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Assessing Mixing Sensitivities for Scale-up

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SOLUTIONS THAT SCALE

Nalas: Solutions that Scale!

Mission

Our mission is to promote technological innovation in the chemicals industry by applying science-based knowledge to solve the problems and achieve the goals of our CUSTOMERS. The creative ideas conceived by the customer will be realized by the Nalas team of scientists and engineers. We will support our customers with all aspects of process engineering that result in a new dimension of performance and enable SOLUTIONS THAT SCALE from the laboratory to commercial production. We will provide sustainable and green processes which can be transitioned to industry, thus enabling lowest-cost domestic production of chemicals critical to our NATION'S military, industrial, and pharmaceutical needs.

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Engineering Services

Solutions | **Services** | Capabilities

Chemical Synthesis
We have experience working with a large number of reaction steps and subsequent workup and isolation stages to identify potential problems in scale-up to pilot plant and production campaigns. >> More

Testing
We have a wide array of testing equipment, ranging from purity measurements, thermal analysis, particle characterization, and small-scale sensitivity for energetic materials. >> More

Safety
Process Safety is critical to any chemical process and the proposed facility, whether you are synthesizing just a few kilograms or planning production of metric tons. >> More

Materials of Interest
We have hands-on experience with a wide range of materials. See a full list of our materials of interest.>> More

Modeling
We are proud users of process models such as DynoChem® and Visimix® to precisely determine potential scale-up failures. >> More

Training / Webinars
We offer training and seminars to help familiarize you with tools such as automated laboratory reactors, real-time heat flow analysis, and other process analytical tools >> More

Solid State Chemistry & Characterization
As experts in solid state chemistry, we offer crystal, cocrystal and polymorph screening and characterization. >> More

Reaction Monitoring
Reaction monitoring is a defining capability that sets Nalas apart from everyone else in the industry.>> More

Broad range of services & capabilities supporting chemical process development…

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Outline

Interplay of scale up and mixing with Examples at Nalas

- Example 1: Identification of the critical mixing parameters
- Example 2: Modeling the mixing of the process at both the large and small scale
  - Requiring multiple experiments to match all scales of mixing
- Example 3: Modeling the mixing throughout the process
  - As the process changes, so can the mixing

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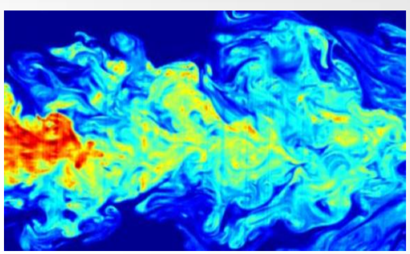
Mixing at Scale or Scale of Mixing?

- Definition of what we mean by “Scale” regarding mixing?
  - The process scale, i.e. lab, pilot, production

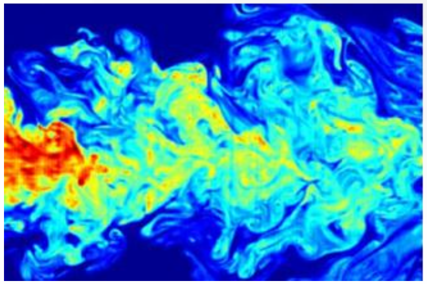
  - Mixing scale, i.e. micro mixing, mesomixing, macro mixing



- We Need to take both definitions of “scale” into account for the process

What is the Scale of the Mixing?

- Micro-mixing is mixing on the smallest scales of motion (the Kolmogorov scale)
- Mesomixing refers to the turbulent dispersion of a feed stream shortly after it enters a mixing vessel.
  - It is caused by the action of the bulk fluid interacting with the feed stream.
  - Mesomixing occurs at a higher scale compared to micromixing, but at a lower scale than macromixing.
- Macromixing, i.e. the blend time in a batch system
- Which one is important?
  - What time scale is your process?



Micro: Fast reactions

Meso: Semi-batch process

Macro: Bulk blending

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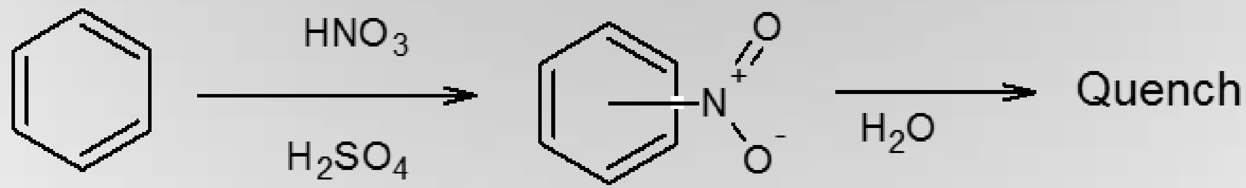
Example 1: Nitration Quench

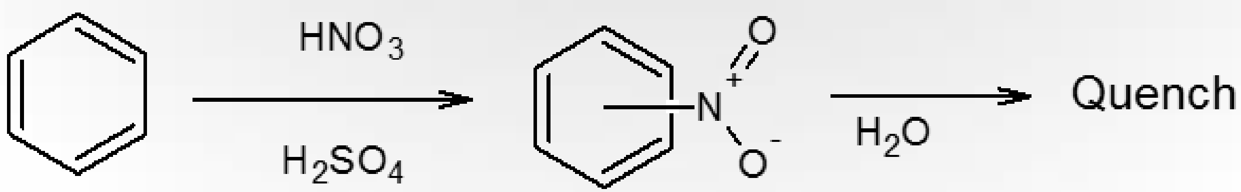


- Product is synthesized by mixed acid nitration
- Material is isolated by Quenching into water
  - Crystallization is instantaneously upon addition to water
- Varying levels of residual acid have been detected in lots of product by IC
  - Larger scale batches have higher acid levels
  - Residual acid has been shown to be due to inclusion in the solids, i.e. not surface acid that can be washed off.

Example 1: Nitration Quench

Statement of the problem:

- Level of mixing present in the quench seems to correlate with acid levels
- How do we design the quench so as to minimize the levels of acid inclusion



In order to Scale up, we need to scale down!

