Scale Up Methodology for the Fine Chemical Industry -

The Influence of the Mixing in the Process

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Abstract- In this article the authors, based on the VisiMix Software, the experience of VisiMix users and personal knowledge from more than ten years of experience using VisiMix for API, Fine Chemicals and others, processes simulation, show a Method for Scale Down – Scale Up of Batch – Semi Batch operations built under Hydrodynamics study of the Mixing procedure in the reactor system. The use of the recommended method will offer the user the possibility to achieve the best results during production stage with saving among time and currency, and at the same time increasing the knowledge of the performed process. Several examples at the end of the article show the benefits of the proposed VisiMix Method Loops for Scale Down - Scale Up and Hydrodynamics Considerations.

Keywords: Mixing, chemical method, stirred tanks, batch chemical reactor, simulation, scale up, scale down.

1. INTRODUCTION

Chemical production is a result of several chemical reactions and purification steps. Purification steps and processes yield are a direct function of the level of understanding of the reaction system. Reaction quality results have a tremendous impact in separation technology. Chemical production is frequently performed on stirred vessels that are operated at batch or semi-batch configuration. The choice process configuration is determined at the development stage of the project. Therefore, if the chemical reaction and mixing are not well understood, wrong selections will be adopted in the process development.

The financial impact of understanding the chemical reaction was assessed. It was estimated that US$500 million can be saved by optimizing a blockbuster drug on the market (Ka Ming Ng 2003). It is estimated that losses by poor mixing is $1 to $10 billion in the US chemical industry alone (Kresta 2001).

Once the process (Chemical, Biological or Physical) 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. If the hydrodynamics knowledge is integrated with the chemical phenomena, it will be possible to set up small and automatic equipment to prove the relationship between mixing and chemistry. In this way, it may be the first time that the process will be evaluated at large scale similar conditions. The main advantage of the methodology is the combination of neither realistic conditions in small equipment and of course catching the main normal gaps between the lab and the production results. The combination of equipment and calculation decrease drastically the experiments work required to solve any topic like scale-up or even improve process that running regularly in the large scale. (Bentolila 2011).

Our goal is to develop a method, based on calculated parameters 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.

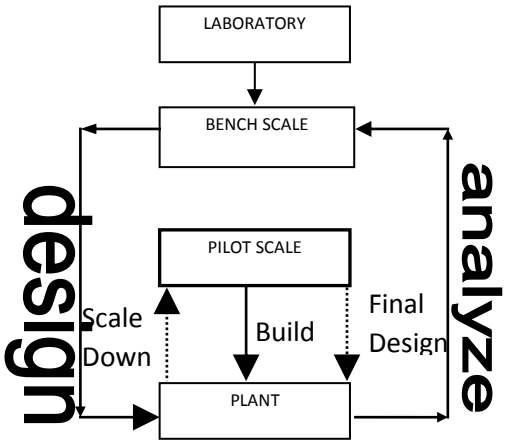
The main parameters changed are the hydrodynamics of the system. If we are able to identify and control these parameters we will be able to achieve the available and optimal solution.

In this proposal we will provide to the chemical industry with a guideline for a combination of hydrodynamics parameters with the chemical process in order to avoid problems during the scale-up of the process.

2. PROPOSED METHOD

Process development at the chemical industry (pharmaceutical, API, food, fine chemicals, biotechnology among others) is performed in small glass reactors. From this lab small glass reactors experience is common to obtain kinetic constants and mixing effects. Akiti [2005] demonstrated the dissimilarity of these reactors since a small glass reactor is not an ideal reactor. Good data for scale up is obtained from the combination of the experimental data with the computation facilities. One of the first authors that thought about this concept was Eng. Berty. In is paper he explained how the computation tools are more developed and the equipment and sensors are more exact. In this way he presents in his paper the follow flow chard, Figure1 and confirmed by Basu [1999] and Ka Ming Ng [2003].

Figure 1. Feedback loops in experiment-design-analysis cycles [Berty 1979].



The basic principle (Fig 1) is to collect data from bench scale equipment, exploit the data by designing commercial-scale process configuration (not for construction but for detailed critical analysis) using mathematical and computation knowledge. After few loops of bench scale experiments and design calculations it will be possible to scale up the designed plant to pilot plant facilities and confirm the hybrid model-experimental data at plant facilities conditions. After the last critical step it will be possible to perform fine tuning and design the commercial process.

Typical flow path for process development in companies are presented in the follow flow chard, Figure 2.

