

# Application Note

## The use of FlexyCUBE in quality/risk analysis

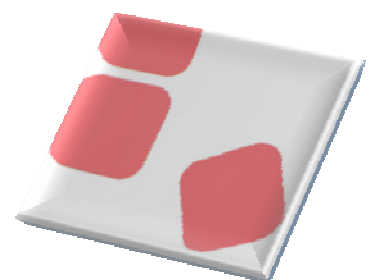
In one reaction step an acid is added with constant TR control and stirrer speed.

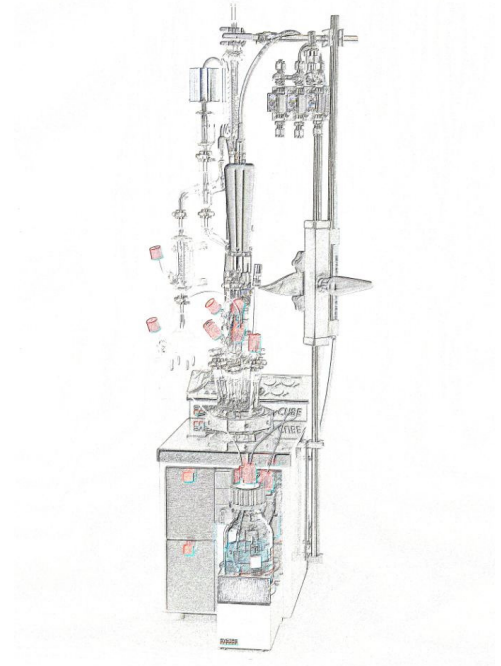
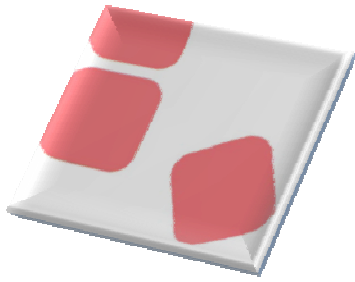
At the same time, pH is kept constant through the use of base. After the addition of acid, pH should be controlled at a defined pH value, and then the reaction mixture is extracted by stirring. Regular in-process controls by means of HPLC record the reaction process.

The suitability of various bases should be examined by means of a series of experiments. It is also necessary to determine the pH range within which the reaction must be carried out in the production operation without quality deterioration.

## Challenge

- ⇒ The current pH (which must be kept constant) at the start of the addition of acid is unknown.
- ⇒ The addition of acid and base is highly exothermic, but the TR that is to be regulated must not exceed a defined deviation from the set-point value.
- ⇒ The duration of the entire reaction takes approx. 10 hours and must be timetabled in such a way that the steps requiring manual handling occur during the times when the laboratory employee is present.





