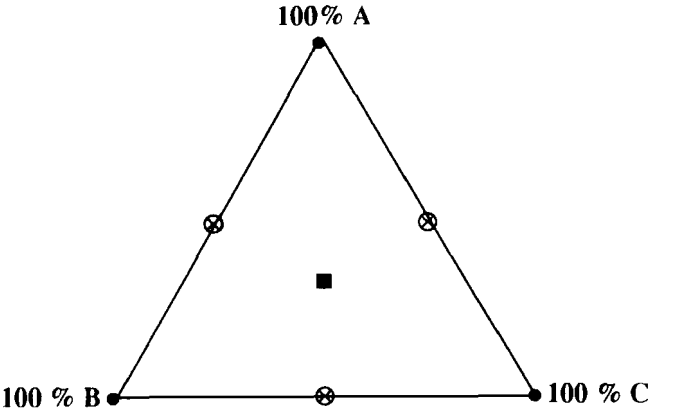

FIGURE 1
Simplex Experimental Design for 3 Components

- ● Experimental points for linear model
- ⊗ { Test points for linear model / Experimental points for interactions model
- ■ Test point for interactions model

The restriction that the percentages of the different components add up to 100% leads to certain differences in the model equations that are used to study mixtures, leading to the elimination of either one component (the so-called filler) in the floating variable form of the model or of the constant term in the canonical or Scheffe equations(1,2). The relationship between the two forms of the equation is discussed briefly in Appendix 1. The canonical form is preferred here.

Provided that there are no restrictions on the proportion of each excipient the factor space for 3 components may be expressed in 2 dimensions as an equilateral triangle (figure 1), that for 4 components in 3 dimensions as a regular tetrahedron. For more than 4 components we need further dimensions but the system and treatment are still relatively simple. Such designs are known as simplex lattices.

These designs are of little interest in formulation because we normally wish to study a very restricted part of the total system. There is little point in testing mixtures with 0% binder or 100% lubricant. If the factor space is still a simplex (figure 2a) we can use the classical designs, knowing that these are optimal (3). This is rarely the case, the factor space having a more complex form (figure 2b). We therefore need to define the

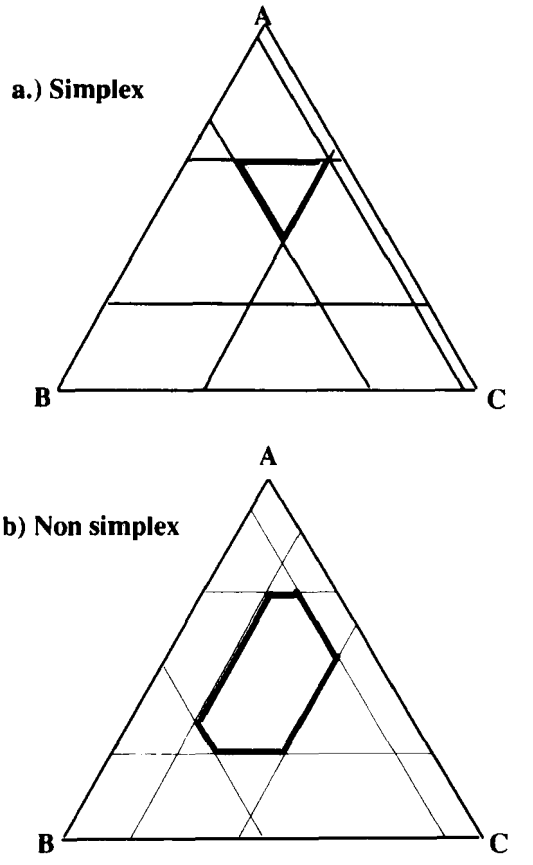

FIGURE 2
Experimental space with restrictions - 3 components

boundaries of the space and select an experimental design, within these limits. Various methods are available for designing the experiment (1). One of the best and simplest is the use of an exchange algorithm to give a D-optimal design.

D-Optimal designs have been used relatively infrequently in pharmaceutical development but future interest will probably be closely correlated with the availability of suitable computer programs. The method is flexible and we believe these designs to be invaluable at different stages of formulation and development.

An exchange algorithm was used to obtain a D-optimal design for characterisation and optimization of a granulation/ tableting process, where

the material available was restricted and the model was not symmetrical (4). This allowed a full factorial design of 72 experiments to be reduced to 22 runs for a model containing 11 terms, the results being analysed using response surface methodology.

D-optimal designs are also useful under circumstances where certain experiments in the classical design are not feasible, requiring the factor space to be redefined. The missing experiments may be replaced by other experiments where the combinations of the levels of factors are feasible, the choice being optimized using the exchange algorithm.

It is possible to impose the choice of certain experiments, for example preliminary tests already carried out, and select the best experiments from the candidate matrix to add to these. D-optimal design methodology is also useful for designing further experiments when moving outside the initial experimental zone, or when changing the model. If a few preliminary experiments have been carried out, which were optimal for a linear model, and we then wish to refine the model we may impose the experiments already done and add an optimal set of points for the extended model.

All of these useful properties of the D-optimal design apply to the use of this method with mixtures. However in the above examples the D-optimal design is chosen because of exceptional circumstances. The classical designs should be used in preference where possible (5). For mixtures in pharmaceutical formulations the use of an optimal design is most frequently in our view the method of choice.