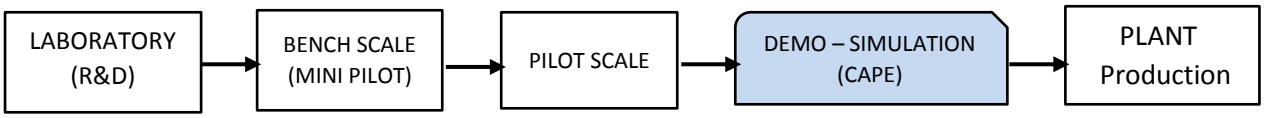


Figure 2. Typical flow path for process development in companies

In this pathway, we can find a vast disconnection between all the required knowledge to develop the process, including here the communication between different departments in the company.
Flow charts for the best organization of scale up activities were presented for different authors. Normally, all of them wrote in industrial journals. The common factor is to try to intensify the number of experiment requires for achieving a good knowledge of the process. Lastly, the scale-down concept is used in order to characterize the process in small scales.

The main question is how after having a good understanding of the scale-down study, we continue to have a gap between lab results, pilot result and production results in the process. A well set up of lab equipment, based on the intrinsic change in the scale up activities will focus the best set of experiments to avoid this gap. Based on the Figure 1, we despoiled the advised flow chard in a completed method that contains the follow steps:

1. - Chemistry or Biological Mechanism of the Process
2. - Design the Future Feasibility according to the Business Company Plan
3. - Calculate by different simulations tools how will be the process in the commercial scale.
4. - Set the lab equipment in the possible scale that will provide the most approximate conditions that in the commercial production scale.
5. - Optimize the process based in the possible range work available in the commercial step.
6. - Use the medium scale to verify your model.

As we consider VisiMix the better simulation tool to estimate Hydrodynamics characteristic parameters for batch and semi-batch process, our proposed method, that take into account upper 6 steps is like in general view from following Figure 3.

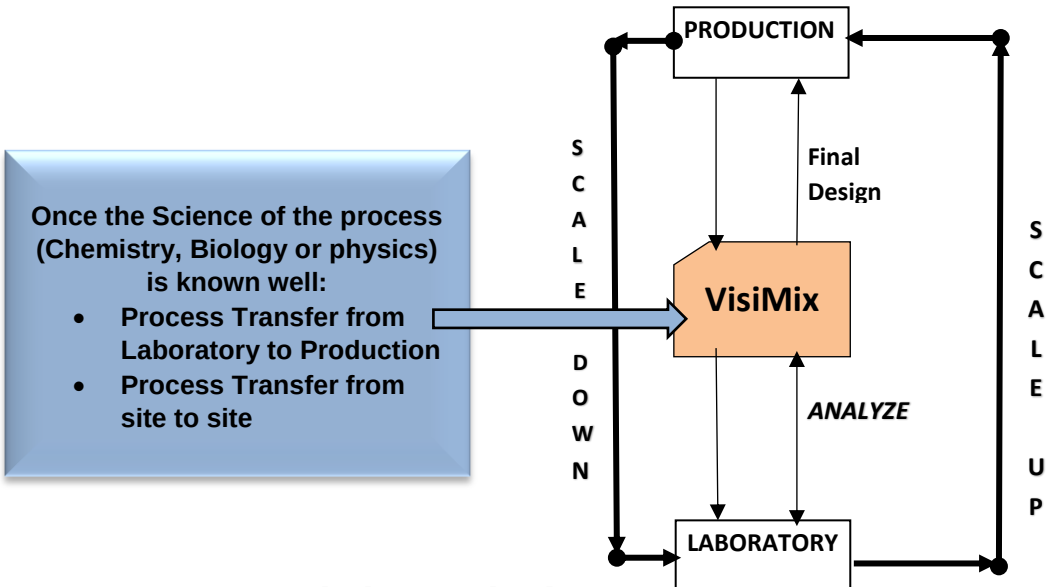
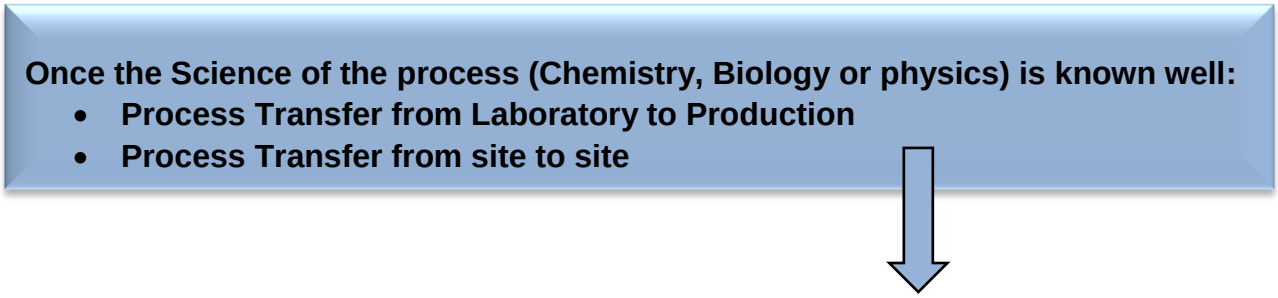


