Simulation of Mixing Processes
VisiMix

Simulation of Mixing Processes

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Contents

• Introduction
• Applications
  – R&D
  – Technical Transfer 1M$ per Project
  – Design 900 K Euros
  – Solid State Production 1.5$
  – Productivity 2M$
• VisiMix Products
• Conclusions
**VisiMix** is a unique software enabling chemical engineers, process engineers and R&D personnel to **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.
About Us

Technology - Simulation of Mixing Processes

- The First and the only tool in the Industry
- Reliable and accurate results
- Based on More Than 300 Man Years of R&D and Industry Experience
- Replacing Pilot Experiments
- Accelerated Time-to-Market process
- User Friendly and easily accessible
Customers and Markets
“VisiMix: This is a highly accessible PC software for mixing calculations available from VisiMix Ltd., an Israeli company. It is a rating calculation tool for both non-reactive and reactive mixing involving blending, solid suspension, gas dispersion, liquid-liquid dispersion, or heat transfer processes in stirred vessels. It calculates the important process parameters for single- and two-phase systems – power consumption, circulation rates, local concentrations of solutes and suspended particles, drop size, concentrations of reactants, etc … ”

Dr. Victor Atiemo-Obeng

Dow Chemicals Co.
Customers and Markets

1.3M, USA
2.Afton, USA
3.Air Products, USA
4.Alkermes
5.AllessaChemie
6.ASEPCO
7.Ashland Hercules
8.BASF, USA
9.Belinka Belles
10.Celgene
11.Chamagis
12.DeDietrich
13.Dow chemical
14.Eni - Milan
15.Evonik Degussa
16.GE Technologies
17.GE Healthcare
18.Global Tungsten & Powders
19.Honeywell-UOP
20.Ineos Styrenics
21.Lubrizol
22.Merck - Schering-Plough
23.Mitsubishi
24.NALAS-Jerry Salan
25.Nan Ya Plastic
26.Nippon
27.Novartis
28.NRDC, India
29.Ocean
30.Pfizer
31.Polimeri
32.Praxair
33.Dr. Reddys
34.Samsung, Korea
35.Sunovion Sepracor
36.SES
37.Solvay
38.Tecnicas Reunidas
39.Tecnimont, Italy
40.Teva Global
41.US Navy, USA
42.Alcon, USA
43.Arizona Chemical
44.JM Huber
45.Jotun
46.Lek
47.Matrix\Mylan
48.MJN - Mead Johnson Nutrition
49.Ranbaxy
50.R.C.Costello
51.Styron
52.Tami
53.Taro
54.Xellia
55.Ash Stevens Inc........

Total > 250 customers
Introduction

• This presentation will focus on the influence of hydrodynamics and mixing parameters in the process for every step of a typical synthesis procedure by connecting between the process and the mixing parameters, and complete our understanding of the main parameters we have to take in account in order to have a complete understanding of the process.

• All the case studies are based in real applications we have collected from our customers during 2012. They show huge savings, in the millions of dollars, in every field including management, development, technical transfer, design, production and troubleshooting.
Simple and Effective

Technology - Simulation of Mixing Processes
The Goal

Once the Science of the process (Chemistry, Biology or physics) is fully understood, 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

Mixing Simulation Software

R&D  Design

Production  QbD
R&D - Example
Application of Visimix to the Characterization of Lab Reactors

Reinaldo M. Machado
Estimating blend time in the Mettler-Toledo RC1 MP10 reactor

VisiMix model of MP10 showing “mean” velocity pattern at 500 rpm

<table>
<thead>
<tr>
<th>rpm</th>
<th>Q (l/min)</th>
<th>uniformity index</th>
<th>time, seconds to achieve 90% uniformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>4.2</td>
<td>0.29</td>
<td>220</td>
</tr>
<tr>
<td>400</td>
<td>5.7</td>
<td>0.31</td>
<td>86</td>
</tr>
<tr>
<td>500</td>
<td>7.4</td>
<td>0.34</td>
<td>53</td>
</tr>
</tbody>
</table>

2 Liter Lab Reactor, T =10 cm; Marine Propeller, D =6.9 cm; Fluid μ =985 cp, ρ =1.25 gm/cc; V =1.2 liters

300 rpm Re = 30
400 rpm Re = 40
500 rpm Re = 50

Characteristic function of tracer distribution

VisiMix simulation for 500 rpm

(c) Reinaldo Machado; rm2technologies LLC 2011
VisiMix predictions and Experiments for Heat Transfer with Anchor Impeller with Glycerol in the RC1 MP10 glass lab reactor

