

**VisiMix in API batch  
manufacturing – Improving  
multi-phase processes.**

**Nuno Louisa**

May 2018



# Agenda

- Hovione worldwide
- How much mixing is enough?
- The VisiMix approach on a hydrogenation.
- Phase-separation times in liquid-liquid extractions.
- Conclusions



In it for life

## Hovione Worldwide

Hovione is a Pharmaceutical Company dedicated to helping Pharmaceutical Customers bring new and off-patent drugs to market. We do well what is difficult, to give our customers what they cannot find elsewhere.



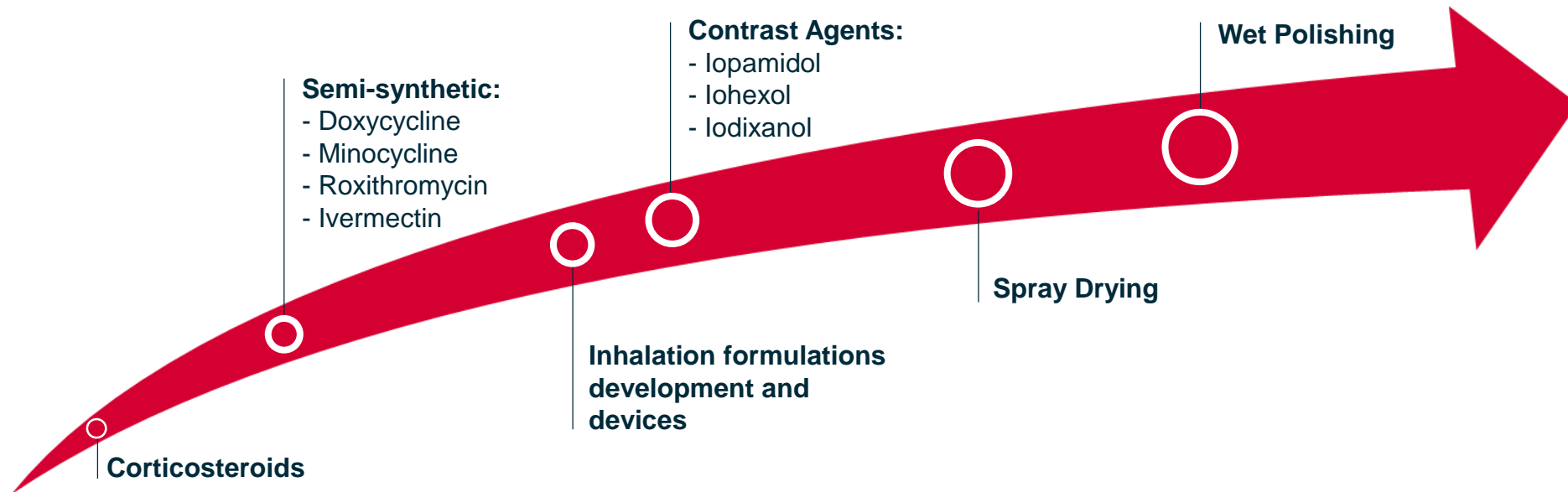
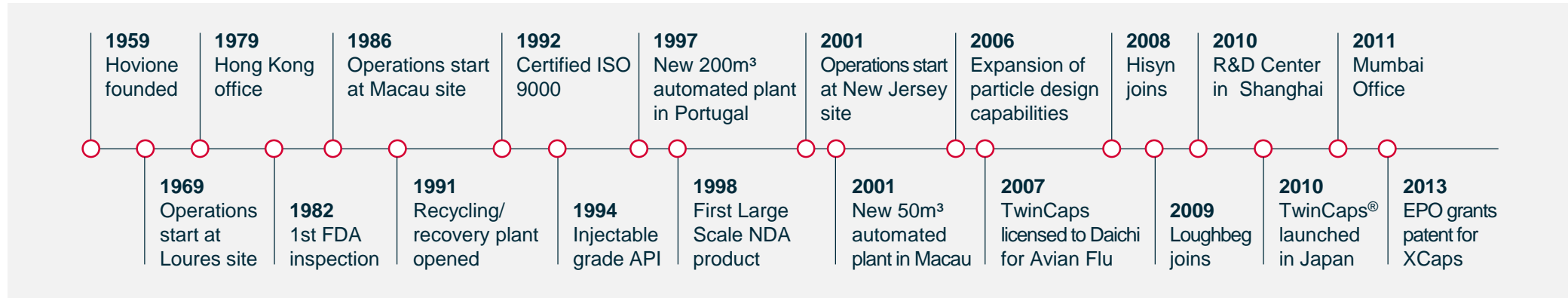
# Hovione is a science based company providing products and services for the Pharmaceutical Industry

- Founded in 1959
- Family business - stable management and long term commitment to pharmaceutical industry.
- Main customers:
  - Biotechs.
  - Medium, speciality and large pharma.
  - Generics pharma.



**Ivan Villax 1926-2003**

# Hovione has continuously increased its offering and its geographic reach



# Hovione has extensive manufacturing capacity spread over three continents



**New Jersey, USA**  
Manufacturing facilities small volume  
R&D Labs, Kilo and pilot plant  
Sales and marketing for North America



**Loures, Portugal**  
Manufacturing facilities including  
R&D Labs, kilo and pilot plants



**Cork, Ireland**  
Manufacturing facilities



**Macau, China**  
Manufacturing facilities

# How much mixing is enough?

How do we define 'good mixing' ?

Using VisiMix to quantify mixing and determine scale-up factors.