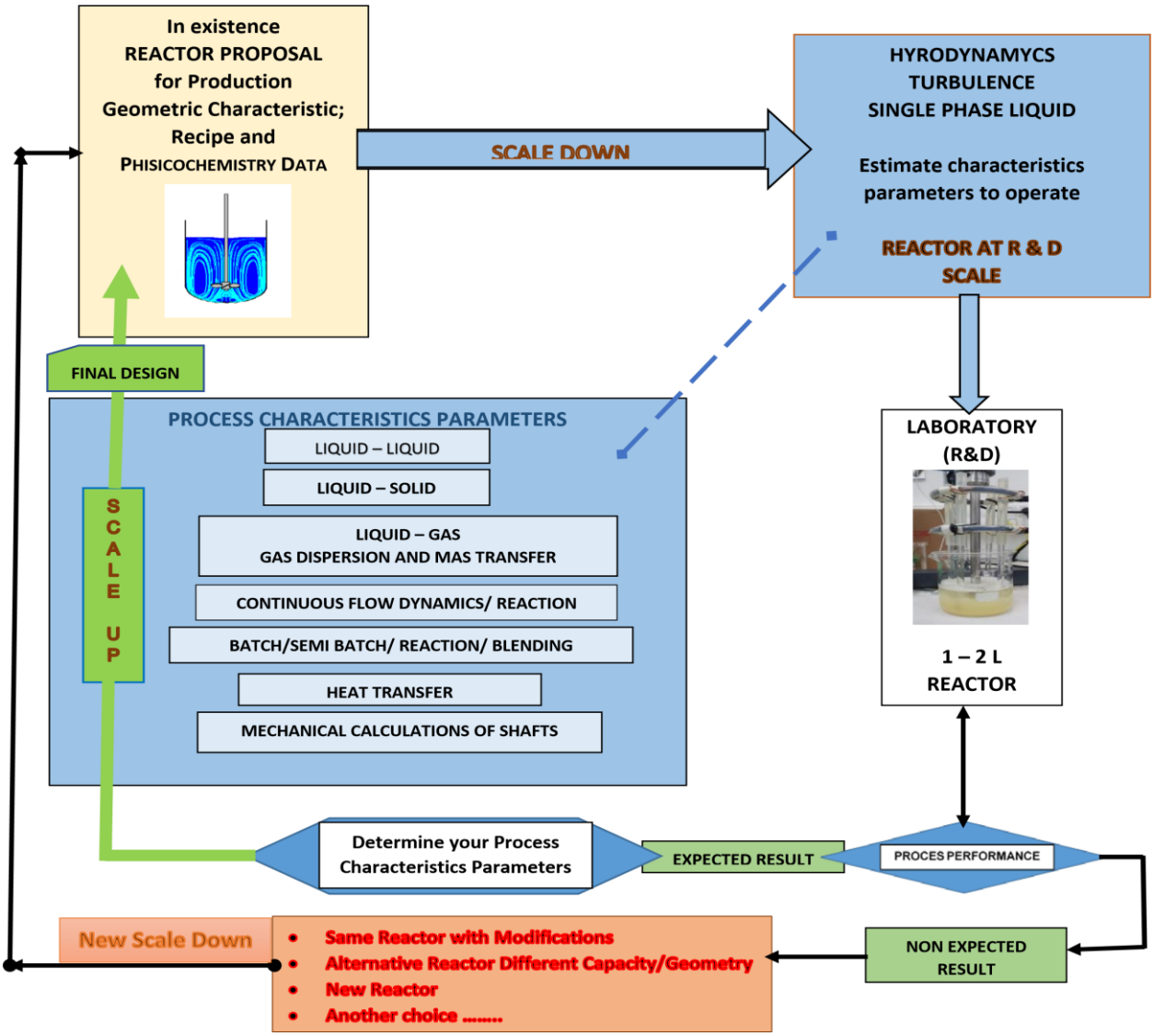
Figure 3. VisiMix Method General Scheme: Lo[illegible]le Down - Scale Up and Hydrodynamics Considerations

The use of VisiMix as Technology Simulation tool is recommended over the judgment of more than 200 companies who have demonstrate with different cases study where they achieve: **Reliable and accurate results**, **Replacing Pilot Experiments and Accelerated Time-to-Market process** all of these with **User Friendly and easily accessible software.**

From Figure 3 a comprehensive flow chart is as follow in Figure 4. Following this flow chart we will clarify the importance of the hydrodynamics parameters characteristics above the scale down – scale up process.