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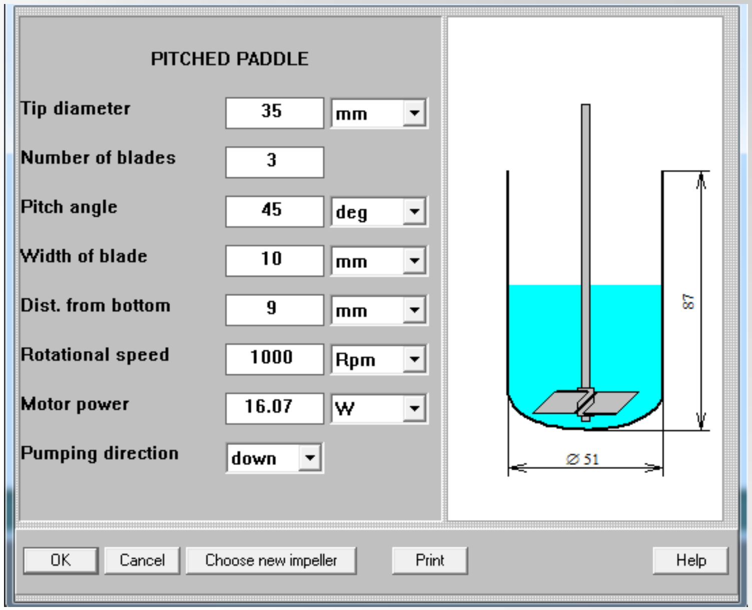
Critical Mixing Parameter(s)?

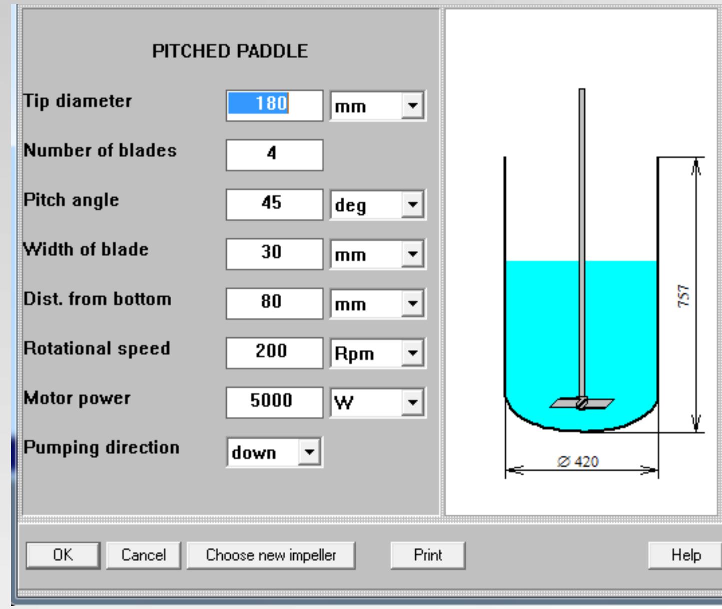
- Need to identify the mixing parameters that are controlling
  - The first step was to run reactions with various degrees of mixing
- Identify a process responds
  - In this case levels of acid inclusion.
- Find the mixing parameters that correlated with the responds
  - The rapid crystallization points to micro-mixing time being critical

Scale down Mixing for Quench

100 ml reactor



100 L reactor



Reactor	RPM	Characteristic time of micromixing
100-L Large Scale	200	4.84 seconds
100-mL EasyMax™ with probes	1000	0.69 seconds
100-mL EasyMax™with probes	500	1.58 seconds
100-mL EasyMax™ w/o probes	320	4.92 seconds
100-mL EasyMax™ with probes	185	4.86 seconds

With VisiMix it was possible to adjust the degree of baffling and rpms to match the micro mixing time in the lab to the large scale reactor

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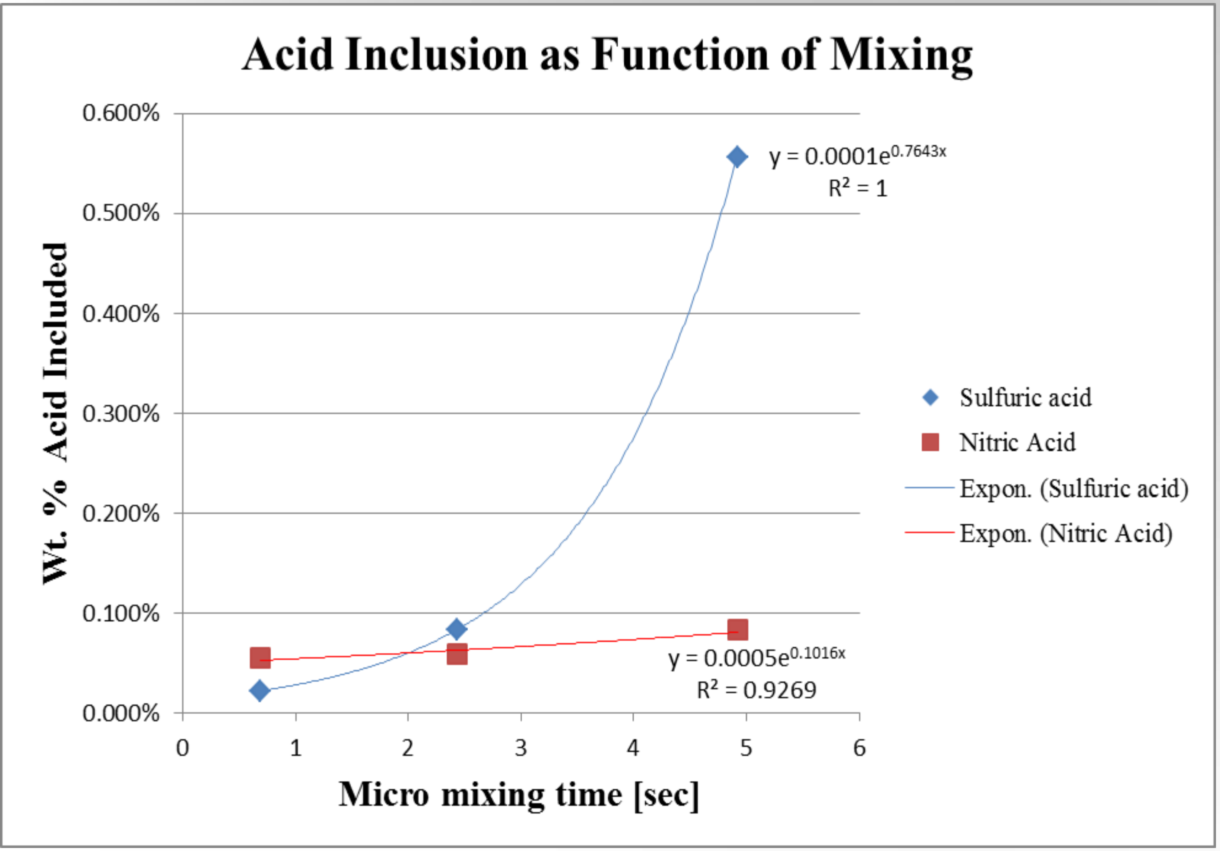
Relationship of Quench Mixing and Acid Inclusion from Lab Experiments



Experiment	RPMs	MicroMixing time [sec]	Sulfuric acid	Nitric Acid
"Poor" mixing	320	4.92	0.556%	0.083%
"Intermediate" mixing	500	2.43	0.084%	0.058%
"good' mixing	1000	0.691	0.022%	0.055%

