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USE OF STATISTICAL EXPERIMENTAL DESIGN IN LABORATORY SCALE FORMULATION OPTIMISATION AND PROGRESSION TO PLANT SCALE

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ABSTRACT

The objective of these studies was to optimise the formulation of a dry powder blend to be filled into hard gelatin capsules and progress the product to plant production. The blend was to contain two active compounds (500mg active A and 10mg active B). Preliminary work had limited the independent formulation variables to levels of filling aid, glidant and lubricant. The effects and interactions of the independent variables were assessed using an augmented factorial experimental design demanding the examination of 31 formulations at small scale (less than 3kg). Critical dependent variables identified were blend homogeneity and flow, capsule weight variation and active dissolution rate.

The study plan was to assess blend flow and active dissolution using formulations manufactured at laboratory scale (less than 3kg), select the optimum formulation, confirm the data and determine blend homogeneity at development scale (upto 30kg) and progress to pilot plant production (250kg).

Statistical software was employed to fit response surfaces to optimisation data and generate 3-dimensional plots which were used to assess interactions of excipients and effects on

dependent variables. From the 3-dimensional plots it was possible to estimate maxima and minima on the response surfaces enabling selection of optimum combinations of excipients. Using this technique a formulation has been devised which has now been successfully manufactured at development and plant scale. Results obtained at laboratory, development and plant scale were compared and found to be not significantly different.

A comparison of estimated resource expenditure indicated that a conventional approach would have required approximately 350 man hours less than the statistical approach. However, using a conventional approach there is a higher risk of production batch failure, rework or troubleshooting exercises resulting in estimated equivalent losses of 350, 250, and 100 man hours respectively.

The statistical approach is proposed as an aid to formulation optimisation and has several advantages in providing an improved data base, ensuring product robustness, giving higher quality assurance and facilitating troubleshooting. In addition, careful experimental design permits accurate resource estimation and allocation with known gains.

INTRODUCTION

Successful pharmaceutical product development is very often dependent on the ability of the scientist to balance variables in a system to achieve satisfactory product parameters. For example, formulation variables may be adjusted to achieve maximum tablet hardness but at the expense of high disintegration time and a compromise may have to be sought. Final product should ideally be an optimum in many respects such as product parameters, materials (both in quantity and quality) and processing costs. It is important therefore to know which variables are critical to the process and fully understand the consequences of changing system variables particularly in terms of effects on important product parameters.

Traditionally, pharmaceutical scientists presented with the problem of developing a formulation or process rely upon experience to devise potential solutions. Certainly, experience with similar products is a key factor in devising product variants or line extensions, particularly if, as is so often the case, development time is restricted. The result is that new products may be developed rapidly but, particularly if based on old products, may retain any defects or problems inherent in the old product. In addition, this approach does not lend itself to the use of novel excipients or techniques.

Subsequent optimisation of that formulation or process, if carried out at all, would be performed by varying one of the parameters at a time whilst keeping all other parameters constant. This approach has the advantage that it may often prove to be a rapid means of product development. However, this empirical approach has a number of disadvantages which result from a lack of understanding or depth of knowledge about the process or product. Product optimisation using an empirical approach is difficult, time consuming and although the final product may be satisfactory it may well be sub-optimal. In addition, changes made to more than one variable may have a compounding effect not immediately apparent and an empirical approach cannot reveal any information on this common problem of variable interaction.

A statistical development approach has been available for some years and has been used by workers in other fields such as chemistry[1], agriculture[2] and engineering[3]. Pharmaceutical scientists are increasingly realising the potential of using a statistical approach to product development which is recognised by many as the most efficient means of generating information needed to understand the effects and interactions of variables[4-7]. Other advantages of a statistical approach include the neccesity for rigorous planning before starting experimental work which leads to improved resource estimation and allocation.

In addition, the generation of an improved data base may facilitate troubleshooting, should it become necessary.

Statistical techniques, until recently, have been difficult to apply, requiring total involvement of a statistician and long hours of manual calculations and graph plotting. Recent advances in computing have facilitated the use of a statistical approach by eliminating manual calculations and automating the production of graphics, leading to easier understanding of the techniques involved. 'User friendly' software systems are now available which assist the formulator in development planning, experimental design and data analysis. Such software systems enable the statistician to make most efficient use of his/her time by keeping involvement to a minimum whilst retaining input essential to the accurate interpretation during data analysis. To maximise the benefit from this approach it is important that the statistician and pharmaceutical scientist collaborate from the initiation of a project throughout planning and data analysis.