Figure 4. VisiMix Method Comprehensive Scheme: Loops for Scale Down - Scale Up and Hydrodynamics Considerations





3. PROCESS SIMULATION FOR SCALE DOWN – SCALE UP

Following Figure 4. Visimix Method, once the science of the process is well-known and guesstimate the reactor to be used for production, you have the necessary information to implement the Scale Down to validate in a laboratory scale reactor if the desired process result could be feasible and scaled up to the level you are investigating.
First estimation to do is associated with the Hydrodynamics- Turbulence – Single Liquid Phase (HT-SLP) characteristic parameters of the process.

Hydrodynamics is a branch of physics that deals with the motion of fluids and the forces acting on solid bodies immersed in fluids and in motion relative to them. Motion of the fluid generate Turbulence which play essential role over the momentum, heat and mass

transfer during the operation with the consequent effect upon the expected times to complete the process performance.
All this complex behavior taking place in a vessel because the energy provided by impeller rotation (or by another mechanism) to the fluid volume (liquid, liquid-liquid, liquid-gas, liquid-solid phases) is commonly known by the code name MIXING.

VisiMix gives the possibility to calculate the mixing characteristic parameters for different applications as show in Table 1. Besides these key process parameters for scale up there are others important to be estimate in order to have a broader knowledge about the process been escalated, among others, following is recommended to calculate:

Mixing Power: Is important to be sure that reactor could operate with the installed motor power. If the calculated mixing power exceeds 0.7 of the motor power rating you have previously entered into the system, the warning "Mixing power is too high for your drive" is issued.
Reynolds Number for Flow: This value is based on the average velocity of the flow and radius of the tank. The lower limit of a turbulent regime corresponds to a Reynolds number value of about 1500. Significant changes in hydrodynamics are observed when the Reynolds number value is lower than 1000. If $Re \leq 1500$ you have to use VisiMix Laminar.
Vortex Parameters: If the vortex is too deep and reaches the impeller, unstable gas caverns may form around the impeller blades. The resulting shaft vibrations may reduce the reliability of the equipment. Gas insertion into the media may also occur. VisiMix lets you know if such conditions are expected. Due to vortex, there is an increase in the level of media near the tank wall. In some cases, this may possibly cause media overflow. In addition, it may increase the heat transfer area in cases of heating/cooling in jacketed tanks.
Gas pick-up from the surface: High intensity of turbulence on the surface of agitated media results in a random formation of cavities and entrainment of gas bubbles into the liquid.
General flow pattern: The visualization is based on the results of approximate modeling the flow with stabilized hydrodynamics. It imitates the motion of tracer particles, which have been injected at random into the tank. The time that has elapsed since loading the tracer particles is displayed on the screen.

As show in Table 1 there are several characteristics mixing parameters frequently applied during Scale Down – Scale Up simulation.
Scale down process means to reproduce in laboratory scale similar values for key process parameters, estimated utilizing production reactor – stirrer system geometric characteristics measurements.

Table 1. Mixing Characteristic Parameters for Different Applications

Application	Key process and scale down – scale up parameters
Newtonian/ Non Newtonian Hydrodynamics and scale up	• Circulation flow rate • Local values of energy dissipation • Turbulent Shear rates
Blending- Single Phase mixing	• Macro and micro mixing times • Max./ Min. concentration difference ΔC
Liquid – Solid Suspension, Crystallization, Dissolution	• Max. local concentrations • Max. shear rate • Crystal collision energy
Liquid - Liquid Emulsification, Heterogeneous org. synth.	• Drop size distribution • Specific mass transfer area • Micro mixing time for disperse phase
Liquid – Gas Gas injection, Absorption, Gas liquid reactors	• Gas hold up • Specific mas transfer area • Specific mass transfer coefficient
Biotechnology	• Oxygen mass transfer rate
Heat transfer in vessels with different heat/cooling devices	• Media temperature • Heat transfer coefficient • Specific heat/cool rate

Circulation Flow Rate: This parameter is calculated as the sum of circulation flow rates in all
main circulation loops in the vessel. Is the base to simulate **General Flow Pattern** and **Mean Period of Circulation**: The average time of a single cycle of media circulation. In many cases, it is recommended to reduce this parameter, for instance, to avoid significant change in concentration near the inlet pipe. To reduce circulation time without increasing the mixing power, try an impeller with a larger tip diameter and lower pitch angle of blades.