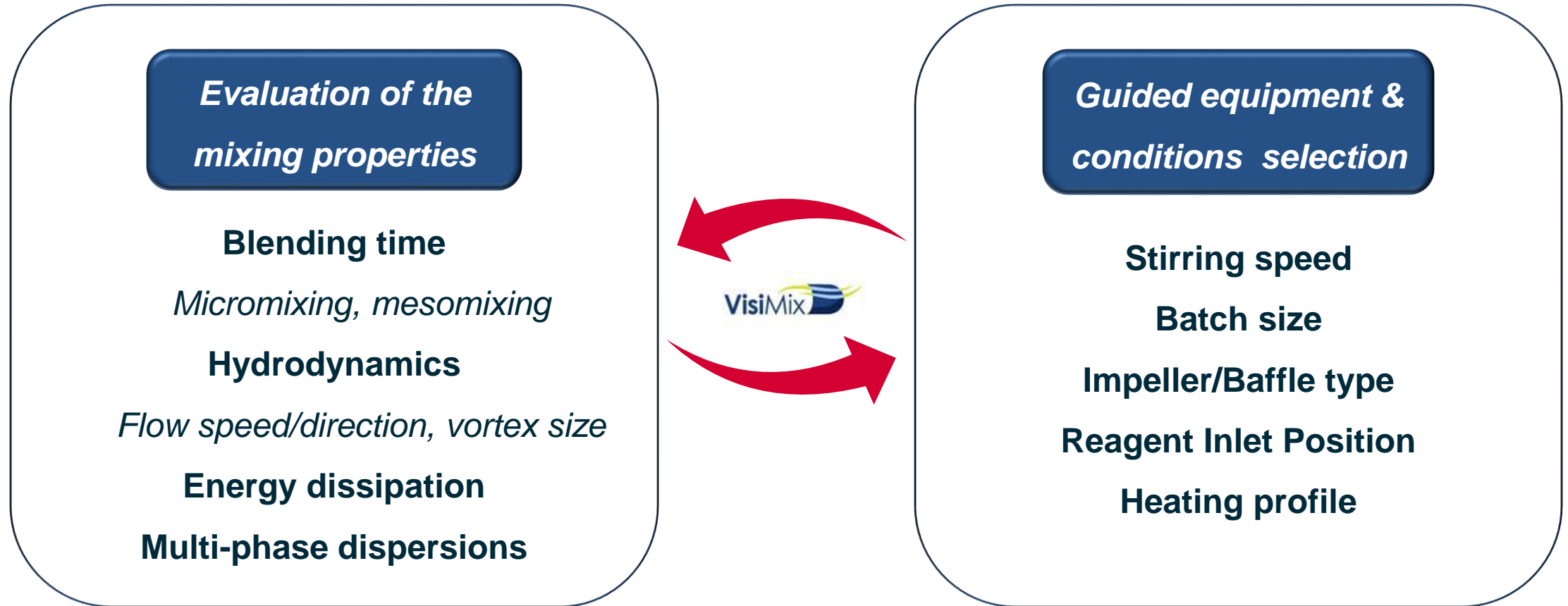


# How much mixing is enough?

- *“I want efficient mixing at this stage.” (customer)*
- *“I don’t want mixing to be an issue (\$\$\$) in scale-up...” (manager)*
- *“Can we avoid wall splashing?” (chemist)*
- *“We have a problem...” (process engineer)*



# How much mixing is enough?



**There is no universal answer.**

**Each application may or may not have its own demand.**

# How much mixing is enough?

- **Technology Transfer & Scale-Up**

- From Lab to PP to Manufacturing
- From customer to Hovione.
- Between Hovione sites.

- **Process Troubleshooting**

- Emulsion formation.
- Particle Suspension/Dissolution.
- Crystallization/Precipitations.

- **Process Safety Assessment**

- Heat Transfer.

- **Process Optimization**

- Hydrogenations/Oxidations.
- Three-phase reactions.

- **Mechanical Design**

- New impeller purchase.
- Reactor internals modifications.

*Benefits...*

Risk Mitigation

Process Improvement

Increased Know-How

Process Safety

# How much mixing is enough?

- **Technology Transfer & Scale-Up**

- From Lab to PP to Manufacturing
- From customer to Hovione.
- Between Hovione sites.

- **Process Troubleshooting**

- Emulsion formation.
- Particle Suspension/Dissolution.
- Crystallization/Precipitations.

- **Process Safety Assessment**

- Heat Transfer.

- **Process Optimization**

- Hydrogenations/Oxidations.
- Three-phase reactions.

- **Mechanical Design**

- New impeller purchase.
- Reactor internals modifications.

1

Hydrogenation

2

Liquid-liquid extraction

# The VisiMix approach on a hydrogenation

Using the software to:

Perform a successful tech transfer

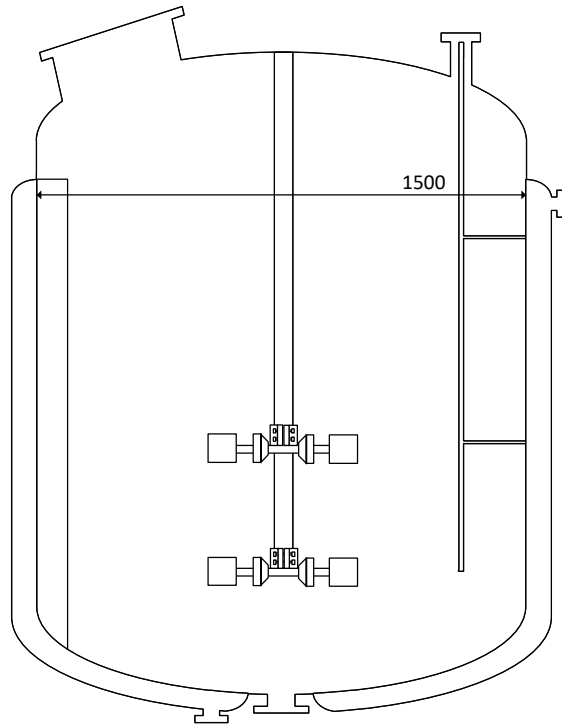
Applying know-how to improve  
impurities and cycle-time



