FlexyCUBE

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.

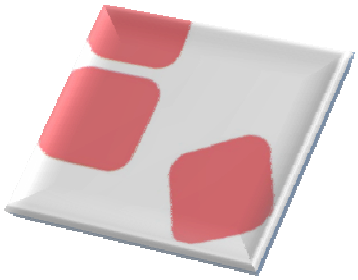
The suitability of various bases should be examined by means of a series of experiments. It is also necessary to determine the pH range within which the reaction must be carried out in the production operation without quality deterioration.

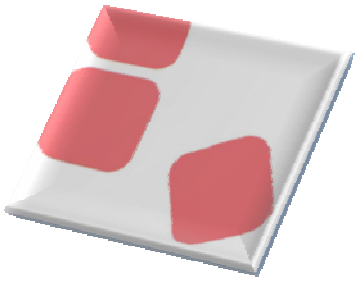
Challenge

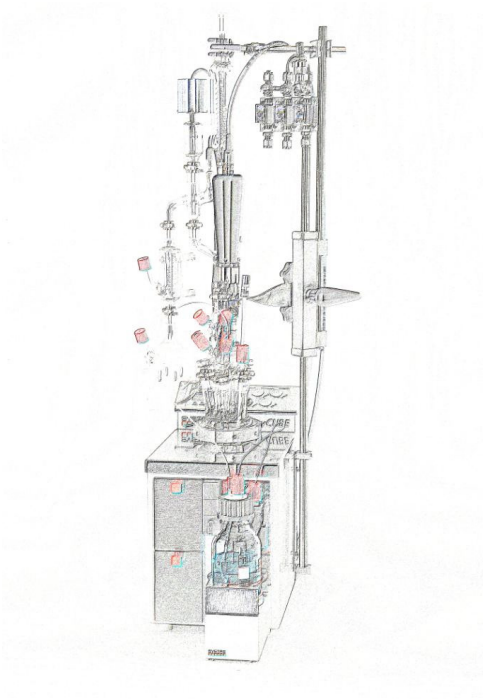
⇒ The current pH (which must be kept constant) at the start of the addition of acid is unknown.

⇒ 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

Temperature control		Stirrer control		pX parameters	
Control mode	Reactor	Control mode	On	Stability band	0.50 pH
End value	20.0 °C	End value	200 rpm	Stability time	5.0 min
Ramp time	5.0 min	Ramp time	0.0 min	P-Term	0.2 pH
Batch mode	Batch	Batch mode	Batch	I-Term	500.0 s
				D-Term	0.0 s
				NL factor	1.50

Phase 2 manual dosage of Pyrrolidin

Hold experiment	
Displayed text	add pyrrolidine
Hold type	Continue only
Jump to	

Phase 3 reaction step with pH-control with base

pX control		Dosage control 1		Dosage 1 limits		pX limits	
Control mode	Maintain	Reactant		Hold if dW >	inactive	Hold if dpX >	inactive
Control type	Base	End value	10.6 g	Hold if dTR >	3.0 K	Hold if dTR >	3.0 K
Reactant		Ramp time	5.0 min	Hold if dpX >	inactive		
End value		Batch mode	Batch	Stop if TR >	inactive		
Ramp time				Stop if TR <	inactive		
Batch mode	Batch			Stop if pX >	inactive		
				Stop if pX <	inactive		
				Stop if tEnd >	inactive		

