Crystal Clear Results

aicos

Statistical Design of Experiments accelerates Crystallization Processes

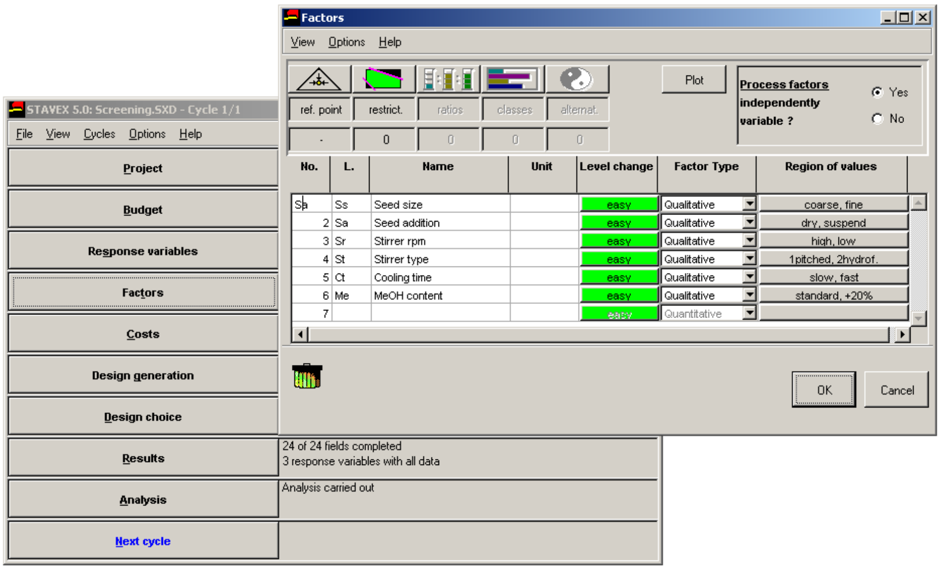
Problems in quality and lack of efficiency can produce substantial financial losses in the process industry. Leading companies of these sectors therefore establish a culture of continuous striving for process improvement and provide their employees with the tools to actually achieve this aim. A useful means in this context is Statistical Design of Experiments.

In order to use Statistical Design of Experiments, the production specialist first defines one or several optimization criteria, for example yield, quantity of residues in the final product, reaction duration. Then he specifies a list of possible influence factors to these response variables, e.g. catalyst quantity, reaction temperature, stirrer form etc. Statistical Design of Experiments makes it possible to develop an experimental design based on these data, which finds the optimal adjustment of the influence factors with the minimum possible number of tests. Modern, efficient computer programs with comfortable user guidance allow the production specialist to use this highly efficient technology also without having extensive statistical knowledge.

Aim: reduction of the cycle time

At Novartis Pharma in Basel Statistical Design of Experiments was applied for the purpose of eliminating a cycle time bottleneck in the production of a pharmaceutical intermediate. The bottleneck consisted in a non-classical reaction/cooling crystallization step with following filtration of the very viscous mother liquor and laborious washing of the filter cake with large solvent quantities. The primary aim of the project was to reduce the cycle time in crystallization, filtration and washing. For this purpose, the specific filter cake resistance was used as the main quality measure in laboratory experiments. On the one hand, it correlates directly to the filtration speed; on the other hand it is also indirectly associated with the crystallization quality (primary crystal size) and the filter cake structure (crystal agglomeration).

For the set-up of the experimental designs the Stavex Software was used, which meanwhile is available as version 5. The program leads the user through the project specification with a clearly structured succession of steps (Figure 1). Dialog boxes with questions and generally understandable comments help the user to precisely define response variables, factors and boundary conditions of the experiments. For special cases, like mixtures, restrictions on the variation ranges of several factors, infeasible experiments and difficult changes of factor levels, a large number of options are available. The menu navigation is however conceived in such a way that the thread of project specification is never out of sight.



1: Main and input screen for the factors

Screening: separate the wheat from the chaff

In the present project, first of all a screening of the potentially important factors for the crystallization was accomplished. These were seed crystal size, seed crystals addition (drying or suspended), stirrer type, stirrer speed, cooling time and solvent quantity. As secondary response variables beside the filter cake resistance, also the primary crystal size distribution (Sympatec Helos laser diffraction, off-line) as well as the agglomerate size distribution in the suspension (Lasentec FBRM probe, in-situ) were analyzed, in order to clarify their relevance for the filter cake resistance and thus the cycle time.

