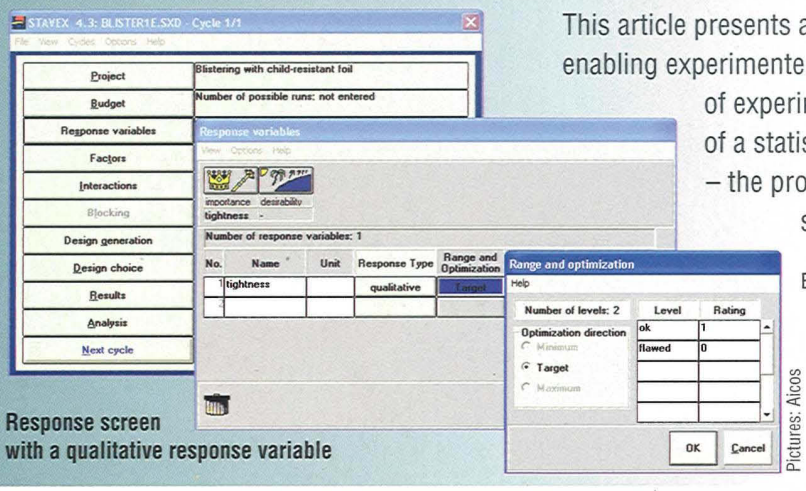
Away from the red zone

Statistical design of experiments identifies and removes quality deficiencies



Response screen with a qualitative response variable

Pictures: Aicos

This article presents a user-friendly PC-based software system enabling experimenters to apply statistical design and analysis of experiments in their routine work independently of a statistician. A project by the pharmaceutical industry – the production of child-resistant blister packages – serves to illustrate the advantages.

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In various branches of the process industry, efficient planning and analysis of experiments is of paramount importance to quality improvement. Aimless trial-and-error is harmful in more than just one way: on the one hand, valuable resources are blocked by redundant experiments; on the other hand, insufficient experiments may even cause greater damage if they lead to poor process parameter settings.

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Design of Experiments is the appropriate method to avoid such problems. It aims at identifying the impact of process settings (so-called "factors") on the quality characteristics (so-called "response variables") of concern. To this end, the set-up of the experiment, typically involving the factors, their range and the responses, has to be specified. From these specifications, appropriate software tools are able to determine an efficient experimental design. Such a design should have as few experimental runs as possible. However, the number of runs must still be large enough for a reliable assessment of the factor effects and interactions between factors.

Experimental design is widely used since decades, often resulting in significant cost cuts and quality improvements. But in spite of this continuing success story, many quality managers do not seem to realize the full extent of potential applications for these methods. Not even the implementation of experimental design methods constitutes an obstacle anymore, thanks to modern software tools.

A project by the development department of a pharmaceutical company might serve to illustrate these points. The production of child-resistant blister packages involves stamping cavities into an aluminum foil. Subsequently, the formed bottom foil is sealed with a lidding foil. Every blister consists of ten cavities. After production, the tightness of the blister is checked by a vacuum test.

As a single deficient cavity ruins the complete blister, it was decided to treat "tightness" as a qualitative response variable with just two possible outcomes, "ok" and "flawed". This is somewhat unusual since experimental design typically deals with quantitative response variables (e.g. a quality deviation in percent). The software Stavex which was used in this study is able to deal with both types of response variables. The factors of interest here are sealing pressure, sealing temperature, pre-heating time and the speed rate of the production line. The first three factors are qualitative and can be varied within the following ranges: sealing pressure 1500 to 2800 kp, sealing temperature 100 to 200 °C, pre-heating temperature 120 to 170 °C. In contrast to these, the speed rate can only be varied in steps. Consequently, it is treated as a qualitative factor. Furthermore, the speed rate may depend on the production lot size. With a small lot size, automatic feeding is too complicated to implement and thus high speed rates may not be available. The factor setting to be identified should therefore yield good results across different speed rates.

Central-composite design

Following these specifications, Stavex suggested four appropriate experimental designs. A so-called central-composite design with 45 experiments was selected.

