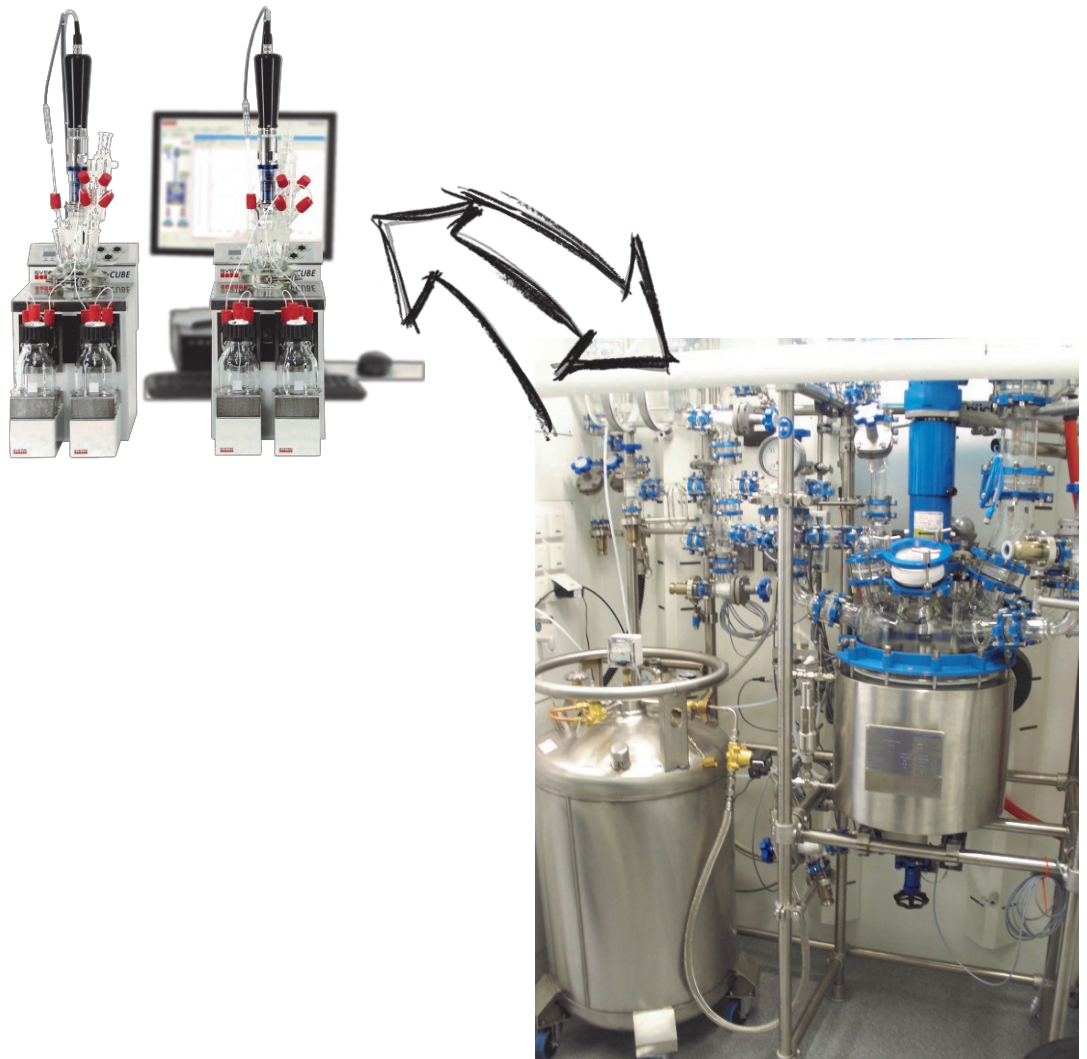


Parallel Process Development and scale-up by factor 300

Application example from the pharmaceutical industry



Introduction

Introduction

In the present application from the pharmaceutical process development, the aim is to transfer processes from the 70ml reactor into the 25lt scale, as efficiently and reproducibly as possible. In most cases, such a scale-up step takes place in different laboratories, in fully diversified plants. A great deal of information is lost, and the knowledge of development Chemists can usually not be implemented optimally.

The integrated automation of laboratory reactors from the smallest scale up to the kilo-batch on one and the same platform is enormously helpful. FlexyConcept from SYSTAG allows this unique feature. All data can be displayed at the click of a mouse in a single chart, whether from milliliter or kilogram scale.



