VisiMix

Simulation of Mixing Processes

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Practical Methods for Process Scale-Up

Moshe Bentolila

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  - Homogenous Reaction
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About Us

VisiMix.Ltd is a unique software enabling chemical engineers, process engineers and R&D personnel to characterize and visualize mixing processes via a simple, user friendly interface.

Our products allow significant savings in time and costs by drastically reducing the need for trial-and-error. They have been successfully adopted by hundreds of companies.

Motivation

Common Questions

- ✓ Did we cover the main parameters during the process development?
- ✓ Will our facilities will be appropriate for the developed process?
- ✓ Does the equipment offer is good for the process?
- ✓ What about safety and runaway scenario?
- ✓ Do our process is robust?
- ✓ Does the operational range parameters are large enough for the manufacture facilities?

The Goal

Once the Science of the process (Chemistry, Biology or physics) is known well, a common situation during the process transfer from lab to production or from site to site is the gap between the old and new results.

- **Our first goal is to develop a process that will run properly in the first trial on a new scale or site, similar to our successful results in the lab or in the old facility.**

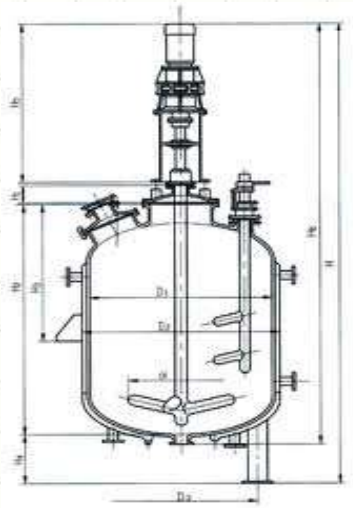
In order to achieve this, we need to evaluate the process with the same conditions we will have in the production phase.

- **The main parameters we change are the hydrodynamics of the system. If we are able to identify and control these parameters we will be able to achieve to the available and optimal solution.**

Data and Results Management

R&D

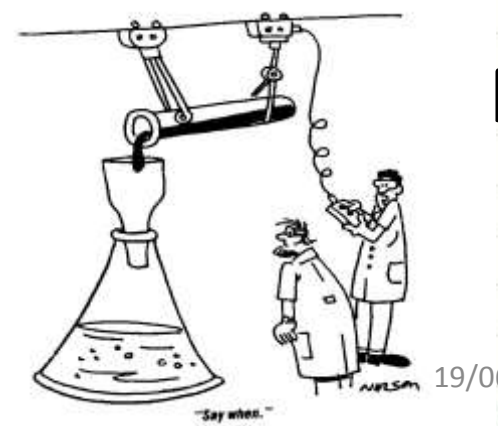
Design



VisiMix

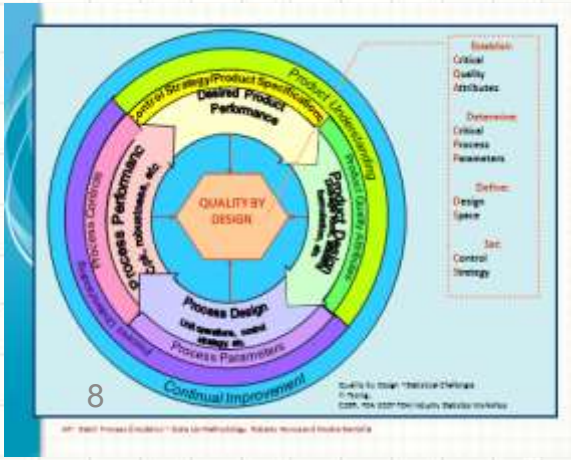
software for chemical engineering

Mixing Simulation Software



Production

QbD



What is Good Mixing?

Troubleshooting in Life Science Industry

Savings of 900,000 Euro!

VISIMIX SOLUTIONS

TURBULENT 2Kx

Low viscosity liquids and multi-phase system

Process: ***Trouble shooting in Life Science Industry after break down of equipment***

Task: ***Understand reason for failed batches and establish new operation conditions with the new equipment.***

The Process

Chemical reaction on porous beads in the life science industry.

The Problem

One product is produced in three slightly different reactors. An intermig impeller was installed in one of the reactors after a breakdown. The flow properties were much higher for batches from the reactor with the new impeller and several batches were out of specification. It was known that oxygen hydrolysis destroys the sugar molecules while the slurry is basic.

