







We empower organizations to realize their Process Improvement Goals



Process R&D Roots (16+ Years)

Council of Scientific and Industrial Research National Chemical Laboratory









Excelerate R&D, Process Development & Operations



With 100+ Man Years of Process Consulting Experience, Tridiagonal has supported Global Companies in Process Improvement Programs





The Enterprise Mixing Analysis Tool

• SimSight



Excelerate your Process Development, Scale-up and improve Mixing Performance

Industry	Processes / Unit Operations	MixIT Solution
Pharma / Chemical	Blending	Mixing Time
	Solid Liquid Operation	Solid Suspension, Cloud Height, Njs
	Crystallization	Meso-mixing time, Particle size distribution, Heating / Cooling rate, and mixing of anti- solvents
	Fermentation	Energy dissipation rate, Volumetric mass transfer coefficient, Oxygen transfer rate
	Hydrogenation	Bubble size estimation, Gas distribution / entrainment rate
	Emulsification	Shear rate & Energy dissipation, Droplet size distribution
	Bio-reactors	Nutrient mixing, Gas distribution, Bubble size estimation, Strain-rate profile of Bio-reactor
Chemical	Extraction	Droplet size estimation, circulation time
	Polymerization	Particle size distribution, Heat transfer, P/V, etc.
	Chlorination / Nitration	Bubble size estimation, Gas distribution / entrainment rate
FMCG	Non-Newtonian Fluids Mixing	Product Quality Control / Estimation

Key Features : Shared Reactor database, Off-centered, Angled and Multi-shaft Agitators, Customizable Impeller Library, Fluid Rheology, Flexible Unit System, Empirical Correlations, Full Automated CFD Analysis



MixIT is the next generation collaborative mixing analysis and scale-up tool designed to facilitate comprehensive stirred tank analysis using lab and plant data, empirical correlations and advanced 3D CFD models. It combines knowledge management tools and mixing science in a unified environment deployable enterprise-wide.



Simulation based Analytics For Decision Support and Knowledge management

Delivering the last mile in Process Understanding



• SimSight Our Value Proposition



Technology Partner

Domain knowledge with 12 years of experience to provide most advanced technologies and solutions for various sectors

End-to-End Solutions

Comprehensive suite of products for all of your Process design and Analysis, Design Automation, data management and sales needs



Support

Robust Support with implementation & customization expertise to meet customers needs.

Training

Customer / User / Product Specific Training Programs & Certifications and knowledge-sharing initiatives for enhanced learning

Consulting

Help improve the competitiveness of our customers and Protect our customers' investments with right consultation & solutions





MixIT – a mixing scale-up tool for Green Process Principles

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Role of Mixing scale-up in Greenness of a process



Time

Mixing is directly related to Green chemistry principle- Prevention- Prevent or minimize waste.

An improper mixing scale-up can result in impurity increase which negatively impact E factor:

$$E = \frac{Kg \text{ waste}}{Kg \text{ product}}$$



Role of Mixing scale-up in Greenness of a process





When scale-up fails due to mixing, waste is created in terms of:

- Higher impurities
- Repeated purification cycles associated with higher solvent consumption and product loss / additional down stream processing like milling
- Time required for root cause analysis and CAPA
- Raw Materials required for repeating scale-up validation, and
- Time required to repeat scale-up validation batches





Mixing sensitive reactions

Reaction Speed Very slow reactions-Kinetically controlled **Batch operation** Semi-batch operation **Kinetics analysis** Thermal risk Layers of protection Scale-up insensitive

Fast reactions-Mass transfer controlled

Homogeneous Solid-Liquid Liquid-Liquid Gas-Liquid

Scale-up sensitive



Typical classification of reactions based on reaction rates

Parameters to consider for scaleup of fast reactions:

- Stirrer type
- Stirrer speed
- Feed point location and type
- Dosed reagent concentration



+ _{H₃C²}

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Mixing sensitive reactions



Coupling reaction L-alanyl-L-proline: Blacklock et al J. Org. Chem. 1988,53, 836-844



Challenges in Scale-up of fast C-C and C-P reactions

What may change with scale increase?

Local concentration near addition point may increase leading to higher impurity formation

Inhomogeneity in turbulent energy distribution rate : $\phi = \varepsilon_{FP} / \varepsilon_{vol avg}$ changes between scales

Macromixing or blend time increases



Mixing regime may change from micromixing at lab scale to mesomixing at plant scale



Mixing sensitive reactions

- C-C and C-P reactions reduce yield by consuming valuable starting materials, and the products of these side reactions can accumulate as impurities that may be difficult to remove from the final product.
 - These impurities may alter the crystal structure of some products, resulting in undesired polymorphic crystal forms
- In a highly regulated industry such as pharmaceutical the presence of mere tenths of a percent of an impurity can result in an entire batch rejection



The consequences are: high production cost with material wastage, lost time opportunities and higher waste generation impacting environment adversly-aggregated over all products is a huge loss in \$\$\$ in bottom lines!!

ing time, $\tau_{-} >$ Reaction time, τ_{-}



Scale-up of Fast C-C and C-P reactions: Damköhler number

The competition between reaction and mixing is well represented by a mixing Damköhler number- the ratio between the reaction rate and the local mixing rate, or conversely, the ratio of the characteristic mixing time, τ_{M} , and the reaction time, τ_{R} :

$$Da_M = \frac{\tau_M}{\tau_R}$$

 $\begin{aligned} \tau_{\rm R} &= 1/k \text{ for } 1^{\rm st} \text{ order reaction,} \\ &= 1/k {\rm C}^{\rm n-1} \text{ for } n^{\rm th} \text{ order reaction, and} \\ \tau_{\rm M} &= \tau_E = 17 \left(\frac{\nu}{\varepsilon}\right)^{1/2} \end{aligned}$



The conventional approach is to keep Da_M constant across scales. However it requires reaction kinetics information.

