Searching for the optimum

Statistical design of experiments improves processes

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Statistical design of experiments sounds like a research and development theme. The same methods are, however, becoming more frequently applied to identify optimal settings for production lines, as well. This enables a manufacturer to fulfil reliably predetermined, often very tight, specifications, so that a constant high quality level is guaranteed.

Siegfried Ltd. is a medium-sized Swiss company which is specialized in custom development and manufacturing of active pharmaceutical ingredients (API) and final dosage forms. In close contact with the customer, the product is developed until it is ready to be brought to the market. A special challenge is the handling of the solid API after synthesis. As no further purification step is possible, it has to be ensured that any cross contamination of the product is avoided. The crystal structure of the final API, as well as its particle size distribution, determines its behaviour in further processing and the effectiveness of the drug. In order to protect employees and environment from dust exposure of the API, additional safety measurements are necessary. Overall, this results in high demands on milling and blending facilities.

Fig. 1: The new milling and blending plant of Siegfried Ltd

Modern milling and blending plant

In 2004, Siegfried Ltd. commissioned an entirely new mixing and blending plant which is fully GMP compliant (Fig. 1). In particular, the ventilation system is designed to avoid any cross contamination by micro particles; e.g. the production rooms can only be entered through separated air locks for employees and materials. Charging and packaging are semi-automated, so that open product handling is nearly never necessary. The production lines are provided with washing-in-place equipment with e.g. spray and jet nozzles.

In pharmaceutical production, product specifications are usually tight in order to guarantee constant quality levels for the API and its final dosage form. For the product we consider in the following example, the specification for the particle size distribution is represented by limits on three size classifications in a laser diffraction system: Helos 10 % (not larger than 10 µm), Helos 50 % (10 to 20 µm) and Helos 90 % (25 to 50 µm). These limits are historically very tight. Furthermore, the requirements for Helos 50 % and Helos 90 % are diametrically opposed.

Statistical design of experiments

The main challenge for production is to find a setting of the variable parameters (the so-called factors, e.g. the speed of the mobile milling tool) such that the specifications are optimally fulfilled. Unfortunately, down-scaling from high-capacity mills to laboratory scale is only rarely feasible. Thus the factor settings must be determined directly at the milling lines. Therefore it is indispensable to use a highly efficient optimisation strategy, which yields reliable prognoses based on a minimum number of experiments. Here the Statistical Design of Experiments provides welcome assistance. It allows the mathematical modelling of the dependence of one or more response variables on the factors. Since in the present case the specifications are given by limits on three size classifications in the particle size distribution, the corresponding particle sizes were chosen as response variables and simultaneously investigated.

For practical applications it is of course very important that the statistical methods can be easily applied without forcing the user to become acquainted with the complete theory. Thus the statistical software Stavex by Aicos Technologies has been used for the project. This software has been conceptualized from the beginning for users without statistical background wanting to plan and evaluate experiments, and is therefore very user-friendly. Thanks to this and its high flexibility, Stavex is used today in many different areas of a large number of companies, e.g. in chemical-pharmaceutical development, for formulations, but also in mechanical engineering.

In the present project, firstly the three quantities which represent the particle size distribution were entered into the software as response variables. As factors, the speed of the mill (turbo tool, up to 10 000 min^{-1}), the dosing speed (1 to 100 min^{-1}) and the sieve size were included. The first two of these factors are quantitative, i.e. they can be

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freely varied in the given region, whereas the sieve size can only be chosen from three different categories, i.e. it constitutes a qualitative factor. Stavex allows treating qualitative as well as quantitative factors; therefore such cases do not pose any problems. Dependent on the sieve size (1000, 2000 or 3000 µm), further restrictions on the other two factors had to be taken into account, otherwise the sieves may block. Other parameters, like the particle size before milling and the speed of the nitrogen flow through the mill cannot be influenced easily. Thus they were fixed at the given level and not included as factors into the optimization.
A complementary analysis option, which is also supported by Stavex, would have been to combine the three response variables to a single one. Here the different quantities may also be weighted differently. In our case, however, the interest was in modelling the dependence structure of the different response variables separately in order to enhance process understanding.