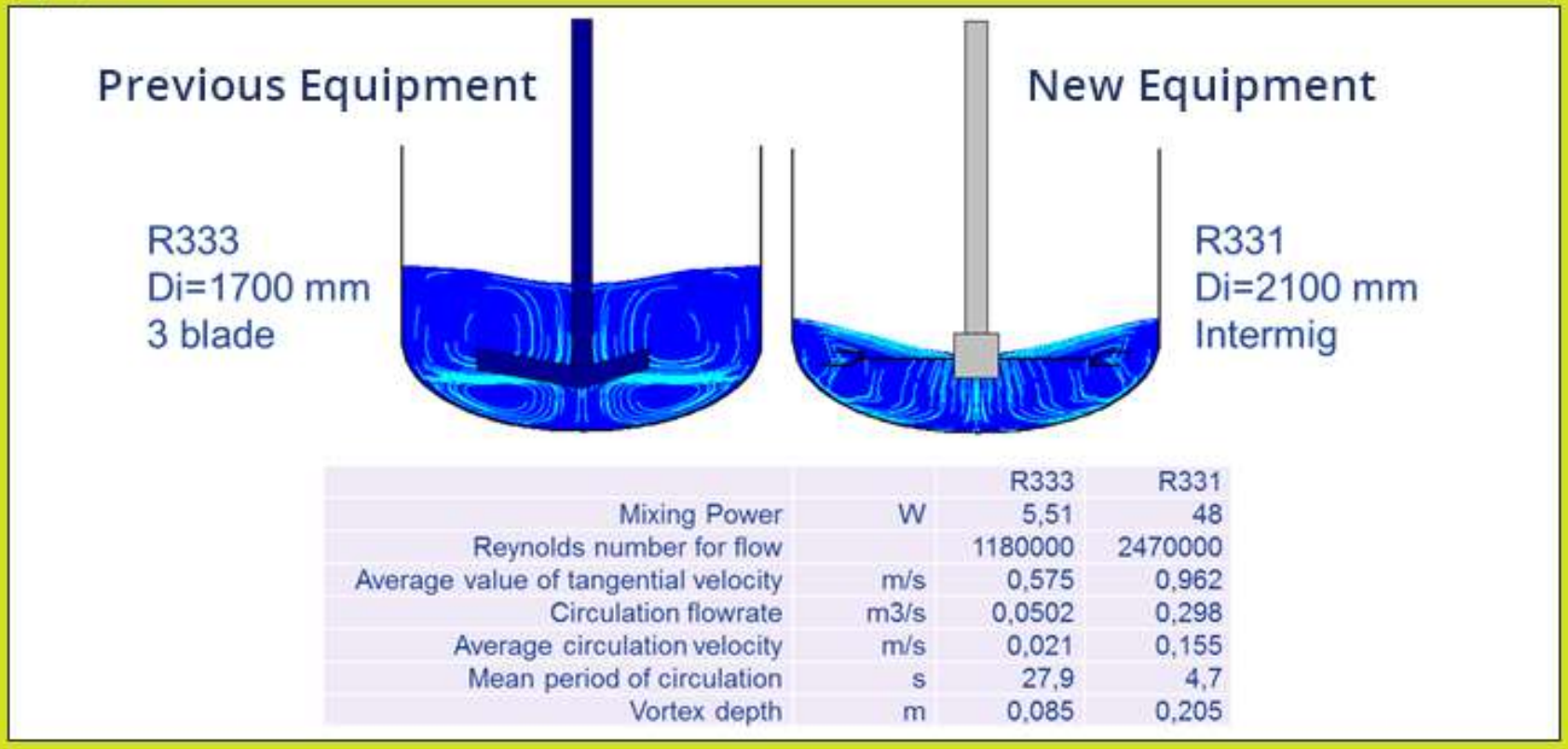
The Traditional Approach	Trial and error in the production facilities in order to do "fine tuning" of the operational parameters in the process. No improvement was observed.
The VisiMix Analysis	VisiMix was used to find out why the process failed and make suggestions to remedy the challenge.
The VisiMix Solution	Due to the design of the old impeller, all beads were found in the lower part of the reactor. VisiMix calculations showed that the improved mixing accelerated hydrolysis. VisiMix also showed that the new impeller was not suited for the process and that the only way to avoid failed batches was to stop using the vessel for this product.
The Results	Oxygen hydrolysis during basic conditions destroys the sugar molecules. Concentration of product much higher below the old impeller. Due to the improved mixing hydrolysis was accelerated.

"From the outcome of this case, we understood that the combination of the company knowledge of the process with VisiMix simulation is more than must – in order to succeed to define new equipment for new processes."

"The Launch was delayed by 6 months and the potential of production during this months is – 1,200,000 Eu and there are some more expenses connected with purchasing equipment"

Technical Description

Process :
Troubleshooting in the life science industry after breakdown and repair of equipment
Task :
Understand the reason for failed batches and establish new operation conditions with the new equipment.



		R333	R331
Mixing Power	W	5,51	48
Reynolds number for flow		1180000	2470000
Average value of tangential velocity	m/s	0,575	0,962
Circulation flowrate	m3/s	0,0502	0,298
Average circulation velocity	m/s	0,021	0,155
Mean period of circulation	s	27,9	4,7
Vortex depth	m	0,085	0,205

Improved mixing accelerated hydrolysis. VisiMix showed that the impeller was not suited for this process, and as a result the production was moved to reactors with appropriate mixing.

Proposed Method

Mixing Calculations in Development

Save with VisiMix (for this example: $1,000,000 per project)!

VISIMIX SOLUTIONS

TURBULENT® 2Kx

Low viscosity liquids and multi-phase system

Process:

Typical Fine Chemical Development

Task:

Decreasing the Number of required batches for Validation Process in the production step.

The Process	Batch and Semi batch Process.
The Problem	Gap between R&D and production results.
The Traditional Approach	Running the process at increasing sized reactors and looking for optimal process and operation parameters at every stage.

The VisiMix Analysis

Implementation of mixing calculations at the first development step as part of the characterization of the process. This activity provides the understanding of the influence of the hydrodynamics in the process. By scaling down calculations, setting the lab equipment according to the output results from the production equipment simulation, it is possible to find the operation surface range for a robust process.

The VisiMix Solution

The relationship between mixing parameters and experimental work based on Quality by Design (QbD) practice, provide the company with a deep " know how" about the process and the scale up activities and decrease the "out of spec." material during the process at different sizes

The Results

As the result of this methodology:

- **Decreasing the required batches for validation in the production step from around 100 to below five;**
- **Savings of at least $1,000,000* per project**
- **Complete the required knowledge for the process understanding.**

The use of VisiMix allowed the company to save $1,000,000 per project by improving the understanding of the influence of the mixing in the process.

