Good planning: the key to success!

Software-aided Design of Experiments reduces the effort needed for the scale-up to a minimum

The scale-up from the laboratory to production is a time-consuming task. Intelligent software tools can however limit the effort needed. Read for instance how Novartis Pharma has optimized the synthesis of Coartem, an important combination drug against malaria, using Design of Experiments.

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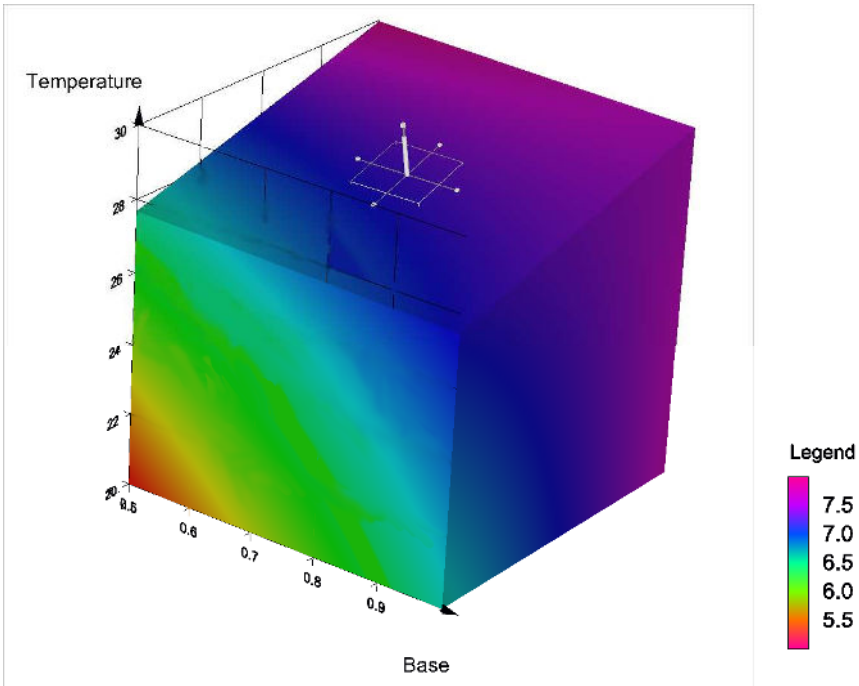
Well designed experiments can make the scale-up more efficient and therefore shorten the time until production start. This measure is especially important for life-saving medications like the combination drug Coartem (arthemether-/lumefantrin) of Novartis Pharma, which was classified as "essential medicine" against malaria by the WHO.

For a production at commercial scale – Novartis Pharma sells the drug to the WHO at production cost – the synthesis procedure of the API lumefantrin had to be considerably modified, in order to optimize systematically the reaction process and to obtain reliably an adequate yield with sufficient quality. Indeed, even if the original production process consisted of only a few steps, it nevertheless exhibited much optimization potential:

- to some extent long reaction times;
- a complex elimination of intermediates;
- a great yield variability (between 56% and 90%) in the last step.

In order to optimize the process, a multitude of experiments possibly has to be performed at several synthesis steps. The use of a Design of Experiments (DoE) software allows to develop optimized designs and thus to reduce the number of experiments, i.e. to find good settings of the factors of influence with a minimum of experiments.

With the software Stavex of Aicos Technologies, the developer can use the advantages of experimental design without needing a deep knowledge of statistical methods.



The 4D contour plot represents the yield (in grams) against the amount of base (x-axis), the reaction time (y-axis, hidden) and the temperature (z-axis). The scale ranges from red (low) to violet (high).

Multiple use

The Design of Experiments software was used several times for the optimization of the process and made improvements possible in the following steps:

- For the first synthesis step, a suitable solvent could be identified, so that the reaction product drops out directly (direct-drop method).
- In the second step, the selectivity of the reaction could be considerably increased.
- For the further steps, the conditions had to be controlled in such a way that, at the production scale also, few by-products arise and the production nevertheless remains in an acceptable range.
- As for the final step, a base-induced condensation, the software use enabled a short and systematic analysis of the four factors seen as critical for the scale-up: the amount of base, that of solvent, the reaction temperature and the reaction time. Because only four factors have been taken into account, their interactions could directly be considered.