A discussion of the many optimisation techniques available to the pharmaceutical scientist is not within the scope of this paper and the reader is directed to published texts for further information[8-9]. The following however is presented as a general guide to the stages involved in planning studies using statistical experimental design :

1. Accurately define the problem.
2. Identify the independent variables and possible ranges.
3. Decide the purpose of the study - if the objective is to optimise a large number of independent variables it will be necessary to perform a preliminary 'screening' study. This will allow a reduction in the number by identifying those not critical to the system.
4. Identify the dependent variables to be measured.
5. Select a mathematical model (linear, quadratic for example) which best describes the relationship between the independent and dependent variables.
6. Provide an estimate of the experimental error.

7. Select a suitable design. That is ; decide which combinations of independent variables are to be examined. A number of classical designs exist which will facilitate data analysis.
8. Perform the requisite number of experiments.
9. Analyse the data and produce optima - this has been facilitated by recent advances in computer technology and software.

This paper reports the use of the above described statistical experimental design technique in the optimisation of a formulation at laboratory scale and the results obtained on subsequent scale up.

OBJECTIVE AND PLAN

The objective of this study was to optimise the formulation of a dry powder blend to be filled into hard gelatin capsules and progress the product to plant production. It was the intention that statistical experimental design should be used to facilitate optimisation of the formulation. In addition, the final product was to be robust enough to ensure successful transition from laboratory to development and pilot plant scale.

The development plan was to define an outline formulation, based on marketing requirements and previous experience, and identify and optimise formulation variables at laboratory (less than 3kg) scale. Results were to be confirmed at development scale (30kg) and the optimum formulation progressed to pilot plant production (250kg).

Selection of Variables

Marketing restrictions were that the product was to contain two actives (500mg active A and 10mg active B) and excipients as deemed necessary to facilitate filling into a size 0 hard gelatin capsule. Active A was obtained with a median particle size diameter of 180micron to optimise capsule filling and dissolution

rate. Active B was available in only one particle size grade with a median particle diameter of 35micron.

Previous experience with similar products had identified filling aid, lubricant and glidant to be potential excipients. Preliminary work limited these independent formulation variables to ; maize starch (0-100mg per capsule), magnesium stearate (0-8mg per capsule) and colloidal silicon dioxide (0-2mg per capsule). Blending time was selected as the independent process variable likely to have most effect on the final product. The effect of blending time on the homogeneity of active B was therefore examined.

Blend homogeneity was considered to be an important dependent variable because of the unavoidable disparity between quantities and particle size diameters of the active compounds. It was also considered that blend flow would have a significant effect on capsule weight variation. In addition, active dissolution rate from filled capsules was known to be important in determining the bioavailability of the actives. Therefore, blend flow and homogeneity, capsule fill weight and active dissolution rates were selected as dependent variables most likely to indicate satisfactory product behaviour.

Experimental Design

A statistician was consulted and an augmented full factorial experimental design was drawn up to assess the effects and interactions of the independent variables. The design required the manufacture of 31 formulations. Essentially, for each level of colloidal silicon dioxide (0 and 1mg per capsule), each level of starch (0,50 and 100mg) was combined with each level of magnesium stearate (0,1,2,4 and 8mg). An additional experiment was carried out to examine the effect of using 2mg colloidal silicon dioxide per capsule. The combinations of excipients examined are given in Table 1.

The workload was further reduced by initially examining only blend flow and active dissolution rate. Formulations selected as acceptable at this stage were progressed to full testing. Examination of results then permitted the selection of an optimum formulation which was fully tested at each stage of scale up (30kg and 250kg).

Resources Comparison

To investigate further the advantages and disadvantages of empirical and statistical approaches, estimates were made of the resource expenditure in developing a product from project brief to pilot scale production. Estimates included allowances for planning, formulation development, quality control, statistical analysis and normal production time losses during scale up and possible rework.

MATERIALS AND METHODS

Materials

Actives A and B were supplied through Sterling Drug Inc. and Sterling Research Group respectively. Maize starch was supplied by Cerestar, Trafford Park, Manchester UK to European Pharmacopoeial specification. Magnesium stearate was obtained from Durham Chemicals Ltd., Birtley, Durham, UK and conformed to European Pharmacopoeial specification. Colloidal silicon dioxide (Aerosil 200) was supplied by Ellis and Everard Chemicals, Wallsend Road, North Shields, Tyne and Wear, UK to United States Pharmacopoeial standard.