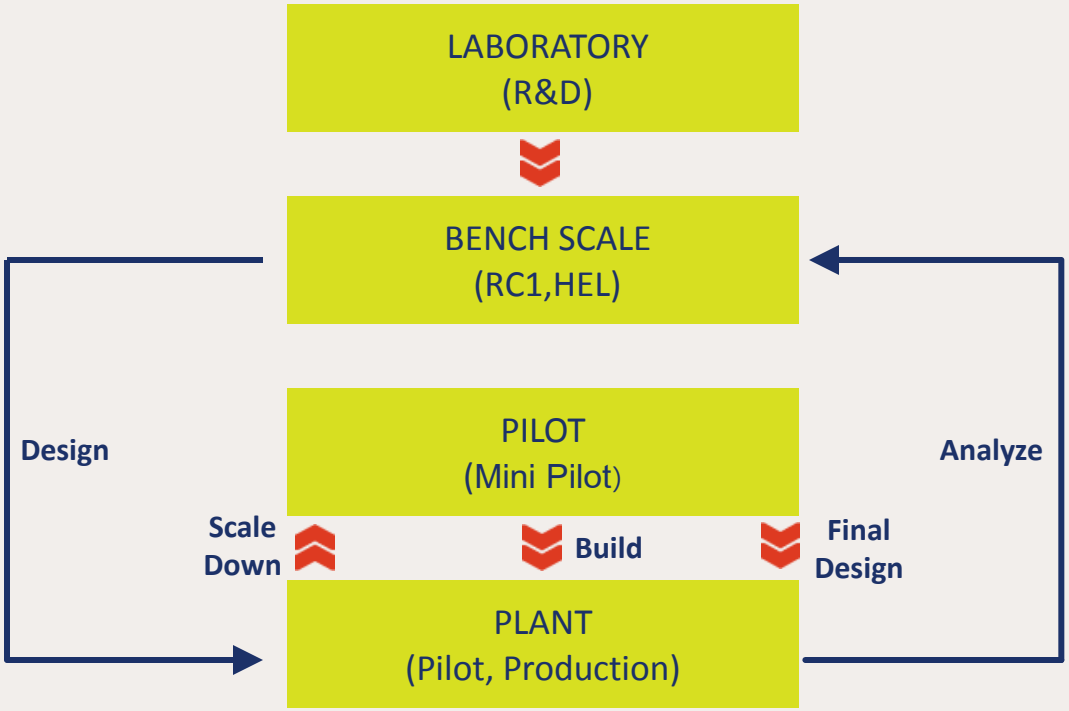
*Based on an average of 25 out of spec. batches in production step with cost of $100 per batch of 400 kg per batch (25*100*400=1,000,000)

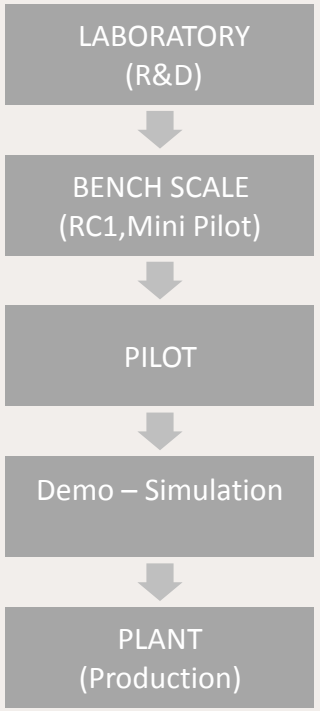
500 rpm

Methodology

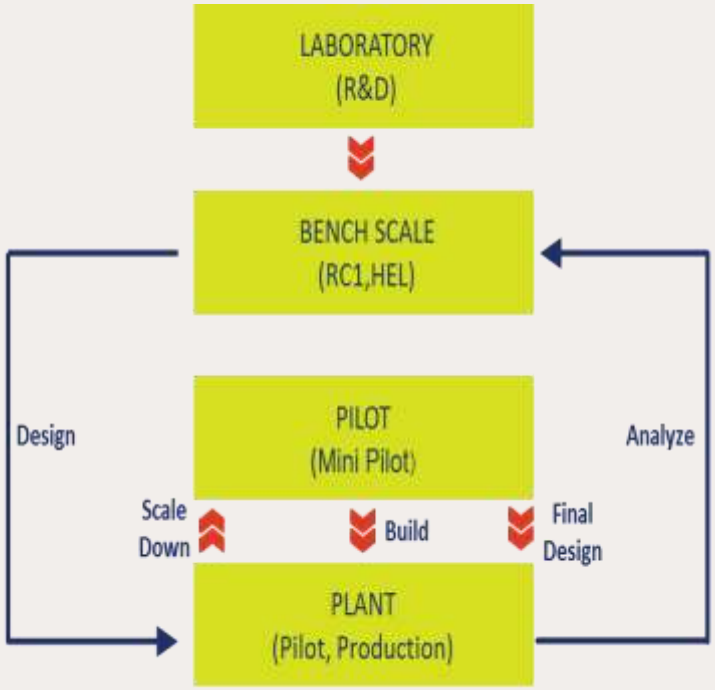
(J.M. Berty, CEP, 1979)

New Process with Mixing





Methodology



- **Step 1**: Know the Mechanism of your Process.
- **Step 2**: Calculate Mixing Parameters will be available to provide in the commercial stage equipment.
- **Step 3**: Set Up Lab or Pilot equipment at the same range of work as calculated in Step 2.
- **Step 4**: Run Statistical Design of Experiments under conditions Set Up in Step 3 and select relevant experiments to proof the mechanism and achieved a good product quality, effective process operation and maximum yield.
- **Step 5**: Model Verification by Scaling down in industrial equipment for sample customer product.
- **Step 6**: Generate a Final Design, Procedure an Operation.

Lab and Prod Calculations

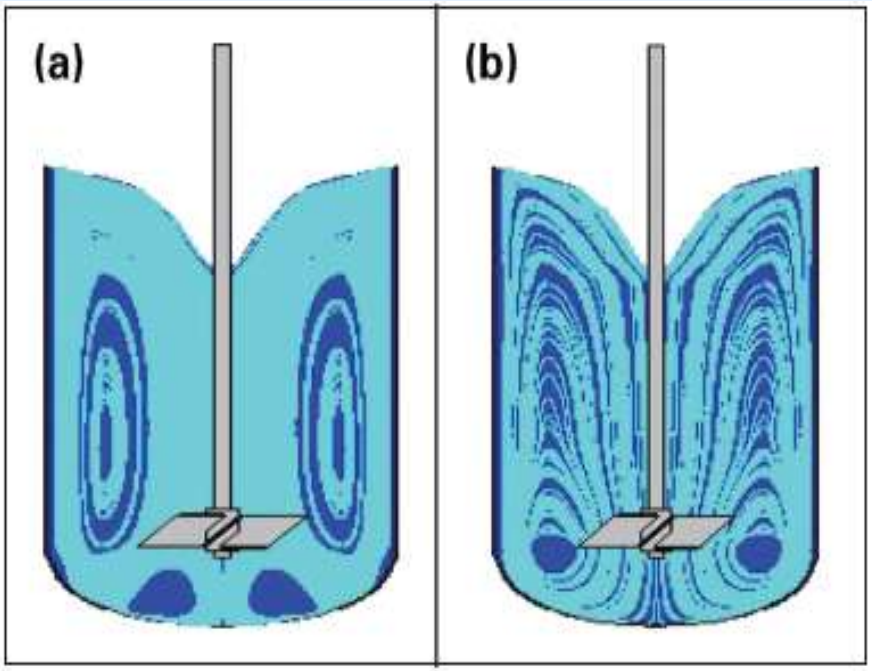


Figure 1. RC–1 General flow – pattern picture, (a) pumping down and (b) pumping up.

