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# EXPERIMENTAL DESIGN FOR PHARMACEUTICAL PROCESS CHARACTERISATION AND OPTIMISATION USING AN EXCHANGE ALGORITHM.

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Efficient experimental design may be used to maximise the information available from a given number of experiments (1, 2, 3, 4). In the development of new molecules the amount of drug available for formulation studies is often restricted. Thus in studying a given process the experiment is designed so that the necessary information is obtained given there is only enough material for a limited number of operations.

We have studied the effects of process variables on the characteristics of a conventional tablet formulation of a soluble drug; the factorial design was optimised by an exchange algorithm.

## FORMULA AND MANUFACTURING PROCESS

The drug substance to be formulated is the hydrochloride salt of a weak base, pK' about 9.3, freely soluble over the

physiological pH range and rapidly absorbed in vivo. The formulation contained about 40 % drug substance, microcrystalline cellulose (37.25 %), corn starch (15 %), sodium starch glycolate (5 %), povidone (2 %) as granulating agent, magnesium stearate (0.5 %) and colloidal silica (0.25 %).

The process studied was one of aqueous granulation. The drug substance and the first three excipients were premixed, a solution of povidone was added and the mixture was granulated, in a Lödige 50 L mixer-granulator. After drying in an oven at 50°C and calibration, the granules were mixed with the lubricant and colloidal silica. The blend was then compressed on a rotary press (Manesty D3RY).

## EVALUATION OF GRANULATE AND TABLET PROPERTIES

The particle size distribution of the granulate was measured by sieving with a Fritsch Analysette.

The friability of the tablets was tested with an Erweka Friabilimeter and assessed in two ways, firstly by the % weight loss, and secondly by the number of broken tablets after the test.

The disintegration time and the dissolution profile were determined by the European Pharmacopeal methods. The dissolution medium was 900 mL purified water and the stirring speed was 50 r.p.m.

The appearance of the tablets was assessed and graded from 1-5. The compression characteristics of the blend were assessed in a similar manner. Evaluation of the results was "blind", the experimenter not knowing which blend he was tableting or which tablets he was evaluating.

## EXPERIMENTAL DESIGN

30 kg of drug substance were available, enough for six granulations each of 12.5 kg total weight.

Five process variables were studied:

$X_1$ : Granulation time

$X_2$ : Concentration of the granulating agent

$X_3$ : Humidity after drying

$X_4$ : Calibration

$X_5$ : Lubrification time

The main effects of these variables were to be estimated, along with second order effects of $X_1$ and $X_5$, and the effects of interactions $X_{12}$, $X_{34}$ and $X_{45}$. The following mathematical model was postulated:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_{11} X_1^2 + \beta_{12} X_1 X_2 + \beta_{34} X_3 X_4 + \beta_{45} X_4 X_5 + \beta_{55} X_5^2$$

(Equation 1)

The method of exchange algorithms was chosen in order to optimise the experimental design for the following reasons:

- The considerable restraints on the number and type of experiment : not more than 4 experiments for a given combination of $X_1$ and $X_2$ (each granulation can be split into up to 4 portions) and not more than 6 combinations of $X_1$ and $X_2$ (no more than 6 granulations).
- The nature of the model, which is incomplete, and asymmetric, and with numerous missing interactions.

These restrictions cannot be satisfied by any classical experimental design (5) such as the composite Box matrices, or those of Box-Behnken, Doehlert or Hoke, nor hybrid matrices.

The presence of the second order terms $X_1^2$ and $X_5^2$ implies that these variables should be studied at least at 3 levels and the remaining factors at two levels. The corresponding full factorial matrix consisting of 72 experiments would allow calculation of all the different effects, main, second order and interaction. It consists of all possible combinations of the three levels -1, 0, +1 for the factors $X_1$ and $X_5$ and the levels -1 and +1 of the two remaining variables.

Because of the restricted amount of active substance available for studying the process it would be possible to carry out only a fraction of these experiments. We used the exchange algorithm to determine whether by carrying out a subset of these experiments we could estimate the coefficients in the model with sufficient accuracy and precision. These calculations were done using the programme NEMROD (6).

The resulting experimental design is known as a D-optimal design. The method of exchange algorithms (7, 8) is described briefly in the appendix.

As the model contains 11 coefficients it was necessary to carry out at least 12 experiments to determine the coefficients. We randomly selected 12 of 72 experiments, and determined which of the 12 experiments had the least information, then replaced it by the remaining point with the most information, the procedure being repeated until the exchange of points gave no further improvement in the precision of estimation of the coefficients.

The process was repeated for 14, 16, 18...28 experiments and the efficiency calculated. This is a measure of information per experiment and is plotted as a function of the number of experiments in figure 1. This shows a maximum at 22 experiments, and another at 28 experiments. Because of the restrictions of material the design with 22 experiments, shown in table 1, was selected. The experiments are grouped to show that it obeys the imposed restrictions and also that it is fairly symmetrical. The inflation factors, relative values of the variances of the estimates of the coefficients are given in table 2. They show that this experimental design, as well as being optimum overall for calculating the coefficients of the model, will enable all coefficients to be calculated with approximately the same precision.

