Quality by Design

Get to the production scale quickly and successfully with Design of Experiments

Quality by design means to design a process from its development onwards so as to avoid the later occurrence of major problems, shall it be during the scale-up or the production. The team of experts of Glatt GmbH has been working successfully for some time according to this method. To this end, the engineers put an emphasis on precise experimental design with the software package Stavex.

Dr. Norbert Pöllinger,
Glatt GmbH
Dr. Stefanie Feiler,
Dr. Philippe Solot,
AICOS Technologies Ltd.

A pharmaceutical product has been developed with a lot of effort, the formulation is correct, even the authorization of FDA is available – and then, at the scale-up, the desired API dissolution profiles cannot be achieved anymore. The support team of the company Glatt is often confronted with such scenarios. It supports its customers from the selection of the appropriate technology to the development of the final production process, as it has been the case in the example just described. The pharmaceutical product consisted of modified-release (MR) pellets. The pellets are spray-coated, whereby the second last layer controls the dissolution dynamics (Figure 1). The API delivery should be pulsatile and occur after eight hours. Unfortunately, many factors influence the product quality. Some effects may be predictable (e.g. yield or agglomeration rate) but one cannot really predict how the agent release will behave depending on the process parameters. Common problems with the processing of modified-release coatings, which are like here based on aqueous dispersions, are in particular due to the stickiness of the coating materials as well as to the adjustment of the optimal film forming temperature.

The expert team at Glatt takes a systematic approach. Overall, a production process should be designed in such a way that it is reliably reproducible and as robust as possible against process fluctuations. And therefore the scale-up process should run as fast and as easy as possible – and with a manageable number of experiments. For a commercial production, attention should be paid not only to the product quality, but also to an efficient and hence economical production method. This is why Glatt makes a point of evaluating and testing all possible problems already during the process design, even for product and process development at a small scale. In case something has to be corrected later on, the effort is much higher.

Efficient approach using Design of Experiments

First, the critical limits of the production processes are evaluated in preliminary experiments. The aim is to be able to choose the parameter setting in the subsequent optimization experiments in such a way that all experiments are feasible. There are some parameters like the system or nozzle configuration, for which the effect can be estimated in advance. However, in the present case, four factors remain, the influence of which on the future quality of the pharmaceutical product is critical and requires a thorough analysis. The volume of the fluidized air flow influences the product fluid bed and the atomisation pressure influences the yield as well as the agglomeration behaviour. The inlet air temperature and the spray rate of the coating liquid influence in turn the stickiness of the coating layers. It is now necessary to examine how these factors are linked to each other.

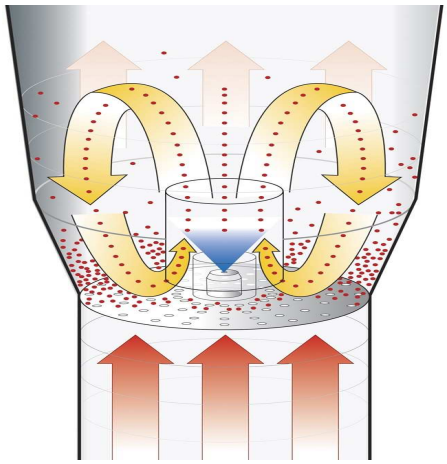

Figure 1: Wurster fluid bed process to produce modified-release pellets.

For the closer examination, Design of Experiments comes into play. If the number of experiments should not escalate out of control, a systematic simultaneous variation of several factors of influence is only possible with the support of a software. Due to the easy handling, the well comprehensible analysis reports and the clear project documentation, Glatt has decided on the software package Stavex of Aicos Technologies. One only has to input the response variables and the factors, and the software then proposes an experimental design, in this case with 19 experiments. Already this small design allows to analyse the influence of all four factors and

