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THE USE OF OPTIMIZATION TECHNIQUES IN PHARMACEUTICAL DEVELOPMENT

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ABSTRACT

The lecture uses selected examples to illustrate the use of mathematical methods to optimize drug dosage forms:

- -Elucidation of compatibility between active ingredient and excipients required in the preformulation phase by factorial design.
- -Calculation of maximum allowable mean of particle sizes for active ingredient and the sum of auxiliary materials to achieve a sufficient content uniformity by applying the Stange-Pool equation.
- -Application of surface response research for identification of the working point in an "innocuous area of landscape" for scaling ups, handing over to production, of trouble shooting by using central composite desing and in the case of multiple constraints doing computerized grid search.
- -Only mentioned and not described in detail will be the methods for pharmacokinetical optimization, necessary for the development of modified release formulations.

Of course not for every development it is mandatory to use surface response research to get the necessary quality. But it is worthwile to apply refgularly factorial design for compatibility

studies to calculate the necessary particle sizes and to compare in vivo results with dissolution rate data.

INTRODUCTION

How Good Is a Product ?

The quality of a drug is determined by the quality of design, which is the Development Department's responsibility, and by the quality of performance, which is guaranteed by the Production Department.

The following table illustrates the essential parameters of quality :

Physical parameters
- aspect
- hardness
- disintegration
- weight uniformity
- friability

Chemical parameters
- content
- content uniformity
- stability

Pharmacokinetic parameters
- dissolution rate
- bioavailability
- optimal blood level curve

Technical realisation
- equipment worldwide available
- excipients,worldwide available and allowed
- trouble-free production, wolrdwide and in different proportions of volume
- harmless for the environment
- no problems for packaging

Consumers' acceptability
easy to take
appearacance, aspect
packaging comfort and security

It is recognised that the requirements as to quality must be defined numerically and that many criteria of quality have opposing effect on, for example, a solid dosage form: dissolution rate versus hardness and friability. Thus, there is no such thing as the best formulation, for a good formulation is always a tolerable compromise between the quality of each of the parameters.

The individual stages in dosage form development are preformulation of laboratory batches, scaling up of pilot batches, handover procedure to production and dealing with any weak points if there are concealed defects in quality of design, and switching to more efficient machines or modernization (face lifting) of "grandfather" preparations.

I should now like to use selected examples to illustrate how we in Sandoz use mathematical methods to optimize drug dosage forms, within the framework of a worldwide corporate strategy.

An important question in the preformulation phase is the compatibility between the active ingredient and the excipients required. To investigate this, we use radioactive labelled active ingredients and the testing is done with the aid of factorial design.

In the statistical test planning by the factorial design methods, we do not simply alter one factor/time. This enables us to recognise the effects not just of one factor, but also the interactions of two or more factors. This test procedure is highly symmetrical as the illustration of a 2^3 design as a cube shows (2 levels, 3 effets, 2^3 = 8 tests).

Assuming that higher interactions, e.g. the treefold interaction ABC in a 2^3 design (8 tests), are not significant, by confounding, a 4th factor D can be introduced instead of ABC,and

only half the number of tests is required, e.g. 8 instead of 16. Indeed, we use 2^4 designs with confounding of a 5th factor E.

The results are analysed by the Yates method, a very simple type of variance analysis which can be used because the system is orthogonal; this provides a qualitative indication of the significant effects and interactions.

This procedure has for years proved to be superior to the conventional method of testing binary muxtures of active ingredient and each particular auxiliary substance.

The particle size of the active ingredient is a particularly important factor as regards, firstly, the quality of mixing and, secondly,the dissolution rate, bioavailability and toxicology.If micronization is unnecessary for reasons of dissolution rate and bioavailability, then there must be 10'000 equally-sized particles of active ingredient per tablet or capsule if 99.7% of all the units of dosage are to have a theoretical content within the limits of $x \pm 3 \quad = 100 \pm 3$ %. This scatter is caused by purely statistical randomness, it may be calculated by means of the Poisson distribution and it has superimposed upon it practical sources of error such as separation, weight tolerances etc.

Stange and Pool's equation is suitable for selecting the mean values of maximum particle sizes of the active drug and the sum of auxiliary materials required; these values can also be tabulated.

$$W_x = (\Sigma fw)_x = \frac{M^4 \cdot \sigma^2}{D(M-D)^2} - \frac{D \cdot (\Sigma fw)_y}{M-D}$$

$$W_y = (\Sigma fw)_y = \frac{M^4 \cdot \sigma^2}{D^2(M-D)} - \frac{(M-D) \cdot (\Sigma fw)_x}{D}$$

D= mass of component x= dose of active drug
M= mass of dosage form, tablet or capsule
(M-D)= mass of excipients y in one dosage form
(fw)i= weighted mean of particle mass

For scaling up and handing-over, and for subsequent trouble-shooting of ofr work on any weak points, it is desirable to be able to formulate a concept as to the "quality of formulation". For this we can use the methods of surface response research; we employed these in Sandoz at about the same time as our colleagues in MSD, as can be seen by the publications and personal communications and personal communications of Schwarz.