The final plan included 22 experiments which could be grouped into six batches of powder granulated under different

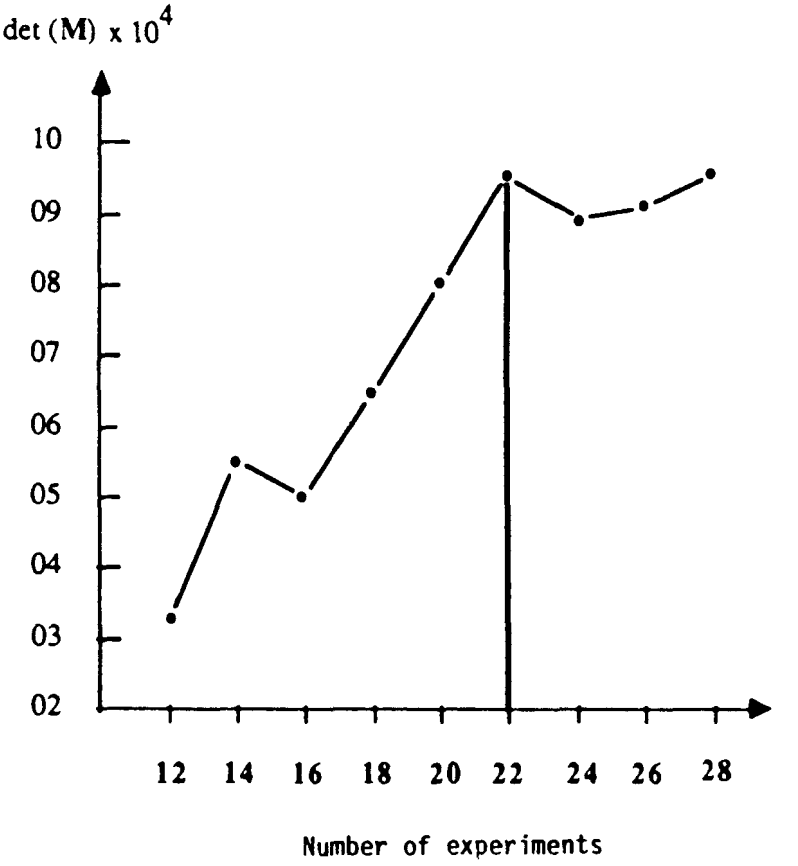


Figure 1 - Variation of the determinant D-eff with the number of experiments

conditions and then split into two or four sub-batches for subsequent stages in the process. Experimental values for the levels of each variable were chosen according to preliminary studies and are given in table 3.

After the granules had been prepared and tableted the physical properties of the granulates and corresponding tablets were examined and the data analysed according to the proposed model by multiple linear regression analysis.

It may be noted that the different experiments are grouped by granulation, and so experiments with the same granulation

Table 1. D-optimal experimental design

| N° | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ |
|---|---|---|---|---|---|
| 1 | -1 | -1 | +1 | -1 | -1 |
| 2 | -1 | -1 | +1 | +1 | -1 |
| 3 | -1 | -1 | -1 | -1 | +1 |
| 4 | -1 | -1 | -1 | +1 | +1 |
| 5 | +1 | -1 | -1 | -1 | -1 |
| 6 | +1 | -1 | -1 | +1 | -1 |
| 7 | +1 | -1 | +1 | -1 | +1 |
| 8 | +1 | -1 | +1 | +1 | +1 |
| 9 | -1 | +1 | -1 | -1 | -1 |
| 10 | -1 | +1 | -1 | +1 | 0 |
| 11 | -1 | +1 | +1 | +1 | 0 |
| 12 | -1 | +1 | +1 | -1 | +1 |
| 13 | +1 | +1 | +1 | +1 | -1 |
| 14 | +1 | +1 | -1 | -1 | 0 |
| 15 | +1 | +1 | +1 | -1 | 0 |
| 16 | +1 | +1 | -1 | +1 | -1 |
| 17 | 0 | -1 | -1 | -1 | 0 |
| 18 | 0 | -1 | +1 | -1 | 0 |
| 19 | 0 | +1 | +1 | -1 | -1 |
| 20 | 0 | +1 | -1 | +1 | -1 |
| 21 | 0 | +1 | -1 | -1 | +1 |
| 22 | 0 | +1 | +1 | +1 | +1 |

Table 2. Inflation factors for the coefficients of the model for the design given in table 1.

| Coefficient | Inflation factor |
|---|---|
| $\beta_1$ | 1.00 |
| $\beta_2$ | 1.07 |
| $\beta_3$ | 1.01 |
| $\beta_4$ | 1.07 |
| $\beta_5$ | 1.00 |
| $\beta_{11}$ | 1.05 |
| $\beta_{12}$ | 1.05 |
| $\beta_{34}$ | 1.00 |
| $\beta_{45}$ | 1.01 |
| $\beta_{55}$ | 1.00 |

Table 3. Levels of process variables selected for the experimental design of table 1.

| | Process variable | Normalised level | Experimental value |
|---|---|---|---|
| $X_1$ | Concentration of binder solution | -1 | 6 % |
| | | 0 | 8 % |
| | | +1 | 10 % |
| $X_2$ | Granulation time | -1 | 2 min |
| | | +1 | 5 min |
| $X_3$ | Residual humidity after drying | -1 | <1 % |
| | | +1 | 2.5 % |
| $X_4$ | Calibration | -1 | 1 mm |
| | | +1 | 2 mm |
| $X_5$ | Lubrification time | -1 | 2 min |
| | | 0 | 6 min |
| | | +1 | 10 min |

conditions but different levels of process variables $X_3$, $X_4$ and $X_5$ are not independent. This is likely to have the effect of artificially improving the repeatability of the experiment (1), and is likely to make interpretation of the statistical significance of the results difficult. This is another consequence of the restricted amount of drug substance available.

Seven response variables were chosen.

$Y_1$ : Particle size distribution before tableting, (percentage of fine particles less than 125 mcm diameter).

$Y_2$ : Compression characteristics.

$Y_3$ : Appearance of the tablets.

$Y_4$ : Disintegration time.

$Y_5$ : Dissolution rate.

$Y_6$ : Friability (loss of weight).

$Y_7$ : Friability (% broken tablets after test).

The coefficients of the model could be estimated for each of the response variables. The coefficients $b_i$ represent the estimation of the main effects $\beta_i$ of the factors $X_i$. Similarly $b_{ii}$ represent the estimations of the second order effects $\beta_{ii}$ and $b_{ij}$ the estimations of the interactions $\beta_{ij}$ between $X_i$ and $X_j$.