Manufacturing method

The following general method was used to manufacture all the formulations.

Active A was passed through a 1000micron sieve into a suitable blender (Apex blenders were used at 3kg and 30kg and a Buls bin blender at 250kg). Active B and maize starch were passed through a 500micron sieve into the blender and the powders mixed for 10 minutes. Magnesium stearate and colloidal silicon dioxide were passed through a 500micron sieve into the blender and the powders mixed for a further 2 minutes. The blended powders were sampled in duplicate and discharged into suitable containers to await analysis prior to capsule filling.

The blend was filled into size 0 hard gelatin capsules using an Hoffliger and Karg model 330 capsule filler fitted with 36 stations and run at a speed of 2000 capsules per hour. Capsules were dedusted and polished (Maschimpex) prior to checkweighing manually (Sartorius balance) at small scale and automatically (Vericap) at large scale.

Analytical Methods

Blend flow was determined by measuring angle of repose and powder consolidation rate. Angle of repose was determined by allowing powder (50g) to flow through a 60° stainless steel funnel suspended 10cm above a flat, level surface. Height (h) and diameter (d) of the powder cone were measured and the slope angle (angle of repose) calculated using the equation : angle of repose = arctan(h/0.5d). An angle of 40° was chosen as minimum for acceptable flow.

Powder consolidation rate was determined by a modification of the method of Hill and Wicks [10] in which a sample of blend (100g) was compacted in a Radon tap density apparatus. The density of the powder bed was measured at intervals of 5 taps for up to 50 taps and a curve drawn representing blend density versus number of taps. A curve of general equation $y = C(1-e^{-rt})$ was fitted to each set of data and the coefficients C and r determined. The coefficient of line curvature (r) was taken to represent the rate of compaction and therefore as an indicator of flow.

Blend homogeneity was determined on duplicate samples taken from top, middle and bottom of the blender. An assay limit of 100%±5% was set.

Analysis of actives was performed using validated HPLC methods. Similarly, individual capsule (n=5) assay was performed using validated HPLC methods.

Dissolution was performed using Hewlett Packard automated dissolution testing apparatus according to the capsule method described in USP XX1. The amount of actives A and B dissolved was determined at 5 minute intervals up to 45 minutes and graphs plotted of percentage drug dissolved with time. Non-linear curve fitting techniques were used to fit profiles to the dissolution data using the equation $y = Q(1-e^{-kt})$. The coefficient of line curvature (k) was taken as a single figure representing the rate of dissolution. A value of 0.05 roughly equated to an acceptable dissolution rate by USP standards : not less than 75% (Q).

Statistical Analysis

Multiple linear regression analysis was performed with the aid of the REG and RSREG procedures in SAS. This allowed the examination of linear and quadratic effects for silicon dioxide and starch and cubic effects for magnesium stearate, together with two factor interactions. An orthogonal transformation was performed. Response surfaces were fitted for angle of repose and dissolution coefficient relating both to the dependent variables (silicon dioxide, starch and magnesium stearate).

Optima were determined with the aid of the RSREG procedure and 3-D graphics generated with the aid of SAS/GRAPH software.

RESULTS

Results are presented in two sections relating to the optimisation studies performed at laboratory scale and those obtained on larger development and pilot plant scale.

TABLE 1

Combinations of Excipients Examined

Variables Combined at Levels Indicated (mg/capsule)			Number of Combinations
Colloidal Silicon Dioxide	Maize Starch	Magnesium Stearate	
0	0	0,1,2,4,8	5
0	50	0,1,2,4,8	5
0	100	0,1,2,4,8	5
1	0	0,1,2,4,8	5
1	50	0,1,2,4,8	5
1	100	0,1,2,4,8	5
2	50	2	1

Formulation Optimisation (Laboratory Scale)

During the optimisation study formulations were manufactured at upto 3kg scale according to the method outlined above and the protocol given in Table 1. Results of flow determination and dissolution were analysed and response surfaces plotted.