Operational Parameter	R 7610	R 7501 Modified
Operation Initial Conditions		
Reactor Volume, L	8	100
Reactor Temperature, °C	70	70
Stirrer Velocity, rpm	450	300
Hydrodynamics		
Mixing Power, W	17	335
Reynolds for Flow	73200	249000
Turbulence Main Characteristics		
Energy Dissipation – Average value, W/kg	2.29	3.61
Energy Dissipation – Maximum Value, W/kg	103	122
Liquid-Solid Mixing Main Characteristics		
Solid Suspended Condition is Expected	OK	OK
Maximum Degree of Non-Uniformity – Axial, %	14	15
Maximum Degree of Non-Uniformity – Radial, %	5	4
Average Concentration of Solid Phase in Continuous Flow, kg/m^3	39	39
Gassing Characterization		
Gas Hold – Up*	0.00024	0.16
Specific Mass Transfer Coefficient Gas – Liquid, 1/s	0.0015	0.655
Gas Mass Transfer Rate*, kg/h	0.0011	6.84
Gas Distribution: Satisfactory, Flooding Not Expected	OK	OK

* Gas Hold-up: represents the average value of volume fraction of gas in the gas-liquid mixture.
* Gas Mass Transfer Rate: rate of gas dissolution corresponding to specific mass transfer coefficient.

Moshe Bentolila, Roberto Novoa, and Wayne Genck, Michal Hasson, Efrat Manoff, "Computer Aided Process Engineering at Chemagis" , PHARMACEUTICAL ENGINEERING July/August 2011. 30-38

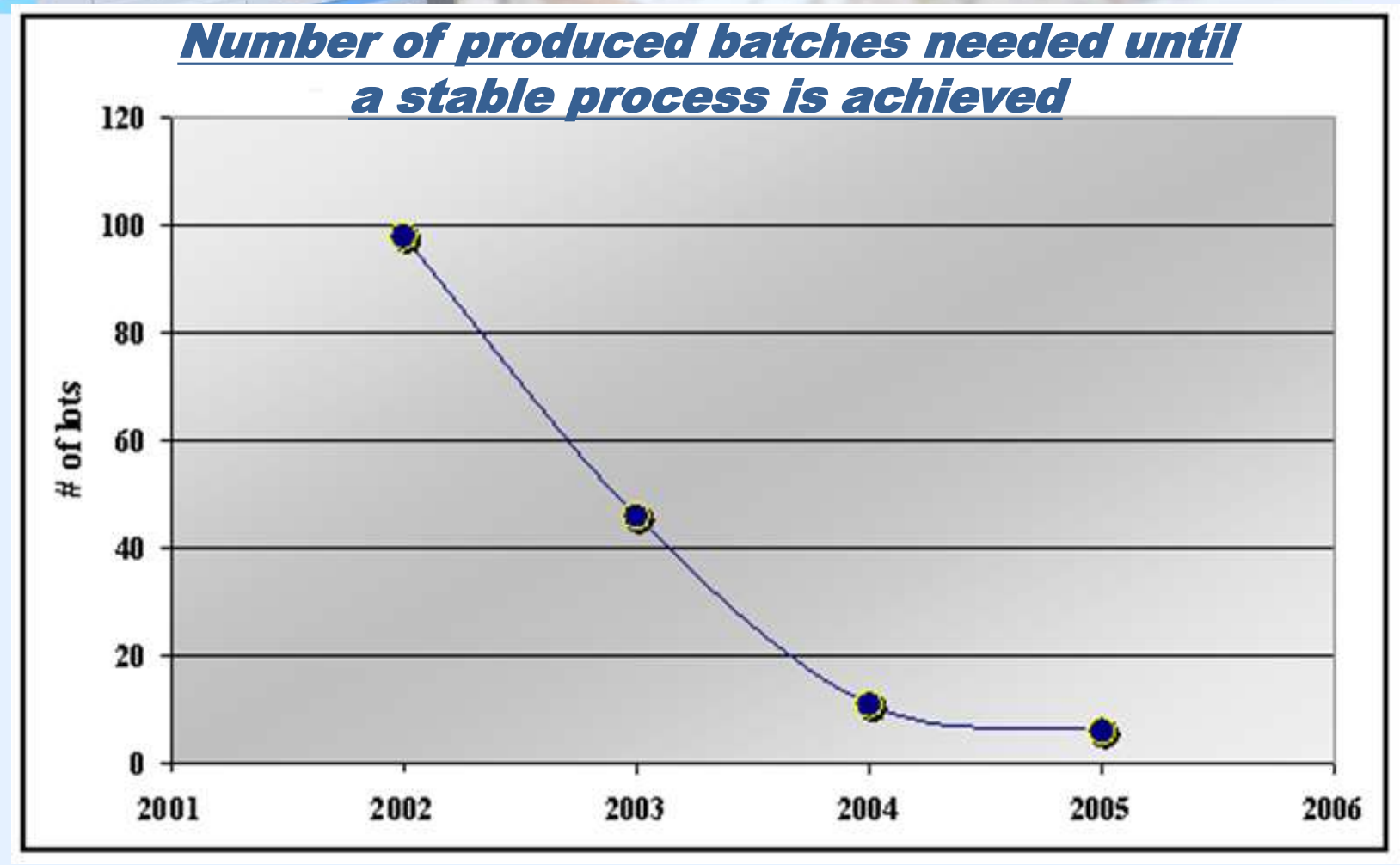
Non Ideal Stirring – Non homogeneity

Before performance of scale up experiments **VisiMix** simulation was used to check suspension at different Mini Pilot Reactors:

Reactor	**7603**	**7605**	**7605**	**7607**
Volume, L	**10**	**25**	**25**	**50**
RPM	**500 (Max)**	**400**	**500 (Max)**	**150 (Max)**
Liquid – Solid Mixing				
Solid suspension quality	Complete suspension is questionable. Partial settling of solid phase may occur.	Complete suspension is expected.	Complete suspension is expected.	Complete suspension is questionable. Partial settling of solid phase may occur.
Max. degree of non uniformity of solid distribution				
AXIAL, %	22.3	10.3	29.1	132
RADIAL, %	65.7	34.3	76.3	90.8

Not all Mini Pilot reactor are capable of full suspension of Reagent

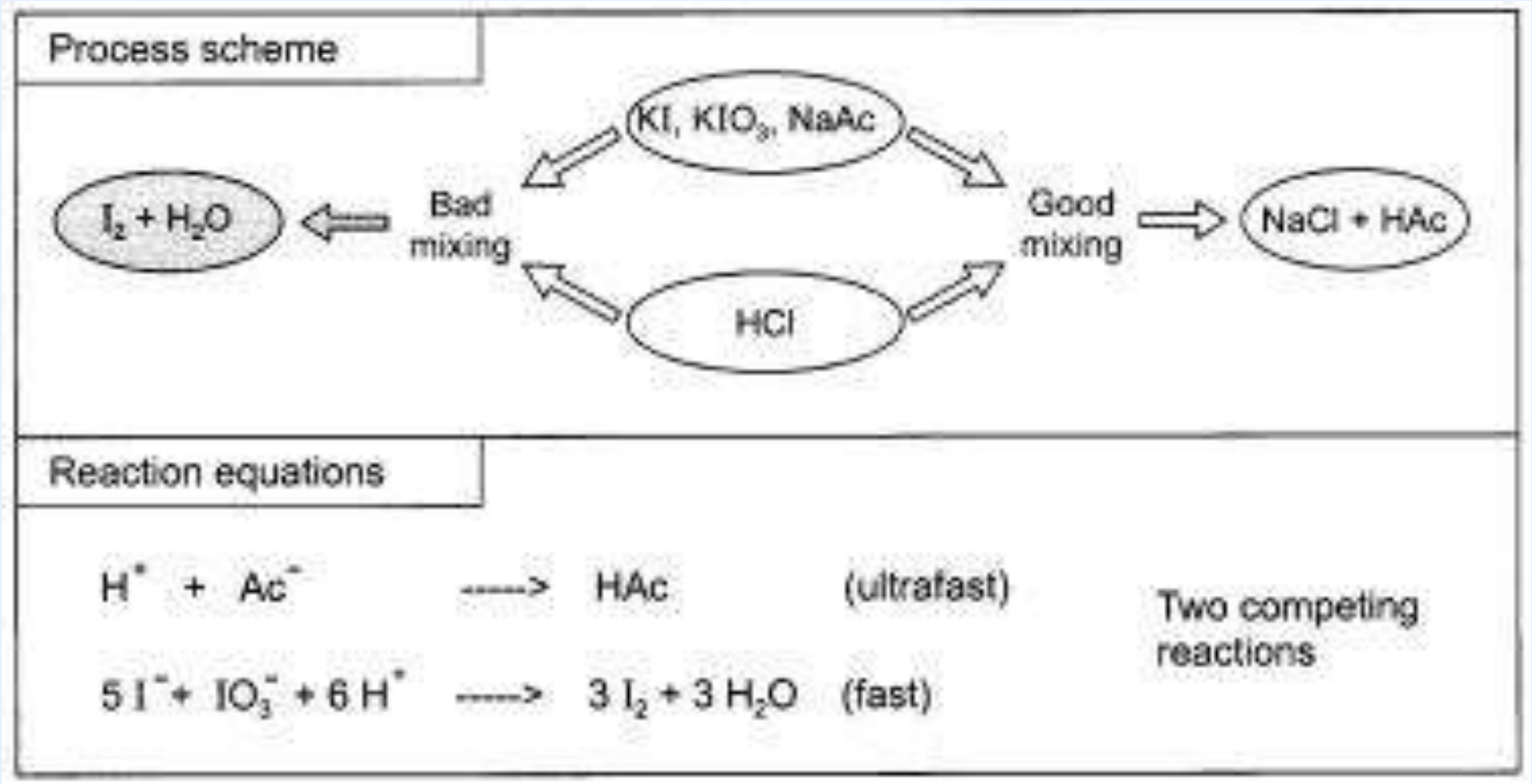
Methodology



VisiMix Application

Homogeneous Reaction

Chemical Reaction



Lab experiment

Feeding HCl without stirring

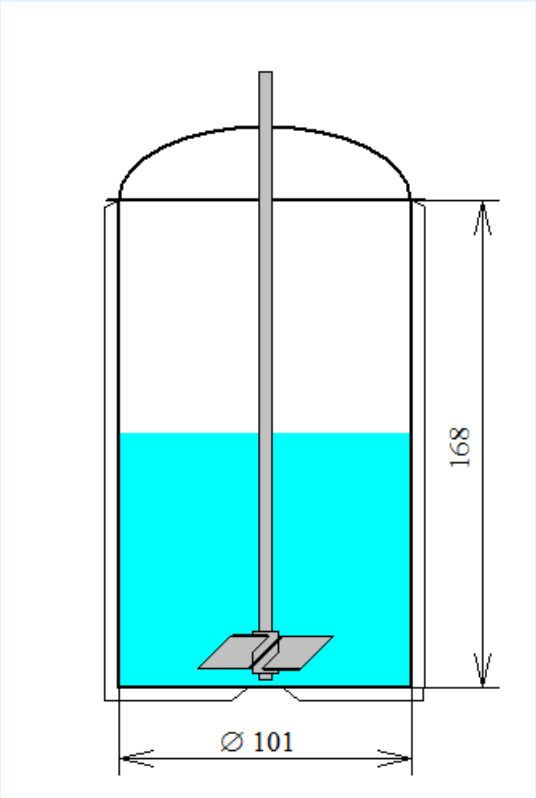
Feeding the HCl upper from the top

Feeding the HCl close to the impeller low rpm

Feeding the HCl close to the impeller high rpm

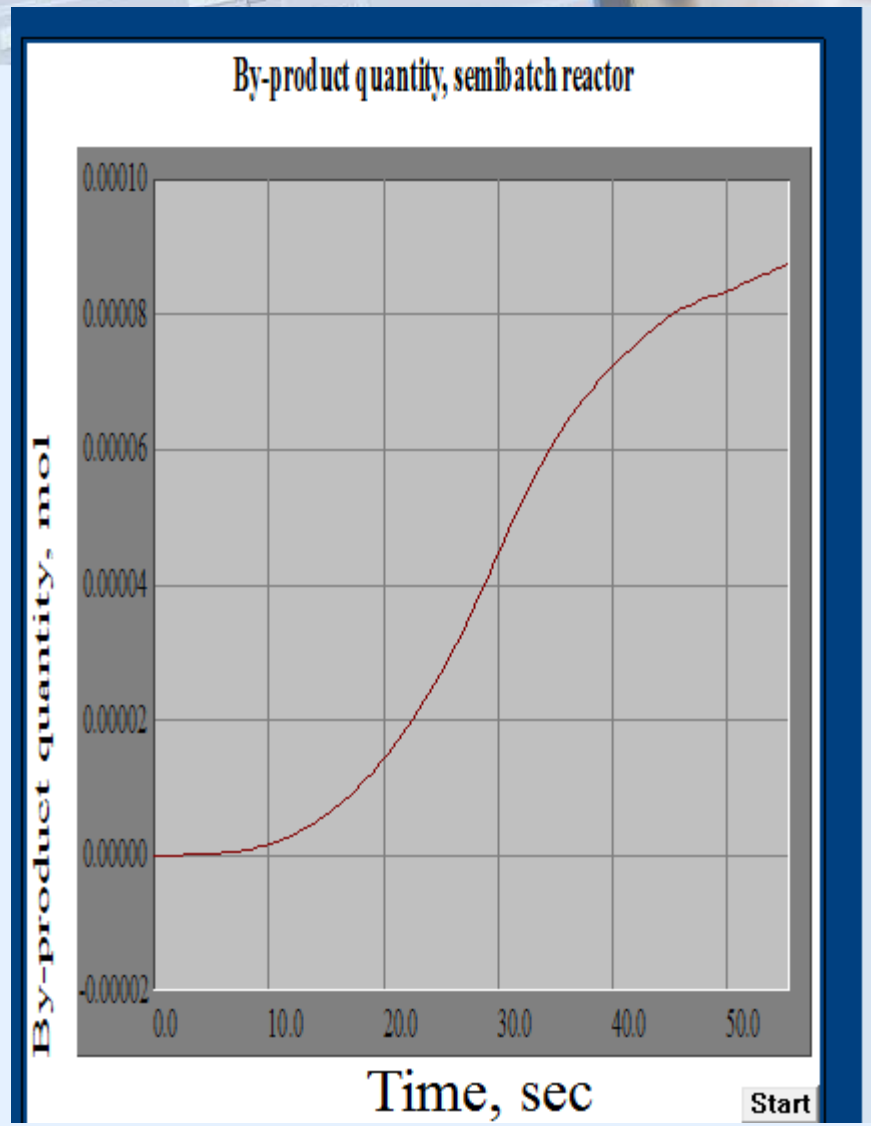
VisiMix Results

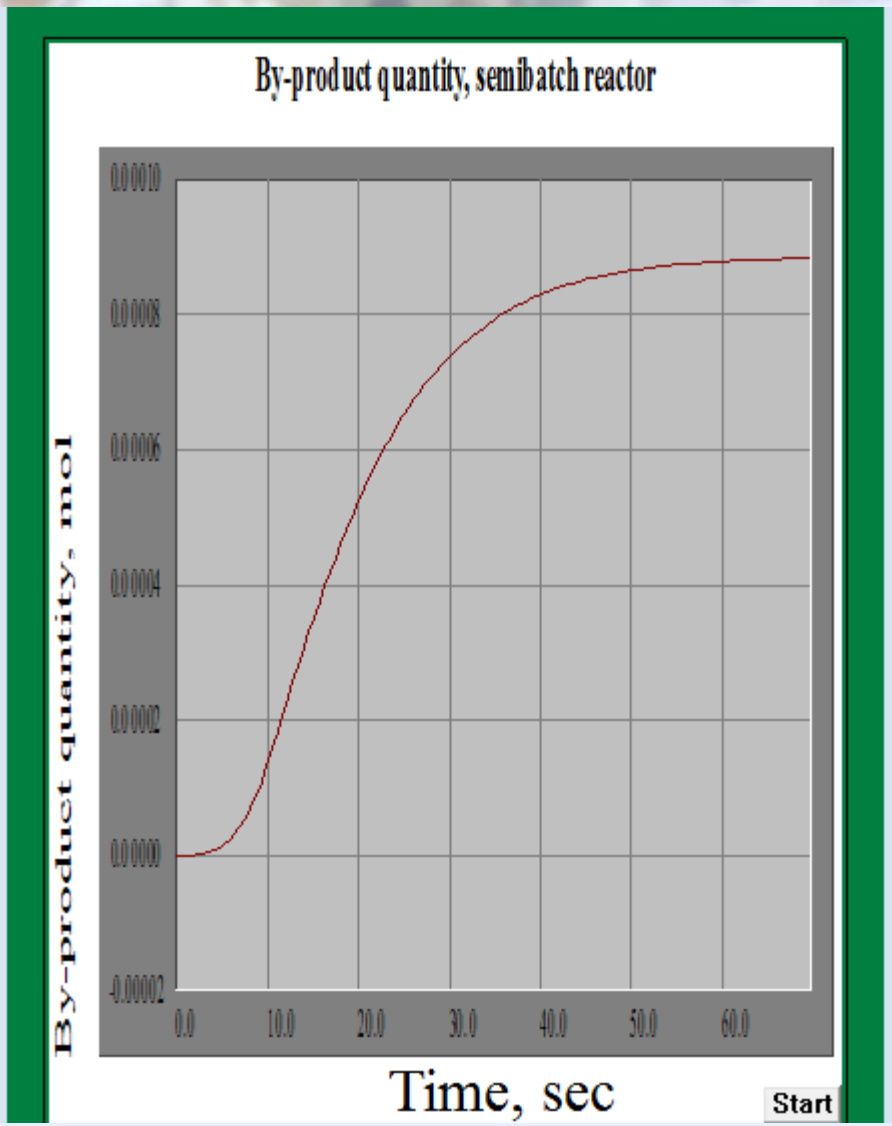
Optimax



VisiMix Optimax Model

VisiMix Results





VisiMix Application

Crystallization

Mixing Parameters for Crystallization Processes

