

TROUBLESHOOTING for CRYSTALLIZATION PROCESSES

» **SAVED \$2,000,000**

Process: **Reactive Crystallization Acid Base in the API industry**

Task: **Impurity rises during scale up activities**

The Process

Reactive crystallization of organic acid with an inorganic base (NaOH) both solids in Ethyl Acetate solvent in the last step to get a final product before the solid treatment. The reaction that generated the impurity was the hydrolysis of the solvent with the base. This impurity resulted in the final product being out of specifications.

The Problem

Failures during scale up in the same system. An additional problem arose when we shifted it to a second system (at the same scale), resulting in a **rise of impurity by about 3 times**.

The Traditional Approach

Try to achieve better homogeneity of solid distribution in the new system.

The VisiMix Analysis

Surprisingly, **the radial distribution of the solids in the reactor where the purity was acceptable was less homogeneous in comparison with the unsuccessful reactor. As a result, the fast reaction is between the solvent and the base and when the homogeneity is higher, the impurity rises.**

The VisiMix Solution

By multiple simulation scenarios, it was proven that it is not possible to reach acceptable conditions in the scale up system to maintain the impurity level of the product. **As a result, the process was changed by adding the NaOH as a solution, and thus achieving satisfactory results.**

The Results

Scale up by a factor of 4 succeeded, and achieved higher productivity by 4 times.



THE USE OF VISIMIX ALLOWS US:

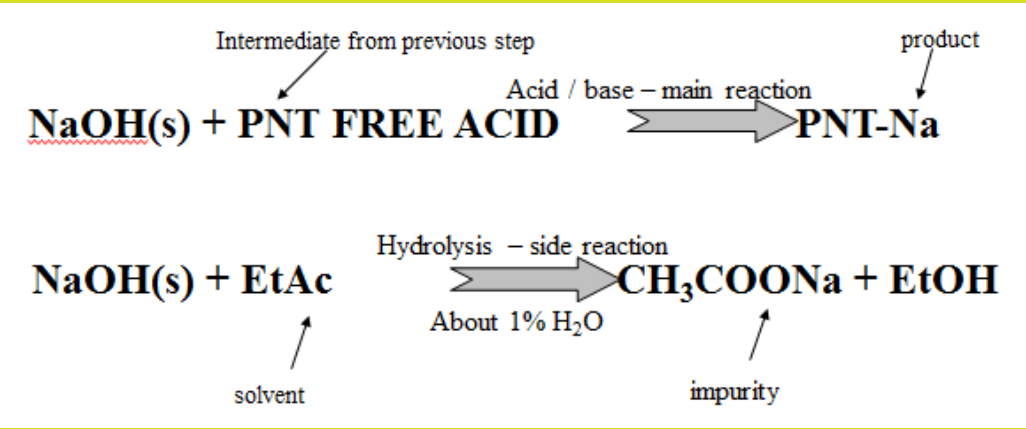
1. To improve out of spec batches from near to 50% to 0 in the new system.
2. Reduce the production by 4 times with no failures in the scale up steps.

The value of this case in the company was estimated at more than \$2,000,000 per year.



TECHNICAL DESCRIPTION

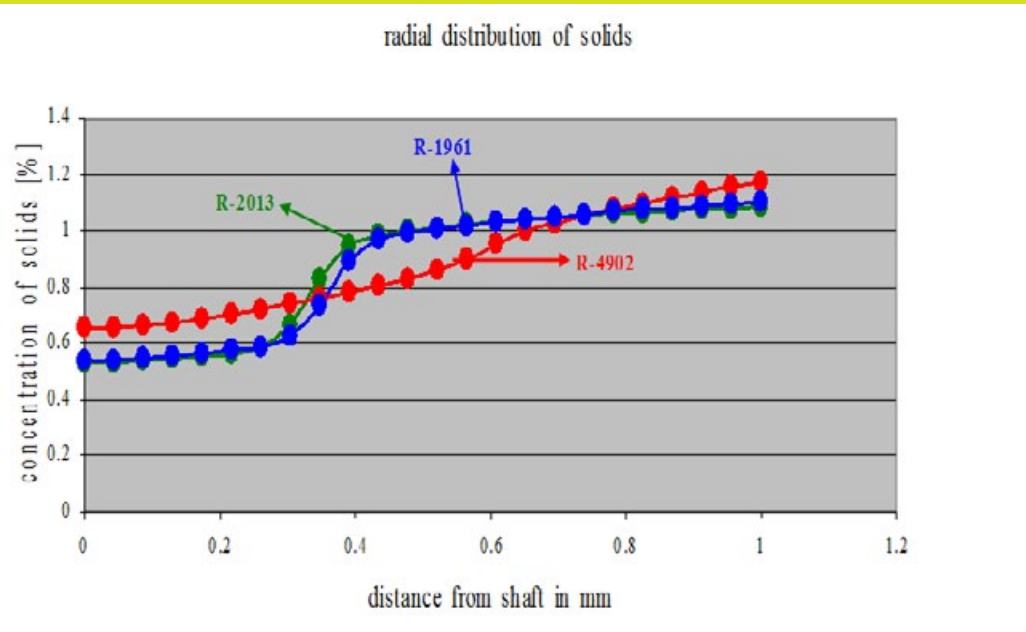
CHEMICAL REACTION



PRODUCTION RESULTS

System	Average imp sodium acetate concentration [%]	Number of batches produced at 2011	% RJ on sodium acetate impurity
R-2013	0.15%	329 batches	1.2%
R-1961	0.19%	195 batches	0.5%
R-4902	0.44%	58 batches	24.1%
specification	NMT 0.50%		

VISIMIX PARTICLE DISTRIBUTION



VisiMix helped us to determine and to implement a new way to think about the continuous process improvement in the production step. Now, every new process must start its activities after evaluating the VisiMix results.