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment</td>
<td>14</td>
<td>25</td>
<td>940</td>
<td>13</td>
<td>58.1</td>
<td>25.0</td>
</tr>
<tr>
<td>VisiMix</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59.5</td>
<td>27.0</td>
</tr>
<tr>
<td>Experiment</td>
<td>31</td>
<td>40</td>
<td>274</td>
<td>43</td>
<td>68.4</td>
<td>25.0</td>
</tr>
<tr>
<td>VisiMix</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70.5</td>
<td>26.2</td>
</tr>
<tr>
<td>Experiment</td>
<td>48</td>
<td>55</td>
<td>89</td>
<td>133</td>
<td>83.7</td>
<td>25.0</td>
</tr>
<tr>
<td>VisiMix</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80.0</td>
<td>23.2</td>
</tr>
</tbody>
</table>

(c) Reinaldo Machado; rm2technologies LLC 2011
Mettler Toledo AP01-0.5

The unique baffle and agitator design is appropriate for mixing diverse liquid chemical systems, from high-viscosity laminar flow to low-viscosity multi-phase turbulent flow.

- **Reactor**
  - $T = 70 \text{ mm}$
  - Maximum recommended liquid height $Z=140 \text{ mm}$

- **Impeller**
  - 1, 2 or 3 depending up reactor fluid and liquid height
  - Non-standard 4 blade pitched ($45^\circ$) blade
  - $D = 38 \text{ mm}$
  - $C = 10 \text{ mm}$
  - Distance between impellers $= 29 \text{ mm}$

- **Baffles**
  - $3 \times 24 \text{ mm} \times 25 \text{ mm}$
  - Pre-positioned between impellers

(c) Reinaldo Machado; rm2technologies LLC 2011
### Comparison of Power Numbers and “macro-mixing”

<table>
<thead>
<tr>
<th>Number of impellers</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>2</th>
<th>3</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation rpm</td>
<td>900</td>
<td>300</td>
<td>300</td>
<td>120</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>Re</td>
<td>26.0</td>
<td>8.7</td>
<td>8.7</td>
<td>3.5</td>
<td>8.7</td>
<td>2.9</td>
</tr>
<tr>
<td>VisiMix 1/T&lt;sub&gt;circulation&lt;/sub&gt; 1/s</td>
<td>0.400</td>
<td>0.087</td>
<td>0.139</td>
<td>0.055</td>
<td>0.166</td>
<td>0.054</td>
</tr>
<tr>
<td>Experimental k&lt;sub&gt;mix thermal&lt;/sub&gt; 1/s</td>
<td>0.113</td>
<td>0.035</td>
<td>0.044</td>
<td>0.017</td>
<td>0.050</td>
<td>0.017</td>
</tr>
<tr>
<td>VisiMix k&lt;sub&gt;mix composition&lt;/sub&gt; 1/s</td>
<td>0.0132</td>
<td>0.0015</td>
<td>0.0074</td>
<td>0.0026</td>
<td>0.0061</td>
<td>0.0020</td>
</tr>
<tr>
<td>VisiMix Power number</td>
<td>4.5</td>
<td>8.7</td>
<td>16.3</td>
<td>40.2</td>
<td>24.3</td>
<td>71.0</td>
</tr>
<tr>
<td>Experimental Power number</td>
<td>4.9</td>
<td>12.7</td>
<td>16.5</td>
<td>39.9</td>
<td>21.9</td>
<td>62.8</td>
</tr>
</tbody>
</table>

Note that thermal uniformity in liquids is achieved much more efficiently than composition uniformity and explains in part the difference between VisiMix and the thermal tracer method.
What about the scale-up of mass transfer?

- plant & lab raw materials & catalyst are from same lots numbers
- mixing in lab reactor measured and $k_L a > 0.4 \text{ s}^{-1}$; mass transfer is very fast compared to reaction so that $C_{H_2,\text{bulk lab}} = C_{H_2,\text{sat lab}}$
- lab reactor pressure was adjusted to match plant rate profile
  - RC1 programmed to match exact temperature profiles of plant
  - when plant = 800 psig and lab = 700 psig the rates are equivalent

$$k_L a_{\text{plant}} = \frac{\text{rate}}{C_{H_2 \text{ saturated plant}} - C_{H_2 \text{ saturated lab}}}$$

<table>
<thead>
<tr>
<th></th>
<th>plant</th>
<th>RC1 HP60</th>
</tr>
</thead>
<tbody>
<tr>
<td>volume</td>
<td>3300 gal</td>
<td>1.0 liter</td>
</tr>
<tr>
<td>agitation</td>
<td>84 rpm</td>
<td>1400 rpm</td>
</tr>
<tr>
<td>Impeller diameter</td>
<td>40 inch</td>
<td>1.8 inch</td>
</tr>
<tr>
<td>Impeller type</td>
<td>2x flat turbines</td>
<td>gassing</td>
</tr>
<tr>
<td>pressure</td>
<td>800 psig</td>
<td>700 psig</td>
</tr>
<tr>
<td>$k_L a$ from scale-down</td>
<td>0.052 s$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$k_L a$ from VisiMix</td>
<td>0.062 s$^{-1}$</td>
<td></td>
</tr>
</tbody>
</table>

(c) Reinaldo Machado; rm2technologies LLC 2011
So what have I/we learned?