IMPORTANT PARAMETERS	ANSWERED QUESTIONS AND NOTES
Axial and radial solids uniformity (distribution)	What is the uniformity throughout the vessel? Ensure that solids do not accumulate on the bottom.
Micromixing time	How long is the micro scale degradation of non-homogenized concentration? This is important for precipitations.
Energy of collisions in bulk	What is the collision energy of particles? A high number of collisions in the bulk can affect breakage and secondary nucleation.
Collisions of maximum energy	How often do the slurry particles see the maximum collision energy? What is the frequency near the zone of maximum turbulence near the impeller blades? Frequent collisions lead to more breakage and secondary nucleation.
Local values of energy dissipation	What is the average energy dissipation in the agitator zone? What is in the bulk slurry? What is it at the baffles? Dissipation controls breakage, nucleation and micromixing in these zones.
Maximum energy dissipation	Manipulating energy dissipation in the area behind the agitator blades controls breakage, nucleation and micromixing in this zone.
Time between strong collisions	What is the average period of uninterrupted crystal growth?
Shear rates	What is the likelihood of rupturing the crystal or agglomerates? What is the impact on growth and desolution for the agitation conditions?

Mixing Parameters for Crystallization Processes

Cooling crystallization of API in 6000 liter reactor.

Campaign	X (v,90)< 250 µm
First	195
Second	325

After investigation it was found that the tip diameter of the Agitator was damaged and the real diameter is a 80 % of the reported one.

ENERGY DISSIPATION - MAXIMUM VALUE

Parameter name	Units	Value
Energy dissipation - maximum value	W/kg	191

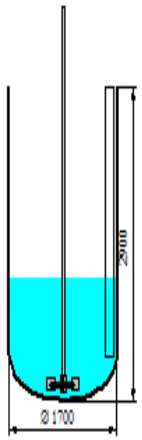
For HELP press F1

ENERGY DISSIPATION - MAXIMUM VALUE

Parameter name	Units	Value
Energy dissipation - maximum value	W/kg	115

For HELP press F1

[VisiMix_R3107] - Drawing of apparatus



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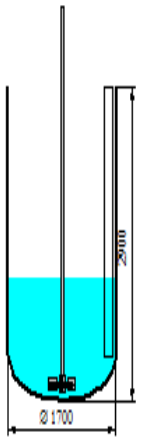
[VisiMix_R3107-new] - Drawing of apparatus



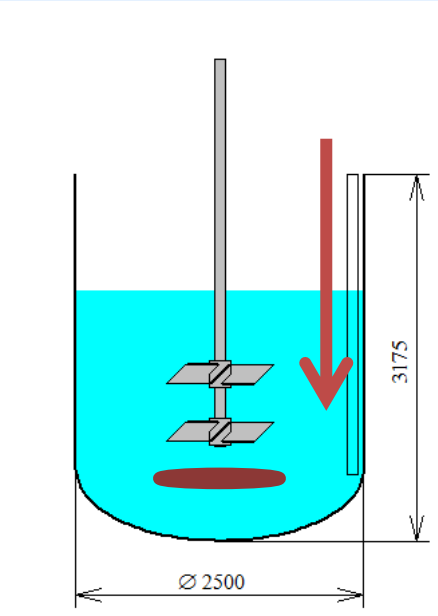
Volume

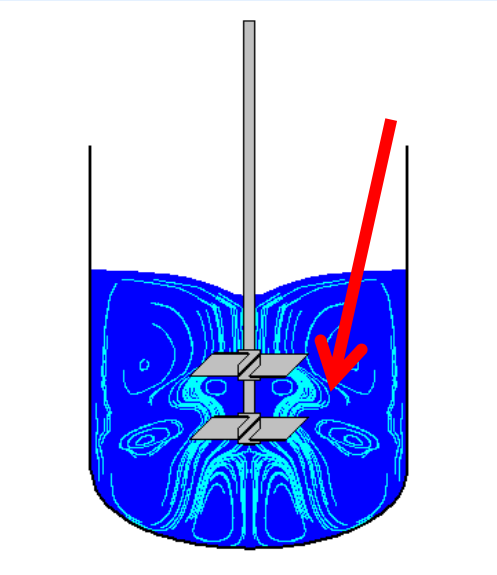
VisiMix Application

Gas Liquid Reaction

Description

- Gas – Liquid reaction in pilot scale ~ 1000 liter is finished after 4 Hour
- Same in Production 4 Days.





