Defining the Design Space

Better process knowledge facilitates validation

The FDA PAT initiative emphasises "Quality by Design": Already during development it should be ensured that a process can later bcontrolled easily. This decreases the effort for scale-up and in production considerably, and allows for a more flexible validation. In order to define the Design Space, only a few steps are necessary when a well-structured design of experiments is used.

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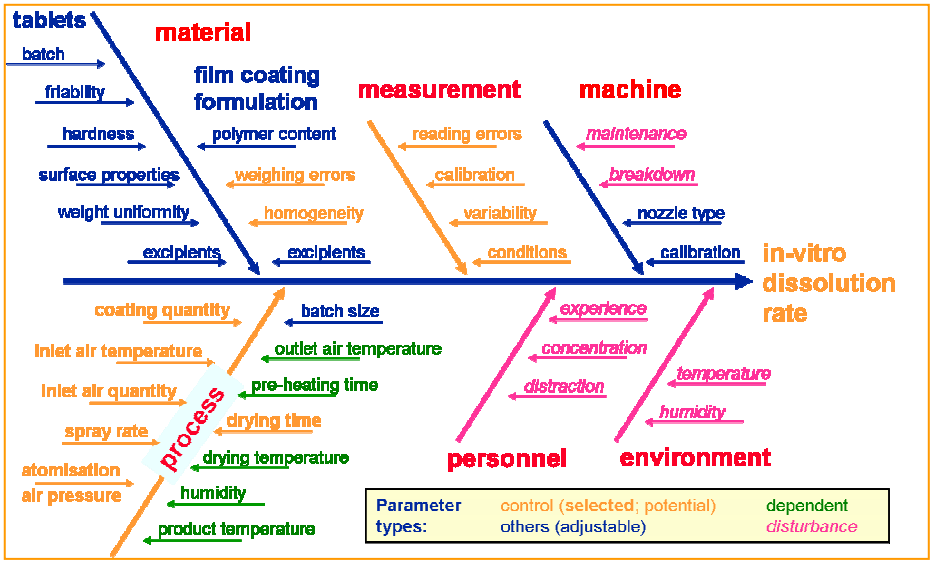

Fig. 1: Ishikawa diagram: Identifying the influence factors for the dissolution rate. For this optimization, the process control factors (orange, bold) were investigated.

The traditional GMP validation of a process is done by showing that, with appropriately fixed settings, a stable quality is obtained. This unfortunately implies that any later change has go be documented. Modifying the process or actually establishing process improvements generates considerable effort. Since the new PAT initiative, more flexibility is possible: when detailed process knowledge can be proven, this will be acknowledged by the FDA. Required is information on how formulation and production process factors impact the product quality and performance. Moreover, process control strategies must be available, which promise to avoid or at least to reduce bad quality in advance.

Reality is complex

For practice this means that first of all the important process parameters have to be identified. When these are known, the optimal process settings are determined. Usually good results can be obtained with several different settings. The entire multidimensional space in which adequate quality is produced is then validated as Design Space. Since the process is well known, an easy control is possible. For instance, the effect of increasing one factor can be compensated by an equivalent adjustment of the other factors. As long as influence factors are changed only within the Design Space, no re-validation is required.
At the Ostwestfalen-Lippe University of Applied Sciences, a Design Space was determined for the coating of modified-release tablets in the context of a bachelor thesis. The aim was to obtain a dissolution profile with specified dissolution rates at given time points.

Spray coating is a complex process in which a lot of factors interact (fig. 1). The quality of the tablets and their dissolution behaviour strongly depend on the selected settings. Nevertheless, it was possible to reach satisfying process settings with only a moderate number of experiments.

Systematic approach with computer aided Design of Experiments

In a first step, the coating film composition was optimised. An indispensable tool to achieve such goals is statistical Design of Experiments (DoE). Only with DoE, sufficient process knowledge can be obtained from a strictly limited number of experiments. Here the choice fell on the expert system STAVEX. It allows applying DoE even for persons without much previous experience in using the method.. The approach is to focus on the problem, not on the methodology. The user enters the response variables - and the potential influence factors. Subsequently, he or she is guided by the software through the entire DoE project. For the spray-coating, the dissolution at the two main time points (2h and 6h) and the qualitative ("yes" / "no") criterion crack formation were chosen as response variables. Amount of coating material, inlet air temperature, inlet air quantity, atomisation air pressure, spray rate and drying time were the process factors. In order to reduce the amount of experiments, it was decided to investigate only five of the fifteen possible pairwise interactions, and to neglect the others. As further restriction, it had to be considered that the factors could only be changed stepwise. Moreover, it turned out that the spray rate could not be varied independently of the inlet air temperature and quantity. In preliminary experiments, a high spray rate required that the other two factors were not set too low.