- VisiMix predictions and lab reactors mixing measurements are in agreement with each other when reactor geometries match and physical properties are known.

- If lab reactor geometries do not match the catalogue of available geometries in VisiMix, geometric approximations must be made.
  - For power and heat transfer, errors appear to be insignificant.
  - For solid suspension, phase dispersion and circulation
    - more detailed mixing data for the lab reactor is necessary to adjust the approximations.
    - validations may be necessary.

- The limitations of lab mixing characterization methods such as thermal tracing must be considered when using them for scale-up or matching more detailed VisiMix models.
Technical Transfer Process

Savings of ~ $1,000,000 per Project
Mixing Calculations in Development
Save with VisiMix (for this example: $1,000,000 per project)!

**VISIMIX SOLUTIONS**

**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)
Methodology (J.M. Berty, CEP, 1979)

- LABORATORY (R&D)
- BENCH SCALE (RC1, HEL)
- PILOT (Mini Pilot)
- PLANT (Pilot, Production)
- Final Design
  - Build
  - Scale Down

- LABORATORY (R&D)
- BENCH SCALE (RC1, Mini Pilot)
- PILOT (Pilot)
- Demo – Simulation (Visimix, Dynochem, CFD)
- PLANT (Production)
Taking into account the hydrodynamic parameters that influence the process results in the early first step in the scaling up characterization and setting the lab equipment according to production simulation results. This focuses the scale up team to find the optimum set of operational parameters based on the evaluation of the process in a real hydrodynamic configuration.

Figure 2: Typical Mixing Parameters Selected VisiMix Outputs

VisiMix helps us to determine an adequate reactor configuration in the different scales in the scaling up activities. Mixing characterization at every stage guarantees a good and stable process.

"With the help of your team and your simulation software. This saved us a lot of money and time. We introduce your simulation software in our plant as part of our scale-up routine and QbD practice..."
Lab and Prod Calculations

Non ideal stirring – non homogeneity

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

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

Not all Mini Pilot reactor are capable of full suspension of POCA.
Methodology

In the three years since the commencement of this process, their engineers achieved a high level of proficiency in the use of the simulation models in order to analyze the results as a function of the process operational parameters.

After three years of working with this integrated plan – they have summarized their knowledge and experiences up to this point, as follows:

1. VisiMix products, when integrated in the validation process (up until they achieved a stable process and confirmed the production) – helped to reduce the number of lost production batches (each batch valued in millions of dollars) - from 100 to just under 10 batches – (review slide 25)

2. VisiMix program used in conjunction with another simulation tool - as reported in this presentation - contributed to the improvement of the teamwork style and professionalism. Net results were observed throughout the implementation of the new solution in better project development: EOR (end of reaction) time reductions, projects development time and cost reduction, and in addition - increasing the expertise and qualification level of the professional staff.

The presentation can be review on the Visimix Website in the References - Users Publications page. (Scale up optimization using simulation experiments-Chemagis presentation)
Methodology

# produced lots needed until till a stable process is achieved
Design

Savings of 900,000 Euro
Troubleshooting in Life Science Industry

Savings of 900,000 Euro!

**VISIMIX SOLUTIONS**

**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.
<table>
<thead>
<tr>
<th>The Traditional Approach</th>
<th>Trial and error in the production facilities in order to do &quot;fine tuning&quot; of the operational parameters in the process. No improvement was observed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The VisiMix Analysis</td>
<td>VisiMix was used to find out why the process failed and make suggestions to remedy the challenge.</td>
</tr>
<tr>
<td>The VisiMix Solution</td>
<td>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.</td>
</tr>
<tr>
<td>The Results</td>
<td>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.</td>
</tr>
</tbody>
</table>

“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”
Due to the improved mixing hydrolysis was accelerated. VisiMix showed that the impeller was not suited for this process and the production moved to reactors with appropriate mixing.

*The actual knowledge and future plan must be coordinated and combined in the company.*
Solid State Production

Saving ~ $1,500,000
Control Morphology and Particle Size in Energetic Material Processes

Save with VisiMix!