## RESULTS

The responses $Y_1$ to $Y_7$ were analysed by regression analysis according to the proposed model. The results are given in table 4. We can see that the concentration of the granulating agent ($X_1$) and the granulation time ($X_2$) have a major effect on most of the response factors. Some second order effects and interactions are important. A number of methods are available for determining optimum conditions for manufacturing (4, 9): direct methods such as simplex and non-direct methods requiring a mathematical model to be postulated, including response surface analysis, canonical analysis, and ridge analysis. In

Table 4. Model parameter estimates.

| | $Y_1$ Particle size | $Y_2$ Compression | $Y_3$ Appearance | $Y_4$ Disintegration | $Y_5$ Dissolution | $Y_6$ Friability (weight loss) | $Y_7$ Friability (broken tablets) |
|---|---|---|---|---|---|---|---|
| $b_0$ | 66. | 4.65 | 3.57 | 7.63 | 15.3 | 0.66 | 15.1 |
| $b_1$ | **23.3** | **0.56** | **1.69** | **-3.59** | **-3.4** | -0.30 | **-10.6** |
| $b_2$ | -4.1 | **-0.27** | 0.04 | **1.64** | **1.3** | 0.16 | **7.2** |
| $b_3$ | 1.8 | -0.06 | 0.00 | **-0.61** | -0.04 | -0.13 | **-8.1** |
| $b_4$ | -2.7 | -0.14 | -0.12 | -0.18 | 0.35 | 0.20 | 0.3 |
| $b_5$ | 2.5 | 0.12 | 0.12 | 0.56 | -0.32 | 0.00 | -0.3 |
| $b_{11}$ | -8.9 | **-0.66** | **-0.40** | -0.39 | 0.51 | 0.20 | -4.9 |
| $b_{55}$ | **-15.7** | **0.59** | **-0.65** | 0.64 | 0.00 | **-0.72** | **8.9** |
| $b_{12}$ | 0.0 | **0.44** | 0.19 | **-0.75** | **-2.31** | -0.32 | 3.1 |
| $b_{34}$ | 1.1 | -0.14 | 0.00 | 0.22 | -0.43 | -0.14 | 1.1 |
| $b_{45}$ | -0.8 | 0.00 | 0.12 | 0.19 | -0.30 | 0.00 | -0.3 |

The coefficients of the model having the greater influence for each response are given in emphasised type. The data are not analysed for statistical significance because the experiments resulting from a single granulation are not independent.
The coefficients are calculated using the coded values of the process variables $X_i = -1, 0, +1$.

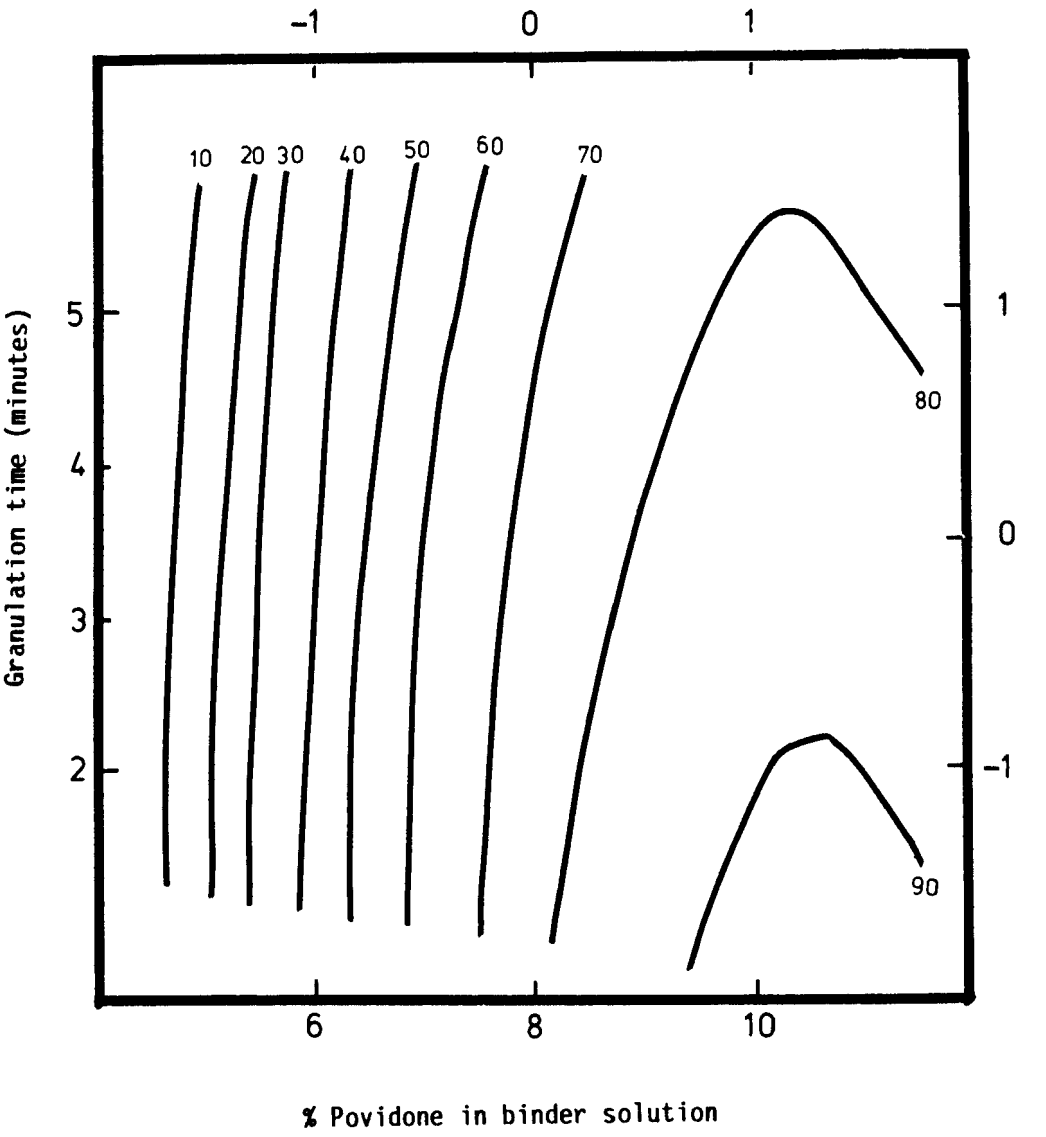


Figure 2 - Particle size of granulate after lubrification (% by mass less than 125 µm diameter) as function of granulation time and concentration of binder.