The subsequent analysis of the experimental results normally uses the well established response-surface methodology.

NON SIMPLEX EXPERIMENTAL DESIGNS

Definition of the experimental space

This operation is trivial for 3 or 4 components, but for more complex mixtures a systematic treatment is necessary. Upper and lower limits are defined for each component. These limits are normally flexible and that after the establishment of these limits it should not be necessary to work outside them in an optimization phase.

We test these limits to make sure that they are coherent or mutually compatible. We then calculate the number of apexes of the factor space. For three components this will be between 3 and 6, for 4 components between 4 and 12, for 5 components between 5 and 30. The coordinates of the apexes are calculated using the algorithm of Anderson and McLean (Appendix 2).

Choice of a D-optimal experimental design

Assume that we have a system of 5 components for which we have fixed the limits. We require certain characteristics and would prefer to carry out a minimum of experiments. If this were a preliminary study we might prefer to neglect interactions between excipients and between drug substance and excipients and use the linear model. To determine the 5 coefficients of the model we must do at least 5 experiments, but it is not simple to decide which ones. If the experimental space were a simplex we could take the apexes, but here we have a choice of up to 20 experiments defining the limits of the factor space (the Extreme Vertices Design). A classical design is not possible and we need answer to the following questions:

1. How many experiments are necessary?
2. For a given number of experiments which will give the most information?
3. Is the experimental design selected on the basis of questions 1 and 2 adequate to obtain the required information.

We arrive at the design by the following stages:

1. Choice of a model for the responses. This may be linear or of higher order. Extreme care must be taken if only certain interactions are selected, particularly if it is necessary, because of the limitations of certain computer programs, to use the floating variable form rather than the canonical form of the equation.

2. Construction of a candidate experimental matrix which consists of:

a) The apexes, determined using the algorithm of Anderson and McLean.
b) The centres of the edges (or in some cases the longest edges only) of the n-1 dimensional factor space.
c) The centres of gravity of the (n-2) dimensional hyperfaces of the factor space.
d) The centre of gravity.

(b), (c) and (d) are added depending on the type and complexity of the model.

3. Analysis of the candidate matrix to determine whether it would be compatible with the experimental objectives.

4. The choice of a limited number of experiments, selected according a criterion of optimality. The normal criterion is of D-optimality (Appendix 3). A computer program is used for the selection, based on the exchange algorithms of Mitchell (6) or of Fedorov (7). Optimum designs are normally determined for different numbers of experiments

TABLE 1.
Modified Release Wax Matrix Tablet

	Limits	Variable
Drug substance	2.5 - 5.0%	x_s
Matrix-forming wax	7.5 - 12.5%	x_w
Acid	2.5 - 5.0%	x_a
Insoluble diluent	10.0 - 30.0%	x_f
Soluble diluent	Q.S.	x_d
Lubricant	1.0%	
Granulating agent	3.0%	
Glidant	0.2%	

The percentages and limits for the variable terms exclude the quantities for the constant constituents, lubricant, glidant and granulating agent.

and the choice made on the basis of the adequacy of the matrix and practical constraints of time and material available.

THE FORMULATION OF A MODIFIED RELEASE TABLET

We wished to design a modified release formulation of a basic drug which dissolved rapidly from conventional rapid release dosage forms at pH 2, but more slowly at neutral pH. The object was to obtain *in vitro* release independent of pH, with a mean dissolution time of about 1 hour. The formula was of a wax matrix tablet, incorporating acid to maintain a constant acid pH within the tablet. The formulation and the limits of the constituents are given in table 1. Because there are no restrictions on the amount of soluble diluent this factor space is fairly simple, and none of the points in the 2^4 factorial matrix obtained by the Anderson-McLean method described in Appendix 2 is outside the limits. Thus the factor space has 16 apexes. This result is general for formulations with a fairly low dose, and single diluent with no restrictions on its levels.

We initially selected a linear 5 component model on the basis of which we obtained a D-optimal design. The experimental design was obtained by first constructing a candidate experiments table, with the 16 apexes of the factor space obtained by the method of Anderson and McLean, and then the centres of the edges of the space, and the centres of gravity of the faces. This gave 118 potential experiments. The optimal matrix was selected for 10, 11, ... 15 experiments, using Fedorov's exchange algorithm (7). The values of det(M) and $\mathbf{d_{max}}$ were calculated for each optimal matrix. These are plotted in figure 3. It is clear that the