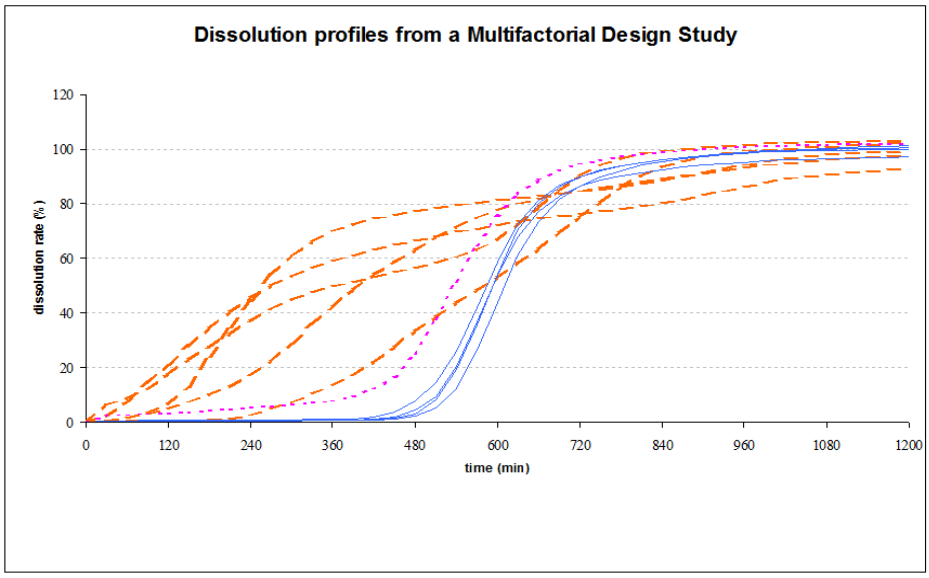

Figure 2: Dissolution profiles for the experimental conditions analysed. The blue curves lie within specifications for the pulsatile API release of the modified-release pellets after eight hours.

of their interactions and to identify optimal settings.
In the case that various experimental designs are possible, these are automatically evaluated and presented with comments by Stavex. The user can simply follow the proposal of Stavex and choose the design recommended. He is also free to take another option. At this point like at many others, it is possible to modify the procedure according to individual priorities.
In the application just described, all factor ranges could be defined quantitatively. For the software however, qualitative factors (e.g. type of nozzle 1 to 5) constitute no obstacle. A further specialty of Stavex is the handling of mixture factors, i.e. of factors that have to sum up to 100% or 20 mg. Stavex even allows several mixture classes, which is in particular useful in galenics. Practical restrictions like “at a high temperature the spray pressure has to be increased” or alternative factors (either filler 1 or 2, either batch size 35 kg with a drying time of one to two days or 40 kg with a drying time of one to three days) can very easily be taken into account.

Optimization of the dissolution dynamics

In order to examine the dissolution behaviour of the API contained in the pellets, one registers its release curve. The API release is characterized by the corresponding values, obtained after 6, 8, 10 and 12 hours, as well as by the value $t_{50\%}$. Besides, response variables can also be specified qualitatively. Such a qualitative value can be the integrity of the coating film. In order to appreciate globally the compliance to specifications of several response variables, a so-called desirability function can be defined in Stavex. In this way, an optimal compromise setting can be determined automatically. Figure 2 represents dissolution profiles obtained with different experimental settings. Those dissolution curves that fulfill the specifications are marked in blue. However, the optimum calculated by Stavex can be different, since another combination of factor settings may lead to an even better behaviour. Overall, in the case presented, one obtains that it is advantageous to work with a high fluidized air flow at moderate temperatures (Figure 3). The spray pressure for the coating liquid however has no noteworthy effect on the product quality “API release”. The system, and therefore the product quality, thus react sensitively to changes in the factor settings.