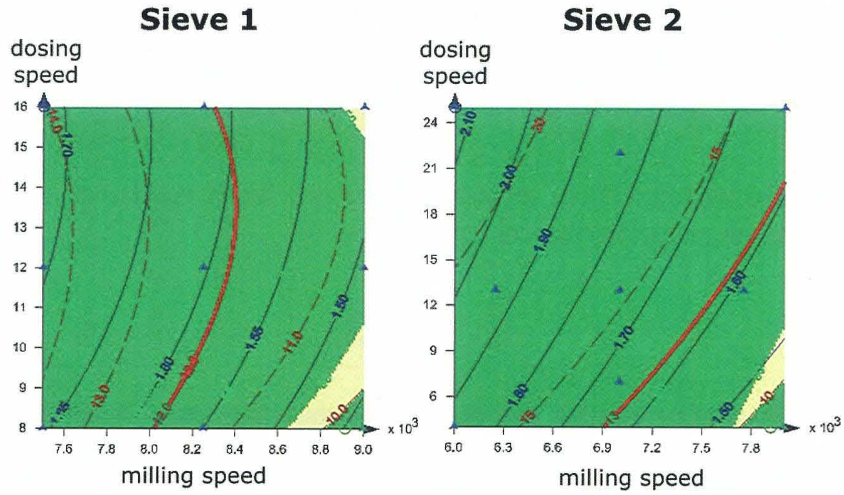

Fig. 3: Contour plots from Stavex: The results for all three response variables are displayed simultaneously. For each response variable the contour lines (Helos 10 % blue, Helos 50 % red and Helos 90 % green) indicate in which region the result lies, as on a map of trails. The green areas are the regions where the specifications are not fulfilled. Furthermore, the parameter settings which have been used for the experiments are marked by blue triangles.

Searching for the optimal process settings

In the subsequent optimisation step, measuring the particle size distribution is overall a difficult task. As the active ingredient in question is an isolator, it is susceptible to electrostatic charge. This can easily result in an aggregation or agglomeration of the particles. Moreover, the analytical method (Sympatec, Helos) was at that time not very reliable with regard to the tight specification limits. However, it was necessary to work under these conditions, as the inherent physical difficulties could not easily be overcome. In our case this meant that electrostatic charge was excluded as much as possible (mills as well as sampling unit grounded) and that certain inaccuracies of the measurement methods were accepted. Because of the strong differences in applying the three sieve types, it was decided to perform separate optimisations for the two finer sieves. Here, a full factorial respectively a central composite design were chosen, i.e. in each case nine different process settings were tested. The parameter combinations used are displayed in figure 3 as blue triangles. As the third sieve was expected to exhibit a lower performance, the investigation of interactions between the parameters was omitted. Thus the number of experiments was significantly reduced compared to the optimisation (4 instead of 9 tests). For the selection of the experimental designs, i.e. the different process settings to be tested, the user can resort to the expert knowledge implemented in Stavex. Depending on the actual problem, the software identifies the most suitable designs and presents them to the user in a commented ranking list.

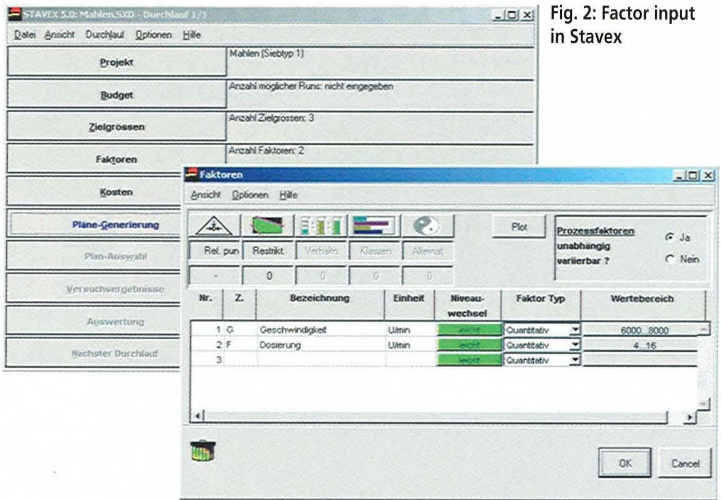

Fig. 2: Factor input in Stavex

Increase in quality and reliability

In all three of the above described cases the speed of the rotating milling tool emerged as the most important factor, i.e. the one exerting the strongest influence on the response variables. Nevertheless, the other factors are mostly not negligible and interactions between different factors have to be taken into account. Stavex summarises these findings in easily comprehensible analysis reports. Thus also here the user is not left alone facing the numerical results. The contour plots computed by Stavex show in which areas the specifications are fulfilled (white areas). Note that the restrictions are mostly due to the response variable Helos 90 %, which also varies most in the analysis method. It can be seen that the finer sieve is preferable. Here the lower dosage speed is advantageous, because then the specifications are fulfilled in a larger region, i.e. the process is more robust against fluctuations. If Helos 50 % (red) lies as near as possible to 10 µm, at a milling speed as high as possible and a dosing speed of around 10 min^{-1}, then the specifications for Helos 90 % are fulfilled as well and stable results are obtained.
Employing Statistical Design of Experiments with the help of the statistical software Stavex for determining the optimal parameter settings has turned out to be advantageous in two aspects. On the one hand a better process understanding has been obtained. On the other hand, the consequence of the conversion to the finer sieve type is that the mill now operates in a region where the specifications are reliably fulfilled and a certain robustness against fluctuations is achieved. Due to the good experience with the Statistical Design of Experiments the analysis method has also been optimised for robustness and precision using Stavex. The insights won from the mathematical approach subsequently led to better understanding and further improvements in the milling process.
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