Local values of energy dissipation: The entire mixing volume is assumed to be divided into zones - the zone behind the impeller blade, the zone behind the baffles, the jet around the impeller, and the bulk volume. This table provides estimates for the energy dissipation values in these main zones. Non-uniform distribution of energy dissipation is important for micro mixing, emulsification, and crystallization. A high degree of non-uniformity has a positive effect on emulsification and a negative effect on crystallization. For single-phase mixing processes and suspension, a more uniform distribution of energy is preferable. To reduce the degree of non-uniformity, try reducing the pitch angle of the blades or the number of baffles.

- ***Energy dissipation - maximum value:*** This parameter is calculated as an average value of the turbulent dissipation rate in the zone with the highest degree of turbulence. In most cases, it takes place in the vortices formed behind the impeller blades. Energy dissipation in this area depends on the difference between the impeller tip velocity and the tangential velocity of the media. The most important micro scale phenomena, such as drop break-up, breaking of crystals, nucleation, and efficient micro mixing take place in these zones.
- ***Energy dissipation - average value:*** This parameter represents the volume average specific power, and is calculated as the mixing power per kg of media.
- ***Energy dissipation in the tank bulk volume:*** This value controls micro mixing in single-phase reactors. To increase this value without increasing the mixing power, reduce the pitch angle of the blades or the number or width of the baffles; alternatively, increase the tip diameter of the impeller and reduce the number of revolutions.

Turbulent shear rates in different zones: This parameter must not be confused with average velocity gradient, and its value is typically one or two orders of magnitude greater than the latter.
The turbulent shear rate, $\Gamma_{turb.}$ is the characteristic shear rate at the micro scale level that governs such processes as mass transport to growing and from dissolving solid particles.
Characteristic time of micro mixing: This parameter represents an estimate of the time required to achieve uniform distribution of the dissolved substances down to the molecular level. It is assumed to depend on the molecular diffusion of solute, while the scale of mixing due to molecular diffusion only is supposed to correspond to the micro scale of turbulence. Micro mixing time is estimated both as the diffusion time, and as the maximum lifetime of a volume element, which has elapsed before the element enters the zone of the maximum dissipation rate. The final value of this parameter is calculated with respect to both estimates. Characteristic size of the volume element is assumed equal to the micro scale of turbulence in the tank bulk volume.
Macro mixing time: This parameter characterizes the time required for the distribution of solute (admixture, tracer, paint, etc.) throughout the entire volume of the tank. It is calculated as the time required to reduce the maximum difference of local concentrations of the admixture to about 1% of its final average value (in batch mixing conditions). The admixture is assumed to be injected instantly. Selection of the real duration of blending is based on the sum of Macro mixing time and the Characteristic time of micro mixing. To reduce the macro mixing time in an un-baffled tank, try increasing tip diameter of impeller or slope angle of the blades. In baffled tanks, reducing the macro mixing time is usually achieved by increasing the mixing power.

Once HT - SLP characteristics parameters for production reactor are computed it will be required to do the same work for laboratory reactor to establish operational specifications to achieve similar values on it.
At this point it will be possible to define and execute a set of experiments (DOE), comprising optimization possibilities. The evaluation of these results will allow to decide if directly go to Scale Up to the initial production reactor proposal or, on the contrary, go for another different proposition as reflected in Figure 4. VisiMix Method.

4. DEMONSTRATIVE REAL EXAMPLES

Following examples were worked up by different VisiMix users from several customers companies. Most of these summarized examples were presented in Boston, July 2011, in the course of the First VisiMix Users Meeting.