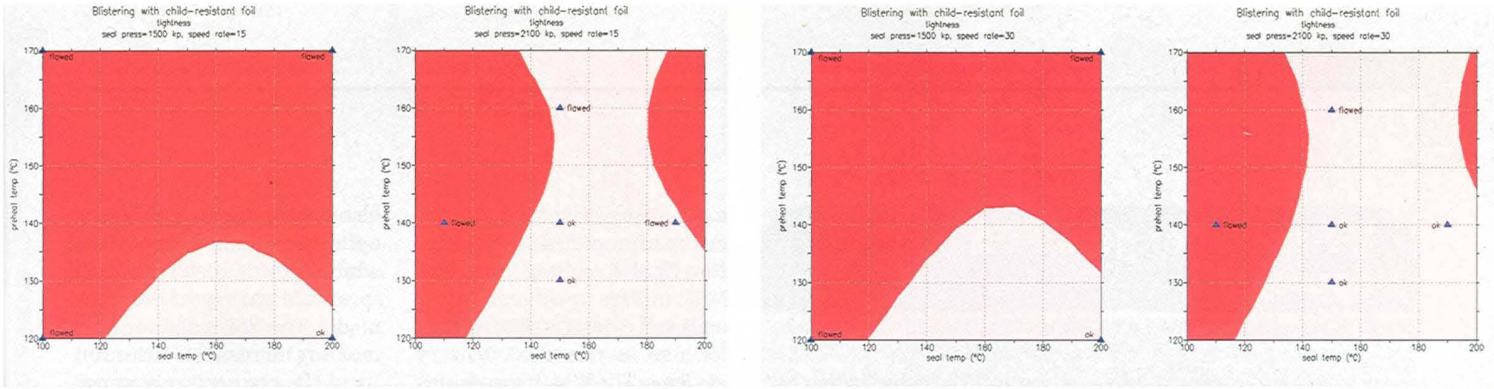
After the experiments had been performed, the software calculated the probability of producing a properly sealed blister depending on the factor settings. This analysis is summarized in an easy-to-understand report. Among other things, this report contains the list of factor constellations at which experiments were done with the corresponding probabilities for a properly sealed blister. These calculations are used for plots where "advantageous" and "disadvantageous" regions within the factor range are indicated by different colors. It is possible to obtain a good impression of the advantageous area by arranging re-

At a glance

Fields of application

Stavex is used by companies from various branches, predominantly the pharmaceutical and the chemical industry, as well as by universities and research institutions. The software is equally well suited for the optimization of laboratory experiments and production processes. For example, Stavex has been used in projects aimed at:

- analysis of dissolution rates for sustained-release dosage forms,
- yield maximization in biosynthesis,
- thermo-sealing of blister packages for tablets,
- optimization of tablet formulations,
- identification of important mixture parameters in the production of adhesives,
- HPLC ruggedness analysis.



The "red zone" is a region of factor settings with a high probability of flawed production. Outside this region, the probability of production flaws is decreasing with the distance from the red zone. Blue triangles indicate the experimental runs in the design with the observed response.

gion plots of two factors at different levels of a third (and possibly a fourth) factor on one page. The software functions offer this possibility (see figure above). On the basis of these plots, one can find a factor setting far away from the red zone. If the advantageous zone is big enough, there might even be a chance to take into account additional considerations when picking a setting. In this case, the plots clearly show that low sealing temperature is a major cause for flawed blisters. Sealing pressure should be relatively high. The following recommendations can be given: sealing temperature: 170 ±10 °C, pre-heating temperature: 130 ±10 °C, sealing pressure: 2600 ±100 kp. These settings are suitable for all speed rates. The recommendations take into account that a very high sealing temperature seals the cavities reliably, but might damage the foil by burning.

On the basis of these results, the production was modified accordingly. The insight gained from the experiment did even prove useful for a number of other blister production processes.

Statistical design of experiments helped the pharmaceutical company to establish the high quality of the process factor settings. Last but not least, an important requirement of the regulation authorities could be met in this way. This application demonstrates how versatile statistical design of experiments really is. Substantial quality improvements can often be reached with little effort. Even in situations where there is seemingly limited information from a single experiment (e.g., just "ok" or "flawed"), the experimenters are able to learn a lot, simply by a smart selection of experimental runs. ■

For further information:

www.pharma-tec.com

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

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