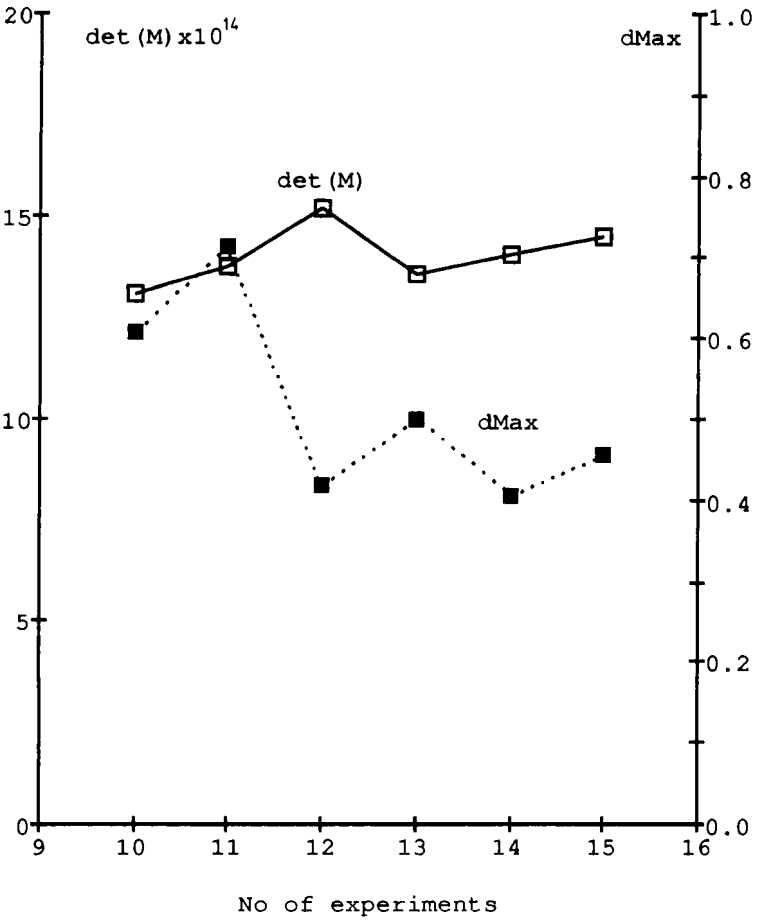

FIGURE 3.
Design optimisation parameters.

influence of the number of experiments on the amount of information per experiment is relatively slight. However there is a maximum at 12 experiments, coinciding with a minimum in d_{max}, indicating that this would give a relative constant variance. The matrix of 12 experiments was therefore selected, to which was added one experiment at the centre of the design. (See table 2, below.)

The dissolution profiles at constant pH were measured, at pH 2 and pH 6.8. The responses chosen for the analysis were the percentage dissolved at pH 2 after 1 hour, and after 5 hours, the percentage dissolved at pH 6.8 after 1 hour and the difference between the percentages dissolved at pH 2 and pH 6.8 after 1 hour.

TABLE 2.
Experimental Designs.

x_s	x_a	x_w	x_f	x_d
Initial design				
5.0	5.0	7.5	10.0	72.5
5.0	2.5	12.5	10.0	70.0
2.5	5.0	12.5	10.0	70.0
5.0	5.0	12.5	10.0	67.5
5.0	2.5	7.5	30.0	55.0
2.5	5.0	7.5	30.0	55.0
5.0	5.0	7.5	30.0	52.5
2.5	2.5	12.5	30.0	52.5
5.0	2.5	12.5	30.0	50.0
2.5	5.0	12.5	30.0	50.0
2.5	2.5	7.5	10.0	77.5
2.5	2.5	7.5	10.0	77.5
Centre point				
3.75	3.75	10.0	20.0	62.5
Exploratory experiment				
5.0	10.0	12.5	10.0	62.5
Additional experiments				
2.5	10.0	12.5	10.0	65.0
2.5	10.0	7.5	30.0	50.0
5.0	10.0	12.5	30.0	42.5
3.75	10.0	7.5	10.0	68.75
5.0	2.5	7.5	10.0	75.0
5.0	10.0	7.5	30.0	47.5

x_s	Drug substance
x_a	Acid
x_w	Matrix-forming wax
x_f	Insoluble diluent
x_d	Soluble diluent

The data were analysed using the linear model, and also other models with potentially important interactions that were compatible with the experimental design. The coefficients of the Scheffe model were determined by multiple linear regression using the programs RS/Explore and RS/Discover (9), and gave a good fit. This did not indicate that the model had any physical meaning, but that it could be used for interpolation within the experimental zone.