- Multiple mixing outputs from VisiMix were compared with the Acid levels
- Micromixing time correlated best with the data
  - As all reactions had the same feed time Data would also correlate with mesomixing time
- Large scale experiments with slower dosing rates did not reduce acid levels
  - this indicats that micromixing time is the correct factor that dictates acid inclusion level

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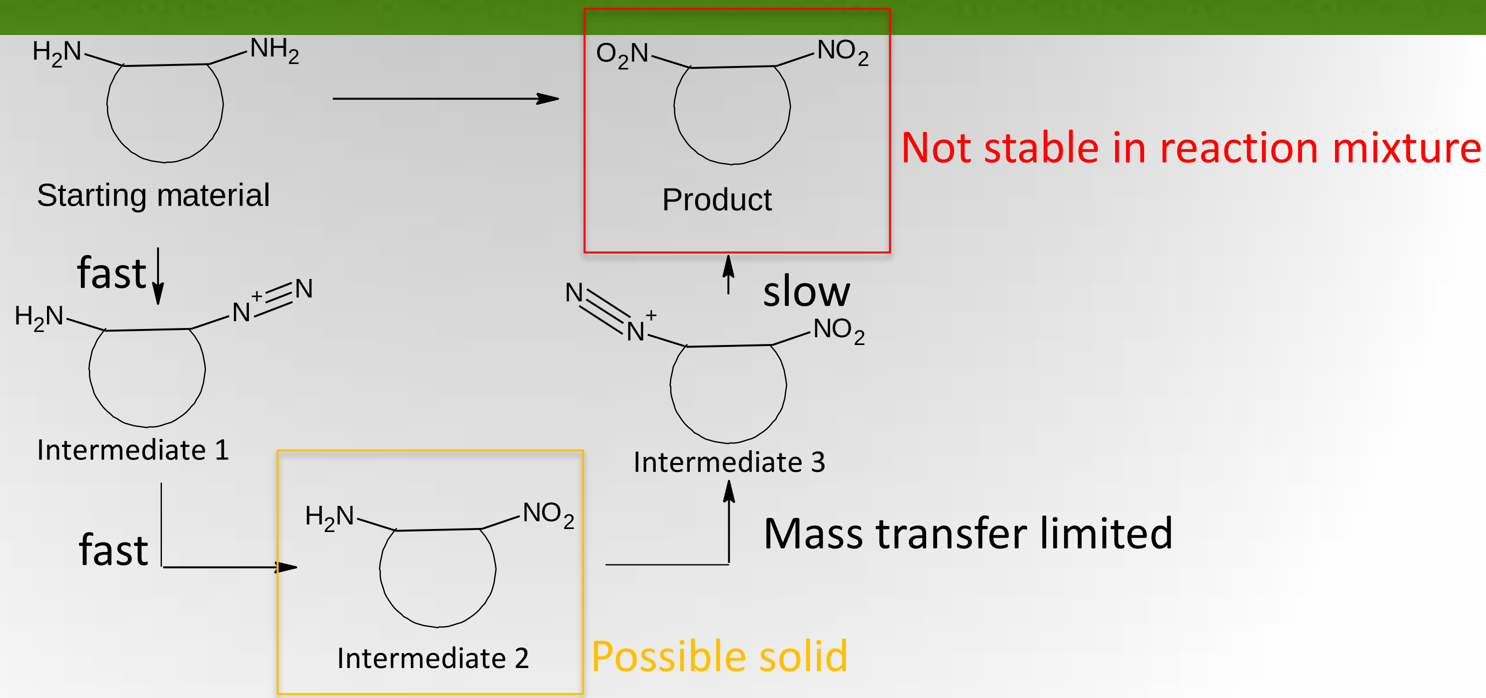
Example 1: Summary

- First identify the critical mixing parameter(s)
  - Select a process responds (quality attribute, yield, etc.)
  - Correlate a mixing parameter with this responds
- Use VisiMix to design the lab scale reaction to match the critical mixing parameter(s) of the large scale equipment
  - The “poor” mixing in the lab equipment was the best that could be achieved at the 100L scale
- Use the data from the lab runs to scale up the process
  - With the correlation of micromixing time and acid levels, it was possible to design an optimal quenching approach
    - The optimal quench is a small scale continuous quench
    - Allows for the required micromixng time to prevent acid inclusion

Example 2: Scale-up of an Energetic, Scale-down of the Mixing



- The reactions to form intermediate 2 are very rapid
  - intermediate 1 is never seen in the reaction.
- Intermediate 2 is above the solubility limit for majority of the reaction.
  - As the reaction is done within the meta-stable zone solids can form.
- Reactions to form product becoming mass transfer limited further slowed formation of product.
  - Product is not stable in reaction mixture

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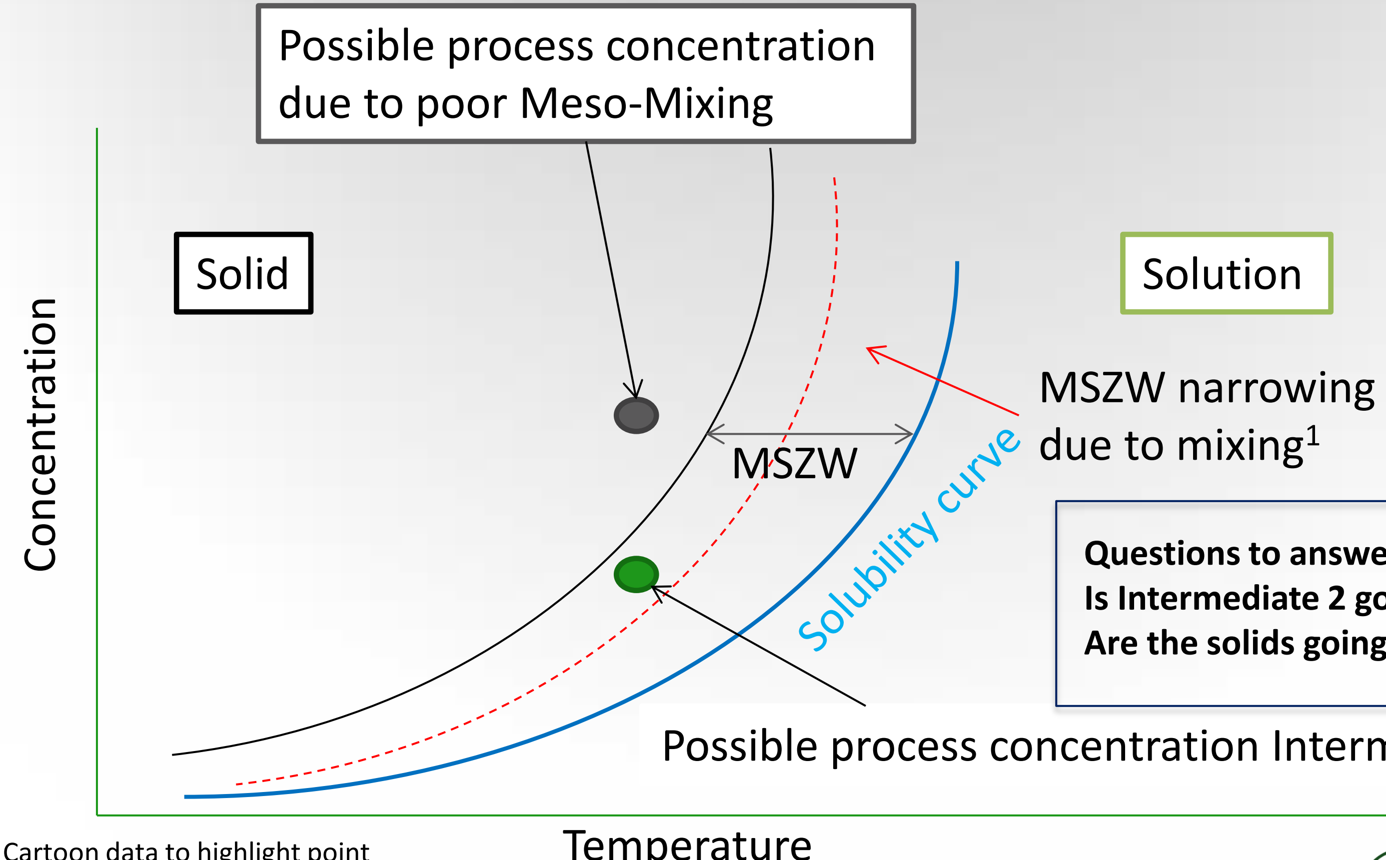
Mixing and Concentrations