# The VisiMix approach on a hydrogenation

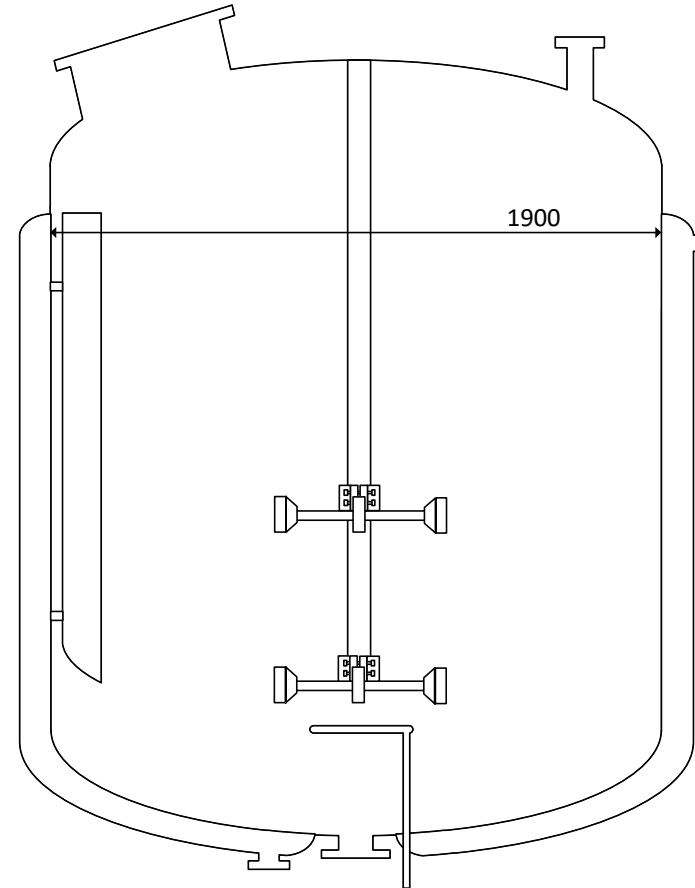
Stage 1 – Setting the RPM for a tech transfer

H3000, Site 1  
**200rpm**



→ → → →  
*A long time ago...*

H6000, Site 2  
**164rpm**

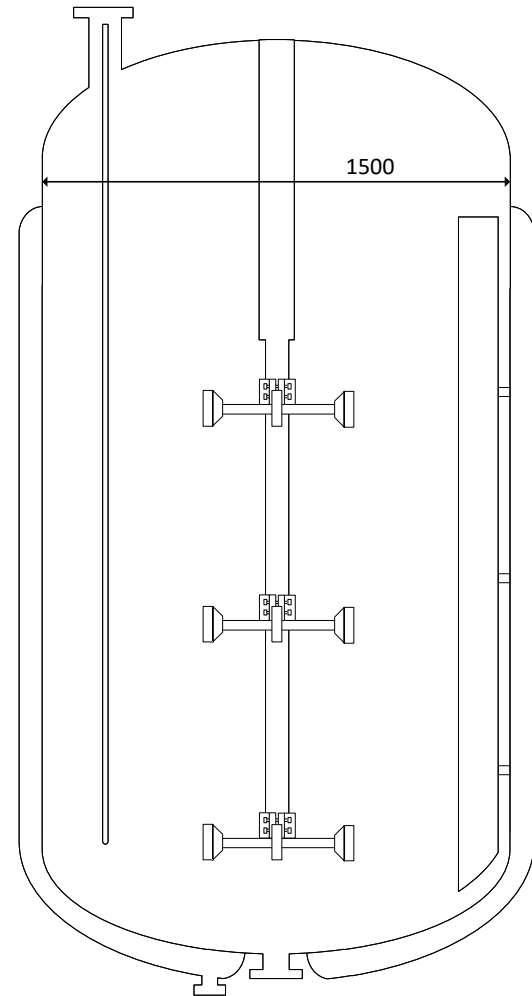


# The VisiMix approach on a hydrogenation

## Stage 1 – Setting the RPM for a tech transfer

**New reactor required due to increased demand...**

**Objective:** to define the proper stirring speed.



**H5000, Site 1**  
**??? rpm**

# The VisiMix approach on a hydrogenation

## Stage 1 – Setting the RPM for a tech transfer

### *Searching for relevant mixing parameters*

Parameter name	Units	H3000	H6000
		Value	Value
Reaction mixture volume	L	2465	4930
Impeller Tip diameter	mm	400	530
Rushton blade nr		8	6
Dist. between stages	mm	500	600
Stirring speed	Rpm	200	164
Energy dissipation - maximum value	W/kg	379	380
Energy dissipation - average value	W/kg	1.7	1.5
Energy dissipation in the bulk volume	W/kg	0.6	0.5
Energy dissipation near baffles	W/kg	1.8	1.4