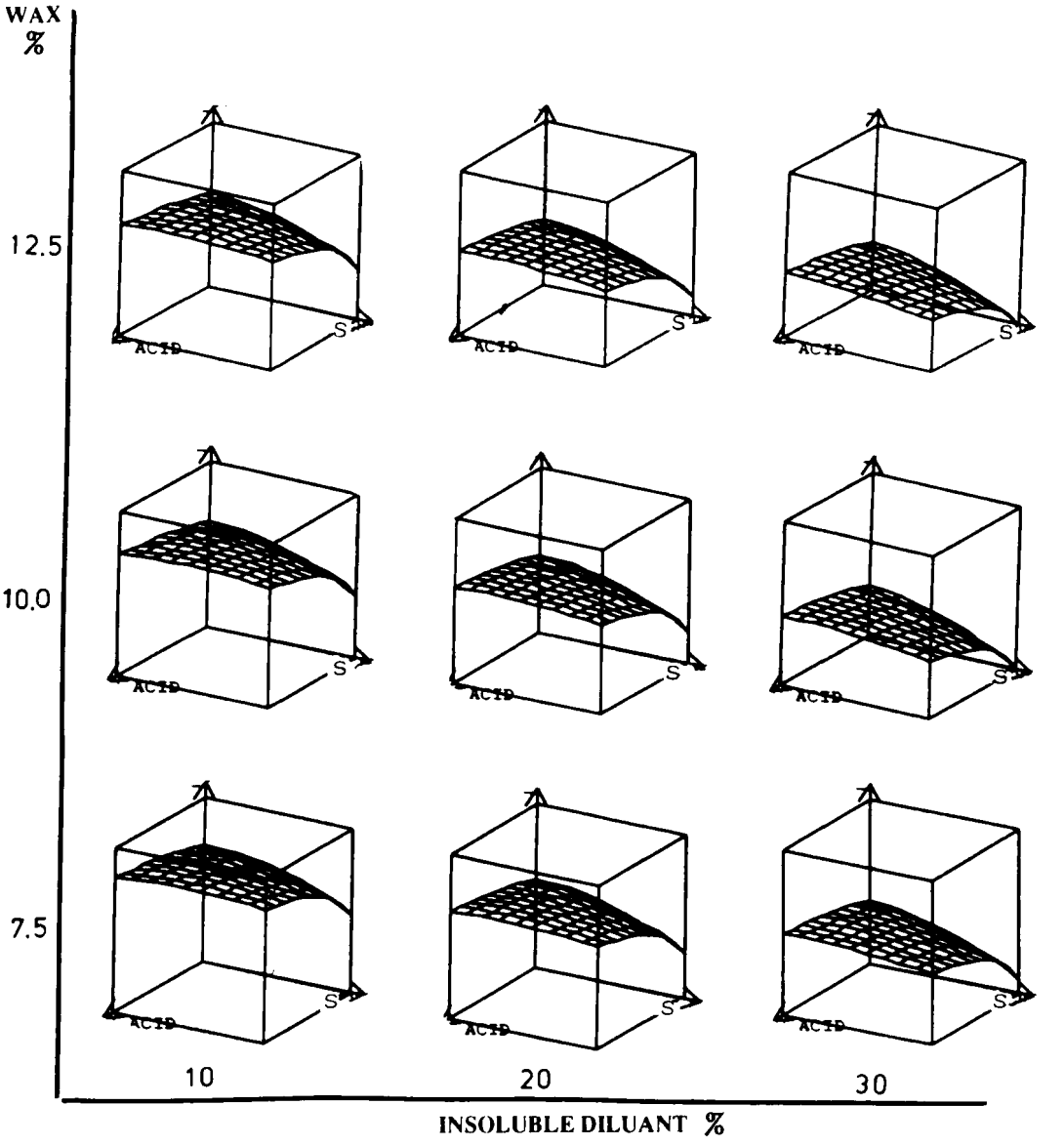

FIGURE 4.
% dissolved at pH 2 after 1 hour.

The limits on the axes of the 3-D graphs are:

% dissolved	40 - 65%
Drug substance	2.5 - 5%
Acid	2.5 - 5%

The soluble diluent is the slack variable.

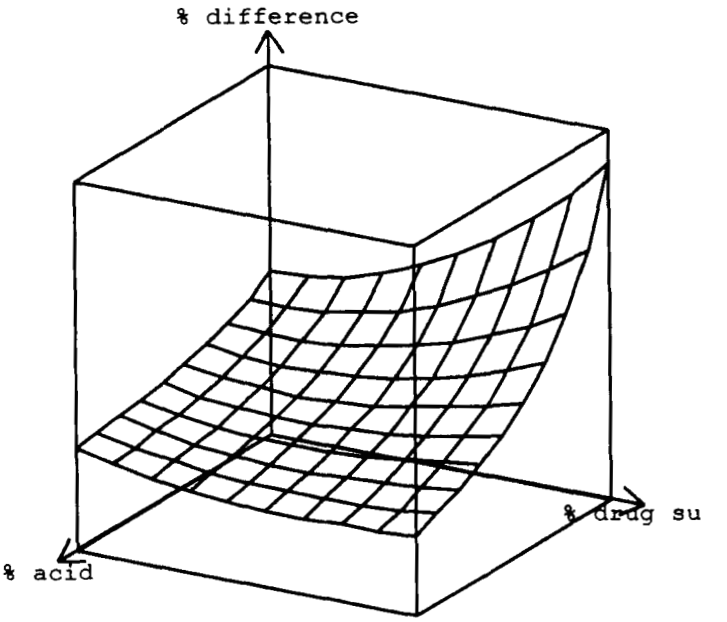

FIGURE 5.
Effect of % acid and drug substance on the pH dependance of the dissolution rate.

Response (% difference):- the difference between the percentages dissolved at pH 2 and pH 6.8 after 1 hour.

Ranges:	Response	0 - 25%
	Drug substance	2.5 - 5%
	Acid	2.5 - 5%
	Wax=10%	
	Insoluble diluent=10%	
	The soluble diluent is the slack variable	

However the fit at the test centre-point was poor, with a difference between predicted and observed values of 10% for the amount dissolved after 1 hour in the pH 6.8 buffer. Inspection of the data indicated that one of the key variables was the excess of drug substance over acid, which as expected from physico-chemical considerations had a considerable effect on the dissolution at neutral pH. It was clear that the pure polynomial model was inappropriate and it was therefore modified, the concentration of the drug substance x_s being replaced by the reciprocal of its square root. Another term, increasing rapidly with the excess of drug substance over