Humidity = 2.5 %
Calibration = 1 mm
Lubrification = 6 min

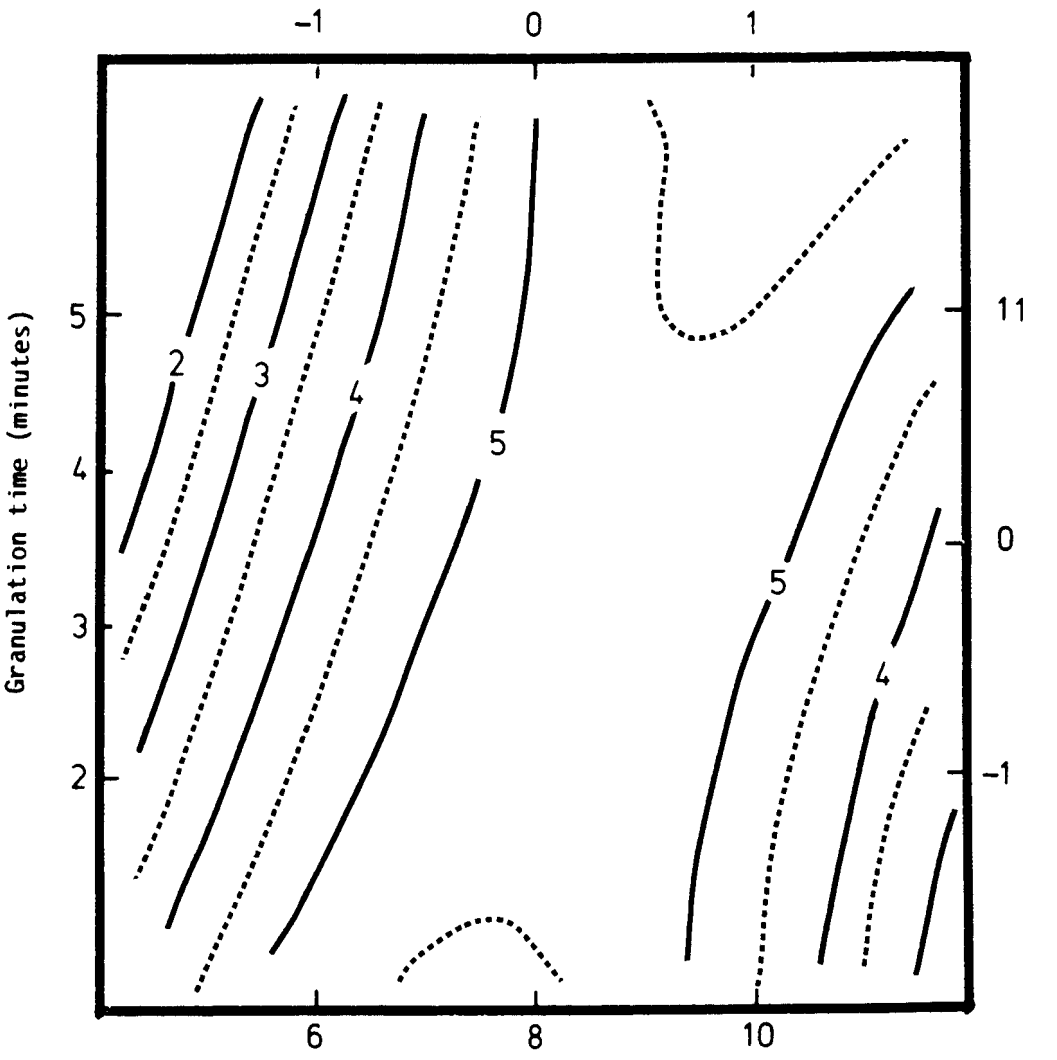


Figure 3 - Compression characteristics of granulate
(1 = poor 5 = good)