**Maximum  
Energy  
Dissipation  
approach !**

# The VisiMix approach on a hydrogenation

## Stage 1 – Setting the RPM for a tech transfer

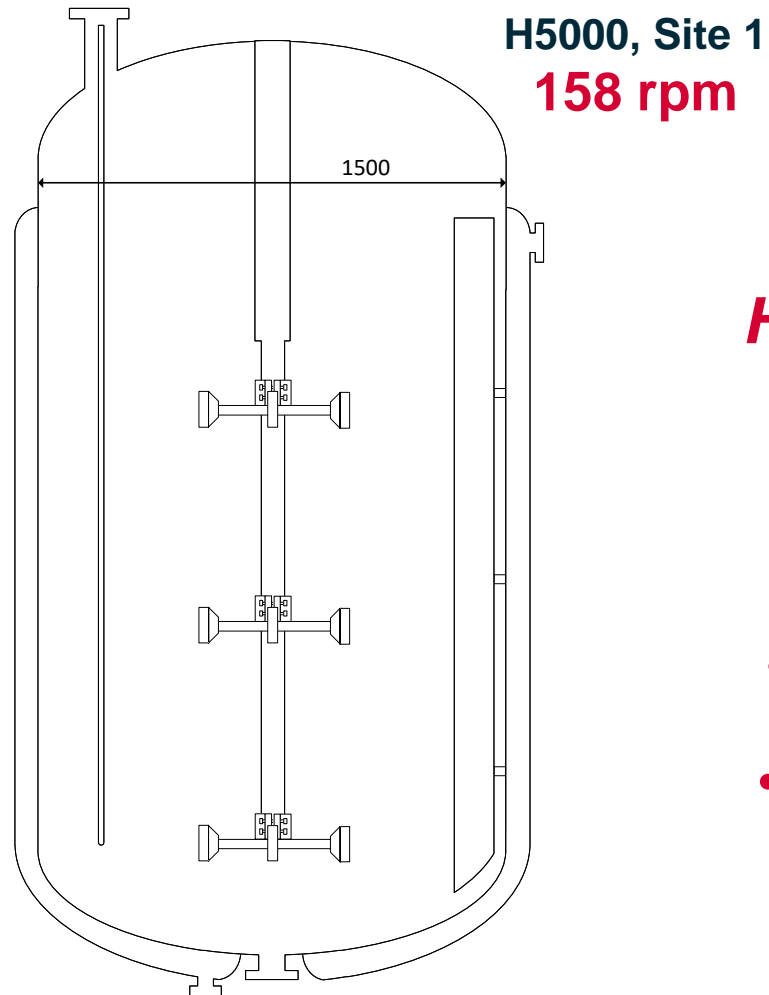
### *Searching for relevant mixing parameters*

Parameter name	Units	H3000	H6000	H5000
		Value	Value	Value
Reaction mixture volume	L	2465	4930	4930
Impeller Tip diameter	mm	400	530	550
Rushton blade nr		8	6	6
Dist. between stages	mm	500	600	1000
Stirring speed	Rpm	200	164	158
Energy dissipation - maximum value	W/kg	379	380	385
Energy dissipation - average value	W/kg	1.7	1.5	2.2
Energy dissipation in the bulk volume	W/kg	0.6	0.5	0.7
Energy dissipation near baffles	W/kg	1.8	1.4	1.9

**New  
reactor  
RPM**

# The VisiMix approach on a hydrogenation

*Stage 1 – Setting the RPM for a tech transfer*



***H5000 performance surpassed all expectations:***

- 45% reduction in reaction time!
- Lowest value of impurities ever!

# The VisiMix approach on a hydrogenation

*Stage 2 – Finding the missing link between mixing and the hydrogenation*

Parameter name	Units	H3000	H6000	H5000
		Value	Value	Value
Reaction mixture volume	L	2465	4930	4930
Impeller Tip diameter	mm	400	530	550
Rushton blade nr		8	6	6
Dist. between stages	mm	500	600	1000
Stirring speed	Rpm	200	164	158
Estimated surface aeration rate	m/s	0.001	0.0005	<b>0.02</b>
Sauter mean bubble diameter	m	0.0015	0.0015	0.0021
Gas hold-up		0.009	0.004	<b>0.1</b>
Specific mass transfer area, gas-liquid	m <sup>2</sup> /m <sup>3</sup>	36.5	15.1	<b>293</b>

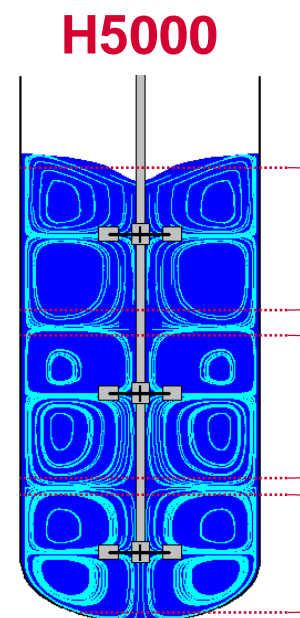
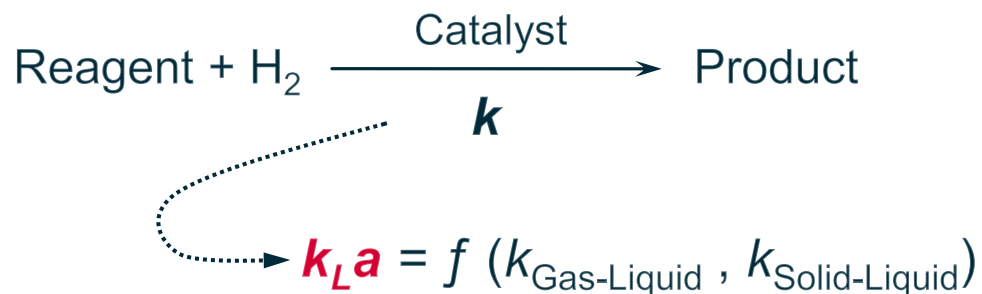
**VisiMix  
Gas-Liquid  
Parameters**

# The VisiMix approach on a hydrogenation

## Stage 2 – Finding the missing link between mixing and the hydrogenation

H5000 has a triple stage impeller system:

- Greater gas hold-up (volume fraction of gas in the reaction mixture).
- Higher  $k_L a$  for Gas-Liquid systems<sup>[1-2]</sup>.



*The flow pattern compartmentalization increases the reactor gas hold-up ability!*

[1] Gogate P., et al., *Biochem Eng J*, 6, 2000, p.109-144; [2] You S., et al, *Rev Chem Eng* 30(3), 2014, p.323-336.

