Two in one sweep

Fast identification of important parameters using “Design of Experiments” (DoE)

Identifying the most important influence parameters already during formulation development simplifies the subsequent scale-up to the production scale. On the one hand, the specification of a Design Space facilitates the process validation acceptance by the regulatory authorities; on the other hand, an increased process knowledge reduces the occurrence of problems. Here, Statistical “Design of Experiments” (DoE) is an important aid, which leads to a clear increase in efficiency.

Natalja Felbusch
Prof. Dr. Gerd Kutz,
Ostwestfalen-Lippe University of Applied Sciences;
Dr. Philippe Solot,
Dr. Stefanie Feiler
AICOS Technologies Ltd.

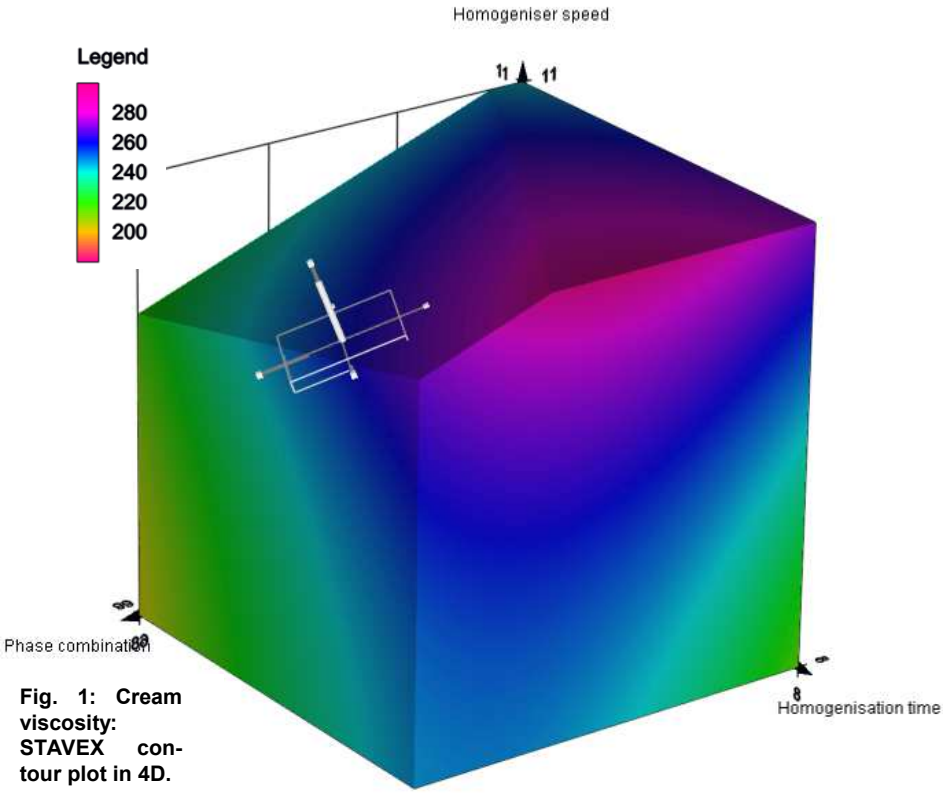

Fig. 1: Cream viscosity: STAVEX contour plot in 4D.

This paper is about the analysis of parameters that influence the viscosity of dispersions. It is well-known that two different kinds of dispersion systems can be produced by means of the Phase Inversion Temperature (PIT) method. Above the PIT, the result is a low-viscosity emulsion (lotion); if one works below the PIT, an emulsion of higher viscosity (cream) can be obtained. Based on a prototype formulation, the critical process parameters are identified and then the optimal settings for both systems are defined.

