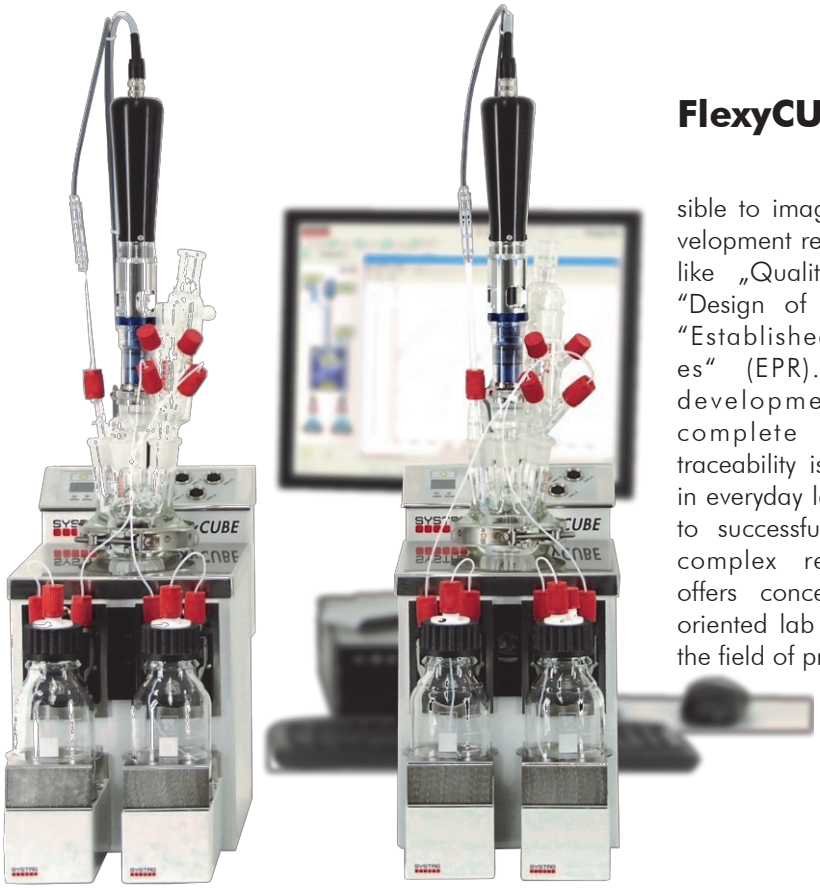
Application note

Efficient synthesis development using the example of determination of the metastable zone



FlexyCUBE

Nowadays it's impossible to imagine operations and development research without keywords like „Quality by Design" (QbD), "Design of Experiments" (DoE) or "Established Parameter Ranges" (EPR). Efficient synthesis development combined with complete logging and data traceability is gaining in importance in everyday laboratory work. In order to successfully meet these entire complex requirements, SYSTAG offers conceptual and application oriented lab automation solutions in the field of process optimization.

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Metastable zone

Introduction

Efficient operations and development research is now, more than ever, an absolute must, especially for custom manufacturer and API developers. New products/operations have to be ready for the market at a faster rate. Development departments are short of resources and the available staff is generally fully stretched dealing with administrative activities. Therefore, it's not surprising that usually there isn't much time left for serious process development, or that the necessary security related research is underfunded. At the same time pressure, concerning logging is building up in early operations research. This again leads to the fact that the new processes pass through the scale-up without further examination and subsequently very often lead to unexpected problems in the production. Downtimes, expensive and time-consuming scale-down measures become necessary.

In order to counteract this successfully, a conceptual lab automation supports chemists in a very early stage of development. On the one hand, time-consuming chores like dispensing, tempering or other tasks are left to an automated laboratory reactor and on the other hand, complex cohesions are noticeable in a very early stage of development, due to consistent data recording and visualization. The scarce, personnel resources can be once again used for more important tasks.

Below, the application of FlexyCUBE in the parallel process development is demonstrated using an application example "Determination of the metastable zone (MSZ) of a product solvent mixture".

Chart 1: FlexyCUBE - Parallel Synthesis Workstation

Metastable zone

Objective

The objective is a successful efficiency enhancement of laboratory work in the general process of development for R&D purposes, as well as in particular in EPR-Operations (Established Parameter Ranges). Reproducible, individual, independent and complete recorded test series are necessary to determine and interpret the metastable zones of a product solvent mixture.