Figure 1 illustrates the response surface obtained for angle of repose with combinations of filler and lubricant in the absence of glidant. Values obtained ranged from 33° to 54° with the majority of the surface above an angle of 40° indicating unacceptable flow. Only at combinations of 0mg filler and 2-8mg lubricant was the flow acceptable. The addition of glidant (1mg per capsule) to formulations caused a reduction in angle of

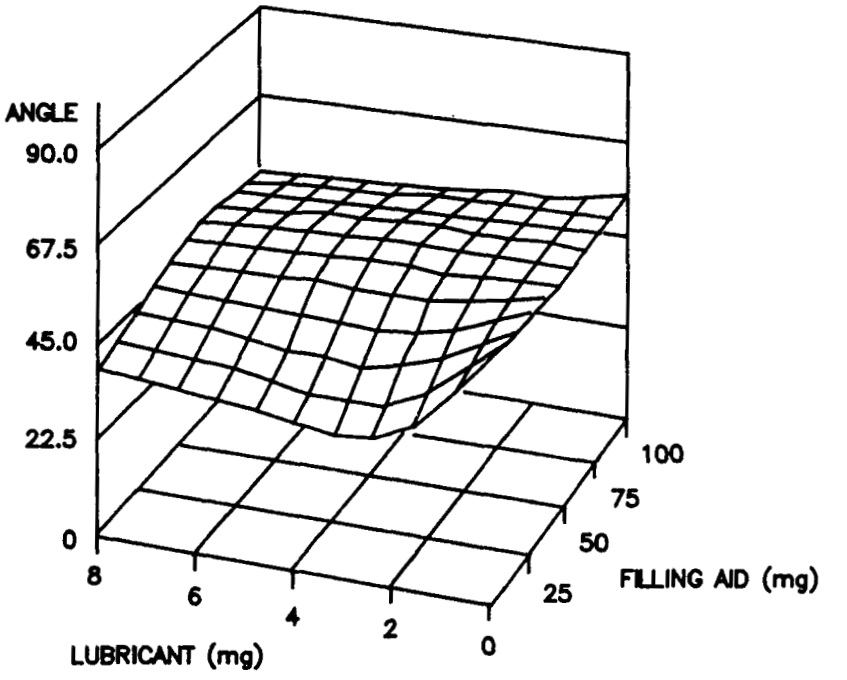

FIGURE 1

Response Surface for Angle of Repose Versus Lubricant and Filling Aid.
(Glidant Absent)

repose over the entire response surface (Figure 2). Values obtained were between 26° and 40° indicating acceptable flow for all combinations of filler and lubricant. Response surfaces obtained for powder consolidation results were similar in profile to those obtained with the angle of repose, confirming the effectiveness of the glidant. Because of the close similarity of the profiles, only angle of repose data are presented.

Figure 3 illustrates the response surface obtained for dissolution coefficient (k) with combinations of filler and lubricant in the absence of glidant. Values obtained ranged from 0.034 to 0.085 with many values below 0.070 indicating slow

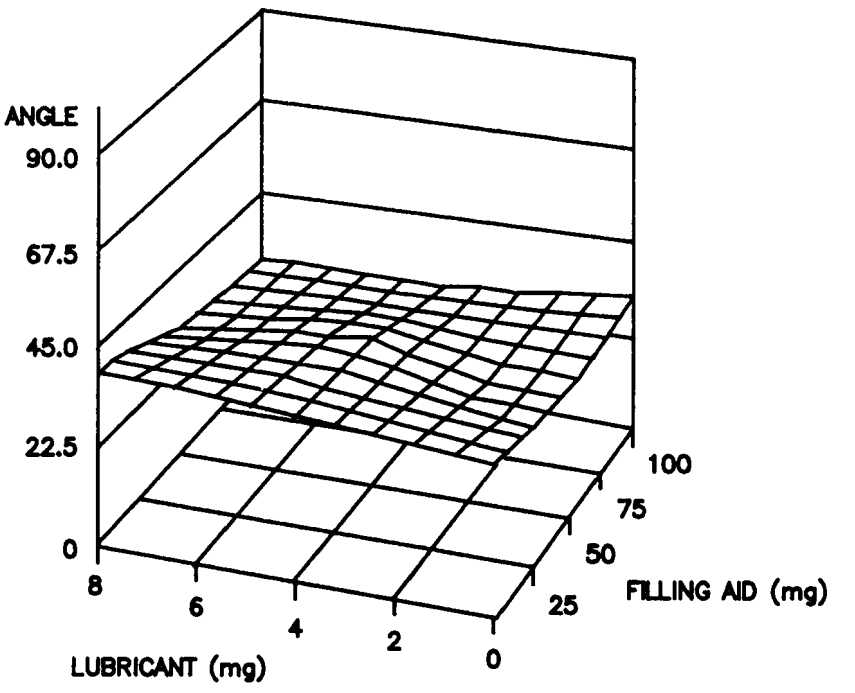

FIGURE 2

Response Surface for Angle of Repose Versus Lubricant and Filling Aid
(Glidant Present at 1mg Per Capsule)

dissolution. In particular, capsules produced with combinations of excipients at the corners of the response surface exhibited coefficient values less than 0.05 and failed to meet USP limits. The addition of glidant (1mg per capsule) to the formulations increased the dissolution rate such that all combinations exhibited dissolution coefficients above 0.05 and passed USP test. Many coefficient values, particularly those obtained with low levels of lubricant, were in excess of 0.1 indicating rapid dissolution. The shape of the response surface obtained (Figure 4) illustrates the complex interaction between filler and