Manager summary

- **For the definition of the Design Space, critical process parameters (CPPs), critical material attributes (CMAs), as well as the desired quality characteristics (critical quality attributes, CQAs) have to be specified.**
- **Enhanced knowledge leads to the development of more efficient processes.**
- **Defining the design space simplifies the scale-up, ensures high quality in production, and facilitates the validation.**
- **The computer-aided statistical design of experiments (DoE) reduces the experimental effort for defining the design-space and allows adapting the investigated factor regions if necessary.**

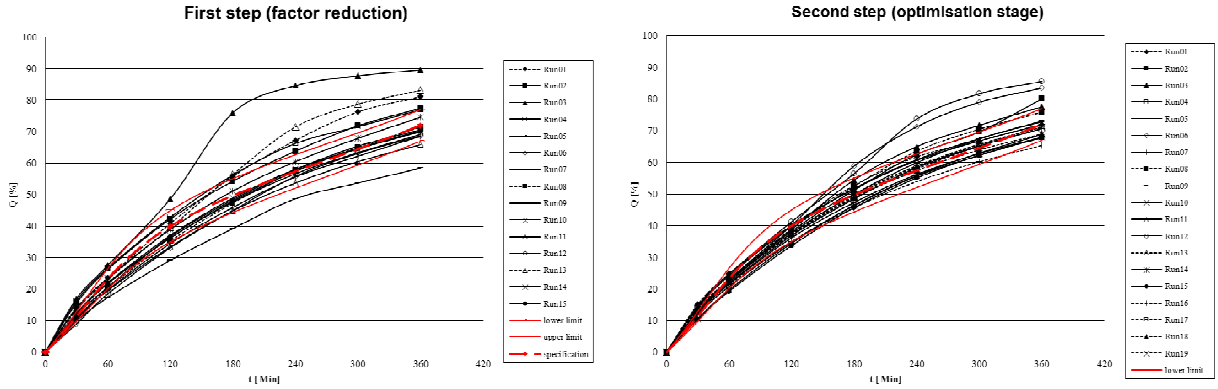

Fig. 2: The dissolution profiles obtained in the two experimental steps. The specification limits are marked in red. Already in the optimization stage, almost all profiles are within the specification.

All these real-life limitations can be taken into account easily in the DoE tool STAVEX. The software then proposes adequate designs of experiments, in this case starting from only 15 experiments.
The analysis report is formulated in natural language, and thus is easily understandable. However, the tool does not omit the necessary statistical tests. The analysis established that inlet air temperature and quantity do not play a role. For the dissolution after six hours, as well as for the crack formation, only the amount of coating material was important. The quality of the coating was also examined with an electron microscope. This confirmed that a too small amount of coating material promotes the formation of cracks, as then the coating does not take place reliably.

Optimisation of the dissolution profiles

In the second step, the process settings were optimised. A sequential approach as implemented in the DoE expert system STAVEX does not only reduce the experimental effort. It also allows to shift the factor ranges if necessary. On the basis of the previous results, the drying time could be reduced, and it was decided to increase the amount of coating material. For the spray rate and the atomisation air pressure however, the ranges were kept unchanged, as an adjustment was impossible for technical reasons. The unimportant factors were fixed. As the system now was to be examined in detail, a design with 19 experiments was selected. Almost all dissolution profiles were within the specification (fig. 2), however at some settings, cracks still appeared. An automatic compromise can be obtained using the implemented desirability function.
The model quality must of course be tested in confirmatory experiments. The optimal settings lie at a low spray rate, a short drying time, the smaller amount of coating material, and a medium atomisation air pressure. A large amount of coating material requires a comparably long drying time and a low atomisation air pressure. With a high spray rate, an irregular film coating can be obtained due to the spray drying and the spray suspension loss. Therefore, the Design Space was defined as the area in which all specifications limits are respected.

Design of Experiments: the efficient way to process knowledge and design-space

The example shows that it is definitely possible to define a design space with a very restricted number of experiments. The systematic experimentation moreover provides important knowledge on the process mechanisms. The Ostwestfalen-Lippe University of Applied Sciences offers to perform such projects within industry cooperation.
Statistical design of experiments (DoE) is in fact only one tool proposed by the FDA. The PAT initiative also comprises process simulation, setting up knowledge databases, as well as implementing online quality control in production. However, DoE is indispensable as first step in product and process development. AICOS Technologies here offers consulting services and training. The final conclusion remains valid: “Quality cannot be tested into products; i.e. quality should be built in by design”.

References

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[2] ICH Guideline Q8, Pharmaceutical Development, (Nov 2005).

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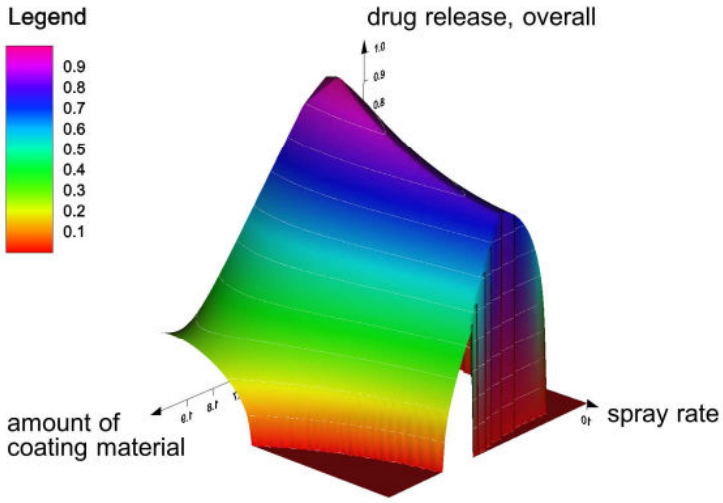

Fig. 3: STAVEX graphic: The desirability function (“Drug release, overall”) vs. amount of coating material and the spray rate. As long as the desirability function is larger than zero, the pro-cess lies within the specifications. Values near one in-dicate a good accordance with the specified targets.