Determination of the metastable zone (MSZ) of a product solvent mixture

When it comes to crystallization processes, the knowledge of the metastable zone is very helpful for a successful scale-up and serves as a basis for a robust procedure at the same time. If located in the sated range of product concentration, one risks a spontaneous crystallization, along with significant problems, like a loss of yield.

In order to determine the metastable zone of a product solvent mixture, in the case at issue, using Isopropylacetate (IUPAC) as the solvent, various exact heating and cooling cycles have to be conducted over a certain temperature range in different concentrations. Exact temperature ramps as well as continuous dosing of liquids play a decisive role. At the same time the solubility and crystallization points are determined through on-line analytics (turbidity measurement, particle measurement). This way the periodical sample taking is also omitted, leading to a simplification of the procedure and an enhancement in the efficiency.

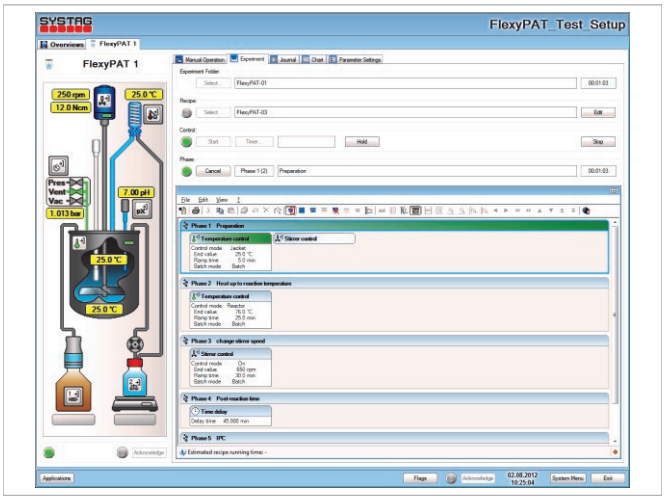

Chart 2: User interface

Metastable zone

Through integrated and intuitive drag & drop recipe editors a procedure can be created, to run through the defined temperature profiles successively. Between the individual heating and cooling cycles, integrated dosages enable a recipe control automation and thus reproducible addition of predefined chemicals/ solvents, even without the presence of lab personnel. If needed, additions can be temperature controlled as well. An optionally implemented turbidity measurement determines the exact clearing and turbidity point, depending on the available product concentration and the current product temperature.

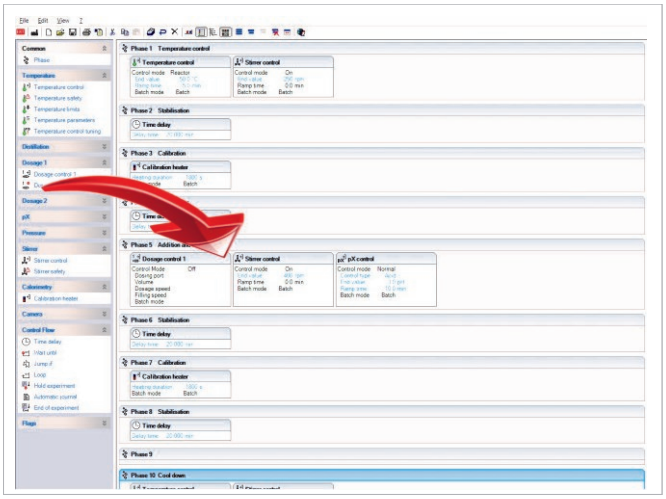

Chart 3: Drag&Drop recipe editor

Based on the measured data, two graphs are formed, which describe the metastable zone of the product solvent mixture. In the current example, it can be immediately recognized that the borderline of the metastable zone can be easily reached in the distillation process sequence through concentration.

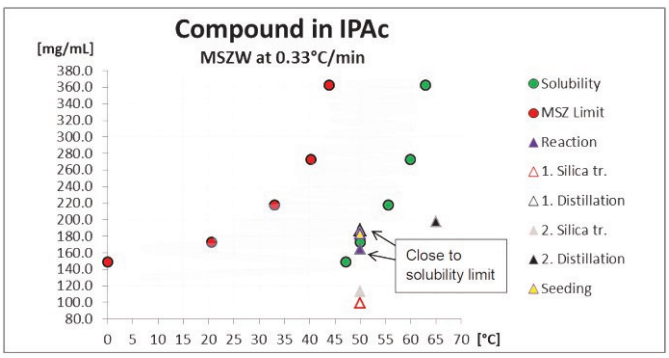

Chart 4: Original procedure

Metastable zone

In this case, the risk of a spontaneous crystallization and several resulting problems has been counteracted with an adjusted procedure (reaction control).