# The VisiMix approach on a hydrogenation

## Stage 3 – Optimizing H6000 performance

Parameter name	Units	H3000	H5000	H6000	H6000 <i>new!</i>
Reaction mixture volume	L	2465	4930	4930	4930
Impeller Tip diameter	mm	400	550	530	530
Rushton blade nr		8	6	6	6
Impeller stage nr		2	3	2	<b>3</b>
Dist. between stages	mm	500	1000	600	600
Stirring speed	RPM	200	158	164	164
<b>Turbulence</b>					
Maximum Energy Dissipation	W/kg	<b>379</b>	<b>385</b>	<b>380</b>	<b>338</b>
Average Energy Dissipation	W/kg	1.7	2.2	1.5	2.0
<b>Gas-Liquid Properties</b>					
Estimated surface aeration rate	m/s	0.001	<b>0.02</b>	0.0005	<b>0.02</b>
Gas hold-up		0.009	<b>0.10</b>	0.004	<b>0.12</b>
Specific mass transfer area, gas-liquid	m <sup>2</sup> /m <sup>3</sup>	36.5	<b>293</b>	15.1	<b>318</b>

# The VisiMix approach on a hydrogenation

## Stage 3 – Optimizing H6000 performance

***Mechanical considerations of adding a new impeller stage  
Power, stability and integrity.***

VisiMix Parameter	H6000	H6000 new!
Mixing Power Required (W) <sup>a</sup>	5830	7940
Critical frequency (s <sup>-1</sup> ) <sup>b</sup>	4.46	4.40
Rotational to Critical freq. ratio	0.613	0.622
Allowable Shear Stress (N/m <sup>2</sup> )	9.95e7	9.95e7
Max. Shear Stress (N/m <sup>2</sup> )	3.19e7	3.19e7
Max. Shear Stress in cross section of the shaft (N/m <sup>2</sup> )	4.76e7	4.76e7

a) The H6000 current motor power is 22kW; b) The H6000 Critical frequency (s<sup>-1</sup>) described by the manufacturer is 4.5

- **The motor has enough power.**
- **The Rotational frequency is below 70% of the Critical frequency value.**
- **The shaft can tolerate the torsion shear stress.**

# The VisiMix approach on a hydrogenation

## *Lessons learned*

1. Software was used to select an adequate stirring speed for a very old process technology transfer:

*The transfer was a success!*

2. New reactor outstanding performance is very likely linked to the improvement in gas-liquid mass transfer:

*Knowledge gain, new process benchmark!*

3. The calculations were used to justify retrofitting an existent reactor with a new impeller stage:

*Improved impurity profile <> Allowed the use of a cheaper raw material!*

*Reaction time decrease <> Increased manufacturing turnover!*

# Phase separation times in liquid-liquid extractions (LLE)

Using the software to:

Develop a methodology to anticipate emulsion formation

LLE troubleshooting – improving yield and cycle time.



# Phase separation times in liquid-liquid extractions

## The background

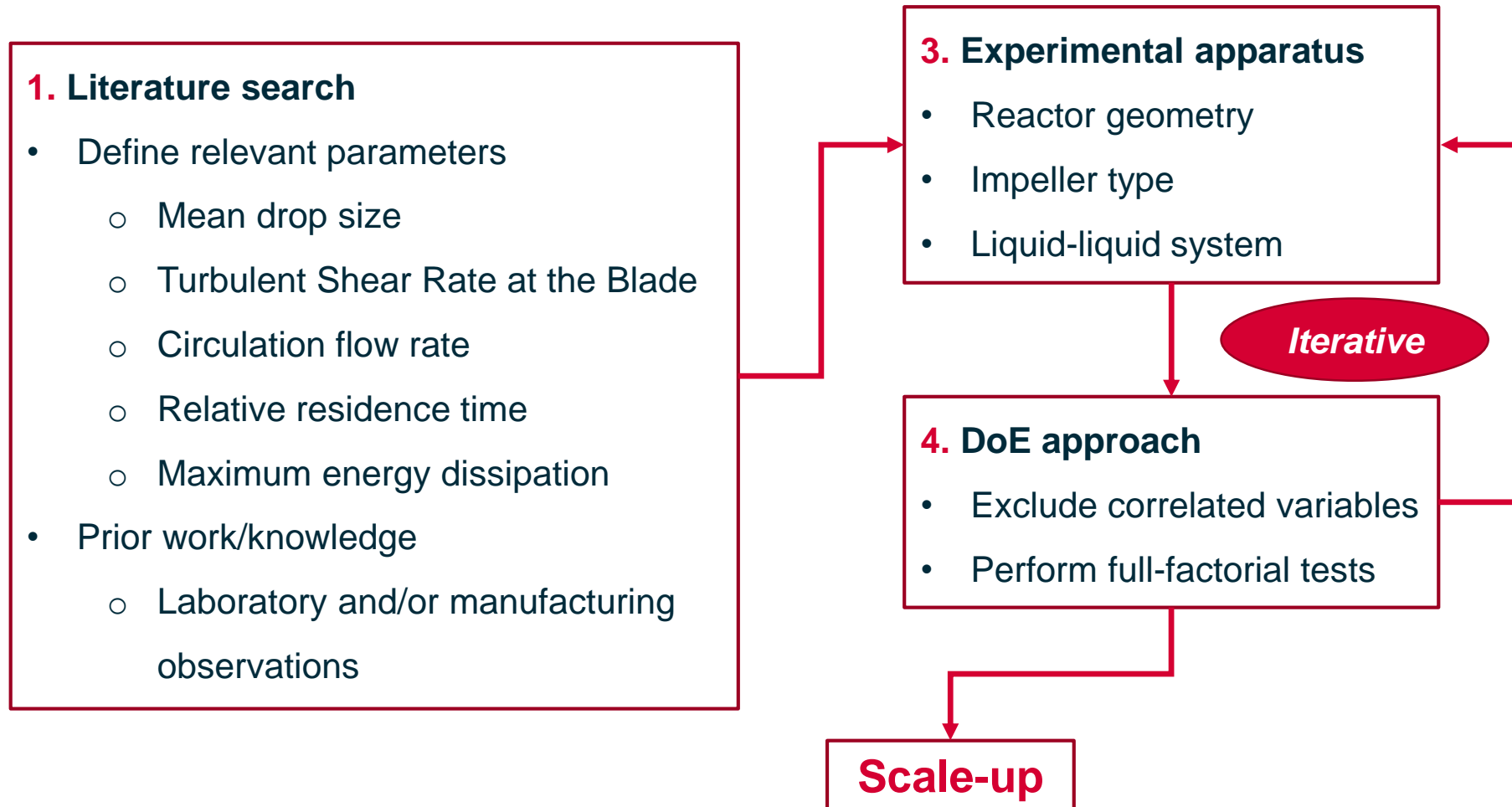
- Two immiscible liquids – a dispersed phase (drop) in a matrix (continuous) phase.
- Mixing has impact in the equilibrium between *drop coalescence vs drop breakup*.
- Lab scale vessels provide unrealistic hydrodynamics which can mask coalescence and dispersion suspension problems.