## FlexyCUBE System Configuration

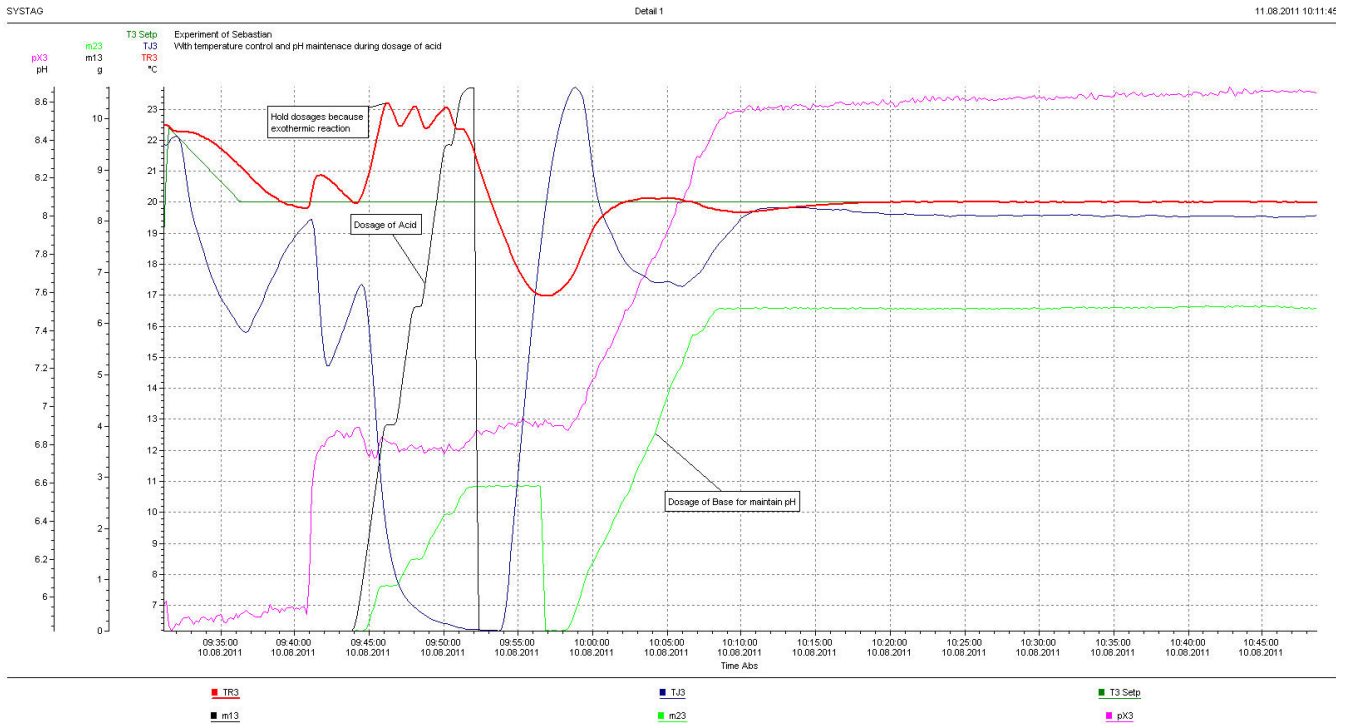
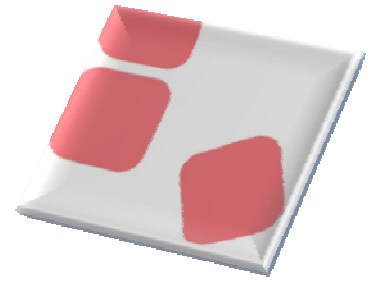
FlexyCUBE Basic System with:

- ⇒ 250ml glass reactor
- ⇒ 2 balances
- ⇒ 2 Pumps
- ⇒ 2x Chemsure peristaltic tube
- ⇒ pH option

## Description of the solution

Since the recipe procedure always takes place in the same way, and only the pH range and choice of base change, a Master Recipe is defined which is used as the basis for each of the experiments. This guarantees the reproducibility and comparability of the data.

Phase 1 Conditioning			
<b>Temperature control</b> Control mode Reactor End value 20.0 °C Ramp time 5.0 min Batch mode Batch	<b>Stirrer control</b> Control mode On End value 200 rpm Ramp time 0.0 min Batch mode Batch	<b>pX parameters</b> Stability band 0.50 pH Stability time 5.0 min P-Term 0.2 pH I-Term 500.0 s D-Term 0.0 s NL factor 1.50	
Phase 2 manual dosage of Pyrrolidin			
<b>Hold experiment</b> Displayed text add pyrrolidine Hold type Continue only Jump to			
Phase 3 reaction step with pH-control with base			
<b>pX control</b> Control mode Maintain Control type Base Reactant End value Ramp time Batch mode Batch	<b>Dosage control 1</b> Reactant End value 10.6 g Ramp time 5.0 min Batch mode Batch	<b>Dosage 1 limits</b> Hold if dV > inactive Hold if dTR > 3.0 K Hold if dpX > inactive Stop if TR > inactive Stop if TR < inactive Stop if pX > inactive Stop if pX < inactive Stop if tEnd > inactive	<b>pX limits</b> Hold if dpX > inactive Hold if dTR > 3.0 K
Phase 4			
<b>Time delay</b> Delay time 5.000 min			
Phase 5 pH-control with base to the end point			
<b>pX control</b> Control mode Normal Control type Base Reactant End value 8.5 pH Ramp time 10.0 min Batch mode Batch	<b>pX parameters</b> Stability band 0.50 pH Stability time 5.0 min P-Term 0.2 pH I-Term 1000.0 s D-Term 0.0 s NL factor 1.50		
Phase 6			
<b>Hold experiment</b> Displayed text check pH Hold type Continue only Jump to			



## Conclusion

The graph shows very nicely how the defined maximum temperature deviation of 3 Kelvin relative to the TR allows the process to be carried out safely and in a controlled way within the desired limits (see acid addition curve: black, and base addition curve: green).

The “Hold” control mode in the basic “pX Regulation” operation in Phase 3 enables the current actual pH value present at phase change to be adopted as the new set-point value.

Reproducible experimental conduct of such a complex operating step is impossible without an automated solution. Thanks to its extensive functional alternatives in carrying out the recipe, FlexySys provides an ideal platform to optimise such processes.