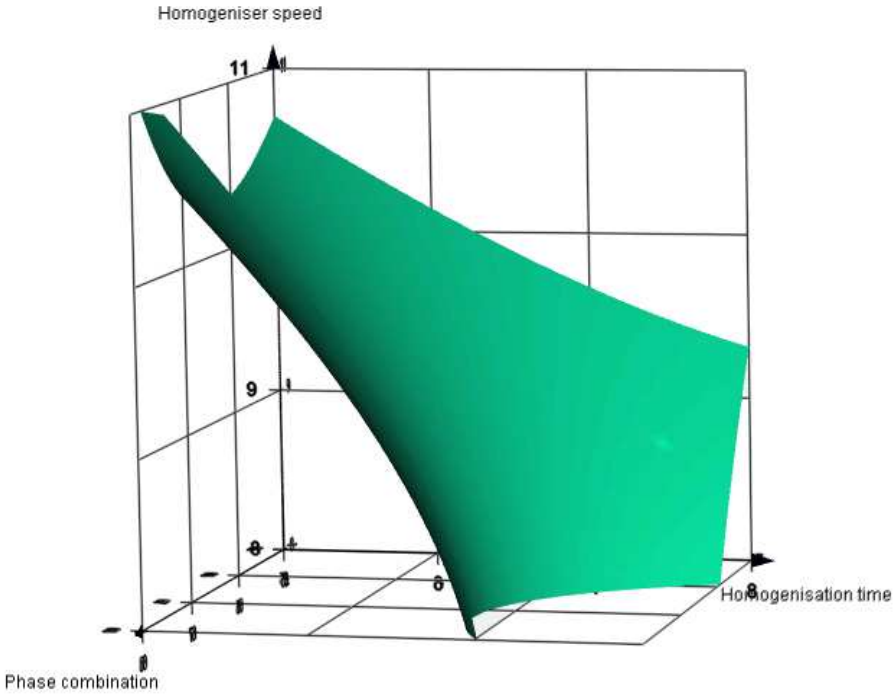

Fig. 2: Cream viscosity: STAVEX isosurface plot for a viscosity of 240 Pa*s. The area limited from below by the isosurface is the defined Design Space.

Structured procedure

Based on a fishbone diagram and a later risk analysis (FMEA), nine potential influence factors remain. Determining optimal process settings in such a complex situation is not an easy task. This is where “Design of Experiments” (DoE) can be used. Through the structured procedure the necessary effort can be minimised: the result is reached in the most efficient way.

The idea of the so-called sequential experimental design is to carry out a simpler or more detailed examination depending on the number of parameters. Thus, the cost-benefit ratio can be kept as low as possible. In case of many parameters, a rough screening allows to reduce the number of factors. With a medium number of parameters, interactions between the factors can additionally be considered; though, the objective still is factor reduction. In practice, there are often only two or three factors that significantly influence the quality of the product. As soon as these factors are identified, optimal process settings can be defined.

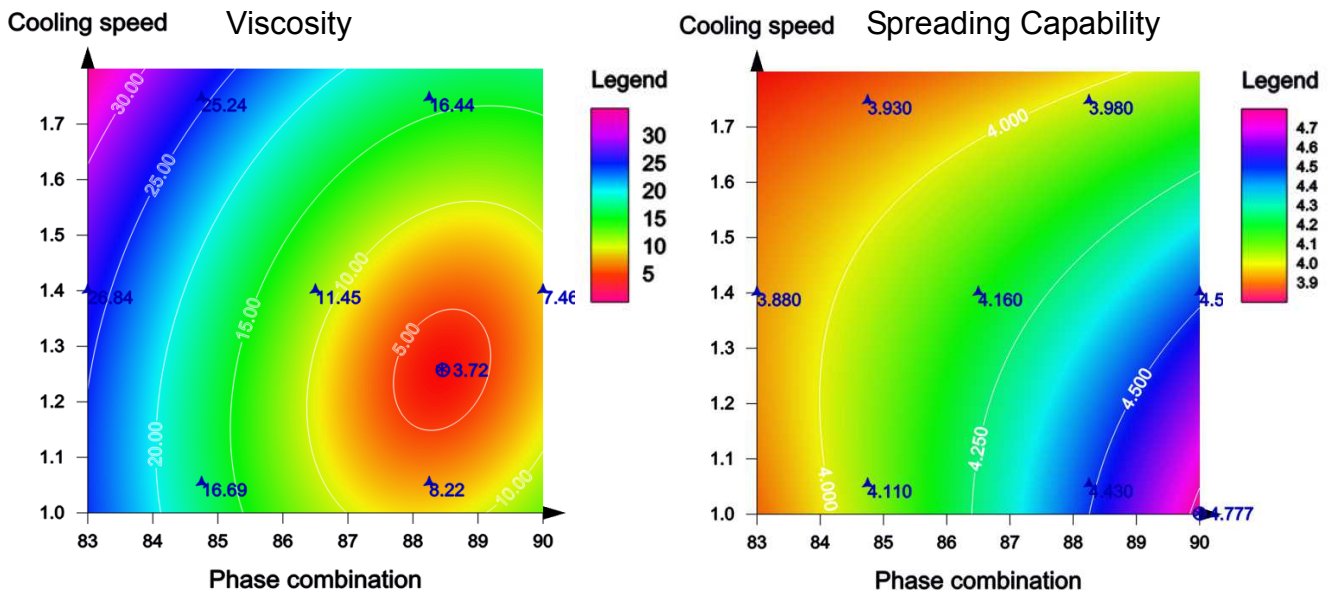

Fig. 3: Lotion: Contour plots for viscosity (left) and spreading capability (right) of the lotion. Viscosity should be preferably minimal, spreading capability should be preferably maximal. The optimal regions are presented in purple.