**VISIMIX SOLUTIONS**

**Process**: Reactive and Continuous Crystallization Process for Energetic Materials

**Task**: Develop a continuous manufacturing process producing energetic materials within desired particle size distribution and of desired morphology.

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**The Process**

Reactive and Continuous Crystallization Process for Energetic Materials

---

**The Problem**

Maintaining particle size distribution and morphology during continuous manufacturing process.

---

**The Traditional Approach**

Running the process in the pilot scale at different degrees of mixing and retention times to achieve desired particle size distribution and morphology.

---

**The VisiMix Analysis**

VisiMix is able to efficiently simulate the degree of mixing influence on solids suspension and predict challenges associated with the specific equipment geometries. The ability to simulate the distribution of the solids in the process as a function of mixing parameters eliminates ‘trial and error’ experiment at the pilot scale. The appropriate equipment (impeller design, tank design) and operating parameters (rpm, feed rates) were identified using in-silico methods, avoiding the ‘trial and error’. This method saved significant money and time while developing a process producing the desired particle size distribution and morphology.
VisiMix predicted that the existing equipment and operating parameters were not satisfactory to suspend the solids resulting from the continuous, reactive crystallization. Changing the design of the equipment (type and number of impellers) and operating parameters (increased rpm) afforded a process producing the desired particle size distribution and morphology.

Each project has unique requirements including number of synthetic steps, process labor, and associated operating costs. Starting material costs are often very high (typically thousands of dollars per kilogram) in development stages. A trial and error approach could have cost over $50,000 in just material with an estimated $60,000 in labor. The modeling approach reduced overall development costs by 60%.

Process development often includes optimization of 10-15 synthetic steps. On average it costs $150,000 per step (10 steps = $1.5M). Modeling reduced process development costs by 60%, or extrapolated to $900,000 in cost savings for a 10 step process.

VisiMix saves you money each time a new process is developed! Have you considered VisiMix for your existing processes?
The “BIG” challenge
Improper pilot-scale design led to particles of a much larger size and morphology than originally seen in the lab-scale proof of concept.

![Image showing lab-scale (inset) vs. pilot-scale]

Lab-scale (inset) vs. Pilot-scale

The “Solution” included VisiMix Modeling
Modeling the specific pilot-scale configuration identified that the impellers were not adequately sized and that the rpm was too low in order to suspend the solids and increase the average concentration of solid phase in the continuous flow. These improvements led to the desired product quality in terms of particle size distribution and morphology.
Equipment Design

<table>
<thead>
<tr>
<th></th>
<th>Single paddle impeller 230 rpms</th>
<th>Single pitched impeller 230 rpms</th>
<th>Dual pitched impeller 230 rpms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max degree of non-uniformity - axial, %</td>
<td>35.4</td>
<td>39.0</td>
<td>97.0</td>
</tr>
<tr>
<td>Average concentration of solid phase in continuous flow (kg/m³)</td>
<td>6.32</td>
<td>6.08</td>
<td>6.86</td>
</tr>
<tr>
<td>Relative residence time (ratio)</td>
<td>1.27</td>
<td>1.32</td>
<td>1.17</td>
</tr>
<tr>
<td>Characteristic time of micro-mixing (sec)</td>
<td>4.63</td>
<td>3.79</td>
<td>2.79</td>
</tr>
</tbody>
</table>

Solid-Liquid Mixing Parameters

<table>
<thead>
<tr>
<th></th>
<th>150 rpms</th>
<th>230 rpms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum degree of non-uniformity-axial, %</td>
<td>298</td>
<td>166</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity - radial, %</td>
<td>13.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Average concentration of solid phase in continuous flow (kg/m³)</td>
<td>4.44</td>
<td>6.31</td>
</tr>
<tr>
<td>Relative residence time of solid phase (ratio)</td>
<td>1.80</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Average concentration of solid phase in continuous flow approaches ideality (8.0 kg/m³)
The Result was a Satisfied Customer

VisiMix can be used at any time during process development. In this case the customer identified a major challenge at the pilot-scale. The challenge was identified as poor solids dispersion in a continuous stirred tank reactor using VisiMix. VisiMix was used to provide suggested changes to the equipment and operating parameters resulting in the desired product.
"Chemical Engineering is not magic! It is a science that assists the team in producing processes that work in the equipment to which you will produce your product."

www.visimix.com
Productivity

Saving ~ $1,600,000
Productivity improvement in API Company
Save with VisiMix (for this example: $1,600,000 per year)!