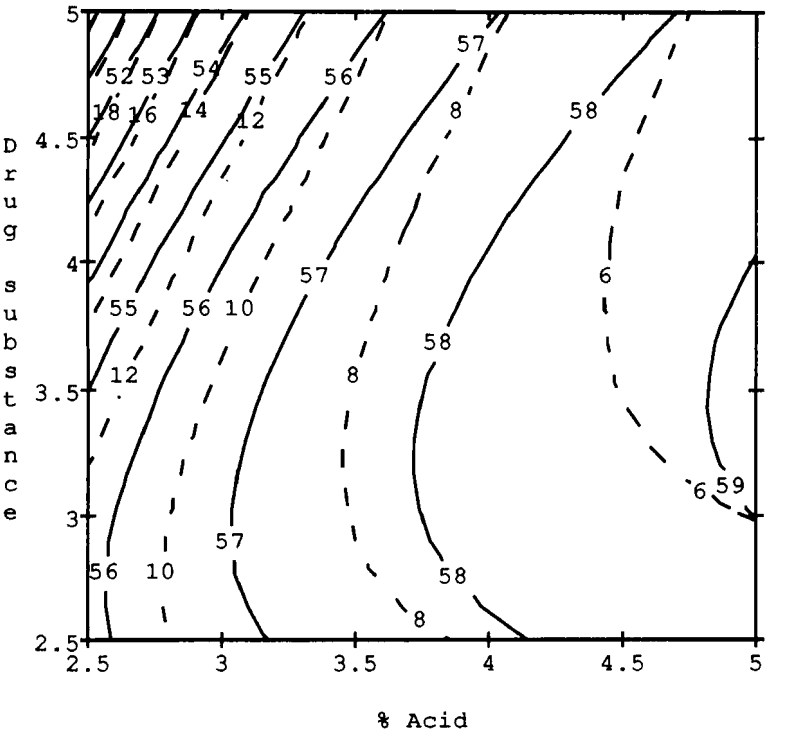

FIGURE 6.
Effect of drug substance and acid on the dissolution profile

% dissolved at pH 2 after 1 hour
Difference between % at pH 2 and pH 6.8 after 1 hour (same response as figure 5)

Wax = 10%
Insoluble diluent = 10%
The soluble diluent is the slack variable

The response surface shows the effect of replacing diluent with drug substance and/or acid. The surfaces are almost identical at other levels of wax and insoluble diluent.

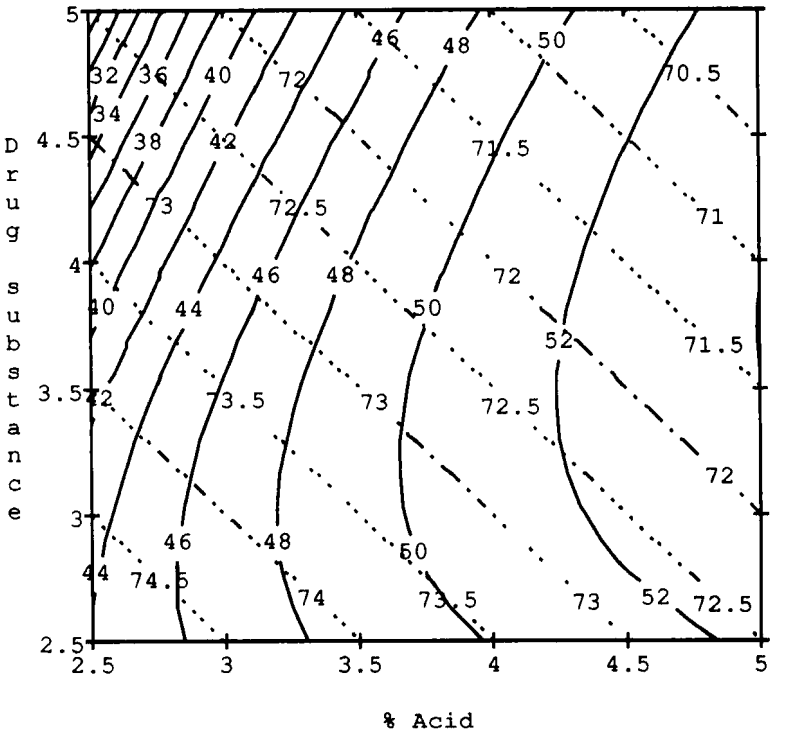

FIGURE 7a.
Slack variable plot of % dissolved at pH 6.8 after 1 hour showing % soluble diluent

% soluble diluent
% dissolved (at pH 6.8 after 1 hour)

Wax = 10%
Insoluble diluent = 10%
The soluble diluent is the slack variable

acid, was introduced. This gave a better fit at the centre for the experimental zone. It must be borne in mind that the design was not D-optimal for the new model.

The equation became:

$$y = \frac{a_s}{\sqrt{x_s}} + a_w x_w + a_a x_a + a_f x_f + a_d x_d + \frac{a_{as} x_a}{\sqrt{x_s}} + \frac{a_{fs} x_f}{\sqrt{x_s}} + a_e exp \frac{x_s - x_a}{x_a}$$