## The moon-shot:

**To develop an efficient and reliable methodology to anticipate emulsion formation and phase separation times at manufacturing.**

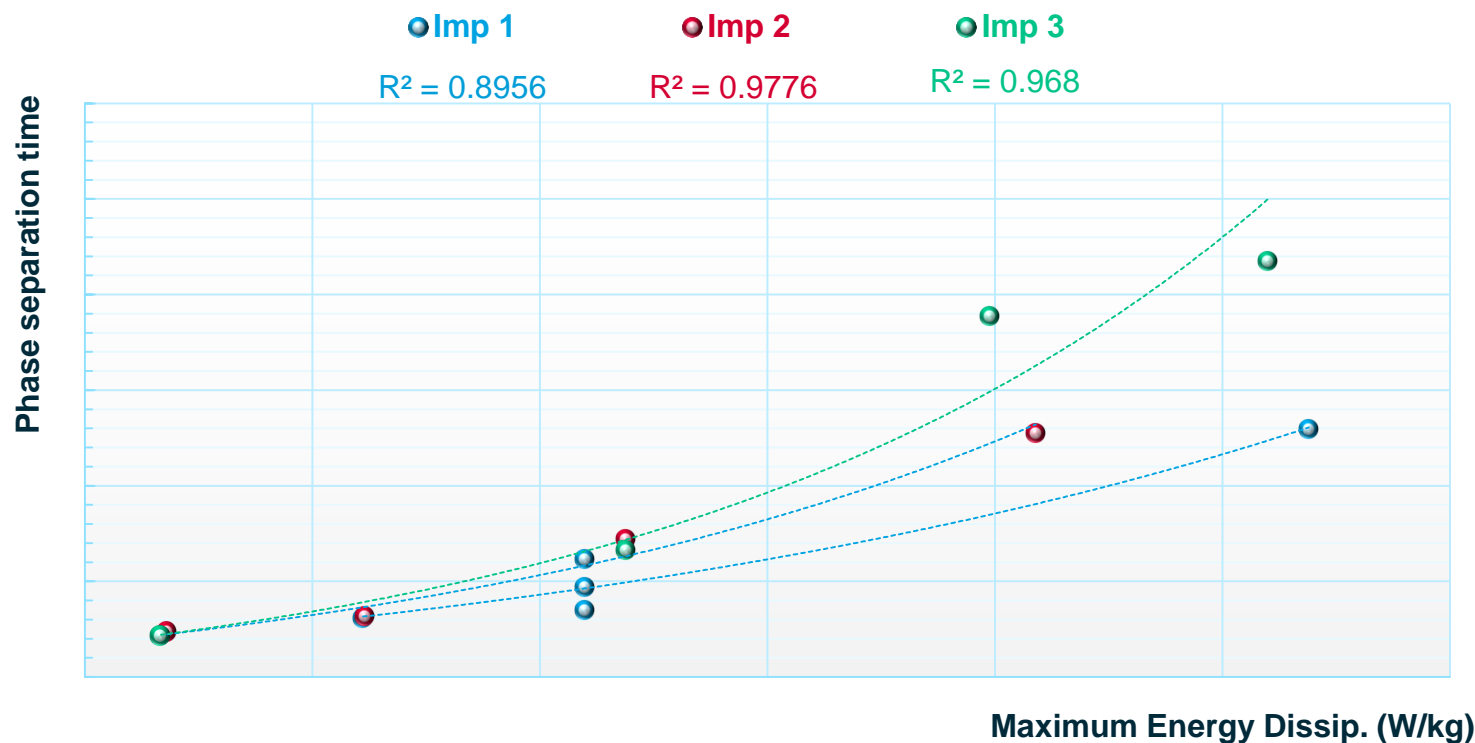
# Phase separation times in liquid-liquid extractions

## Stage 1 – Developing in-house knowledge



# Phase separation times in liquid-liquid extractions

Stage 1 – Developing in-house knowledge (bench scale DoE)