- Depending on the Meso-mixing the local concentration can be higher
  - very high local concentrations could rapidly form solids
- Mixing could narrow the MSZW due to high shear, resulting in solids



Questions to answer:
Is Intermediate 2 going to precipitate out?
Are the solids going to reduce the yield?

*Cartoon data to highlight point

1. Chianese, A., Contaldi, A. and Mazzarotta, B., *J Crystal Growth*,**1986**, *78*: 279–290.

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Evaluation of the mixing

- Evaluate the mixing in the 100 gallon reactor
  - Need to match the micro mixing time, meso mixing time, and the max energy dissipation and shear
- It will not be possible to match all three in one experiment
  - We will run three reactions, each matching one of the mixing parameters.
  - Evaluate each reaction for solid formation and impact on reaction rates and yield

Scale Down of the Mixing:
VisiMix Modeling of 100 Gallon and Lab Reactor

	100 gal	0.5L Tr,Cal, Raman, pH	0.5L Tr,Cal, Raman, pH	0.5L Tr,Cal, Raman, pH
	175 rpms	935 rpms	535 rpms	300 rpms
Volume at end of dose	81 gal	0.35 L	0.35 L	0.35 L
Max energy [W/kg]	73.9	74	13.9	2.45
bulk energy [W/kg]	**0.193**	1.030	**0.194**	0.0341
average energy [W/kg]	0.624	2.07	0.389	0.0686
micromixing time [s]	2.28	0.983	2.27	4.83
Shear rate in: [1/s]				
bulk	440	1020	442	185
near impeller	8630	8640	3740	1570
tip speed [m/s]	3.37	1.84	1.05	0.589
Mixing power [W]	191	0.726	0.136	0.024
Reynolds # for flow	3.28E+05	13400	7640	4280
Avg tangential velocity [m/s]	0.802	0.233	0.133	0.0744
Avg circulation velocity [m/s]	0.0842	0.296	0.169	0.0949
Feed rate[m^3/sec]	2.20E-05	2.50E-08	2.50E-08	1.32E-07
[mL/min]	1320.00	1.50	1.50	7.92
k (Turbulent diffusivity)	6.81E-01	2.03E-01	6.62E-02	2.08E-02
Dt (energy dissipation rate)	2.41E-01	4.01E-03	2.26E-03	1.27E-03
Td(Meso mixing time) [sec]	1.09E-03	2.11E-05	6.56E-05	1.09E-03
Dose time [min]	90.15	90.00	90.00	17.05

Reaction formed solids

Baldyga and Bourne mesomixing time for dispersion of feed[1] $\tau_D = Q_B/UD_t$

Q_B=Volumetric feed rate

U= Fluid velocity in surrounding fluid at feed point

D_t= local turbulent diffusivity $=0.1k^2/\varepsilon$ and $k \sim 0.06U^2_{tip}$

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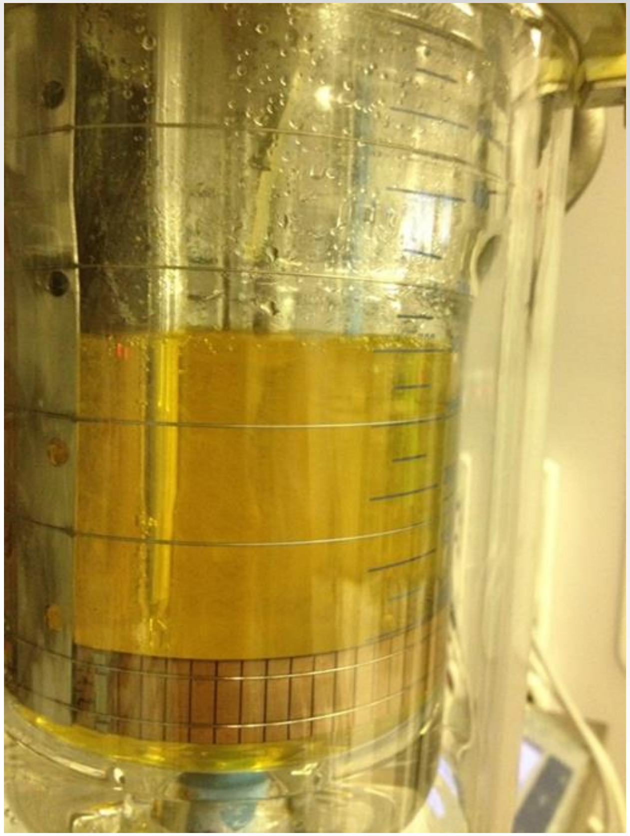
1. Edward Paul(ed),Handbook of Industrial Mixing Science and Practice, 2004, John Wiley & Sons. ISBN: 0-471-26919-0. p772.