Phase 4

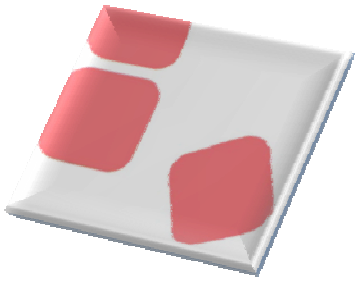
Time delay	
Delay time	5.000 min

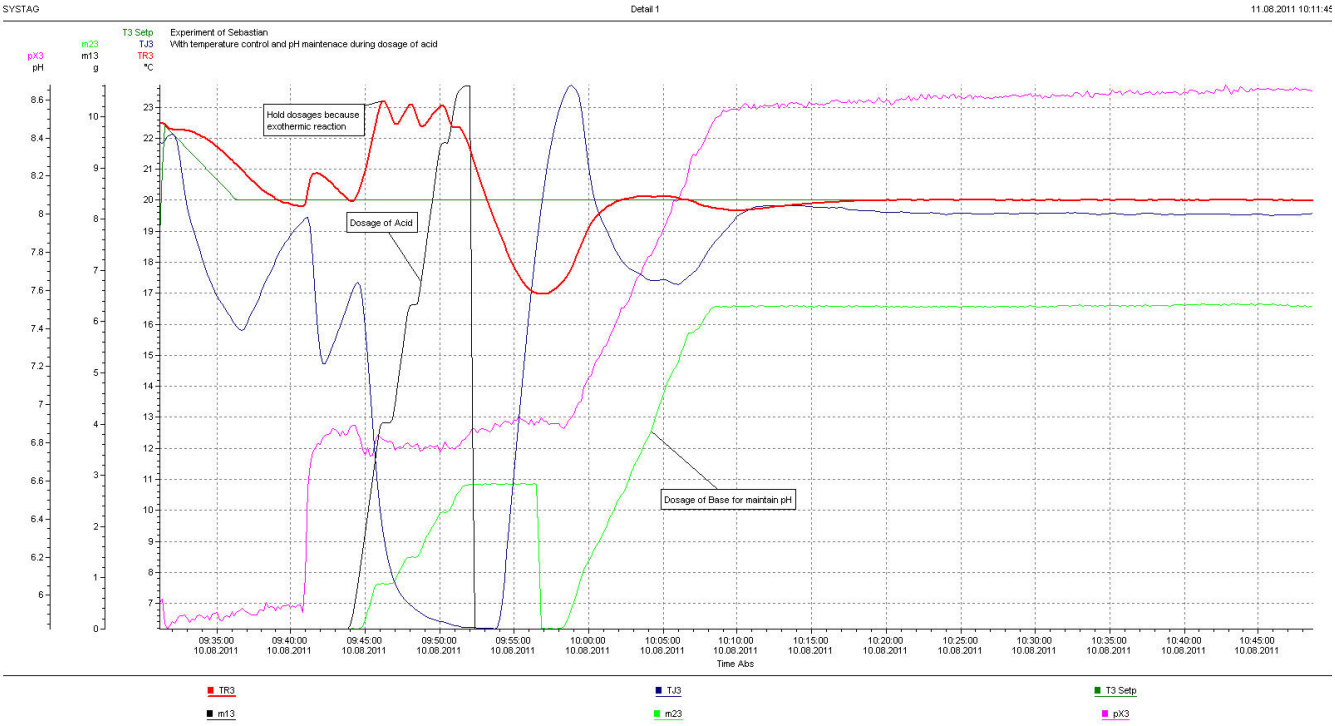
Phase 5 pH-control with base to the end point

pX control		pX parameters	
Control mode	Normal	Stability band	0.50 pH
Control type	Base	Stability time	5.0 min
Reactant		P-Term	0.2 pH
End value	8.5 pH	I-Term	1000.0 s
Ramp time	10.0 min	D-Term	0.0 s
Batch mode	Batch	NL factor	1.50

Phase 6

Hold experiment	
Displayed text	check pH
Hold type	Continue only
Jump to	



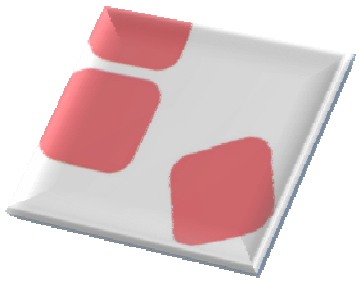


Conclusion

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.



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