Equation 1

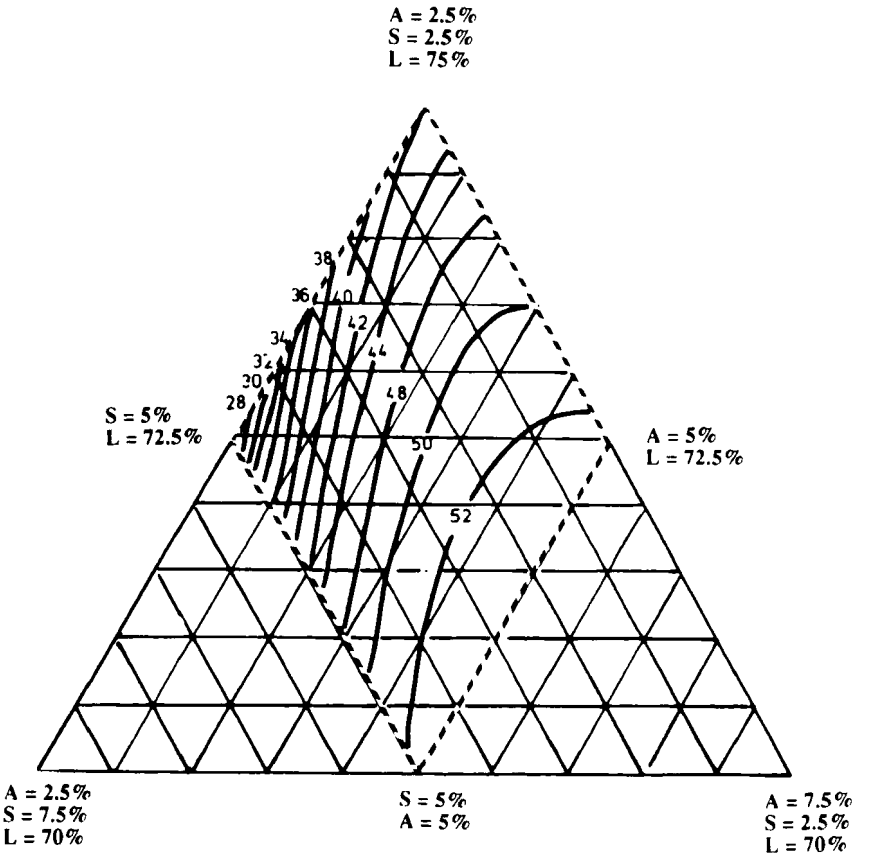

FIGURE 7b.
Canonical plot of % dissolved at pH 6.8 after 1 hour.

A = Acid
S = Drug substance
L = Soluble diluent
Wax = 10%
Insoluble diluent = 10%

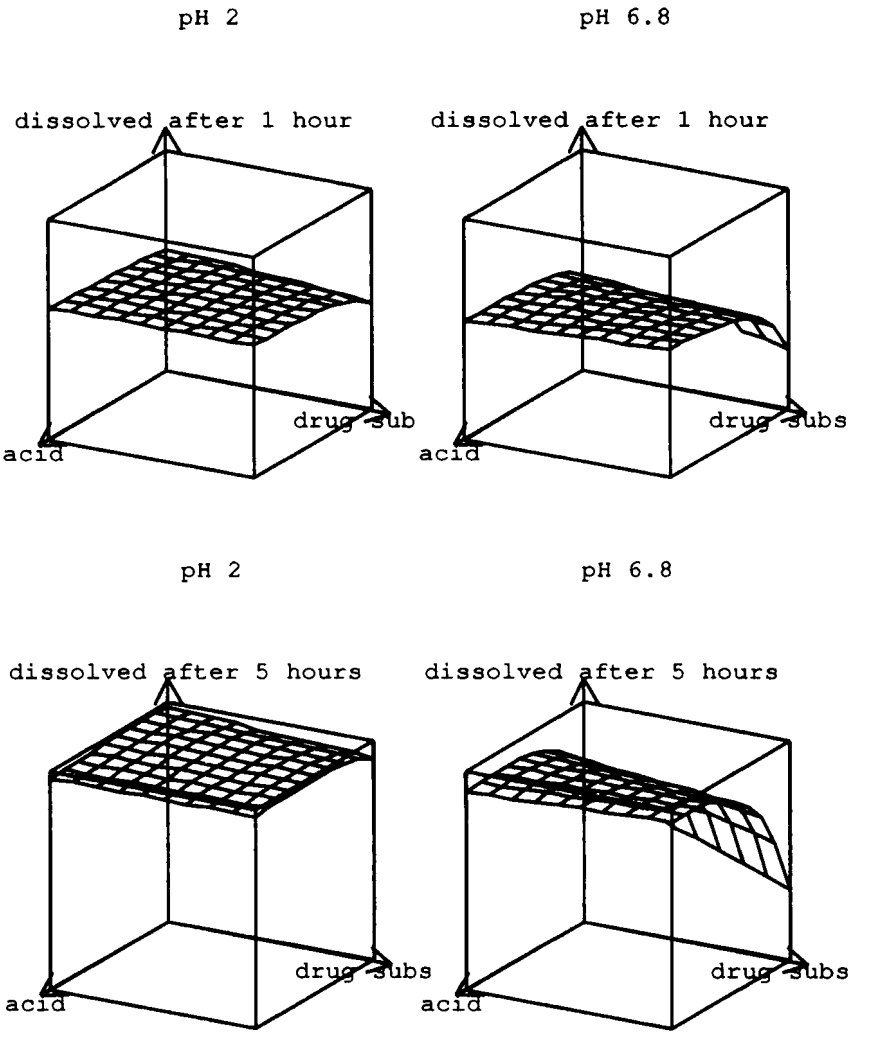

FIGURE 8.
Results of enlarged design.
% dissolved after 1 hour and 5 hours at pH 2 and pH 6.8

RANGES:	% dissolved	0 - 100%
	Drug substance	2.5 - 5%
	Acid	2.5 - 5%

The soluble diluent is the slack variable

This equation is purely empirical and a different treatment would have been used if a new experimental matrix had been planned, with terms of the form x_a/x_s and $(x_a/x_s)^2$.