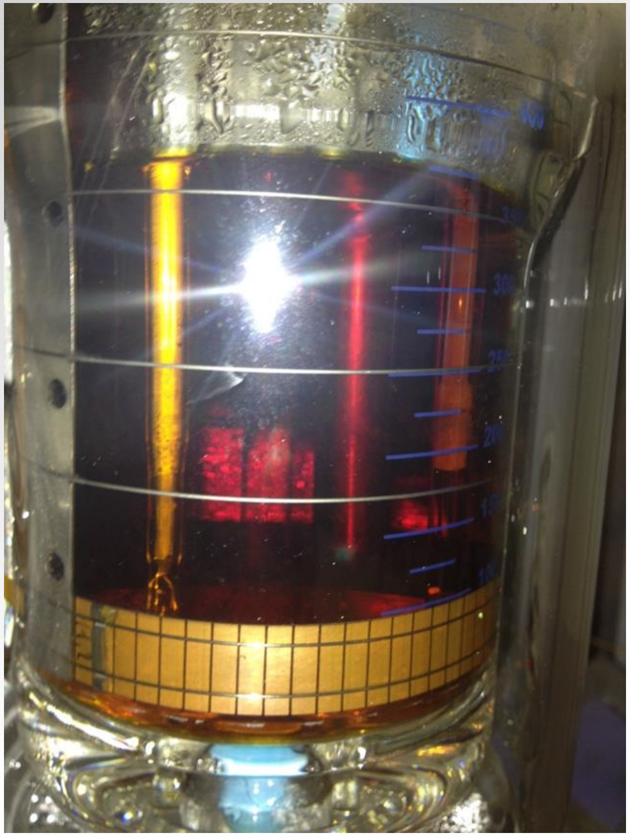
Matching Micro and Meso Mixing,

No Mass Transfer Limitation for Reactions

During the dose, no solids seen



Next morning, no solids seen



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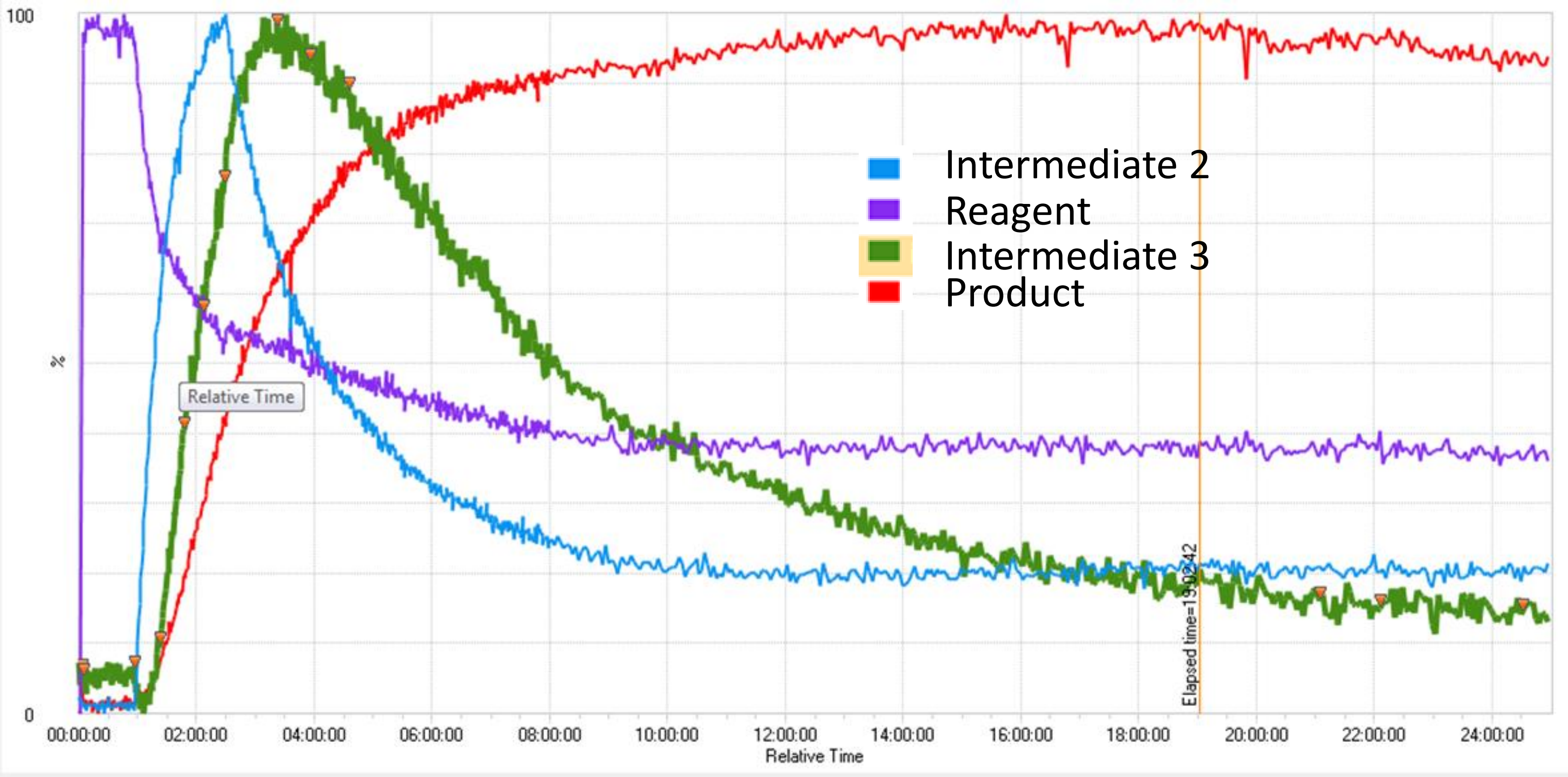
In Situ Raman Spectroscopy for Reaction Matching Micro-Mixing

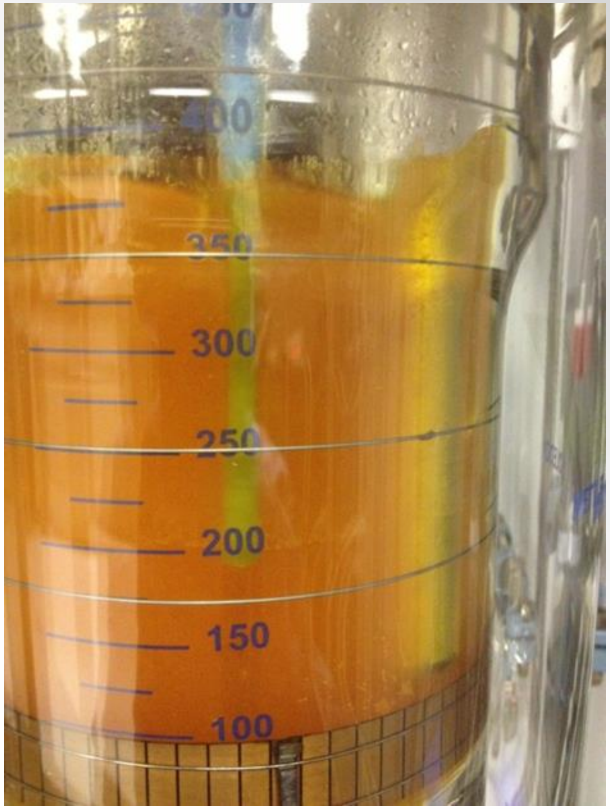
No mass transfer limitation seen in Intermediate 2 profile, In situ Yield of 71% at 18 hour reaction time