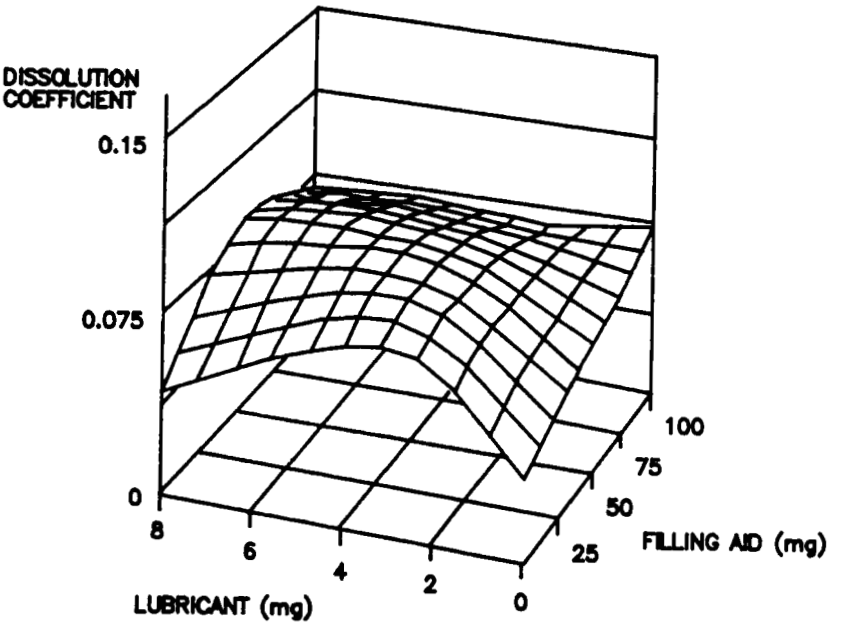

FIGURE 3

Response Surface for Dissolution Coefficient Versus Lubricant and Filling Aid (Glidant Absent)

lubricant. The addition of 2mg glidant to the formulation had no beneficial effect on dissolution above that seen with 1mg per capsule.

The above results indicated that a product containing excipients within the following ranges would prove acceptable in terms of flow and dissolution : 10-90mg filler, 2-6mg lubricant and 1mg glidant. The optimum glidant level (1mg per capsule) was therefore fixed for all future work and a lubricant level of 2mg was chosen to minimise product cost.

Three formulations : 0,50 and 100mg filler plus 2mg lubricant and 1mg glidant were chosen for further examination

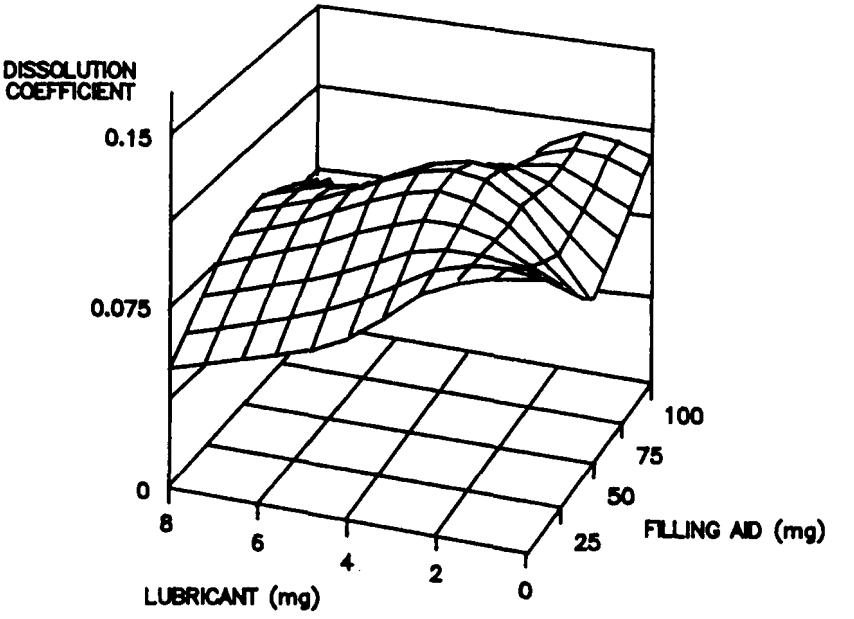

FIGURE 4

Response Surface for Dissolution Coefficient Versus Lubricant and Filling Aid
(Glidant Present at 1mg Per Capsule)

