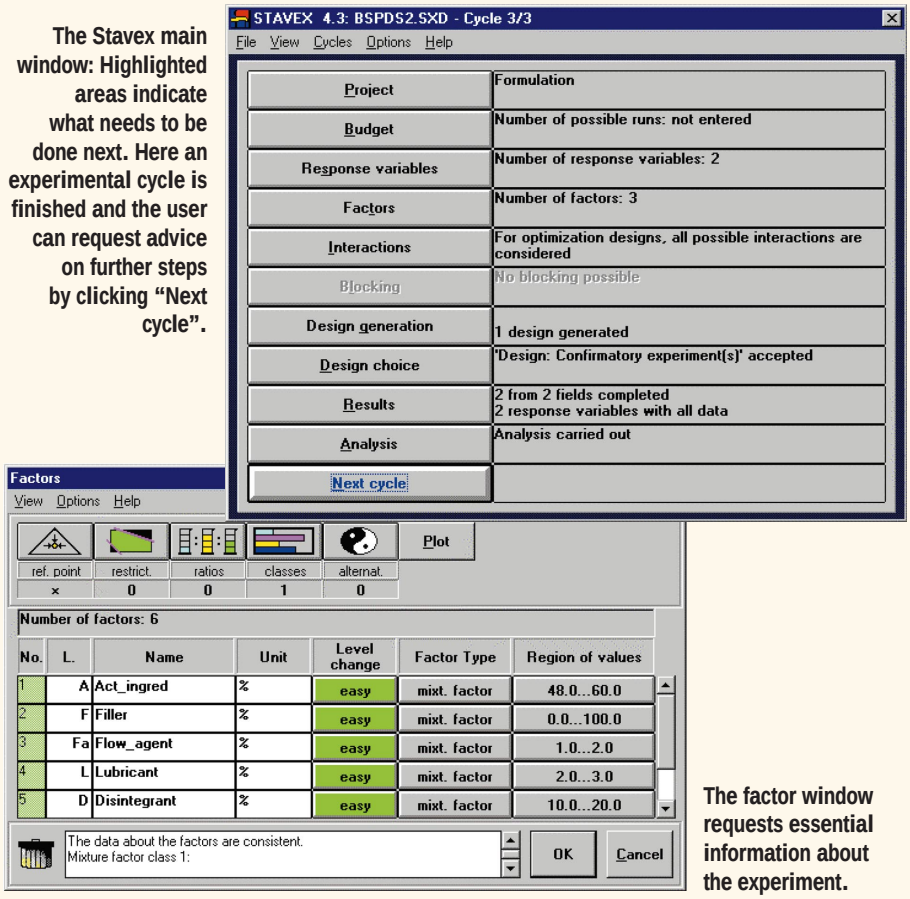
Straight from lab to market

How to get the most of your lab with optimum experimental designs

Sick of experiments? Does this sound familiar to you: excessive experimentation, poor test records, redundant tests, and test results that defy interpretation? This article presents a user-friendly PC-based software system enabling experimenters in research and development to apply statistical design and analysis of experiments in their routine work independently of a statistician.

DR. EKKEHARD GLIMM, MARKUS OTZ AND DR. PHILIPPE SOLOT



The Stavex main window: Highlighted areas indicate what needs to be done next. Here an experimental cycle is finished and the user can request advice on further steps by clicking "Next cycle".

The factor window requests essential information about the experiment.

Time-to-market is crucial for the success of new pharmaceutical and chemical products. A lot of money and resources are squandered by inefficient experimentation. Likewise, quality problems in production require immediate problem identification for prompt countermeasures. Experimental design techniques are the tool for getting the most information from a minimum number of experiments. Based on the specification of factors and responses, they calculate optimum experimental designs. In practice, these techniques require powerful software tools that do not only calculate the designs, but also perform the subsequent statistical analyses of the outcome. To be really useful, the software should state the main results in plain, non-technical language, thus requiring only little background in mathematical statistics.

Tailor-made designs

Formulation processes of solid and orally administered sustained-release drugs are one of the many areas where efficient experimentation is of paramount importance. In laboratory experiments, Novartis Pharma investigated the 60-min-dissolution rate of a sustained-release dosage form in 0.1 N HCl and the 65-min-dissolution rate in phosphate buffer. The experimental design software Stavex by Aicos Technologies was used for this purpose. It analyzes the two responses simultaneously. The subsequent discussion will focus on the more important 60-min-dissolution rate. In this particular application, both dissolution rates should be maximized. In general, maximum, minimum or target value optimization might be required. In the latter case, often upper and/or lower specification limits are present, too. Two types of factors have an impact on the dissolution rates: Roller compaction speed is a so-called process factor. This factor can be varied between 16 and 45 rpm independently of all other factors. In addition, formulation processes typically involve so-called mixture factors. Usually, these are the ingredients of the end product and add up to 100%. Therefore, they cannot be fully independently varied, making the calculation of optimum experimental designs a difficult task. Stavex can handle such cases, taking account of all restrictions. It even allows further restrictions on process or mixture factors as well as several mixture groups.