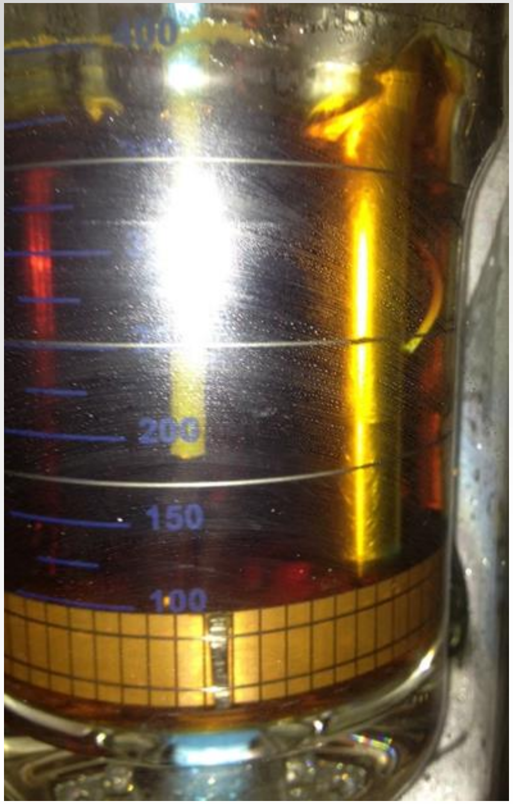
Matching Max Energy Dissipation

Mass transfer limited Reaction

End of Dose solids seen, but not "gummy"



Next morning, no solids seen



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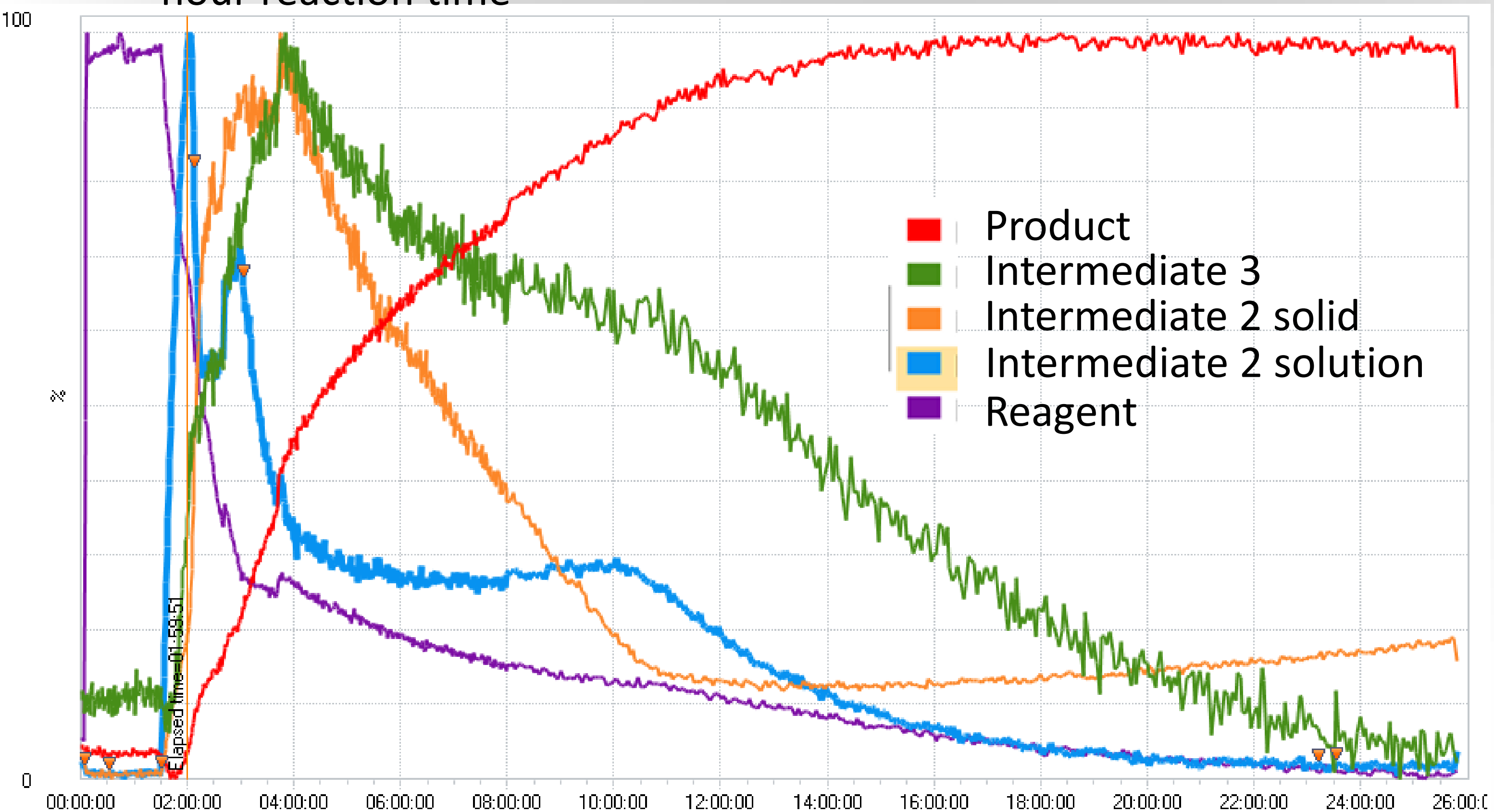
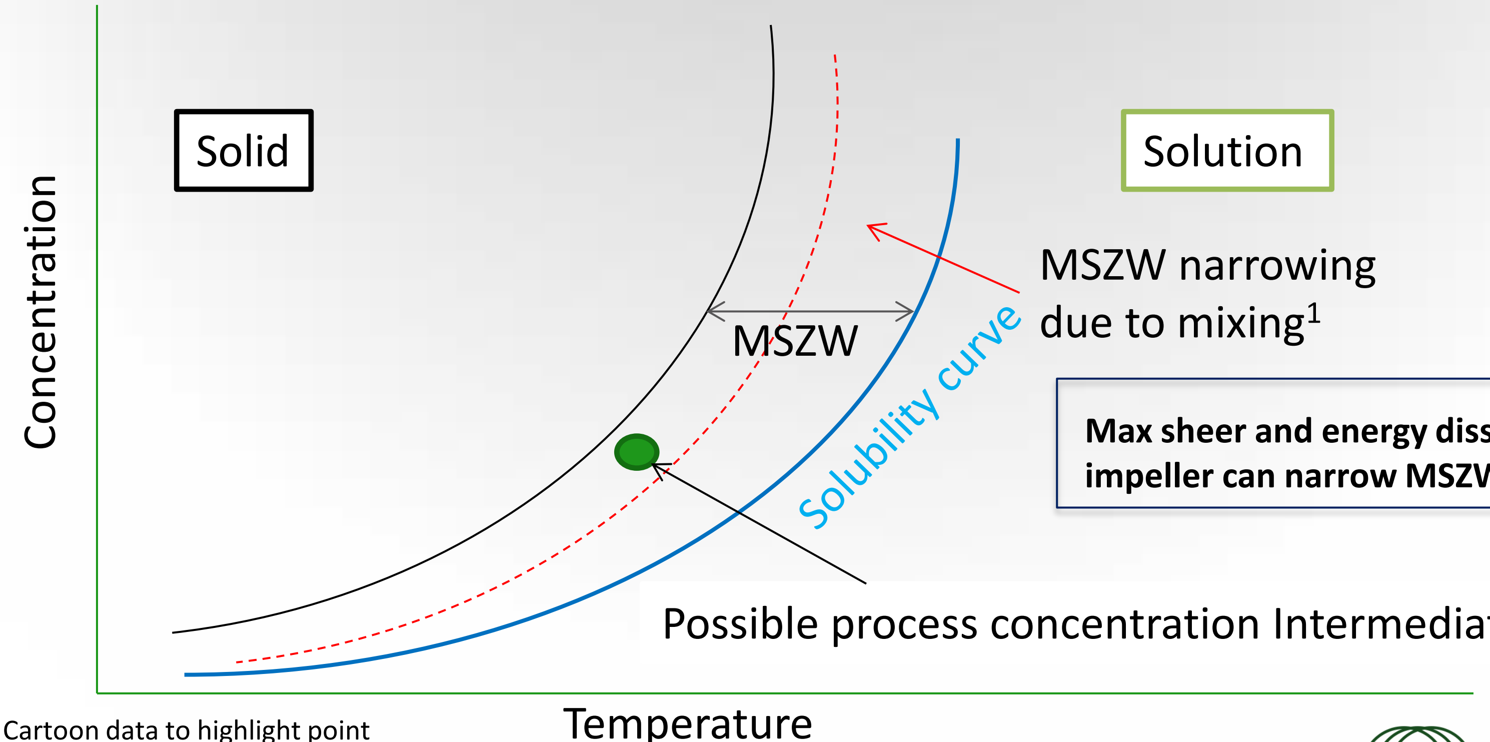
In Situ Raman Spectroscopy for Reaction Matching Max Energy Dissipation