**Process:**
Two Phase Reaction – Production

**Task:**
Improve performance, reproducibility and operation time

**The Process**
Batch reaction

**The Problem**
Long Operation time. Poor reproducibility.

**The Traditional Approach**
After a few batches, it was clear that the problem was in the equipment. The results were non reproducibility and log time of the reaction time
The VisiMix Analysis

Operation in this reactor was evaluated using VisiMix in combination with QbD practices. A 25 liter Reactor will operate with 10 L volume. Stirrer Speed around 100 rpm is the maximum to avoid Dangerous Vortex formation. These hydrodynamic characteristics of the production reactor induce to predict kLa lower than wished for, resulting in longer EOR time and possibly uncertain reaction results. The chosen production reactor was not recommended to perform this API reaction.

The VisiMix Solution

Two new reactors were evaluated for API reaction operation. Installation of two baffles was enough to stabilize and reduce the reaction time from 25-50 hours to 9 hours.

The Results

In the modified system,

- Reproducibility of the reaction time;
- Saving at least $1,600,000 per year*
- The analysis of the problem, and the solution took just 2 weeks.

The use of VisiMix made it possible for the company to save $1,600,000 by adding a new baffle configuration. Additional savings were achieved by decreasing the process time and improving the quality of the product.

*Calculated for cost of $200 per hour per Batch and an average saving of 20 hrs per batch during a year’s work for 400 batches (200*20*400=$1,600,000)
The VisiMix simulation showed that mixing in the existing system was good. Comparison with two new configurations gave better results.

<table>
<thead>
<tr>
<th>Characteristic/Reactor</th>
<th>RC-1</th>
<th>R4504-1</th>
<th>R4504-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum useful volume, L</td>
<td>2</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Operational volume, L</td>
<td>0.6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Stirrer speed, rpm</td>
<td>500</td>
<td>285</td>
<td>285</td>
</tr>
<tr>
<td>Reynolds</td>
<td>13700</td>
<td>70300</td>
<td>56400</td>
</tr>
<tr>
<td>Energy distribution average, W/kg</td>
<td>1.18</td>
<td>1.83</td>
<td>2.5</td>
</tr>
<tr>
<td>Energy distribution in bulk, volume, W/kg</td>
<td>0.623</td>
<td>0.72</td>
<td>0.90</td>
</tr>
<tr>
<td>Micro mixing time, s</td>
<td>1.53</td>
<td>2.71</td>
<td>2.27</td>
</tr>
<tr>
<td>Complete Suspension Expected</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity Axial, %</td>
<td>1.74</td>
<td>2.77</td>
<td>1.52</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity Radial, %</td>
<td>0.77</td>
<td>12.9</td>
<td>0.63</td>
</tr>
<tr>
<td>Maximum energy of collisions, J</td>
<td>4.4E-9</td>
<td>7.7E-9</td>
<td>1.17E-8</td>
</tr>
<tr>
<td>Characteristic time between two strong collisions, J</td>
<td>5.05</td>
<td>4.5</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 1: Main Hydrodynamics-Turbulent-Mixing Characteristics for lab and production reactors,
5 Test results:

- $T = 20 - 23 \text{ C}$
- $\text{EOR} = 23 - 50 \text{ h}$
- $\text{Yield} = 97 - 98 \%$

2 Test results from R4504-1:

- $T = 23 - 25 \text{ C}$
- $\text{EOR} = 11 \text{ h}$
- $\text{Yield} = 97 - 98 \%$

Similar results were obtained in R4504-3 but:

- $\text{EOR} = 9 \text{ h}$

**VisiMix** helped us to determine adequate reactor/stirrer system and the best Hydrodynamics/Turbulent Mixing characteristics during the operation process to guarantee desired steady results.

"With the help of your team and your simulation software, the solution was simple: we have installed new baffles, and obtained good mixing with reproducibility and decreased the reaction operation time. This saved us a lot of money and time. We introduce your simulation software in our plant as part of our scale-up routine and QbD practice..."
Productivity

Saving ~ $2,000,000
Troubleshooting for Crystallization Processes – Saved $2,000,000

Save with VisiMix!