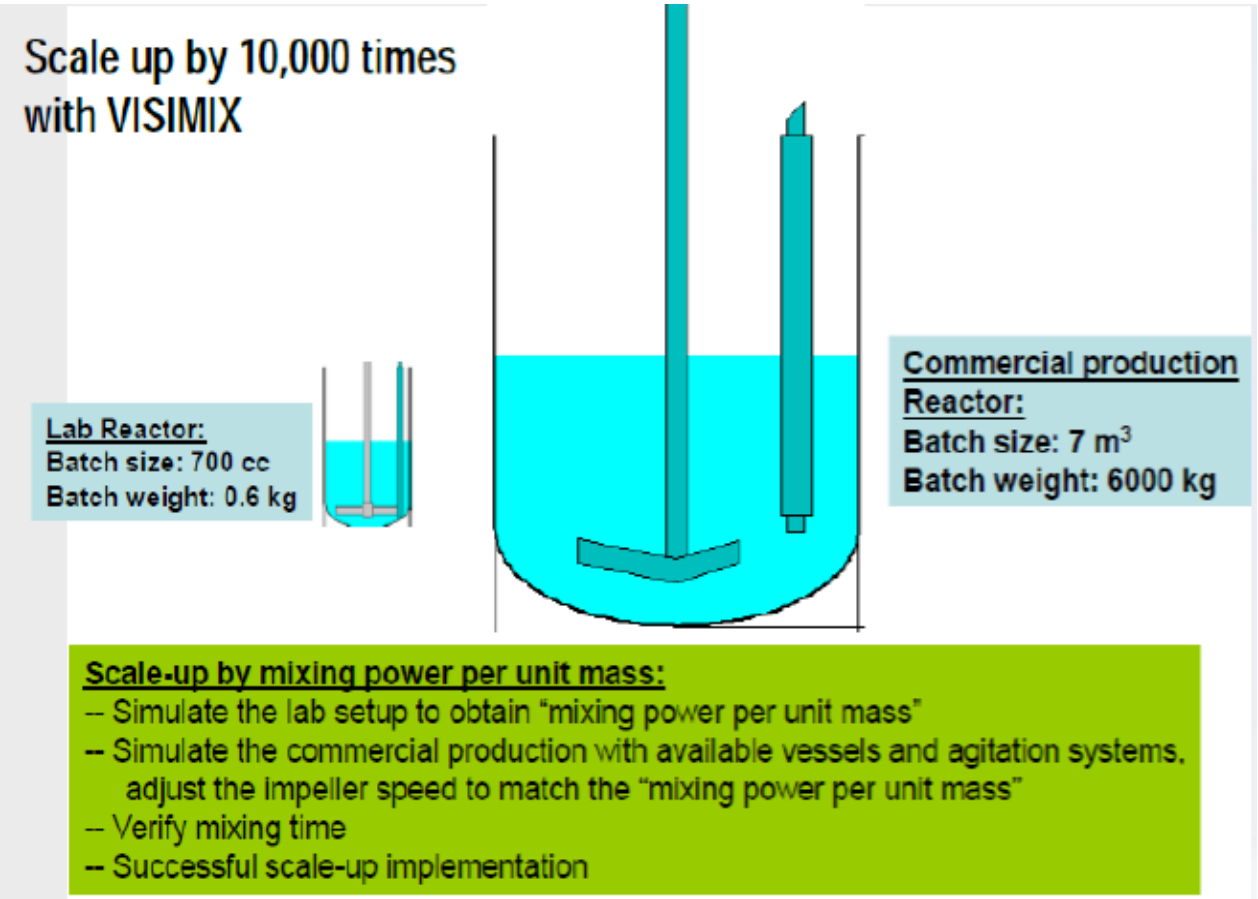
EXAMPLE 1

Scale up from Laboratory to Commercial Production (DOW Chemicals)

Problem definition: Scale up from Laboratory Reactor, 0.7 L; to Commercial Reactor, 7000 L

- What reactor to choose? From a few available vessels and agitation systems to reduce capital.
- How to scale up agitation? Laboratory tests show that the product quality was very sensitive to mixing or agitation. Too much or too little agitation would negatively affects product.
- What is the mixing time?

Result:



EXAMPLE 2

Crystallizer. Scaling Up (Genck International, Inc., USA)

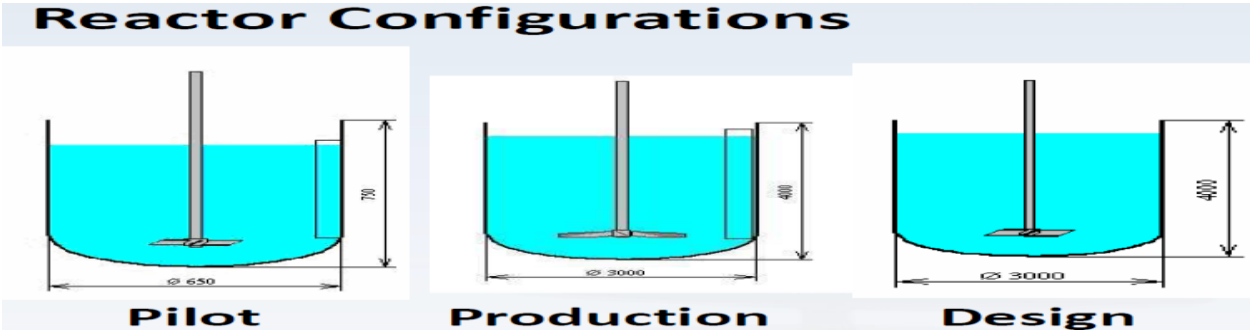
Problem definition:
The process rate and particle size distribution in crystallization and precipitation processes are dependent on chemical composition and physic-chemical properties of the system.