including process optimisation studies. Analysis of blend samples taken from the mixer at 1, 2, 5, 10, 15, and 20 minutes indicated acceptable homogeneity of actives (99-102±1%) at all times greater than 5 minutes for formulations containing 50 and 100mg filler and 10 minutes for 0mg filler. Ten minutes blending time was chosen for all future work. Capsules filled with the above three blends demonstrated acceptable fill weights (99±3%) and dissolution rates (88-94% dissolved at 45 minutes). In comparison with the use of 0mg filler, formulations containing 50-100mg demonstrated shorter time to homogeneity and higher dissolution rates (Figure 4) and a level of 87mg filler was chosen for the

final formulation to bring the total capsule fill weight to 600mg.

The following formulation was, therefore, selected as optimum and progressed to scale-up:

Active A	500mg
Active B	10mg
Filler	87mg
Lubricant	2mg
Glidant	1mg
Total	600mg

Plant Scale Up

The above optimised formulation was manufactured at 30kg scale. Results of analyses (Table 2) indicate acceptable blend flow ($33\pm1^{\circ}$ angle of repose), capsule fill weight ($100\pm1\%$), assay (99-100$\pm$2% for both actives) and dissolution rate (87-89% dissolved in 45 minutes). Optimum blending time was confirmed as 10 minutes.

The product was manufactured at 250kg scale and results of analysis (Table 2) were similar to findings at 3kg and 30kg scale confirming acceptable formulation and process.

Resources Comparison

Resource estimation indicates that the statistical approach required a total of 850 man hours in comparison with 500 man hours for an empirical development. However, optimisation has given rise to a formulation which is known to be robust and unlikely to be affected by minor changes in material or process parameters, such as mixing time or excipient quality. The product is unlikely therefore to be the subject of plant batch failure and subsequent rework procedure. Had the product been developed using the empirical approach it would have been more likely to

TABLE 2

Results of Blend and Capsule Analyses

Formulation Manufactured at 3kg, 30kg and 250kg scale

Parameter	Target Value	Result at each scale (mean ± c of v) 3kg	30kg	250kg
Blend Homogeneity (% Active B)	100±5%	99±2	99±3	99±3
Blend Flow (angle of repose	less than 40°	30±1	34±2	28±2
Capsule Weight (% theoretical)	100±5%	100±2	103±2	100±2
Active Dissolution (% in 45 minutes)	not less than 75% (Q)	96±6	93±9	86±8

exhibit problems at plant scale for which the estimated resource expenditure is from 100 man hours for a troubleshooting exercise to 350 man hours, or the equivalent, for the loss of one production batch.

CONCLUSION

Using statistical experimental design and analysis, a product was developed at laboratory scale (3kg) with a formulation and process known to be optimum in terms of product acceptability and cost. The database generated was considerable,

providing valuable information on product robustness. No problems were encountered on increasing batch size to development (30kg) and pilot plant (250kg) scale and results of analyses confirmed findings at laboratory scale.

A number of advantages of a statistical approach were highlighted during this study. Formulation optimisation using statistical design demands that the scientist spends time carefully planning development work prior to starting experimentation. This detailed planning, in collaboration with a statistician ensures that all relevant factors are taken into account and little is therefore left to chance. Resource requirements can be estimated and allocated from the outset permitting accurate development programmes to be drawn up by all parties involved. Statistical analysis of the data can detect any interactions in the system which would not otherwise be apparent. In addition, it ensures an objective assessment of results obtained. In this respect care should be taken to apply a modicum of common sense in distinguishing between differences which may be statistically significant but not necessarily clinical relevant.

Recognising that the accumulation of data is not a substitute for formulator experience, statistical experimental design and analysis is proposed as an aid to formulation optimisation. For a relatively small initial investment, statistical design and computer aided evaluation of data may contribute to the understanding of formulations and reduce the risk of costly batch failure at plant scale.

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