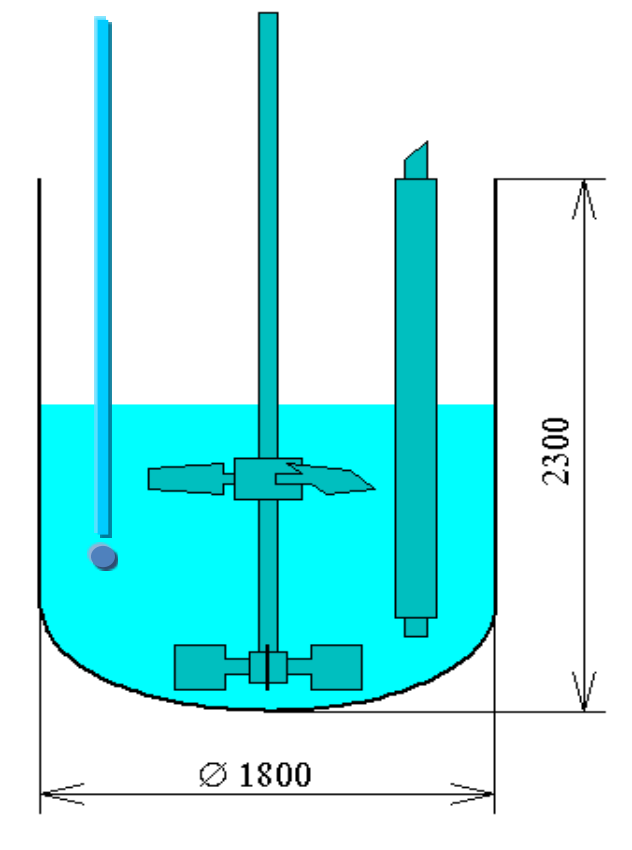
After Change Position the process take around 14 hours

VisiMix Application

High Shear Rate in Semi Batch Homogeneous Reaction

Process and Quality Problem

Feed R-Cl



R-6826

Process

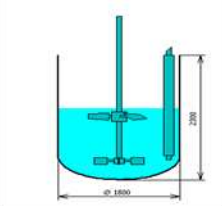
$R\text{-}NH_2 + R'\text{-}Cl \longrightarrow t\text{-}D\text{-}R\text{-}R'$

Impurity

t-L-R-R’

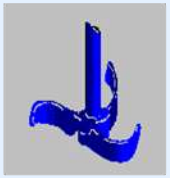
Impurity Results at Laboratory and Production

[%]impurity	RPM	Impeller type	system
0%	15,000 rpm	rotor stator	Laboratory reactor
0.3%	1,500 rpm	3-blade	
0.6%	800 rpm		
1.5%	100 rpm		
0.3% - 0.6%	140 rpm	bottom – flat blade up - turbofoil	R-6826



R-6826

Rotor stator



Lab impeller

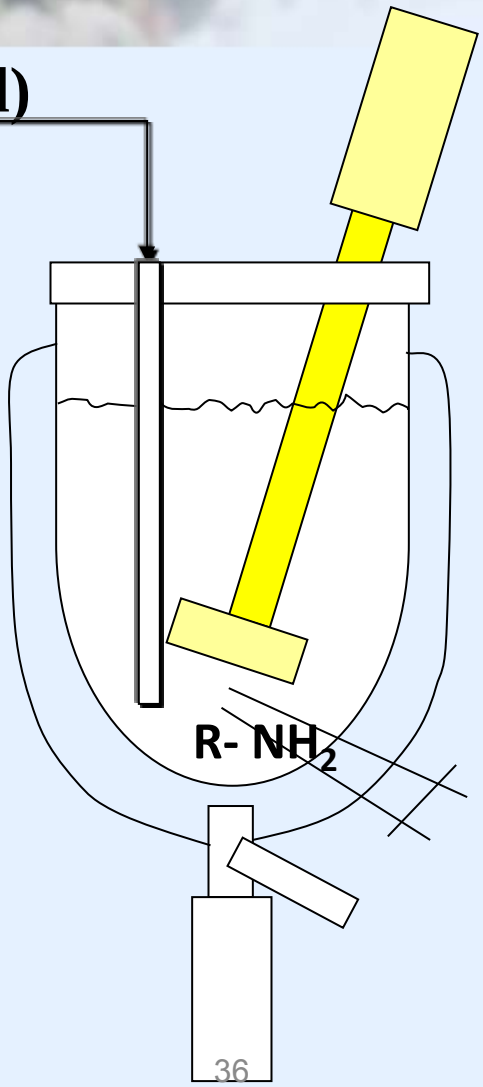
Working with Rotor Stator at Laboratory Scale

Problem

How to scale up ?

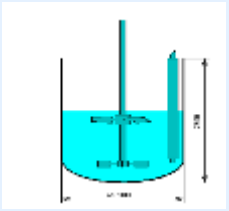
Potential Saving :

MORE than 250 K$



Calculating Shear Forces with VisiMix

Turbulent shear rate [1/s]	[%]impurity	RPM	Impeller type	system
780,000	0%	15,000 rpm	rotor stator	Laboratory reactor
32,900	0.3%	1,500 rpm	3-blade	
12,900	0.6%	800 rpm		
580	1.5%	100 rpm		
15,200	0.3% - 0.6%	140 rpm	bottom – flat blade up - turbofoil	R-6826



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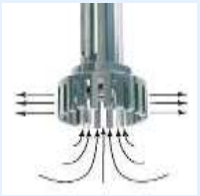
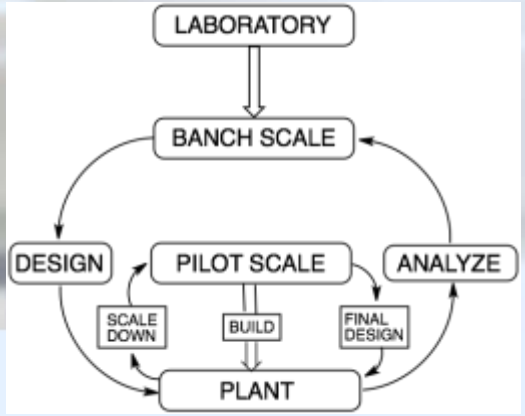


Rotor stator

Lab impeller

Summary



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Conclusion

- Using VisiMix Products support you can
  - understand better your processes
  - Reduce dramatically your Scaling up processes and Scaling down
  - Save a huge amount of Time & Money ($1,000,000 +)
- The VisiMix Products are friendly and easy to use with very quick results.
- The VisiMix results are based on a systematic and seriously experimental checking – and found very reliable.
- VisiMix Projects Parameters and Data Base allows you to share and transfer the data with colleagues in the company.

Thank you for your attention

VisiMix

VisiMix

Thank You

For your attention

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