- In the same time they can be substantially dependent also on some phenomena that are functions of mixing conditions – for example, on primary and secondary nucleation, attrition and breakage of crystals, distribution of solid phase and liquid-solid mass transfer.
- The following example is related to a particular case when the crystallization is controlled mainly by these parameters, and scaling-up conditions include reproduction of these phenomena.
- The corresponding parameters selected from the list of VisiMix outputs and used below for crystallization scale-up are presented in the Table.

Table 1. Scaling-up parameters for crystallization.

VisiMix Menu section	Output parameters
	Energy dissipation – maximum value
	Turbulent shear rate near the impeller blade
	Relative residence time in zone with maximum dissipation
Liquid-solid mixing	Axial and radial distributions of the solid phase
	Maximum energy of collisions
	Frequency of collisions of maximum energy
Liquid –solid mass transfer	Mass transfer coefficient

For calculation of the **Mass transfer coefficient**, it is necessary to enter a number of additional initial data, including the **Diffusivity of the solute**. **In our case the problem consists not in prediction, but in reproduction of the same value of the Mass transfer coefficient**.



Result

Menu section	Parameter	Pilot	Production with A310	Production with Pitch paddle
Turbulence	Energy dissipation – maximum value	106 W/kg	204	96.4
	Turbulent shear rate near the impeller blade	9660 1/s	13400	9200
	Relative residence time in zone with maximum dissipation	0.00133	0.000278	0.00127
	Energy dissipation – average value	0.380 W/kg	0.359	0.313
Liquid-solid mixing	Maximum degree of non-uniformity- axial	16.8%	13.0	12.9
	Maximum degree of non-uniformity- radial	1.13%	0.445	0.485
	Maximum energy of collisions	8.71e-11 J	1.34e-10 J	8.15e-11 J
	Frequency of collisions of maximum energy	0.0181 1/s	0.00474 1/s	0.0168 1/s
Liquid-solid mass transfer	Average mass transfer coefficient (approx.)	0.000038 m/s	0.0000375	0.00365

EXAMPLE 3

Typical Fine Chemical Development. Batch and Semi Batch Process

Problem definition:

- GAP between R&D and Production result

Task: decreasing the number of required batches for validation process in the production step.

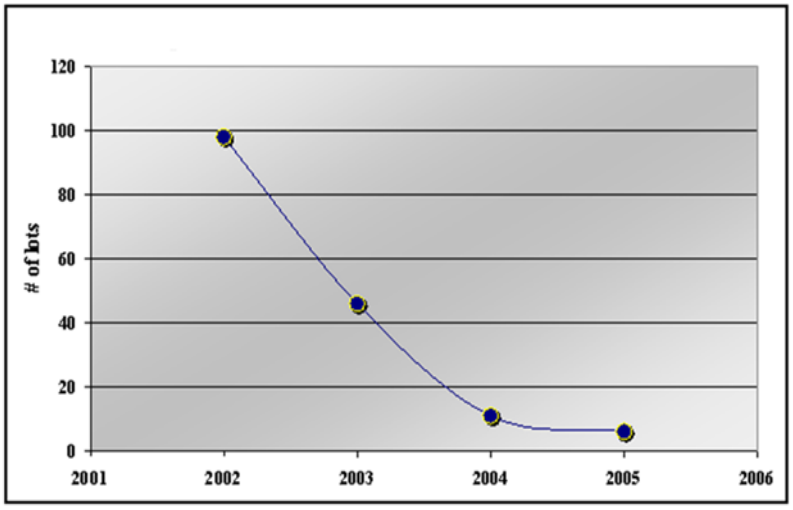
The traditional approach: running the process at increased size reactors and looking for optimal process and operational parameters at every stage.

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 QbD practice, provide the company with a deep "know how" about the process and the scale up activities and decrease the "out of specifications" material during the process at different sizes.

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.

Batches/Year Using VisiMix Method



The Result:

- 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.

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EXAMPLE 4

Productivity improvement in API Company

Problem definition: For a batch process two phase reaction (Liquid-Solid), long operation time and poor reproducibility in production stage.