Mass transfer limitation seen in Intermediate 2 profile, In situ Yield of 68% at 18 hour reaction time



Mixing and Concentrations

- Meso-mixing local concentration will not lead to solid formation



Max sheer and energy dissipation near impeller can narrow MSZW

*Cartoon data to highlight point

1. Chianese, A., Contaldi, A. and Mazzarotta, B., *J Crystal Growth*, **1986**, *78*: 279–290.

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Example 2: Summary

- Not possible to match all the mixing parameters at each scale in one reaction
  - Requires multiple experiments to isolate each mixing parameter of interest
- Possible Mixing impact on process, the chance exists for solids to form in the 100 gallon reactor
  - Due to max energy dissipation and shear near impeller
    - The solids will not be problematic for the process and would result in only a slight yield loss, 68% vs. 71%.

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Case study 3: Non-Newtonian Fluid and Mixing Throughout the Process

- Customers is scaling up a deprotection of a polymer solution.
  - Solution is a non-Newtonian fluid that changes throughout the process
- Wanted to know if their process would perform at the 1000 gallon scale
  - Process had already been scaled to the 275 gallon scale
- Needed to evaluate additional process parameters (total amount of off gas)
  - Wanted to scale down the mixing in the lab equipment to be sure the data would be representative of the large scale equipment.

Non-Newtonian fluids

- A Non-Newtonian fluid is one where the viscosity is not constant with shear rate.
- In this case the fluid is shear thinning (viscosity decreases as shear increases)
- Viscosity as a function of sheer rates was supplied by costumer as well as densities at three points in the process

Shear rate (s^{-1})	viscosity(cP)		
	Time zero	Phase Transition	Final (3 hours)
1.7	114	3695	180
3.4	84	1569	123
6.8	77	737	80
17	64	271	42
34	60	129	28

- This data was fit to a power-law model for viscosity in VisiMix
  - The Herschel-Bulkley form of the equation.

$$\tau = \tau_0 + K * \gamma^n$$

$$\mu = \tau_0 * \gamma^{-1} + K * \gamma^{n-1} ,$$

where μ -effective viscosity, Pa*sec;
γ -shear rate, 1/sec;
τ -shear stress, Pa;
τ_0-yield stress, Pa.

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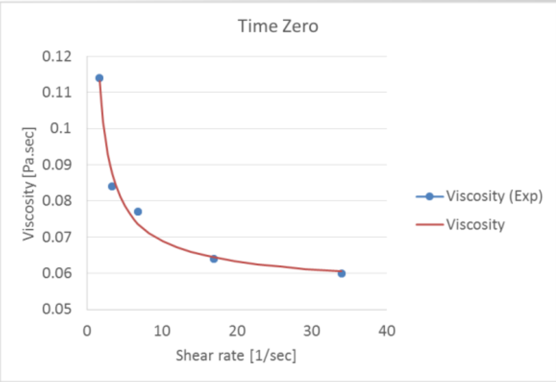
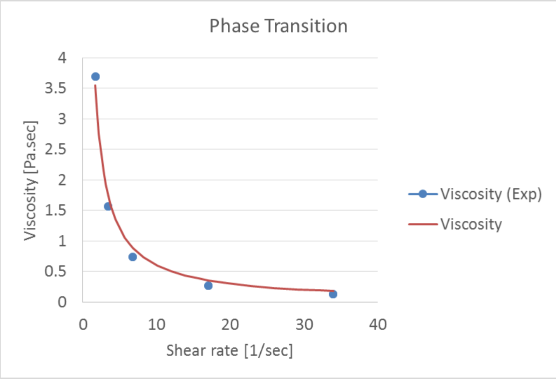
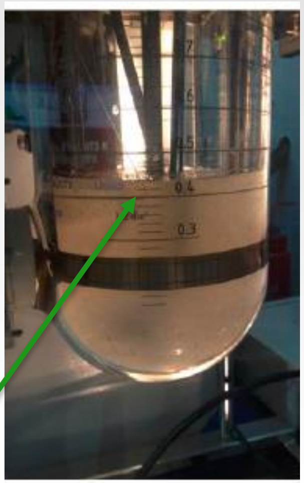
Non-Newtonian Fluid Viscosities