This procedure is implemented in a very user-friendly way in the software STAVEX of AICOS Technologies. The integrated expert system suggests suitable experimental designs based on the number of factors specified. Usually, one simply follows the recommendations of the software. Advanced users can of course very flexibly adapt the recommendations to different needs, e.g. in order to let the software complete their own preliminary experiments to a complete design.

The first screening cycle establishes that the number of factors can be reduced to four for the lotion and to six for the cream. It should be mentioned here that STAVEX presents the results as an easily understandable HTML report and makes many graphics available for the visualisation. If required, the statistical details can still be retrieved via links to the long form of the analysis report.

The smaller number of factors obtained now permits a more precise examination of the dependences in the so-called modelling cycle. Here it should not be forgotten that the objective still is a further reduction of the number of factors. Therefore, fractional factorial experimental designs are now used: for the cream, a design of 16 experiments is chosen; for the lotion, 8 experiments suffice. Such designs are too small for calculating the pairwise interactions between all the factors. However, this should obviously happen if their interactions are not clear yet and this is therefore the default software setting. But STAVEX definitely allows to reduce the number of experiments if previous knowledge about the system is available. This can be done by defining which interactions can be considered as negligible. It concerns, for example in the case of the lotion, the interaction between the homogeniser speed and the cooling speed, whereas the interactions between the other factors should be examined in any case. The software thereupon suggests suitable designs.

At the end of the modelling cycle, it is established that for the cream only three factors (homogenisation time, homogeniser speed and phase combination temperature) are really decisive, for the lotion even just two (phase combination temperature and cooling speed). As the number of factors is now small enough to search for the optimal settings, the next step is the so-called optimisation cycle. The software chooses a central-composite design with 15 experiments for the cream. For the lotion, the project team resolves to switch from the design suggested originally with nine experiments to the smaller hexagon design with seven runs. Both series of experiments provide acceptable (cream) to very good (lotion, especially viscosity) model fits. Therefore, optimal process settings were found, based on the nine potential factors, in 43 experiments for the cream and in 27 experiments for the lotion. The confirmatory experiments performed prove the validity of the models obtained. By the way, a further advantage of the sequential design of experiments is that the factor ranges can be adapted from one cycle to the next according to the result obtained. Here for instance, the range examined for the homogenisation time, which was from 2 to 10 minutes in the screening, was reduced to the more accurate area from 5 to 8 minutes in the optimisation phase.

Main results

Figures 1 and 3 show contour plots of the results. One directly sees that a longer homogenisation time, a high speed of the homogeniser as well as a medium phase combination temperature are ideal for the viscosity of the cream. Two quality characteristics are interesting for the lotion: besides a minimal viscosity, a maximal spreading capability. They are illustrated in the contour plots of Figure 3. Here a good compromise may for instance be found by means of a joint (overlay) contour plot or using a so-called desirability function. In the case observed, the latter is not necessarily required because both plots of Figure 3 show a similar trend, namely that the best setting of the factors lies in the lower right quarter of the area. Also design spaces are easy to define. A value of at least 240 Pa*s is considered as desirable for the viscosity of the cream. This area is limited by the turquoise zone and can for example be well illustrated by an isosurface plot (Figure 2). The regulatory authorities permit a simplified process validation with sufficient knowledge of the correlations because it is then known how to countersteer undesirable effects. Within the design space the settings can be flexibly modified.

In the present case of the cream, a deviation of the phase combination temperature from its medium setting can easily be compensated by increasing the values of the homogenisation time and of the homogeniser speed (Figure 2). The additional process knowledge obtained through and besides the experiments furthermore reduces problems later during scale-up and thereby also the corresponding effort in time and material. So statistical design of experiments is indispensable for “Quality by Design”; it can be performed easily with user-friendly software tools such as STAVEX from AICOS Technologies.