VISIMIX SOLUTIONS

Process: Reactive Crystallization Acid Base in API industry

Task: Impurity rises during scale up activities

The Process

Reactive crystallization of organic acid with 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 generates 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 factor of 4 succeeded, and achieved higher productivity by 4 times.
Chemical reaction

Intermediate from previous step

\[
\text{NaOH(s)} + \text{PNT FREE ACID} \rightarrow \text{PNT-Na}
\]

Acid / base - main reaction

Hydrolysis - side reaction

\[
\text{NaOH(s)} + \text{EtAc} \rightarrow \text{CH}_3\text{COONa} + \text{EtOH}
\]

About 1% H₂O

solvent

impurity

Production Results

<table>
<thead>
<tr>
<th>system</th>
<th>Average imp sodium acetate concentration [%]</th>
<th>Number of batches produced at 2011</th>
<th>% RJ on sodium acetate impurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-2013</td>
<td>0.15%</td>
<td>329 batches</td>
<td>1.2%</td>
</tr>
<tr>
<td>R-1961</td>
<td>0.19%</td>
<td>195 batches</td>
<td>0.5%</td>
</tr>
<tr>
<td>R-4902</td>
<td>0.44%</td>
<td>58 batches</td>
<td>24.1%</td>
</tr>
<tr>
<td>specification</td>
<td>NMT 0.50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

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

**VisiMix** help 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 **VisiMix** results evaluation.
Impeller Design for Liquid-Liquid Dispersion Using VisiMix RSD/Turbulent
Impeller Design for Liquid-Liquid Dispersion Using VisiMix RSD/Turbulent

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860-460-9611

Jerry Salan
jerry.salan@nalasengineering.com

Available for public release
What do we do?

• Transition chemical processes to the plant environment
  – Identify engineering challenges including heat transfer, mass transfer, and mixing
  – Evaluate chemistry in the laboratory using in situ tools (IR, Raman, FBRM, PVM, heat flow)

• Evaluate pilot and production equipment. Validate processes through scale-down experiments

• Develop low-cost chemical processes
Background

• Design an automated laboratory reactor to replace the current lab system for the evaluation of raw materials in the production of Propylene Glycol Dinitrate (PGDN).

• Maintain same degree of mixing as traditional system
Laboratory Reactor Constraints

• The main point of the automation is to increase worker safety, while maintaining same degree of mixing
  – Allow for comparison back to historical data
  – Droplet size may impact separation times
  – Identify problematic lots of propylene glycol
• Match the mixing that they have in the current setup
  – VisiMix to model both existing and proposed lab reactor
Simulant Testing

- Test system was Toluene/water.
- Direct comparison of the ‘existing’ laboratory system vs. the ‘proposed’ laboratory system

Existing Setup
“Disperserator”

Proposed Setup
Traditional Impellers
VisiMix Inputs for Liquid-Liquid Mixing

- Interfacial Surface tension between the two phases
- Density of both phases
- Index of admixtures
  - This is a measure of the system to stabilize drops
    - Electrolytes
    - Surfactants
    - Etc.

![Properties of continuous and disperse liquid phases](image-url)
Required Inputs

**Interfacial tension**

\[
\sigma_{12} = -\sigma_{1a} \frac{\cos \theta_{1a}}{\cos \theta_{12}} + \frac{gr}{2\cos \theta_{12}} (\rho_1 h_1 + \rho_2 h_2 - \rho_1 L_1)
\]

Were:

- \(\sigma_{12}\) = interfacial tension between the two liquids
- \(\sigma_{1a}\) = surface tension of the light phase
- \(\theta_{12}\) = angle of contact of the liquid-liquid meniscus with the capillary wall
- \(\theta_{1a}\) = angle of contact of the light phase meniscus with the capillary wall
- \(g\) = acceleration due to gravity
- \(r\) = radius of the capillary
- \(\rho_1\) and \(\rho_2\) = densities of the respective phase.
- \(h_1\), \(h_2\), and \(L_1\) are measurements taken as shown in figure.
• Densities of the two phases were measured after the phases had been mixed and allowed to separate.
• This is to account for the change in density due to the solubility of the two materials with each other.
Required Inputs

\[
\sigma_{12} = -\sigma_{1a} \frac{\cos \theta_{1a}}{\cos \theta_{12}} + \frac{gr}{2 \cos \theta_{12}} \left( \rho_1 h_1 + \rho_2 h_2 - \rho_1 L_1 \right)
\]

- Photograph of Toluene/water interface
- Measured interfacial tension our system (Toluene/Water)
  - 0.0327 N·m\(^{-1}\)
- Reported/reference interfacial tension for Toluene/Water
  - 0.0364 N·m\(^{-1}\).

\[\theta_m = \cos^{-1}\left(2k/(k^2+1)\right)\]
\[\theta_{12} = 180 - \theta_m = 155.01^\circ\]
Particle Vision Microscopy: PVM

In situ probe that allows for:

- Detect multiple phases: Gas, Bubbles, Droplets, Oil
- Characterize Particle Shape
- Polymorphic crystallization characterization
  - Visualize morphology changes
  - Understand dynamics of polymorph transitions
- Characterize surface roughness
- Understand particle dynamics and interactions: growth, nucleation, agglomeration, and breakage phenomena
- Determine root cause of particle processing problems
Validate Model Using PVM

• Taking the PVM data at one setup to test the model for the admixture value.
• Comparing drop size distribution to the VisiMix values
• By matching the shear between systems we hope to match drop size, surface area, and mixing.