We know from mathematics that at least two points are needed to describe a straight line and at least three points to describe a quadratic function. Therefore if, for example, five factors or process variables are being investigated, for a quadratic model a 3^5 = 243 tests (!) should be employed. However, if we dispense with higher ihteractions of the type $x_1x_2^2$ etc. and confine ourselves to a quadratic mode, then a "central composite design" is the design of choice.

With five test-variables and an abbreviated design, 27 tests are necessary instead of 243, added to which, when devising a central composite design, one starts with a quite normal 2^n factorial design. This design is then expanded, by conducting one test per factor x_i with the extreme values at a distance of $\pm$ alpha from the test centre. In these experiments, the remaining factors are kept constant at level 0 (mean between level + 1 and - 1). At least one further test ib also carried out in the design centre.

The tests are randomized better statistically and carried out in blocks, that is to say starting with the 2^n factorial design, and then the additional tests necessary for constructing the central composite design are performed. The magnitude of alpha depends on the number n of the factors investigated and on whether

it is considered important that the quadratic regression coefficients are also determined independently of the other factors investigated (orthogonality).

After implementing a central composite design with, for example, five factors, with four target parameters (hardness, disintegration time, dissolution rate and friability) four different mathematical morels are obtained. The quality for the model can be estimated from the correlation coefficients of the regression equation and residual is the difference between the measured value and the value of criterion of quality designated on the basis of the mathematical model.

"Carthographic" or three-dimensional perspective diagrams vividly illustrate the dependence of the criteria of tablet quality on the individual factors.

Generally, the true optima for each of the criteria of quality are not in the same place, i.e. not in the same formulation. Therefore, we have to search for a reasonable compromise. Where there are only a few factors, this can be done by superposition of the "carthographic" landscapes; this sets limits on the area of the optimum formulations. Where there are more than two factors,this process becomes laborious and it is more sensible to entrust the task of finding the area of the optimum formulations to a computer. For example, the whole factor test area which is technically feasible can be conceived as a spatial grid, and similarly in the three-dimensional case as a cubic "crystal grid". Each point on the grid then corresponds to a possible formulation and the computer calculates the corresponding values of the target parameter, i.e. the criteria of quality (grid search). By starting with standards, for example hardness 4 kp, friability 1 %, disintegration time 2 min. etc. the area of the optimum formulations is narrowed down and the computer prints out the formulations (grip points) which comply with all the requirements.

The results obtained by mathematical modelling illustrate very clearly and graphically the complexity of multiparameter

tablet formulation. A comprehensive knowledge of the pharmaceutical system (i.e. the "landscapes") provides a means of interpreting the various "pharmaceutical" effects, whichare at first sight contradictory or inexplicaple. Conflicting reports in the literature regarding correlations between criteria of tablet quality and process variables can also be explained as follows: if the scrutinized area of the formulation lies in one of the sides of the "landscape", which is ascending to a maximum of the criterion of quality, then in this section we find a positive correlation to the test parameters. Beyond the maximum, however, in an area of the landscape, which may have been otherwise investigated, there is automatically a negative correlation.

Where is the optimum formulation to be found in the landscape? On what criteria should the choice be based ?

The "working point", i.e. the composition and the process, should be in an innocuous area of the "landscape". A "working point" in a steep side of a lahdscape would be a very poor choice. A slight change of compression pressure or in the quality of the lubricant may mean failure to comply with the hardness criterion. It is much better to site the "working point" corresponding to the criterion of quality in the centre of a flat maximum or minimum.

There are, of course, a further lot of quite different problems, inherent in the concept of strategies in formulating drug dosage forms:

a.Peroral Modified Release Formulations are designed to modify in a controlled way the kinetics of drug input from the gastrointestinal tract into the systemic circulation, to improve the tolerability by decreasing the peak plasma circulation and to prolong the duration of action, leading to better patient compliance. Here the pharmacokinetical optimization can be done by in vitro-in vivo correlation, further by estimating the in vivo release kinetic by deconvolution and finally, establishing the pharmacokinetic-pharmacodynamic connection using the Sheiner approach.

b. Establishing tolerances and selecting a suitable sampling scheme, which provide a proper balance between the outlay on inspection and the risk to the user, and which take adequate account of what is technically feasible.

c. Developing suitable compositions and processes, in order to comply in every case and in every country with the already very stringent quality requirements, laid down by the licensing authorities, for example cross contamination, microbiological contamination, list of allowed excipients, list of allowed food colours, permission of gamma-ray-sterilization and so on.

d. Developing reproducible analytical techniques, sufficiently fast, sensitive and precise, which lend themselves to automation and which are economic from the point of view of investment and testing costs.

The following parameters have been found to be essential:

Tolerances Statistical confidence of the results Technical feasibility Analytical feasibility	degree of perfection
Process costs Testing costs	costs

If we plot degree of perfection against costs, the degree of perfection rises, the costs increase exponentially. However, the user, usually the general public, is only willing to pay the price, which is commensurate with the necessary quality.

CONCLUSION

If we wish to preserve the research capacity of the pharmaceutical industry and enable industry to grapple with high-risk problems, we are going to need a common, international, scientific platform for specialists of all fields, the licensing authorities and manufacturers, to assess the relative merits of all the parameters, their benefit-risk-ratio for the patient, to evaluate the necessary quality and not only to ask for the best one.