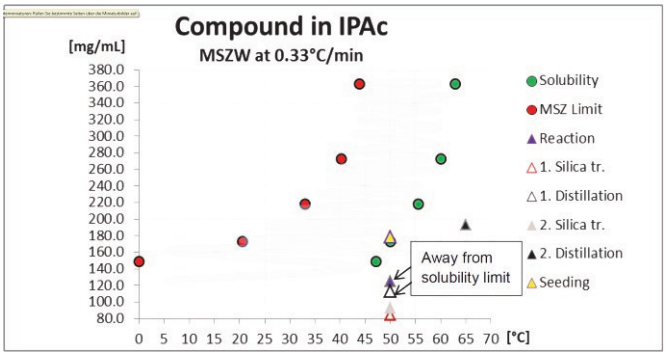

Chart 5: Optimized procedure

Equipment

In order to determine the metastable zone, a FlexyCUBE with 2 reactor units and with a reaction volume of 250 ml was on hand. The parallel reactor system allows an expansion of up to a maximum of 6 reactors with different reactor volumes (70 ml / 100 ml / 250 ml / 400 ml). The robust sulfonation flask-like, single-walled reactor is easy to use, open, change and clean.

Additionally each reactor unit has 2 individual, gravimetric dosages. The dosages can also be programmed using temperature control for general process development. Different dosage lines enable a wide area of application, sometimes also dosage of stirred suspensions or pre-tempered solutions. In order to cascade reactors, even a liquid transfer from reactor to reactor is possible. It can be optionally extended, through a pH-measurement or even with a one-sided pH-control, based on an available dosage.

The efficient mixing of reaction solution is attained through the stirrer motor with different stirring shaft options. A low-maintenance and absolutely sealing stirring shaft execution enables even distillations in vacuum.

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Conclusion

The determination of the data and the trial, with the help of 2 FlexyCUBE reactor units with the volume of 250 ml/resp. 400ml, was very easy. The data collection via a turbidity probe (Solvias/Trb8300), represented on-line and directly in the same chart as temperature, dosage, speed etc., simplifies the evaluation and interpretation of data. Three attempts were necessary to determine various data, with approximate experiment duration of 24h each. Creating the recipe requires roughly 30 minutes and bears very good proportion to this trial. The conceptual lab automation solution with integrated safety monitoring and customized alarm management allows unsupervised operation around the clock.

With a conventional trial, without the support of FlexyCUBE, the operation would be considerably more time-consuming and the data analysis and evaluation would be many times more complex. In addition to that, the continuous presence of lab personnel would be required to conduct manual dosage and to record in detail. Recognizing the correlation between temperature, concentration and turbidity without consistent laboratory automation and data gathering would also be limited. The required amount of time to get equivalent and meaningful results, without using FlexyCUBE, would be twice as long in the case at issue. Furthermore, the evaluation of data based on automatic data recording is significantly simplified.

The combination of laboratory automation and on-line analytic shows clear advantages and increases lab efficiency significantly, especially when it comes to time-consuming tasks, without neglecting the safety factor. With automated reactors like FlexyCUBE, parallel running experiments can be reproduced accurately and independent of operators. Consistent implementation leads automatically to an improvement in quality and will save time, which leads to medium-term savings in costs.

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FlexyCUBE

Parallel Synthesis Workstations for R&D

SYSTAG designs systems for chemical research, process development and scale-up applications. The company offers FlexyCUBE and FlexyPAT, which helps in the research, optimisation and manufacture of fine chemicals and active pharmaceutical ingredients (APIs) for synthetic process development. Modular and integrated automation solutions are provided for millilitre scale and small-batch production. The FlexyCUBE parallel synthesis workstation enables processes to be developed efficiently, allowing rapid and robust scale-up and in-depth quality risk analyses. SYSTAG uses standardised processes to cut costs from early development stages to deliver a high level of reproducibility and informative analyses through an integrated logging function.

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