Here, five mixture factors adding up to 100% are considered:

- the active ingredient (48-60% of the end product),
- a disintegrant (10-20%),
- a lubricant (1-2%),
- a flowing agent (2-3%),
- a filler (0-100%).

Such complex settings require a software user interface that guides the user through the steps necessary to set up the experiment by a sequence of windows.

In general, three different experimental design stages can be distinguished: screening, modelling, and optimization. Screening is the first step when there are many potentially influential factors and very little is known about their impact. It aims at sorting out irrelevant factors. Subsequently, modelling takes a closer look at the more relevant factors, especially at

www.process-worldwide.com

- More about Stavex
- Here you will find a fax-request form for a free test installation

Dr. E. Glimm is consultant in applied statistics, Dr. P. Solot is CEO, both AICOS Technologies Ltd., Basel/Switzerland; M. Otz is statistician at Pharmaceutical and Analytical Development of Novartis Pharma, Basel/Switzerland.

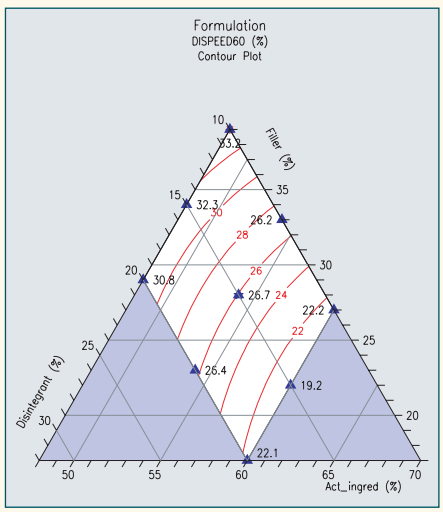
their interactions. This allows to eliminate further factors. Finally, one can concentrate on finding an optimum setting for the remaining most important factors. This is done in the optimization stage.

Based on the number of factors, Stavex suggests a design stage and corresponding designs that provide maximum information with as few runs as possible. The user can override the recommendation concerning the design stage, thus causing the software to calculate additional designs. He or she might even include own designs and just use the software for analysis. Full compatibility with Windows facilitates copy and paste from or to Microsoft Excel and other spreadsheets.

For the sustained-release formulation problem, the number of factors allows to skip the screening stage and start with modelling right away. Stavex suggests a so-called vertex-centroid design with nine experimental runs. After the experiment results have been entered, a statistical analysis is done and summarized in an easy-to-understand analysis report. Here, the report indicates that the percentages of active substance, disintegrant and filler have an impact on the response, whereas the other factors are negligible.

A wide variety of graphs

In many cases, visualization is one of the keys to a true understanding of the analysis results. Consequently, the software offers a wide variety of graphs, such as contour and surface plots. Those with a penchant for statistics can take a closer look at information that is only displayed on user request: details of the model fit include parameter estimates as well as various diagnostic goodness-of-fit measures.



Pictures: Aicos

The ternary contour plot visualizes the impact of the mixture factors on the dissolution rate. Small blue triangles mark the experimental runs.

At a glance

Fields of application

More than 100 companies and universities all across Europe are currently using Stavex. Mostly, the companies are from the chemical and pharmaceutical industry with some from the food industry as well. The software can be used to optimize laboratory experiments and production processes alike. For example, the software has been used in projects concerned with

- analysis of dissolution rates for sustained-release dosage forms,
- stress resilience of dyed fabrics,
- thermo-sealing of blister packages for tablets,
- identification of key parameters in pigment production,
- HPLC ruggedness analysis,
- conservation of dairy products.

Moving from modelling to optimization, the next Stavex design focusses on the factors "active ingredient", "filler" and "disintegrant". Only these are varied in nine new runs. The extra information is used for a more precise estimation of the response from a more sophisticated mathematical model. Again, the main results are summarized in a concise analysis report with hyperlinks to plots and details. The "best level combination" is reached with 48% active ingredient, 10% disintegrant, 39% filler and other parameters arbitrary. The predicted dissolution rate is 33.3% with a 90%-confidence interval of [30.4, 36.2]. While no mathematical model can capture all aspects of reality, it is important that it provides an adequate approximation to reality. Here, model diagnostics show that the model fits well, so the investigation is essentially finished at this point. However, it is part of the Stavex quality philosophy to recommend a confirmatory experiment to validate the prediction at the best level combination. This extra experiment indeed confirms the prediction.

In the end, it took Novartis just 19 experimental runs to identify the best combination of ingredients for the sustained-release form. With modern experimental design tools like Stavex excuses like "It's too early to use statistical methods" or "Let's just vary one factor at a time, so we don't get confused" are no longer a reasonable justifying explanation. Such groping about in the dark can gobble up hundreds of experiments with no substantial progress towards a solution. Avoiding such detours, experimental design aims straight at the heart of the matter.

For further information in connection with this article, mark code number **304**