The model was then transformed to the slack variable form for plotting 3 dimensional figures. These are shown in figures 4 and 5 for the amount dissolved at 1 hour at acid pH and the difference in the amount dissolved at acid and neutral pH at 1 hour. Figure 6 shows the same data at a given level of wax and insoluble diluent content, as a contour plot. Figure 7a and 7b compare the slack variable and Scheffe representations for contour diagrams.

Analysis of the results indicated that the original choice of limits for the acid was too narrow and the upper level should be raised above 5%. The model was used to extrapolate to determine a zone suitable for further experimentation. These relatively few further experiments could be selected using the exchange algorithm, by establishing the candidate matrix with the new upper limit for the acid and imposing the experiments already carried out, along with the experiment at the centre and one exploratory experiment, upon the final design. A number of different models were proposed as indicated above with ratio terms in drug substance and acid. Using the exchange algorithm six experiments were selected to give a matrix compatible with the proposed models (table 2). It may be noted that most of the new experiments were at the new upper limit of acid concentration. The model with ratios of drug substance to acid was found to give the best fit over the new factor space (Equation 2)and pH-independent dissolution was predicted over a wide range of constituent concentrations (Figure 8).

$$y = a_s x_s + a_a x_a + a_w x_w + a_f a_f + a_d x_d + a_{s/a}\left(\frac{x_s}{x_a}\right) + a_{s/a2}\left(\frac{x_s}{x_a}\right)^2 + a_{af} x_a x_f + a_{sd} x_s x_d + a_{sf} x_s x_f$$

Equation 2.

CONCLUSION

The use of D-optimal designs for mixture experiments enables the systematic development of formulations, such as that described in the above example, with the required characteristics. The information obtained on the influence of the different excipients would be expected to prove useful on further development when formulations of differing dissolution

characteristics might be required, or where scaling up imposed minor formulation changes.

The strategy may with care be reconciled to the more usual stepwise approach of industrial pharmaceutical formulation, allowing feasibility tests as well as preliminary linear experimental designs to be included in the optimization design. Finally, process factors may be included as interactions in the mixture model, allowing minor formulation changes during optimization of the process.

This will result in a more systematic approach to formulation, but maintaining a certain flexibility. A pharmaceutical formulator, experienced in the use of these designs, and with a good understanding of their properties, advantages, as well as their limitations, will be more able to develop optimised and fully characterised formulations, without the need for an excessive amount of experimentation.

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APPENDIX 1: SIMPLEX DESIGNS FOR MIXTURES AND THE SCHEFFE AND SLACK VARIABLE FORMS OF THE MODELS

We consider a mixture of 3 components. If the fraction of each component i is x_i and the response is y then the linear model for three components in the Scheffe canonical form is

$$y = a_1x_1 + a_2x_2 + a_3x_3 \qquad \textit{Equation 3a}$$

In the non-canonical form, with x_3 considered as a "filler" or "slack variable", this becomes:

$$y = b_0 + b_1x_1 + b_2x_2 \qquad \textit{Equation 3b.}$$

Note that in equation 3a there is no constant term. The coefficient have different physical meaning in the two equations. In equation 1a the coefficients a_i describe the property of the pure substances. In equation 3b the constant term is the property of the pure filler and b_1, b_2,.. describe the effect of replacing filler by the component.

The relationships are:

$$b_0 = a_3$$
$$b_1 = a_1 - a_3$$
$$b_2 = a_2 - a_3$$

The Scheffe simplex design can be used to determine the coefficients a_1, a_2, a_3. The three additional experiments marked in figure 1 can be carried out at the same time in order to test the adequacy of the model. If the linear model does not describe the system the second order model may be used. In the canonical form it is:

$$y = a_1x_1 + a_2x_2 + a_3x_3 + a_{12}x_1x_2 + a_{23}x_2x_3 + a_{13}x_1x_3 \qquad \textit{Equation 4a.}$$

In the floating variable form this is equivalent to the quadratic model for two independent constituents.

$$y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_1x_2 + b_{11}x_1^2 + b_{22}x_2^2 \qquad \textit{Equation 4b.}$$

The coefficients are related as follows.

$$b_{11} = -a_{23}$$
$$b_{22} = -a_{13}$$
$$b_{12} = a_{12} - a_{23} - a_{13}$$
$$b_1 = a_1 - a_3 + a_{13}$$
$$b_2 = a_2 - a_3 + a_{23}$$

The Scheffe form is normally to be preferred . Interpretation is easier and there is no apparent reason why one component should be distinguished from the others, unless it is in considerable excess (for

TABLE 3.

Illustration of the Anderson-McLean algorithm for 3 components

Limits:

$$0.20 \le x_1 \le 0.50$$
$$0.20 \le x_2 \le 0.70$$
$$0.05 \le x_3 \le 1.00$$

	x_1	x_2	x_3
1.	0.2	0.7	0.1
2.	0.5	0.7	-0.2
3.	0.2	0.2	0.6
4.	0.5	0.2	0.3

Point 2 outside limits

Degenerate points

	x_1	x_2	x_3
2′	0.5	0.45	0.05
2″	0.25	0.7	0.05

example, the solvent) or it is totally inert. This may however be necessary to use this form for certain computer programs (9).