  – Mean drop size
Calculating Drop Diameter from PVM

Average of drop diameters from PVM image

Repeat with another image

The average diameter for all three images is then averaged again and that value is the drop diameter for that RPM

Repeat a third time
RC-1 Experiments

Pitch blade impeller with PVM and Tr as baffles.

PVM mean ≈ 280 µm

VisiMix calculated mean = 282 µm with admixture value set to 0.75
RC-1 Experiments Using PB-Impeller

VisiMix Cal Mean = 689µm
PVM Mean = 670µm

VisiMix Cal Mean = 403µm
PVM Mean = 397µm

VisiMix Cal Mean = 314µm
PVM Mean = 301µm

VisiMix Cal Mean = 281µm
PVM Mean = 275µm

400 rpms
600 rpms
800 rpms
10000 rpms
VisiMix RSD enables you to quickly calculate—

- Shear rates and stresses in internal spaces of the High Shear Mixer
- Pumping capacities
- Power consumption and torque
Modeling

- VisiMix models both traditional type impellers (Turbulent 2K) and rotor stator mixers (RSD)
- First calculate mixing parameters using rotor stator model
- Match the output using Turbulent 2K
  - Trial and error by simply changing rpm

<table>
<thead>
<tr>
<th>RPMS</th>
<th>4000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shear Rate [1/sec]</td>
<td>30800</td>
</tr>
<tr>
<td>Shear Stress [N/sq.m]</td>
<td>54.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RPMS</th>
<th>1860</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shear Rate [1/sec]</td>
<td>30800</td>
</tr>
<tr>
<td>Shear Stress [N/sq.m]</td>
<td>54.6</td>
</tr>
</tbody>
</table>
Disperserator Experiments

Modeling:

Mean diameter = 138 µm

Experimentation:

Mean diameter ≈ 130 µm
Conclusions

• **VisiMix** accurately predicts mixing parameters for both traditional impellers and *rotor/stator systems for liquid-liquid mixing*

• By modeling the dispersion in the historical laboratory equipment we are able to identify automated reactor configurations that will maintain the same degree of mixing.
High Shear Rate at Chemical Fast Reactions
Process and Quality Problem

R-6826

Feed R-Cl

Process

R-NH₂ + R’-Cl → t-D-R-R’

Impurity

t-L-R-R’
### Impurity results at laboratory and in production

<table>
<thead>
<tr>
<th>[%]impurity</th>
<th>RPM</th>
<th>Impeller type</th>
<th>volume</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>15,000 rpm</td>
<td>rotor stator</td>
<td></td>
<td>Laboratory reactor</td>
</tr>
<tr>
<td>0.3%</td>
<td>1,500 rpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6%</td>
<td>800 rpm</td>
<td>3-blade</td>
<td>0.63 lit</td>
<td></td>
</tr>
<tr>
<td>1.5%</td>
<td>100 rpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3% - 0.6%</td>
<td>140 rpm</td>
<td>bottom – flat blade up - turbofoil</td>
<td>2,978 lit</td>
<td>Production R-6826</td>
</tr>
</tbody>
</table>

Correlation between shear rates and the impurity concentration
Working with rotor stator at laboratory scale

Problem

How to scale up?

Potential Saving:

MORE than 250 K$
Rotor Stator Technology
Calculating shear forces with VisiMix

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

The required shear rate can not be achieved in the production reactor
Millions Saved By Using VisiMix!
A Real Return On Investment (ROI).

VisiMix LTD, is pleased to provide you with some very important new information on VisiMix Savings, which we have compiled for publication. These documents, show **savings of millions of dollars per year**. Please click the links directly below to view the following savings examples:

**Mixing Calculations in Development** (Saved - $1,000,000)
**Productivity Improvement In API Company** (Saved - $1,600,000)
**RSD Application in a Chemical Reaction Process** (Saved - $250,000)
**Control Morphology and P.S. in Energetic Material Processes** (Saved - $900,000)
**Troubleshooting for Crystallization Processes** (Saved $2,000,000)
**Troubleshooting in Life Science Industry** (Saved €900,000)
**Three Phase System – Solid-Liquid-Liquid** (Saved €1,200,000)
**Improve Dissolution of Organic Solid** (Saved €1,200,000)

**Physical Properties of the Final Product (Solid) – Ensuring Regulatory Compliance of $20,000,000 Sales**

We also invite you to view some highlights from our very successful **International Conference in Boston** that took place in **July 2011**, which united users and future users of the VisiMix Software to share some insights into the various uses and benefits of the software.
VisiMix Products
VisiMix Products

The latest VisiMix products are:

- VisiMix 2K8 Turbulent
- VisiMix 2K8 Laminar
- VisiMix 2K8 Different Impellers
- VisiXcel- Data Base
- Pipe Line
- Rotor Stator Disperser – RSD

NEW!
VisiMix Products

VisiMix Software Products

• VisiMix 2K8 Turbulent – for low-viscosity liquids and multiphase systems.