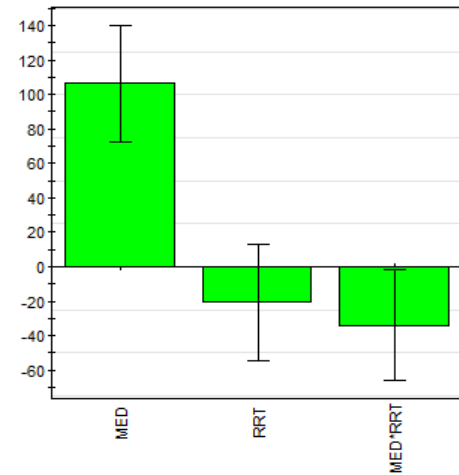


Impeller (RCI)	Tip Ø (mm)	Width (mm)
1	45	15
2	75	15
3	50	10

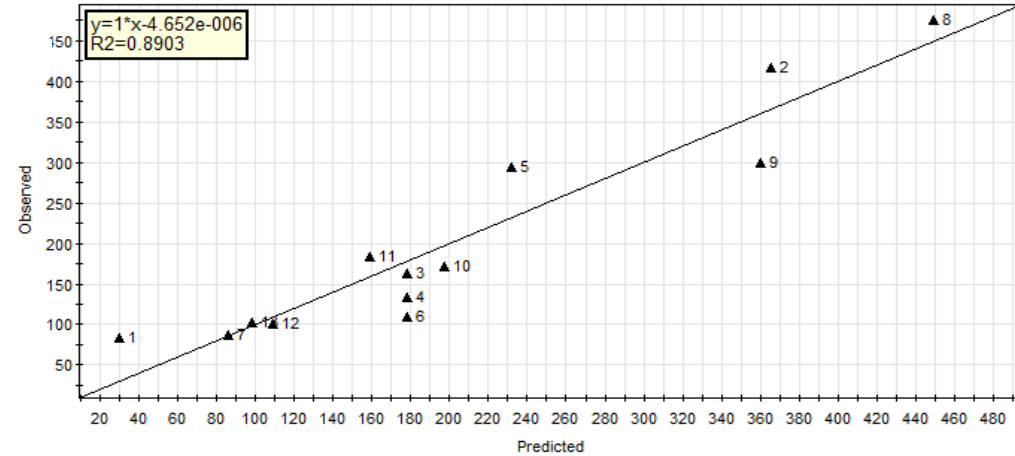
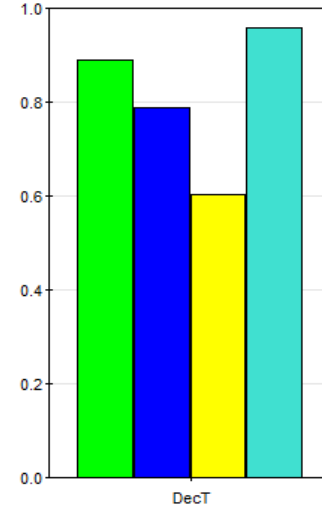
- Higher maximum energy dissipation (MED) leads to longer separation times.
- For the same MED, different impellers yielded similar separation times.
- **Interaction with other mixing variables?**

# Phase separation times in liquid-liquid extractions

## Stage 1 – Developing in-house knowledge (bench scale DoE)



N=13  
DF=9  
R2=0.890  
Q2=0.789  
RSD=49.63  
Conf. lev.=0.95



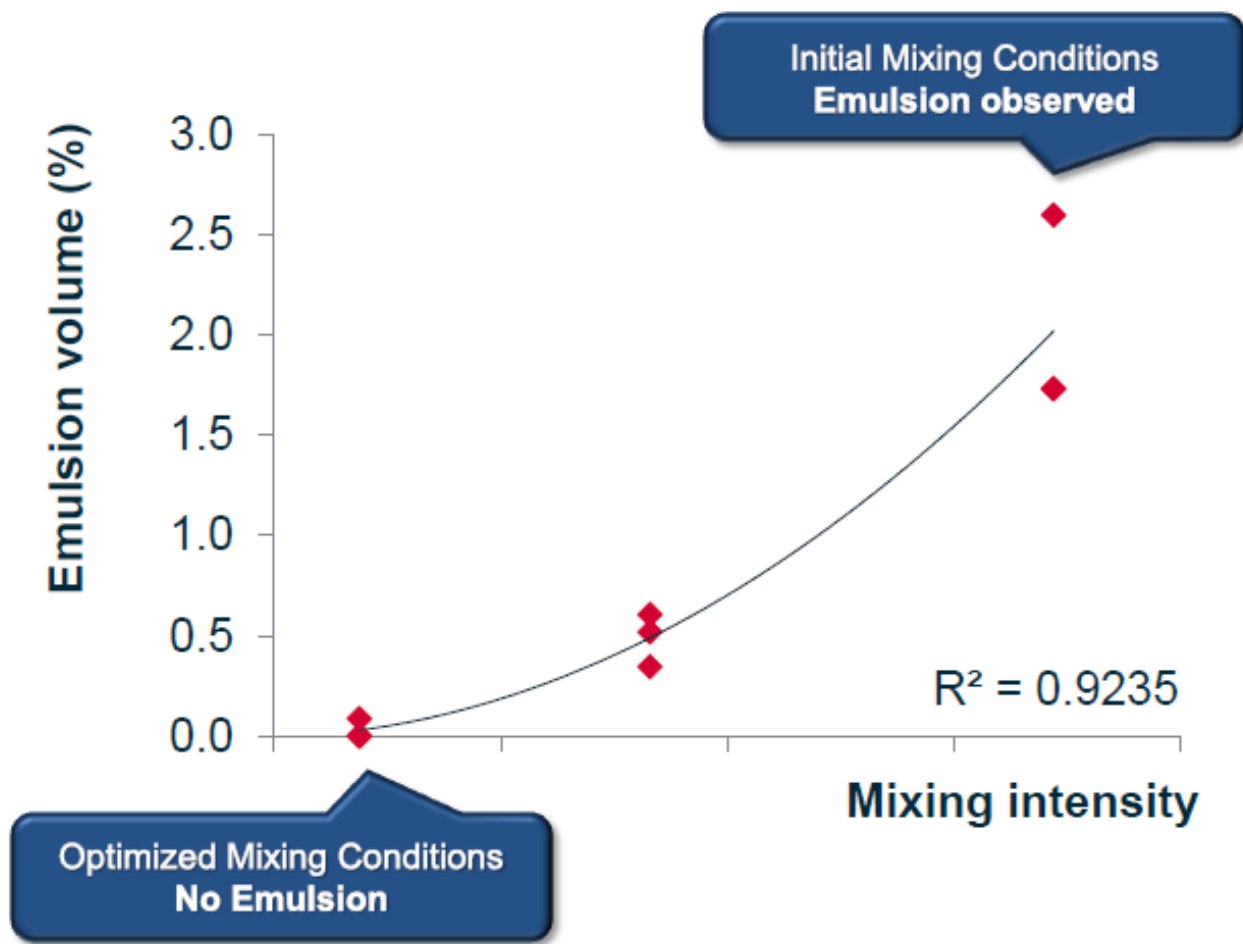
N=13  
DF=9  
R2=0.890  
Q2=0.789  
RSD=49.63

- High maximum energy dissipation (MED) lead to larger separation times.
- High residence time in the zone of MED led to centrifugal separation – swirl effects
- Power and Geometry effects can now be anticipated!