Humidity = 1.5 % (level 0)
Calibration = 1 mm
Lubrification = 6 min

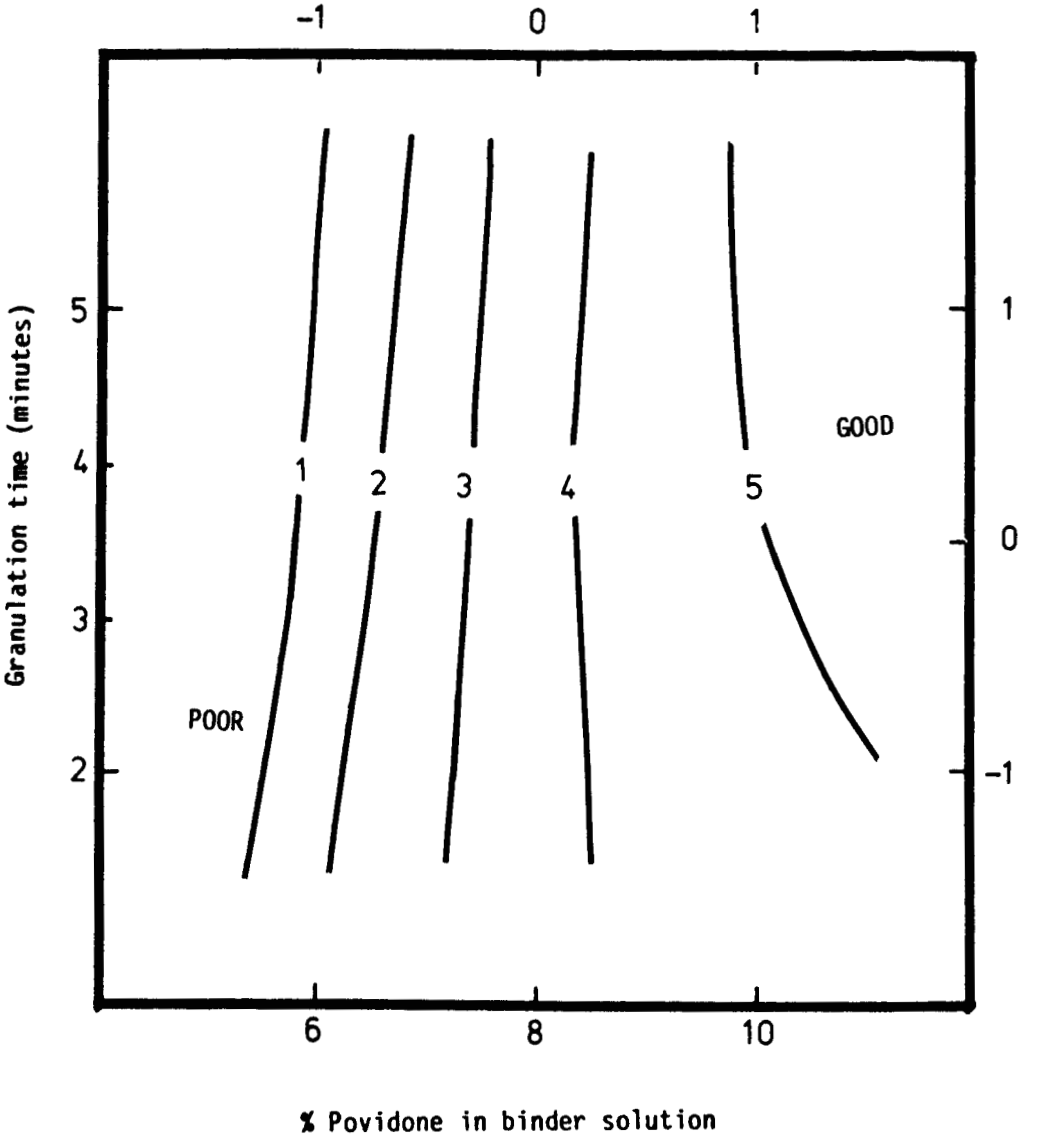


Figure 4 - Appearance of tablets as function of granulation time and concentration of binder.

Humidity = 1.5 % (level 0)
Calibration = 1.5mm (level 0)
Lubrification = 6 min

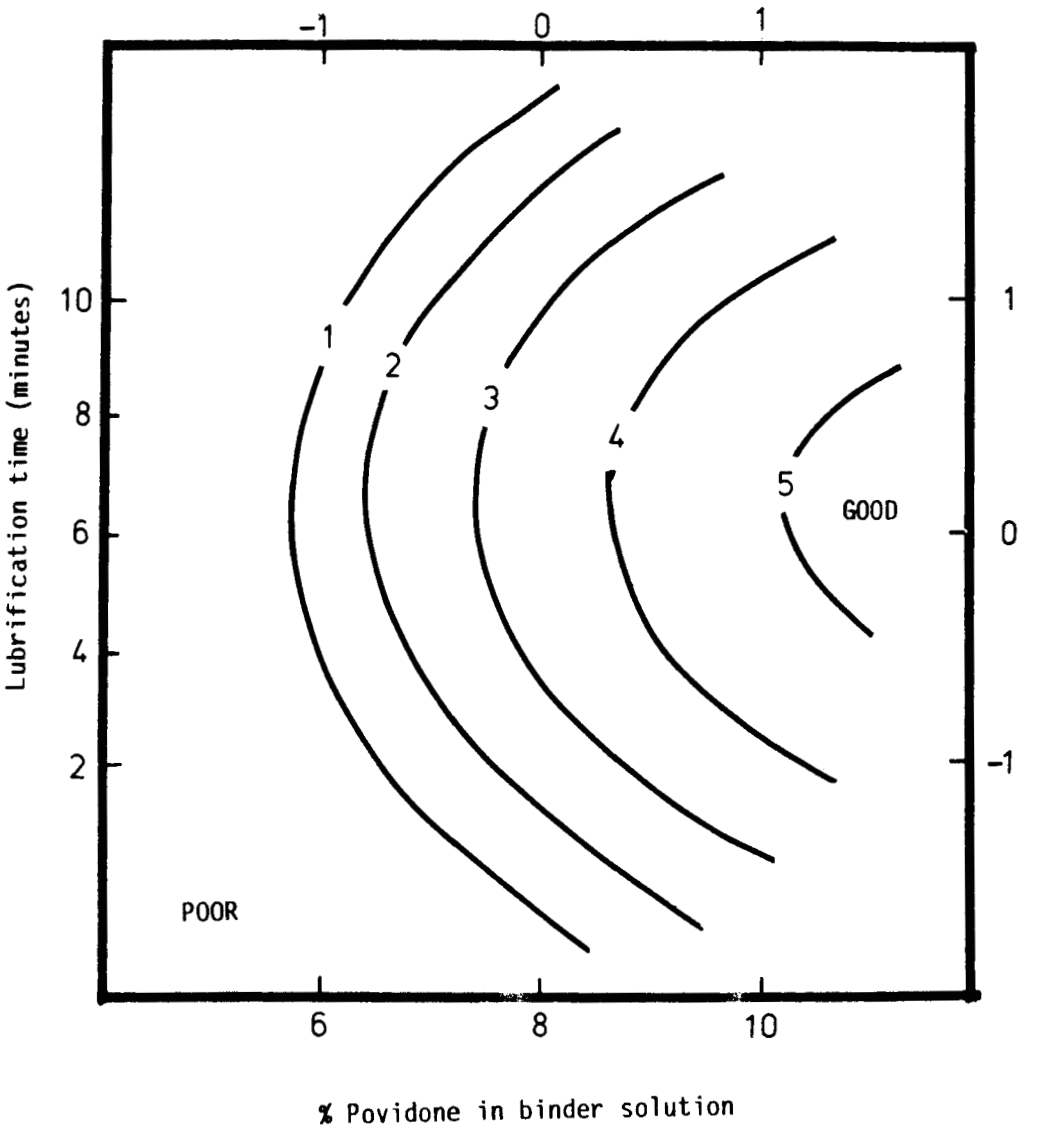


Figure 5 - Appearance of tablets as function of lubrification time and concentration of binder.