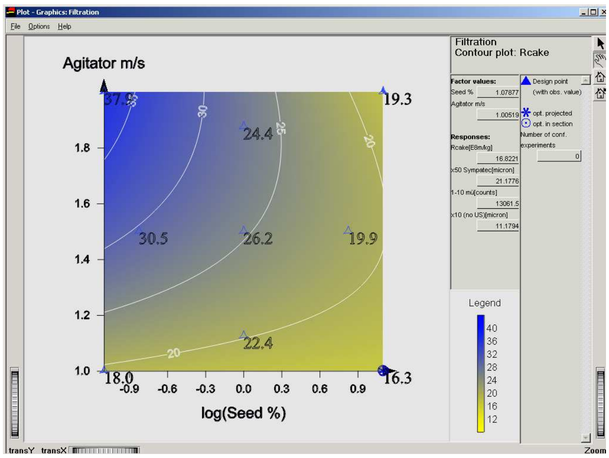
After the input of these variables the software produces suitable experimental designs with systematic variation of the factor settings. In this case, a so-called Plackett Burman experimental design with eight tests was selected from the list of the suggested designs. This design aims first of all at a distinction of important and unimportant factors and not yet at the optimal factor constellation.

After performing the experiments and recording the results, Stavex provides an extensive analysis report in the HTML format which is formulated without jargon. It shows that only the suspended seed crystals, slow agitating speed and an increased solvent quantity substantially reduced the filter cake resistance. The assumed correlation between primary crystal (respectively suspension agglomerate size) and filter cake structure (respectively filtration time) was not confirmed.

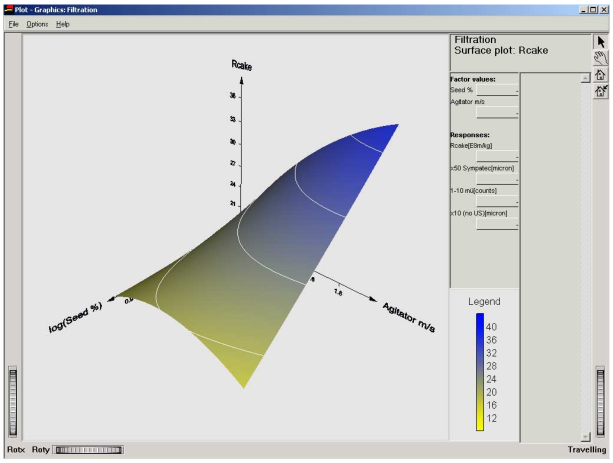
Optimization: the best factor setting

On the basis of the results of the analysis, the software also gives recommendations regarding further processing. In this case it suggests rendering the obtained results more precise by an optimization experiment. This was done, based on the agitating speed and a newly introduced factor: the ratio of seed crystals to batch size. All other factors were either fixed at their best level (if they had proven to be important in the preceding analysis, but could only to be varied in discrete steps), or they were set on the "most comfortable" level (if they had proven to be unimportant).

Stavex suggested for these new conditions an experimental design with nine experiments. In contrast to the design from the screening stage, now the fine tuning of the two examined factors stands in the foreground. As "compromise stage" between screening and optimization Stavex includes also a modeling stage, where a medium-sized number of factors (typically four to eight)



2: Contour plot of filter cake resistance versus seed crystal ratio and stirrer speed



3: Surface plot of filter cake resistance versus seed crystal ratio and agitating speed. The picture can be rotated interactively.

is examined with regard to interactions. However, this stage was skipped here.

The best results are obtained with small stirrer speed and high seed crystal ratio. The analysis however also shows that, due to interactions between stirrer speed and seed crystal ratio, a high stirrer speed can be balanced by a high seed crystal ratio and vice versa. Good results thus are obtained at a low stirrer speed, independently of the seed crystal ratio, as well as with high seed crystal ratio, independently of the stirrer speed. Above all, the latter result is important: In the production the reduction of the stirrer speed is limited due to restrictions imposed by heat transfer and mixing quality requirements.

The Stavex analysis report makes these insights possible by identifying the important factors and interactions and by quantitatively estimating their effect. Here the software uses an empirical mathematical model that describes the correlation between influence factors and response variables. It examines automatically the model quality. In the case of deficits, it gives recommendations regarding possible modifications, for example by transforming the response variable. Very useful for the model diagnosis, but in particular also for a better understanding of the results, are the many different types of diagrams which are available in Stavex.

The graphical tools have been extended in version 5 compared to the older versions. The numerous options include, beside new plot types, also extended facilities of user interaction, like rotating pictures, changing colors and symbol sizes, and more possibilities for combining several figures into a multiple picture. Figure 2 shows the modeled correlation between the influence factors and the principal response variable filter cake resistance. The effectively obtained results are also plotted. They agree well with the predicted values, which indicates an adequate model. In Figure 3 the same situation is represented as a surface plot.

Running time halved

Thanks to the insights gained from the systematic experimental design approach and to suited measures taken in the production, the cycle time of the filtration could be decreased from more than 46 to 37 hours.

Additionally, important incitations for further improvements arose as a result of the deepened understanding of the crystallization process. Due to the insight that stirrer speed, seed crystal suspension and seed crystal quantity are important factors for the filterability of the crystal suspension, it was decided to introduce an optimized stirrer as well as a separate, well-mixed seed crystal container. Moreover, the solvent ratio was optimized. By these measures, the crystallization and filtration time could be reduced both to less than 24 hours.

Authors: Dr. E. Glimm, AICOS Technologies AG, and Dr. U. Meier, Novartis Pharma AG