**Let's go to manufacturing!**

# Phase separation times in liquid-liquid extractions

## Stage 2 –Applying knowledge at manufacturing

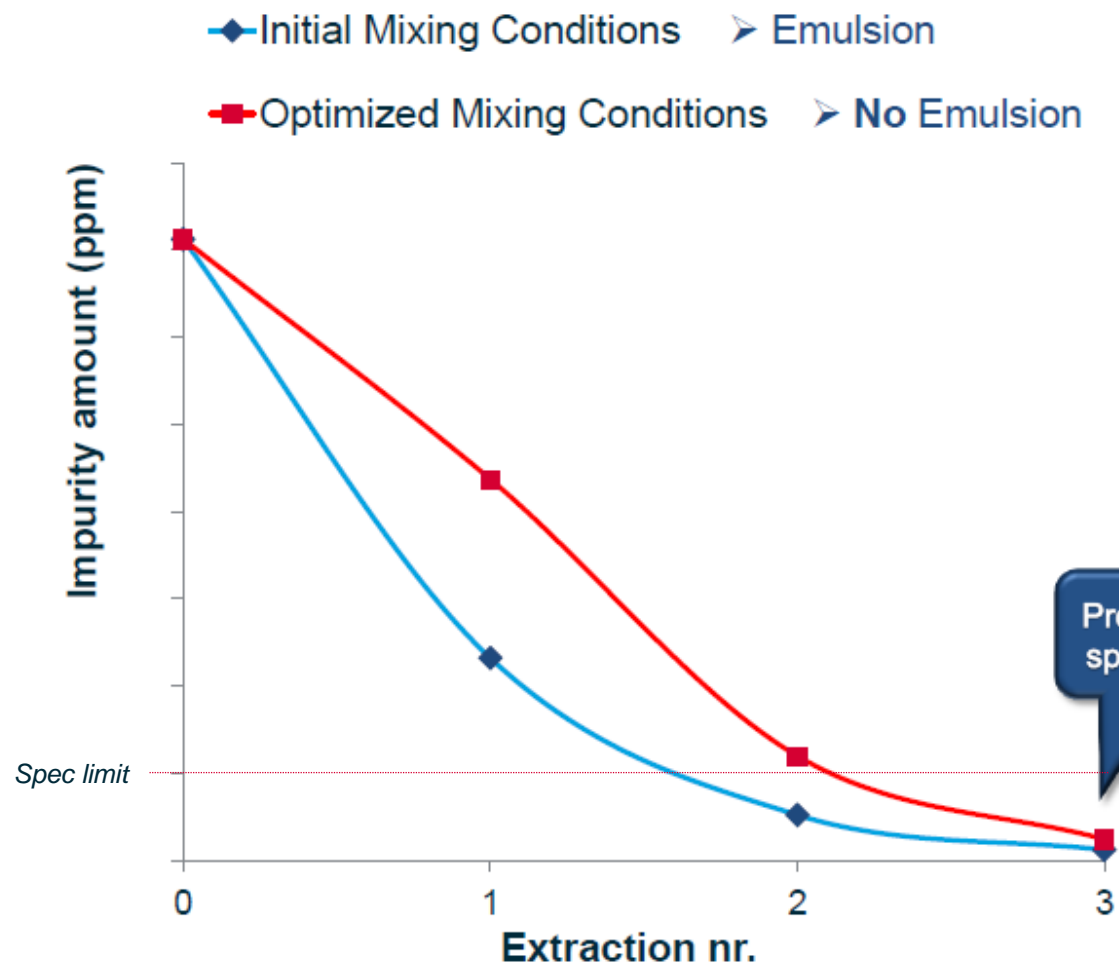


- Scaled-down the manufacturing reactor to a 2L bench reactor.
- Found a correlation between the maximum energy dissipation and the amount of residual emulsion at the end of the procedure.

In Lousa N, et al., *Chemistry Today*, 2015, 33(5), p.63-66.

# Phase separation times in liquid-liquid extractions

## Stage 2 –Applying knowledge at manufacturing



- The new optimized mixing conditions, yielded the desired product. Besides stirring speed, no changes are made to the manufacturing technique.

# Phase separation times in liquid-liquid extractions

## *Lessons learned*

**1.** Software was used to study the effect of geometric variables in oil-in-water systems.

*Key mixing parameters are identified!*

**2.** A reasonable acceptable prediction model was generated and integrated in a QbD methodology.

*Increased know-how! Right-first-time!*

**3.** The software was used for the optimization of an important manufacturing liquid-liquid extraction process.

*Increased batch yield and cycle-time! \$\$\$*

# Conclusions

Summary of the benefits highlighted during the presentation:

Risk mitigation

Increased Know-How

Process Improvement



# Conclusions

**Mixing simulations have an important role in Hovione's *development by design* approaches, allowing:**

- Scientists **to develop** process knowledge – Hovione delivers 'packed knowledge'.
- Process engineers and chemists **to evaluate** the mass transfer phenomena – Right first time.
- Mechanical engineers **to design** equipment – Process requirements overcome supplier recommendations.

**New medicines are made available in a safer, faster and cheaper way!**

# Thank you for your attention



**Nuno Lousa**

Chemist, R&D Technologies and Process Safety

[nlousa@hovione.com](mailto:nlousa@hovione.com)

## ***Acknowledgements***

Carlos Alvarez, R&D

Pedro Santos, Manufacturing

Hélio Lourenço, Manufacturing

Luis Olival, Engineering

[www.hovione.com](http://www.hovione.com)



**In it for life**