Granulation time = 3.5 %
Humidity = 1.5 % (level 0)
Calibration = 1.5 mm (level 0)

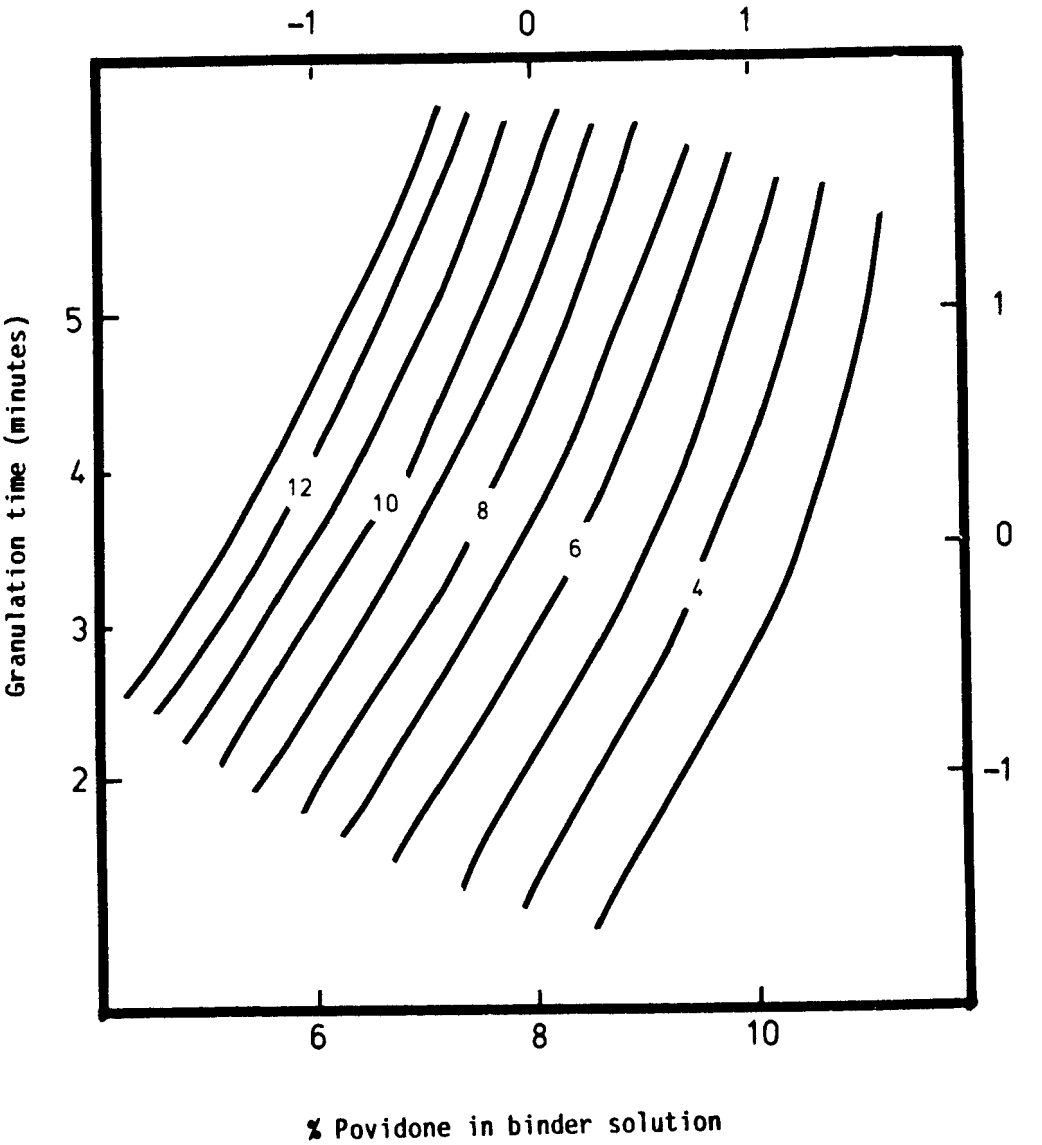


Figure 6 - Disintegration time in minutes as function of granulation time and concentration of binder.