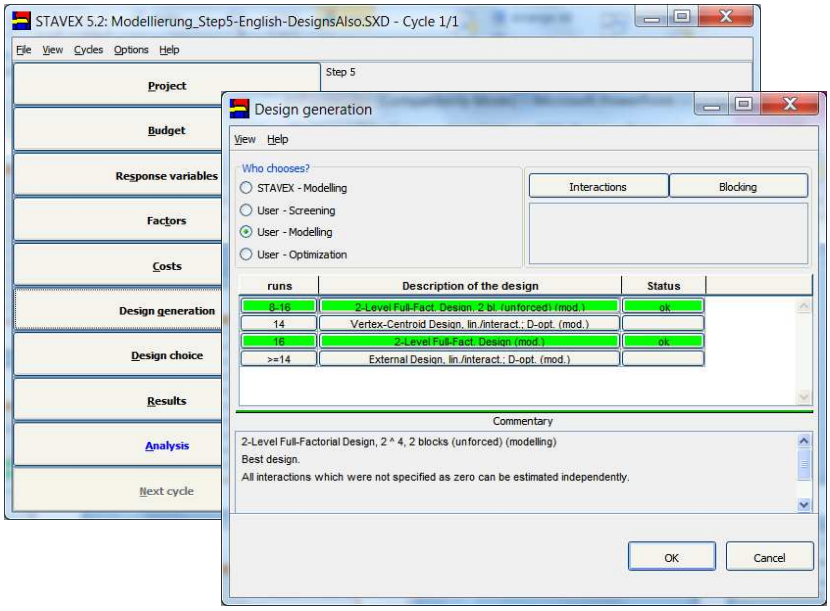
Identifying relationships

The analysis of the experimental results showed that the amount of solvent has no significant influence on the yield. On the contrary, the other three factors are important; furthermore, strong interactions can be observed. This can be seen in the graphics as well; there, the color gradient is not parallel to the axes. The 4D cube (see Figure) makes clear that the lowest yield is the result of a low amount of base, a low temperature and a reaction time (y-axis, in the back of the figure) of one day; a long reaction time however leads to a high yield. The yield is specified in grams; the best value corresponds to a prediction of 86%. Considering this, one could have stopped there, especially because the experiments had already confirmed this value. However, the experts of Novartis Pharma did not settle for this result. In order to reduce the unsatisfyingly long reaction time, further experiments were run with a low amount of base, high temperature, but reaction times of one to two days only. As the yield then constantly lay between 81 and 87%, it was decided to run the final detailed

optimization in this area, but to fix the reaction time to one day. To be on the safe side, the amount of solvent was included again. And indeed, also with the short reaction time, yields of 87% can be achieved reliably. This means that the reaction time was decreased by two thirds without making concessions on the amount or quality of the product. An additional observation allowed to identify the reaction mechanism. Next to a successful scale-up, which has led to a high and reliable yield with a high quality, a deep process knowledge was gained. This is in particular due to the flexible use of the Design of Experiments software.

At a glance: This is how Stavex works

The software makes use of the concept of sequential Design of Experiments. The developer provides the parameters to be optimized and the factors that possibly influence these response variables. Then, suitable experimental designs are proposed. Initially the aim is a stepwise reduction of the factors, because in practice it is already possible to achieve very good results if only the two to four most important factors are set optimally. Including more factors into the detailed optimization would only slightly improve the result, but would mean a higher experimental effort. The analysis of the experimental results is clearly commented, so that one does not need to extract the information oneself from the statistical results. The latter are though fully available and can easily be accessed over the long form of the report. An extensive graphic library makes the result visualization easy. After the completion of every step, suggestions for the next one are made, e.g. which factors can be excluded in the following experimental cycle.



The user-friendly user guidance of the experimental design software also enables the practitioner who is not a specialist in statistics to take profit of the advantages of a systematic Design of Experiments.