Chart 1: FlexyCUBE - Parallel Synthesis Workstation

The benefit

The benefit

Three different reactor systems (FlexyCUBE 70ml, FlexyPAT 2lt and ChemReaktor 25lt) are operated on the same PC using the application software FlexySys.

Benefit 1: Minimum training and maximum acceptance

Via a remote terminal, the systems can also be monitored and operated at any time from the office workplace or anywhere.

Benefit 2: Increased safety and maximum operating comfort

Thanks to this unique combination of process research, process development and scale-up, the process engineer can realize the complete synthesis and Scale-up of the entire process on the same plant. The seamless data recording from the different reaction variables can be compared easily and quickly with one another. Automation steps or complete recipes can be exchanged between the individual reactors by drag & drop.

Benefit 3: Efficient space utilization and the highest possible throughput of the individual processing steps

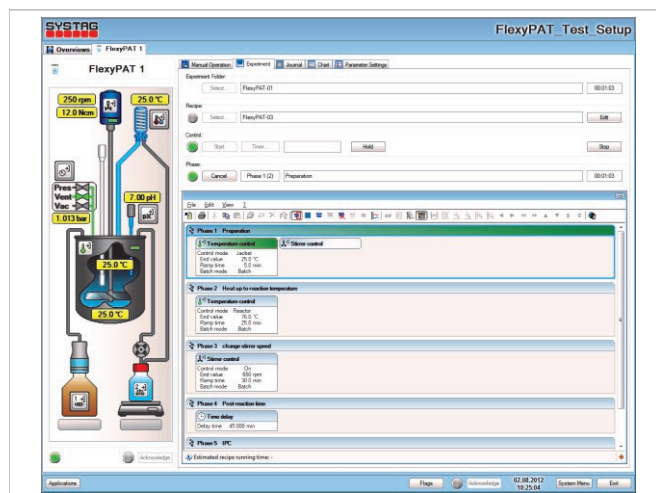


Chart 2: User interface

Screening from 70-250ml

FlexyCUBE-2 for Screening

Reactor system with 2 (up to max 6) reactor vessels

Specification Reactor:

- Size: 70ml and 250ml
- Material: Glass
- Temperature range: -80 ... 280°C

Automated functions:

- 2 parallel feeds
- Stirrer control 50-700 rpm
- Temperature control mode TJ / TR
- pH – measurement and control

Advantages:

Efficient process development thanks to the parallel operation of two or more reactors.

High reproducibility thanks to recipe control.



Chart 3: FlexyLab Parallel Workstation with 2 reactors

The Application

The two FlexyCUBE (Parallel Synthesis Workstation) units with different reactor sizes from 70ml up to 400ml are used as multifunctional instrument for process research (route scouting) as well as for process development. Thanks to the simplicity of the operation and the robustness of the components, the units are already used at a very early stage of the development cycle. Thanks to the fully automated control system, important insights can already be gained from small tests for the next scale-up step.

The system is, of course, also predestined for the processing of test plans (DoE) due to up to 6 reactors for individual operation. The high reproducibility and fully data acquisition enable more and more meaningful results from the experiments. This ultimately leads to fewer attempts and a higher quality of processing.

The integrated on-line and off-line trending makes it easy to compare the different experiments of the 70ml reactor, as well as those from the 25lt reactor.

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.

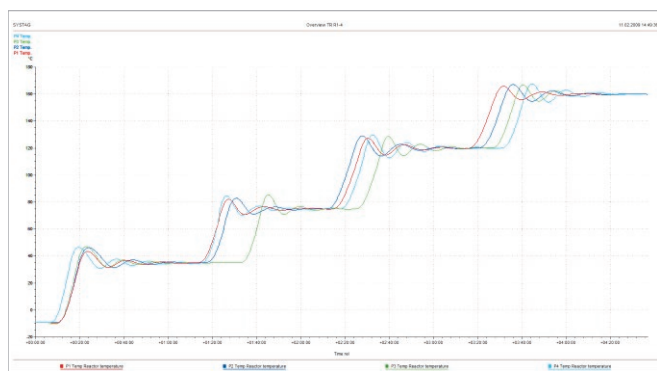


Chart 4: Trend overlay from different experiments

Scale-Up by a factor of 20

FlexyPAT-1 for 1st Scale-Up step

- Triple jacketed glass reactor

Specification Reactor:

- Size: 2000 ml
- Material: Glass, vacuum jacketed
- Temperature range: -60 ... 250°C

Automated functions:

- 2 parallel feeds, optionally also usable for the ChemReactor
- Stirrer control 10-200 rpm
- Temperature control mode TJ / TR
- pH – measurement and control
- Pressure measurement
- Pressure-/ Vacuum and Venting control



Chart 5: FlexyPAT - Controlled Lab Reactor

The Application

After optimizing the experimental parameters by FlexyCUBE, a scale-up of factor 20 may be performed.