  The program provides process parameters necessary for analysis, scaling-up and optimization of mixing tanks and reactors with all types of impellers.

Calculations of:

✓ Blending
✓ Suspension
✓ Dissolution
✓ Emulsification
✓ Gas dispersion
✓ Heat transfer
✓ Chemical reactions
✓ Mechanical stability of shafts
VisiMix Products

VisiMix Software Products

- **VisiMix 2K8 Laminar** - for highly viscous media
  - Newtonian and non-Newtonian
  - Macro-scale blending
  - Micromixing in high-shear areas
  - Heat transfer
  - pastes
  - creams
  - shampoos
  - liquid soaps
  - gels
  - ointments
  - paints:
  - coatings
  - slurries
  - polymer solutions
VisiMix Products

VisiMix Software Products

- **VisiMix 2K8 Different Impellers – for combined mixing devices**

  The program handles mixing devices consisting of any 2 – 5 impellers.
  Different distances between impellers
  Used in combination with VisiMix Turbulent.
  Provides parameters of hydrodynamics, turbulence and heat transfer.
VisiMix Products

VisiMix Software Products

- **VisiMix VisiXcel – Data Base (DB)** – automatic conversion tool: Visimix Output to Excel Spreadsheet

- Integrates VisiMix report parameters in standard Excel worksheets
- Analysis VisiMix results in Excel
- Builds a Database of mixing tanks and reactors.
- Builds a Database of projects - for processes
- Makes correlation between plant equipment nomenclature to VisiMix database of mixing tanks and reactors in VisiMix Project Database.
- Easy access to design data of the mixing tanks, to process parameters and to corresponding results of VisiMix modelling.
- Results of VisiMix mathematical modelling in the **VisiMix VisiXcel-DB** and arrange the data according to the reactor nomenclature.
- Easy access to recalculation of the VisiMix modelling from the Database of the reactors & the projects
VisiMix Software Products

• VisiMix Pipe-Line

• Calculates hydraulic resistance of simple pipelines for liquid viscosity and non-Newtonian products.
• *Chemical engineers benefit from a quick and user friendly method for charging times* and the *bottle-necks* in the line.
• *Includes*: - Pipes - Riffled hoses – Elbows – Valves - And more
• Also comes with a *database containing rheological constants* for the typical commercial non-Newtonian products - pastes, creams, shampoos, paints, etc. (*see Help Section for details*)
• *The first and only tool* calculating flow resistance for liquids that correspond to *Carreau rheological model*. (*See Help Section for details*)
VisiMix Products

VisiMix Software Products

• **VisiMix RSD (Rotor Stator Disperser)**

The **revolutionary** new VisiMix RSD - Rotor Stator Disperser software is the first product of its kind that provides support for mixing devices for media subjected to high sheer stress:

*Based on 3 years dedicated research in a lab with dedicated equipment*

*Works with all types of media - both high and low viscosity liquids, Newtonian and Non-Newtonian.*

Input geometrical data and process parameters and obtain fast and reliable results with one click

VisiMix RSD enables you to quickly calculate

- Shear rates and stresses in internal spaces
- Pumping capacities
- Power consumption and torque
VisiMix Orientation

VisiMix Demonstration Tools

The VisiMix Demonstration Tools:

- VisiMix Turbulent – Examples & User Guide
- VisiMix Laminar - Examples & User Guide
- VisiMix Different Impellers – Examples & User Guide
- VisiMix RSD– Examples & User Guide
- VisiMix Turbulent SV – Trial & Education
- VisiMix Review of Mathematical Models
- Selected Verification Examples

*The Comparison between Published Experimental Data and VisiMix Calculations*

http://www.visimix.com/
Conclusion

- Using VisiMix Products support you can
  - Better understand your processes
  - Dramatically reduce your Scaling Up and Scaling Down processes
  - 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 serious experimental checking – and found to be very reliable.

- VisiMix Projects Parameters and Data Base allows you to share and transfer the data with colleagues in the company.
If You Are Interested In Learning More

• India:
  – Please call Dinesh Malviya at +91 9321024445
  – e-mail Dinesh at dmalviya@helindia.com

• Mexico:
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