Task: Improve performance, reproducibility and operation time.

The traditional approach: After a few batches, it was clear that the problem was in the reactor. None results reproducibility and long reaction time.

5 Test results:
T = 20 - 23 C
EOR = 23 – 50 h
Yield = 97 – 98 %

2 Test results from R4504-1:
T = 23 - 25 C
EOR = 11 h
Yield = 97 – 98 %
Similar results were obtained in R4504-3 but:
EOR = 9 h

The VisiMix analysis: A 25 liters reactor will operate with 10 liters volume. Stirrer speed around 100 rpm is the maximum allowable to avoid dangerous vortex formation. These hydrodynamic characteristics of the production reactor induce to predict lower KLa (mass transfer coefficient) than wished for, resulting in longer end of reaction time and possible uncertain reaction result. The chosen production reactor was not recommended to perform this API reaction.

The VisiMix solution: Two new reactors were evaluated for this API reaction operation. Installation of two baffles was sufficient to stabilize and reduce the reaction time from 25 -50 h to 9 h.

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

The Result.
In the modified system:

- Reproducibility of reaction time and yield.
- Saving at least 1,600,000/year
- Analysis of the problem and solution take around 2 weeks.

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EXAMPLE 5

Effect of Impeller Design and Power Consumption on Crystal Size Distribution [13]

In referred experimental work, Doraiswami Ramkrishna, Jyeshtharaj B. Joshi and collaborators, studying "Crystallization processes in a 500 mL stirred tank crystallizer with computational fluid dynamics (CFD) and population balances toward estimating how crystal size distributions (CSDs) are influenced by flow inhomogeneity's", using three different impellers at three different stirrer velocities.

Main results Table (from Table 3 [13])

Impeller Type	Speed (r/s)	Mean Crystal Size (microns)	Power Consumption Expt. (watt)	Power Consumption CFD (watt)
DT 	2.5	532	0.0232	0.02583
	5.0	413	0.1805	0.20239
	10.0	344	1.4010	1.58488
PBT 	2.5	544	0.0142	0.01564
	5.0	451	0.1115	0.12395
	10.0	378	0.6154	0.69037
Propeller 	2.5	549	0.0033	0.00361
	5.0	467	0.0251	0.02770
	10.0	396	0.2101	0.23361

Simulation results using VisiMix Turbulent, with the same input data [13], in the following table:

Main Parameters results using VisiMix Turbulent Mixing Simulation software

Speed (r/s)	Mixing Power Watt	Energy dissipation in Bulk Volume W/kg	Shear rate Maximum Value 1/s	Solid suspension	Maximum energy of collisions J	Frequency of collisions of maximum	Characteristic Time between two Strong Collisions

						energy 1/s	s
2.5	0.0247	0.0144	1460	Questionable	1.98e-11	0.0410	23.90
5.0	0.1980	0.115	4130	Complete	7.90e-11	0.0835	12.00
10.0	1.5800	0.924	11700	Complete	3.16e-10	0.1670	5.99
2.5	0.0133	0.0103	688	Questionable	7.24e-12	0.0560	19.80
5.0	0.1060	0.0827	1950	Questionable	2.89e-11	0.1010	9.89
10.0	0.8470	0.6620	5490	Complete	1.16e-10	0.2020	4.95
2.5	0.0019	0.00183	400	Questionable	3.51e-12	0.0213	46.9
5.0	0.0152	0.0147	1130	Questionable	1.40e-11	0.0426	23.5
10.0	0.1220	0.117	3190	Questionable	5.61e-11	0.0852	11.7

Particular and general analysis of the results and conclusions in referred article [13] are the same when simulation is performed using VisiMix software [1], with the VisiMix advantage related to the calculation of more specific Hydrodynamics – Mixing parameters, usefulness for Scale Down – Scale Up working. For example, Solid Suspension column, solid suspension and distribution during crystallization have influence over crystals size. As observed in upper table, when solid suspension is questionable, crystal size tendency is to growth, possible because the crystals accumulation in the bottom of the tank induce crystals seize.

5. CONCLUSIONS

VisiMix method brings the possibility to calculate the main hydrodynamics parameters of the process. Reaching similar values at any scale it will be possible to achieve the available and optimal solution of the process. In this environment we can: Understand better your processes, reduce dramatically your Scaling up processes and Scaling down and save a huge amount of Time & Money ($1,000,000 +)

The VisiMix Products are friendly and easy to use with very quick results, based on a systematic and seriously experimental checking – and found very reliable.

Finally VisiMix Projects Parameters and Data Base allows you to share and transfer the data with colleagues in the company.

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