Humidity = 2.5 %
Calibration = 1.5 mm (level 0)
Lubrification = 10 min

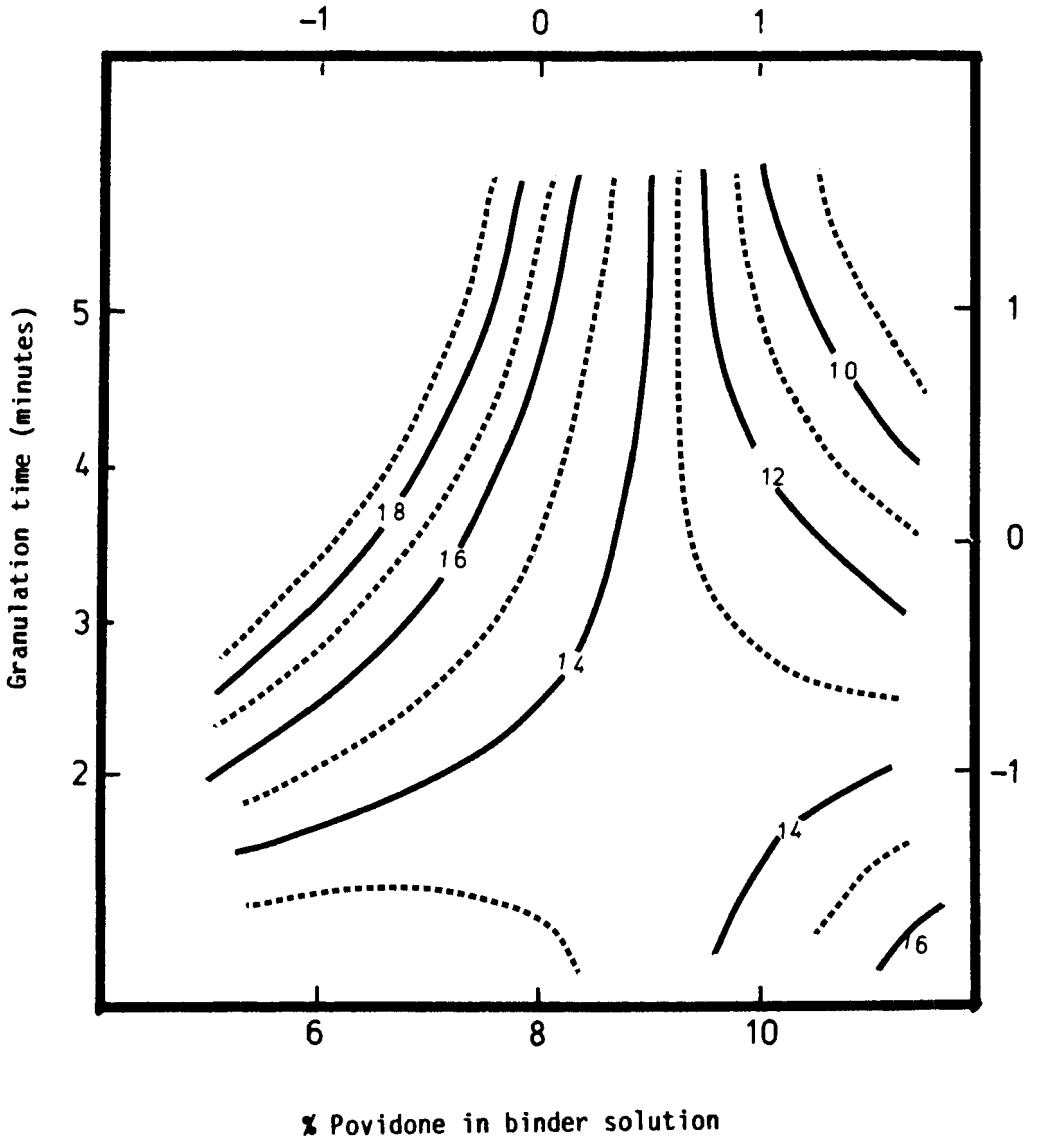


Figure 7 - Dissolution time as function of granulation time and concentration of binder. (Time for 75 % dissolution, in minutes)

Humidity = 1.5 % (level 0)
Calibration = 1.5 mm (level 0)
Lubrification = 6 min

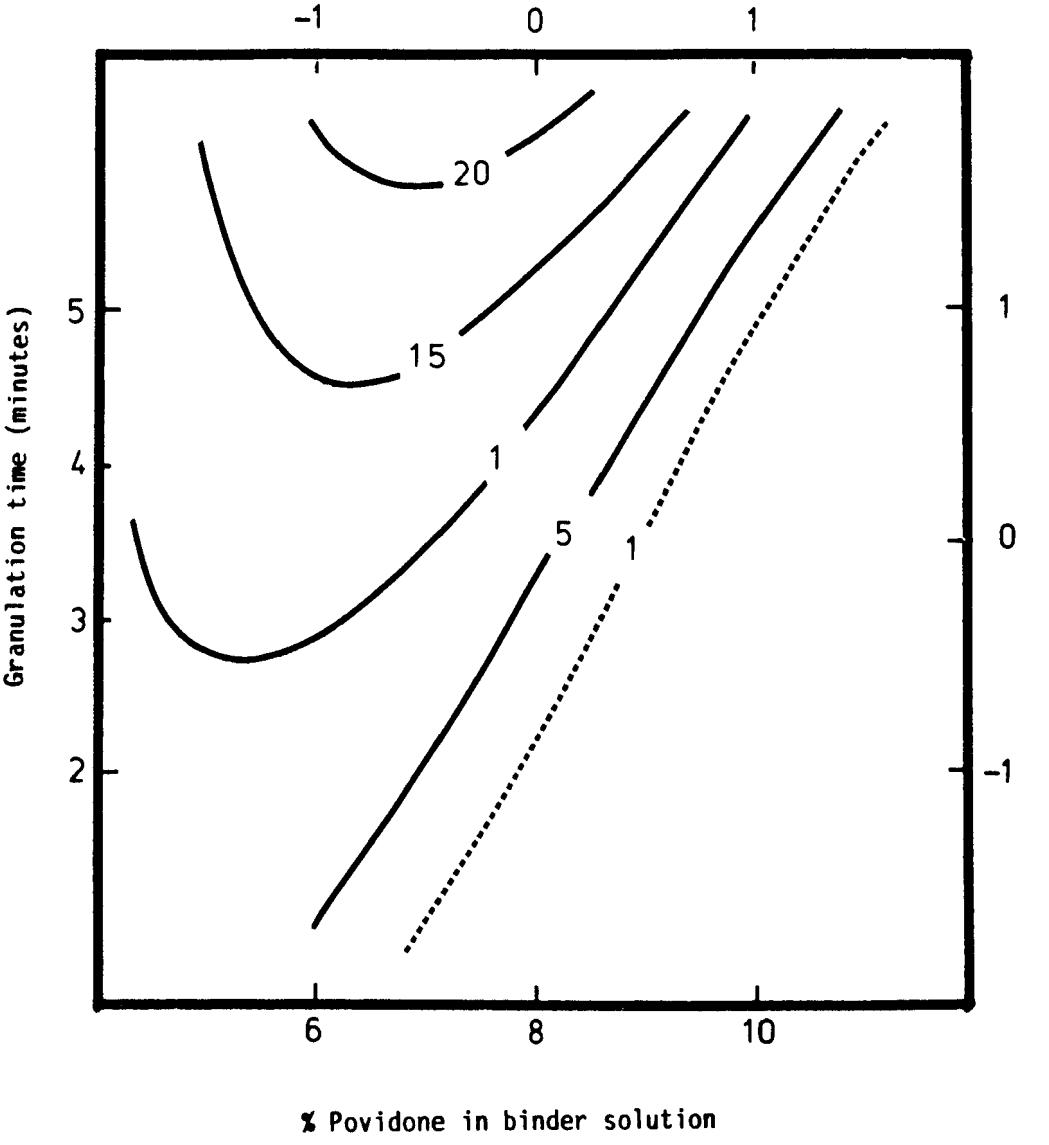


Figure 8 - Friability -(% of broken tablets after test)- as function of granulation time and concentration of binder.