In this volume dimension, attention may now be focused on the physical aspects, especially during work-up process.

Whether phase separation in the context of extractions or optimization of crystallization. The combination with online analysis tools such as FTIR or particle size analyzers provide an in-depth and comprehensive insight into the process flow.

With conventional trial, without the support of FlexyPAT, 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, feed rate and pH-value without consistent laboratory automation and data gathering would also be limited.

Furthermore, the evaluation of data based on automatic data recording is significantly simplified.

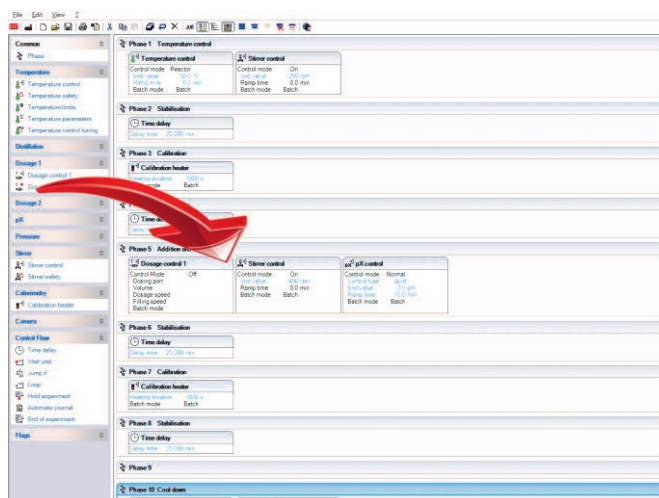


Chart 6: Drag & Drop Recipe Editor

Kilo-Lab

Automated ChemReactor

Specification Reactor:

- Total size: 25 Litre
- Nominal size: 15 Liter
- TR-range: -100/+200°C
- TJ-range: -200/+200°C
- Inside material: Hastelloy C22
- Lid: Borosilicate glass 3.3
- Pressure range: -1/+0.5 bar
- EX-proof Ex II 2G T4 (Zone 1)

Automated functions:

2 parallel feeds, optionally also usable for FlexyPAT

Stirrer speed: max 2000 rpm

Temperature control: TJ / TR

pH – measurement and control

Pressure measurement

Pressure-/ Vacuum and Venting control



Chart 7: ChemReactor 25lt

The Application

Customized

Two independent half-pipe coils are drawn into the reactor bottom part. This allows heating / cooling with heat transfer oil via a thermostat, an in addition, an inexpensive rapid cooling into the low-temperature range by second coil via the evaporation of liquid nitrogen.

The control is completely automated and requires no manual intervention.

The control behavior is excellent and allows ramp speeds up to 10K / min.

Application

A further scale-up step with factor 10 confirms the quality and robustness of the process on the way to production.

The plant is used as a multifunctional production plant for small quantities of active ingredients. The glass structure permits a reflux cooling or subsequent distilling off solvent. After crystallization of the product in the vessel, the suspension can be transferred into a Büchi suction filter for filtration.

Advantages

- Universal control concept from Lab to pilot plant
- Interchangeability of recipes
- Automatic data acquisition and logging
- cGMP/CFR 21 Part 11-compliant qualification

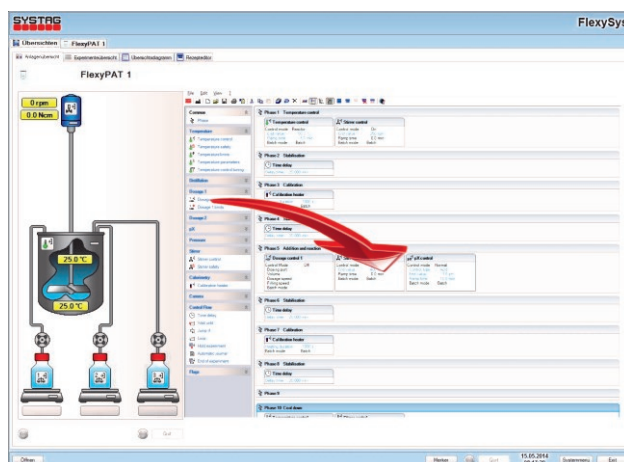


Chart 4: User interface