Bourne J. R., Organic Process Research and Development, 2003,7, 471-508

Kresta S. M. et al, "Mixing and Chemical Reactions" in HANDBOOK OF INDUSTRIAL MIXING SCIENCE AND PRACTICE ed by Paul E. L., et al Wiley Interscience, 2004





Case Study: Scale-up of Competitive-parallel Fast bi-phasic pH neutralization reaction

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Scale-up of Competitive-parallel reaction: the chemistry

In this case the substrate is in solution in an organic solvent and aqueous sodium hydroxide is added to raise the pH from 2 to 7. The rapid parallel reactions are the acid-base neutralization and a base-catalyzed hydrolysis.

The absolute value of the hydrolysis rate constant, k2 is not known in this pH range but has been observed to be many orders of magnitude lower than the acid-base neutralization rate.





Scale-up of Competitive-parallel reaction: Lab trials



Effect of feed location at low RPM and fast addition

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Approach of analyzing Local Tracer concentration



Monitor points:

M1: Added reagent local concentration close to Feed point

M2: Added reagent local concentration in organic phase

Added reagent concentration profile can be generated by multiplying tracer concentration with feed concentration.



MixIT CFD analysis with tracer simulation





Scale-up and scale-down approach for Fast reactions

	Parameters	Unit	LAB Top addn @ 200RPM	Plant Top addn @ 96RPM	LAB Top addn @ 400RPM
	Power Per-Unit Volume	kW/m³	0.092	0.734	0.735
	Volume Average Velocity	m/s	0.122	1.343	0.256
	Volume Average TDR	m²/s³	0.057	0.554	0.463
	Micro-Mixing Time calculated based on Average TDR (epsilon)	S	0.066	0.021	0.023
6L 200RPM	Micro-Mixing Time (At Addition location)	S	0.152	0.034	0.038
	Meso-Mixing Time (At Addition location)	S	0.155	0.068	0.043
	Macro-Mixing Time (95% Homogeneity)	s	6.44	5.04	2.8
6300L, 96RPM	Average Droplet Size	mm	0.617	0.192	0.266

Addition as fast as possible at highest possible mixing rate to avoid local regions of high concentrations and adjustment of feed concentration to match lab condition



Scale-down simulations for Fast reaction





Based on the tracer simulation, the scale-down in 6 L reactor should be run at 400 RPM and with 2.5M NaOH in-place of 7M NaOH to avoid excess impurity formation



Scale-up of Fast reaction – Optimum Feed concentration





Scale-up of Fast reaction – Optimum Feed concentration







Case Study: Scale-up of a reactive crystallization

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Reactive Crystallization

- Production of API salt is a mixing sensitive reaction and equipment dependency is a well known phenomena in such cases
- CFD Models were use to understand mixing performance across the scales
 - Flow Pattern
 - Shear Distribution
 - Macro-mixing and Meso-mixing Profiles
 - P/V
- Results obtained from CFD models were critically analyzed to understand similarity and differences in mixing performance across the scales



Reactive Crystallization- Flow Profiles



- The flow profiles indicate more axial flow in lab-scale and kilo-lab scale reactors which will lead to good mixing across the volume
- The pilot scale shows more rotation flow which may lead to poor mixing across the volume



Reactive Crystallization: Shear Rate Profiles



- The CFD results shows that similar shear profile across the scales
- The pilot plant shows less shear compared to lab and kilolab scale
- So shear may not be impacting the lower particle size observed in the pilot scale







Reactive Crystallization: Meso-mixing profiles



- The CFD results shows regions with higher mesomixing in pilot plant reactor compared to lab and kilolab reactors
- Poor mesomixing may be leading to supersaturation and thereby impacting PSD





Reactive Crystallization: Results - Macro-Mixing



- Analysis of tracer based mixing profile shows poor /delayed mixing in the pilot plant reactor compared to lab and kilolab scale
- Poor mixing is a result of more rotational flow in the pilot scale reactor





Case Study: Reactive Crystallization-Performance Parameters

Parameter	Lab scale	Kilolab-1	Kilolab-2	Pilot-Plant
Tip Speed (m/s)	0.4712	0.589	0.754	1.5708
Impeller Power Number, Np (-)	0.841	0.748	0.622	0.2464
Power per unit volume (kW/m3)	0.018	0.013	0.019	0.0359
Vol. Average Velocity (m/s)	0.1734	0.254	0.2805	0.5458
Vol. Average Shear Rate (1/s)	17.671	9.4567	7.5744	4.822
Macromixing Time (s)	8.61	5.75	7.96	14.85

Based on the simulation results, it is clear that:

- The pilot plant agitator generate multiple mixing loops and the surface addition of the solution is not dispersed within the whole reaction mass fast enough
- It created local regions of high supersaturations- which lead to higher nucleation rates and lower particle size.
- The Pilot scale agitator type is not suitable for the process.



- In the scale-up of mixing sensitive fast reactions or antisolvent and reactive crystallizations, indepth analysis of mixing is required to ensure successful right first time scale-up to avoid waste during plant scale-up validation campaigns.
- MixIT simulation software platform allows CFD based three dimensional mixing simulation and analysis and enables process engineers to replicate lab mixing environment at plant scale to ensure same process quality in terms of mass transfer.
- Using MixIT platform, one can quickly select most suitable reactor from available list or quickly modify agitator design to suit the process requirements.





The Enterprise Mixing Analysis Tool

Thank you !!!

Many thanks to IGCW team !!!