Humidity = 2.5 %
Calibration = 1.5 mm (level 0)
Lubrification = 6 min

Table 5. Choice of optimum conditions

| Process variable | Optimum zone | Conditions for 50L & 130L batches |
|---|---|---|
| $X_1$ : concentration of the granulating agent | > 8 % | 9 % |
| $X_2$ : granulation time : | < 3.5 min | 3 min |
| $X_3$ : humidity after drying | 2.5 % | 2.5 % |
| $X_4$ : calibration : | 1 mm | 1 mm |
| $X_5$ : lubrification time : | 6 min | 6 min |

Table 6. Results for "optimal" conditions.

| Responses | Experimental results | | Theory |
|---|---|---|---|
| | 50L batch | 130L batch | |
| Particle size % less than 125 mcm | 83% | 86% | 80% |
| Compression | 5 | 5 | 5 |
| Appearance of tablets | 5 | 5 | 5 |
| Disintegration | 7 min | 4 min | 6 min |
| Time for 75% dissolution | 14.5 min | 11 min | 16 min |
| Friability (% loss of weight) | 0.16% | 0.49% | 0.37% |
| Friability (% broken tablets) | 0 | 0 | 0 |

this case response surfaces were drawn over the experimental factor space using the program NEMROD, (5, 6). Examples are given in figures 2 to 6.

Superimposing the graphs obtained for the different responses gave an optimum zone (table 5). A batch of tablets was manufactured at the same scale as the factorial study using conditions within this optimum zone, also given in table 5. The properties of the granulate and the tablets were measured as before.

The same conditions were used for the manufacture of a larger batch using a 130L mixer.

The results for both batches are given in table 6 where they are compared with the theoretical responses calculated from equation 1 and the estimates of the coefficients in table 4. The optimum that had been determined at 50L proved suitable, though not necessarily optimal, for scaled up manufacture at 130L. It would normally be possible to correct for problems on scale up using the information already obtained on the influence, and interactions of the process variables at a smaller scale.

## CONCLUSION

D-optimal experimental designs obtained using exchange algorithms are useful in pharmaceutical process characterisation and optimisation, in particular where there are restrictions in the amount of raw material or in the number of times a given stage of the process may be carried out. The method is also to be recommended when we use mixed models, at different numbers of levels, and where certain combinations of factors are not experimentally feasible, and can be used for a more rational choice of experiments at each stage in a sequential approach to problem solving.

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## APPENDIX: Exchange Algorithms

It is not always possible to use a "classical" experimental design, as for example in the following cases:

- for a postulated mathematical model which is not symmetric in all the variables,
- restrictions in the experimental zone (restrictions in the proportions allowed of certain constituents for mixtures, impossibility of combining certain factors, etc),

- economic factors, differences in cost of individual experiments,
- ability to use experiments already carried out as part of the design.

In these cases and in certain others it is possible to use exchange algorithms (7, 8, 10).

The conditions required to use these algorithms are the following:

- postulation of a model (assumed here to be a polynomial).
- it is wished to determine the coefficients of the equation of this model within a fixed experimental factor space. Contrary to normal practice this factor space must be expressed in terms of a list of N possible experiments.

Let N be the number of experiments in the final experimental matrix. We select the n experiments which are the most representative of the experimental space, that is to say those which give the most information. The iterative process consists of three main steps:

- initialisation: random selection of n experiments from the total set of N candidate points, to construct an initial matrix.
- progression: determine the experimental point in the matrix which gives the least information and exchange it for the candidate point which gives the most information.
- continue this process until the exchange no longer improves the quality of the design.

The criterion for assessing the quality of the matrix, is termed D-optimality:

Let p be the number of coefficients in the postulated model and X the model matrix, consisting of n lines corresponding to the n experiments and p columns corresponding to the p variables of the model. Let Y be the vector of n lines, describing the experimental results for each experiment. The coefficients of the model can be estimated by the least squares method, according to the formula:

$$B = (X'X)^{-1} X'Y$$

where B is the vector of the p estimates of the coefficients

X' is the transpose of the model matrix X

X'X is the information matrix

$(X'X)^{-1}$ is the inverse of the information matrix and is known as the dispersion matrix.

It may be shown (11) that the precision of the coefficients increases with the determinant of X'X. An experimental matrix of N experiments is termed D-optimal when the experiments are chosen so that det(X'X) is maximal. Maximising this determinant is equivalent to minimising the determinant of the variance-covariance matrix of B. Det(X'X) maximisation gives low values for the variances and covariances of the model parameter estimates. It is this criterion which is used in the exchange algorithm method and which enabled us to construct the experimental design given in table 1. A single iteration in the algorithm corresponds to the exchange of two experiments which increases det(X'X) by the greatest amount.

The determinant of the information matrix increases with the number of experiments. However the increase in the precision of estimation of the coefficients does not necessarily justify carrying out extra experiments. A useful parameter in making this judgement is the D-efficiency of the experimental matrix, which is a measure of the amount of information per experiment and which enables us to compare matrices which consist of different numbers of experiments.

It is defined as:

$$D\text{-eff} = \det(M) \times 100$$

where M, the normalised information matrix, is equal to $1/n\ (X'X)$

It follows that:

$$\det(M) = \det\ (X'X)/n^p$$

We consider therefore that the optimum matrix with respect to the above criterion of efficiency, provides the best precision per experiment for estimation of the coefficients.

Values of D-eff are plotted in figure 1, and on this basis we could have selected the matrices for either 22 or 28 experiments. Taking into account the time required and the amount of material available we selected the former.