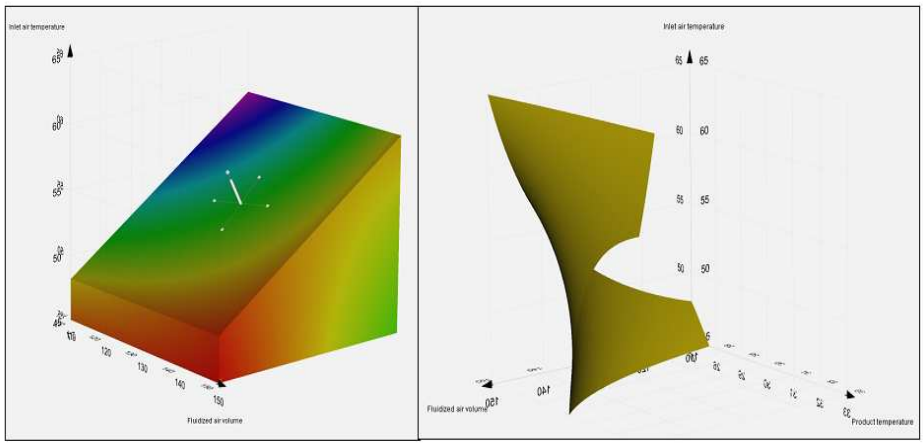

Figure 3: 4D-graph generated by Stavex. X-axis: fluidized-air volume, y-axis: product temperature, z-axis: inlet air temperature; the response variable “API release after eight hours” is coded in colour. The colour scale ranges from 2% (red) to 65% (violet). The target value is 10%. The area concerned (orange) is represented separately (right picture) in form of an iso-surface.

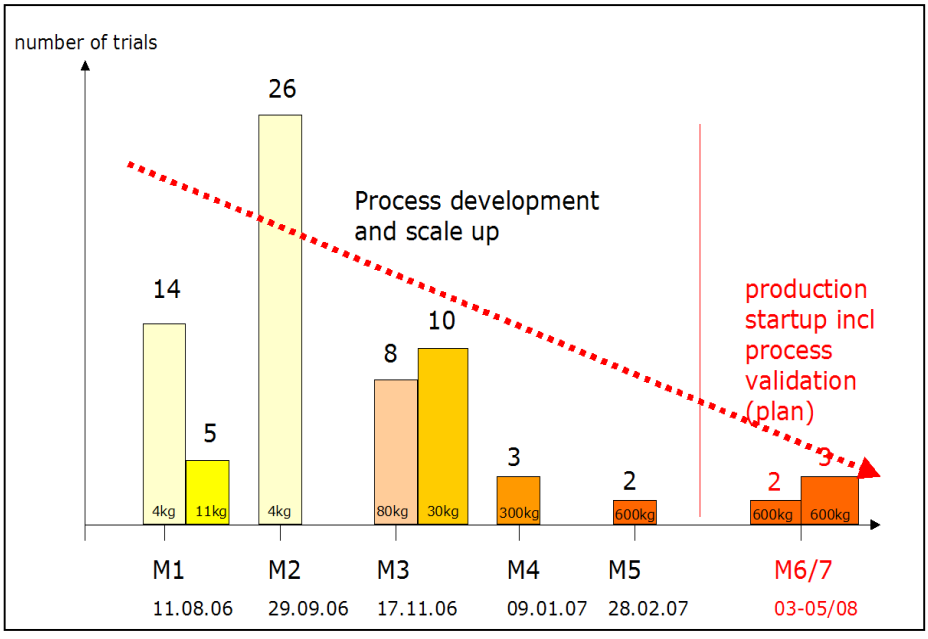

Figure 4: Experimental effort during various phases of a process development project of Glatt GmbH. By applying early targeted Design of Experiments the experimentation at production scale can be reduced to a minimum.

Experimenting in a planned and controlled way

The combination of the experience and the expertise of the process developers at Glatt with a powerful Design of Experiments system like Stavex allows a fast and efficient process optimization. If the quality is already ensured at the design phase, unpleasant surprises during the scale-up can be avoided. Figure 4 shows, using a typical project of Glatt, how the scale-up process can be run with very little effort by applying early Design of Experiments. Moreover, this methodology – the controlled and planned experimentation – enables to gain advanced knowledge of products and processes. In the project described, the influence of the parameter setting on the agglomeration behaviour as well as on the dissolution kinetics could in particular be examined and clarified in detail.