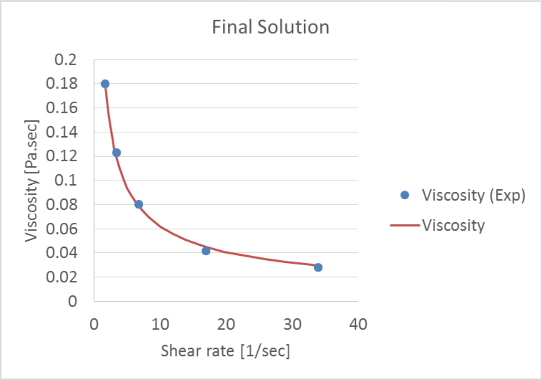
- The values for the parameters in the power-law were regressed to allow for modeling viscosity over the range of shear rates seen in the tank

	K	n	τ_o
Time zero	6.63E-02	9.62E-01	8.18E-02
Phase transition	1.00E-05	5.00E-02	6.03E+00
Final	2.51E-01	3.94E-01	0.00E+00





Highly viscous with no vortex at this point



Viscosity dramatically decreases, over 100 ml of volume increase due to vortex

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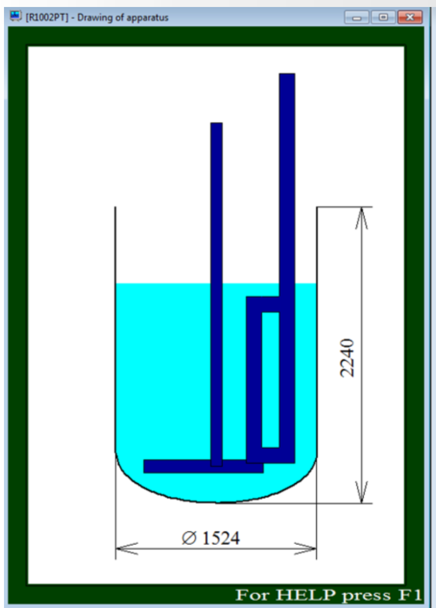
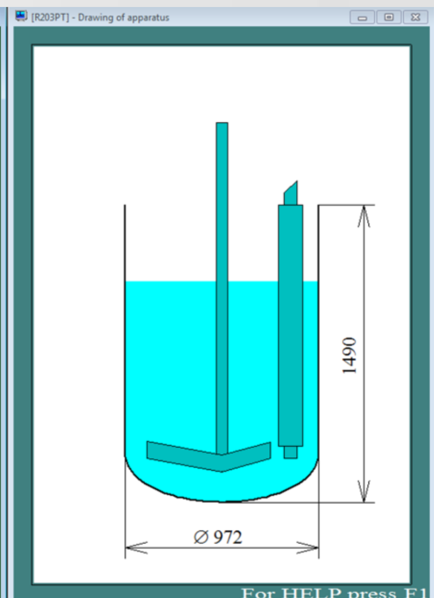
Visimix ® Model of reactors

- The geometry for the RC-1, the 275 gallon reactor, and the 1000 gallon reactor were input into Visimix ®

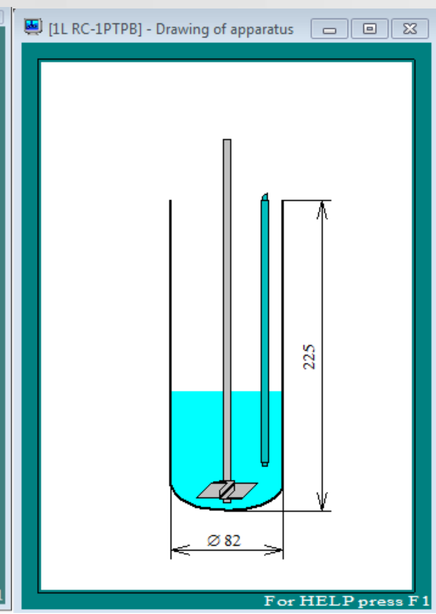
737 gallon fill
(1000 gallon reactor)



200 gallon fill
(275 gallon reactor)



0.1 gallon fill (0.4 L)
(0.26 gallon reactor)



What Mixing Parameters are Important?

- In practice it is not possible to match all the mixing parameters at various process scales.
  - rpms, tip speed, etc.
- Important to identify parameters that describe and impact the process.
  - Comparison of apparent viscosity at different zones in the tank (cP)
  - Average energy dissipation (W/kg)

Visimix ® Results

	275 gallon R-203 @110 RPMs	1000 gallon R-1002 @90 RPMs	RC-1 Pitch Blade @750 RPMs
Time Zero			
Viscosity bulk volume (cP)	53.8	53.8	
Viscosity near baffles (cP)	50.1	51.7	50.4
Viscosity near impeller (cP)	45.9	45.4	45.7
Average energy dissipation (W/kg)	1.65	1.66	2.53
Phase Transition			
Viscosity bulk volume (cP)	87.6	85.2	52.1
Viscosity near baffles (cP)	7.37	23.6	3.8
Viscosity near impeller (cP)	0.3	0.2	1.12
Average energy dissipation (W/kg)	1.6	1.64	1.34
Final			
Viscosity bulk volume (cP)	10.1	10	7.87
Viscosity near baffles (cP)	3.5	5.7	2.61
Viscosity near impeller (cP)	0.9	0.7	1.5
Average energy dissipation (W/kg)	1.6	1.64	1.42

- R-203 @ 110 RPM is best matched in R-1002 @ 90 RPM
- Viscosity (across the entire tank), and average energy dissipation values are in good agreement at all three stages of the process that were modeled.

- The RC-1 was able to come close to matching the viscosity and energy dissipation as compared to the larger equipment

- **The mixing in 1000 gallon can be adjusted to match that of the 275 gallon.**
- **Data from RC-1 is representative of the large scale equipment.**

Reynolds number for the Time zero material in the RC-1 were in the Laminar region and calculations were done using Visimix ® Laminar. All other calculations done using Visimix ® Turbulent.

Example 3: Summary

- As the process changes the mixing can as well
  - Physical changes in the process can change how the energy from the impeller is transferred through the material
- Need to compare the mixing at multiple points in the process to be sure the mixing will be sufficient.

Summary

- VisiMix is a valuable tool in the scale up of chemical processes.
- VisiMix helps in the identification of the critical mixing parameters
- VisiMix allows for modeling the mixing of the process at both the large and small scale
  - Test the process at the small scale
  - Ensure that the results at the small scale represent the large scale
  - May (**will**) require more than one experiment
- Identify and solve problems before scale…Save $$$!