APPENDIX 2 METHOD OF ANDERSON AND McLEAN

The Anderson and McLean algorithm (10) for determining the corners of the experimental factor space is illustrated in table 3 and figure 9 for 3 components. A complete 2 level factorial design is established for all but one of the components, using values at the upper and lower limits. Then the corresponding fraction of the last component is calculated for each point. Some points may lie outside the defined limits. In this case we set the fraction of the diluent to its defined limit and adjust the values of the other components in turn. If these values are within their limits then the point is an apex of the polyhedron or hyper-polyhedron. (We have already seen that if there are no restrictions on the amount of diluent the points are frequently all within the limits and the factor space is fairly simple.)

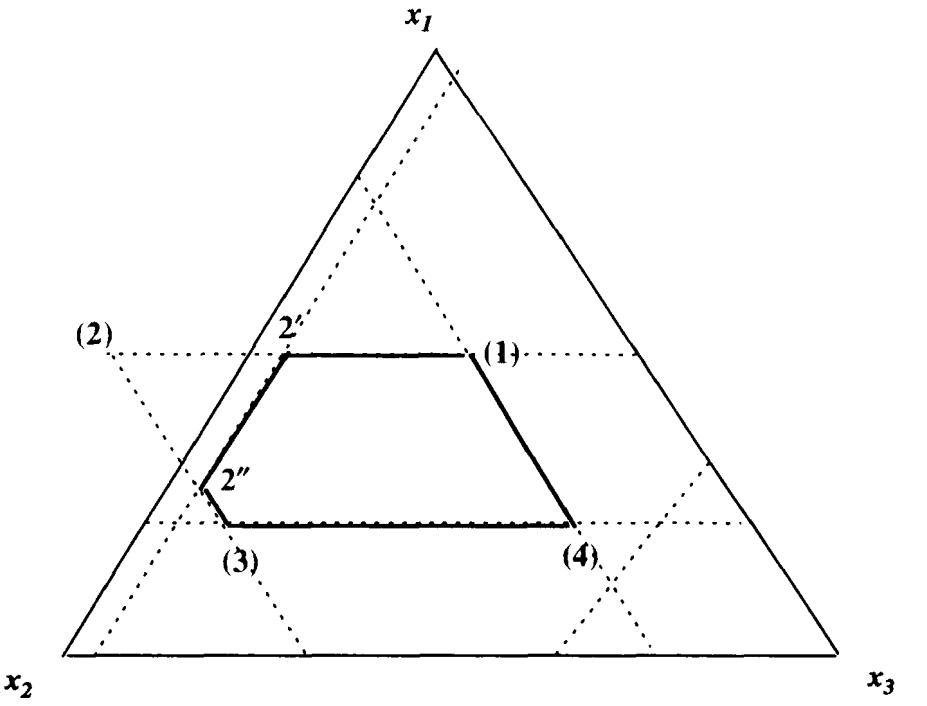

FIGURE 9

Illustration of the Anderson-McLean algorithm for 3 components

In the example points 1, 3, 4 are valid but point 2 is not only outside the limits but cannot physically exist. We set x_3 to 0.05, its lower limit and subtract the difference, 0.25, from the values for x_1 and x_2 in turn. This gives points 2′ and 2″ which are both inside the imposed limits. This example could just as easily be treated graphically but more complex examples in more dimensions may be treated easily by this method. Thus for the n components we define the 2^{n-1} full factorial design, identify the points outside the experimental limits, and define the degenerate points, as described above for 3 components.

APPENDIX 3 CRITERIA FOR OPTIMUM DESIGN MATRICES

D-optimal

We wish to obtain the best overall precision in estimating the model coefficients. For this we minimise the 'volume' of the confidence ellipsoid, which involves maximising the determinate of the information matrix X′X.

A-optimal

In order to calculate all these coefficients with approximately the same relative precision the design should be chosen so that the diagonal elements of the variance-covariance matrix are of about equal magnitude. The trace (or sum of the diagonal terms) of the variance-covariance matrix $[X'X]^{-1}$ is minimized.

E-optimal.

To reduce correlation of the estimations of the model coefficients we reduce the ratio of the largest to the smallest eigenvalue of the variance-covariance matrix. This leads to a near-orthogonal design in which the non-diagonal elements are as small as possible.

Criteria related to the **precision:**

a) The variance does not depend on the direction from the centre of the design (rotational iso-variance).

b) There is uniform precision over the experimental space.

c) There is minimal rate of change of the precision at the boundaries of the experimental space.

(a) and (b) are closely related to the **G-optimal** criterion. d^*_{max}, the maximum variance in the factor space, is minimised.

The D-optimal criterion is almost universally employed. One reason for this is the fact that it is not necessary in this case to invert the XX' matrix at each step. The optimization is thus less costly in computer time. However this method gives experimental designs that are usually good with respect to the other criteria. It is advisable to verify the different factors for each D-optimal matrix designed, trace, d^*_{max}, variance-covariance matrix, in order to be sure of the quality of the design.