Understanding Mixing Strategies
for Drug Substance Process Development and Scale-Up

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Inspired by patients.
Driven by science.

Agenda

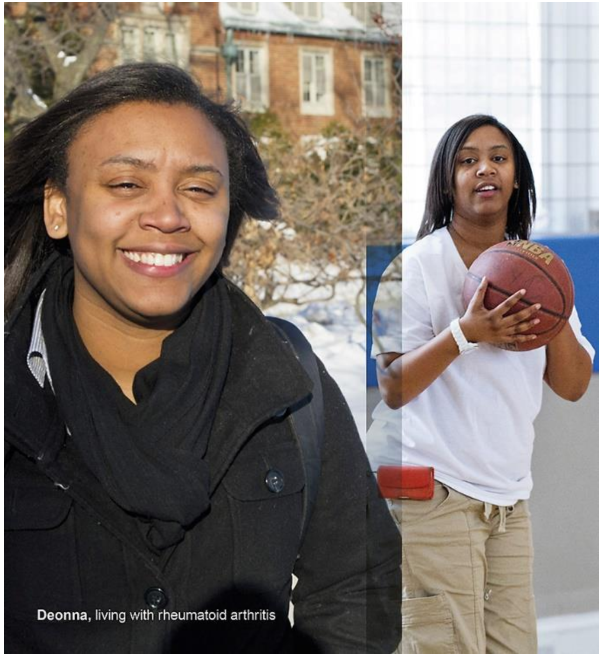
- Introduction to UCB and work of Chemical Engineers @ UCB
- Solid-Liquid Separation – Crystallisation development and mixing strategy to develop a robust process
- Final Highlights

UCB: creating value for patients

Bringing solutions to people living with ***neurological*** or ***immunological*** diseases

Key facts and figures 2017:

- **Revenue**: **€4.5 billion**
- **rEBITDA**: **€1375 million**
- About **7500** employees globally
- Operations in ~**40** countries
- R&D Spend: **23%** of revenue
- Listed on **Euronext**



UCB: reinventing itself, leveraging a solid heritage

1928: Emmanuel Janssen establishes UCB in Brussels

1936: UCB enters the United States

1952: UCB discovers Atarax® U.S. license awarded to Pfizer

1972: A new state-of-the-art R&D center in Braine-l'Alleud, Belgium

1980s: UCB registers its novel antihistamine Zyrtec®

1990s: approval of Keppra®, a novel anti-epileptic

2004: UCB acquires British biotech company Celltech

2006: UCB acquires German pharma company Schwarz Pharma

Launch of Cimzia®, Vimpat® & Neupro®

Launch of a new anti-epileptic

Combine leadership in antibody research & chemistry expertise to better treat severe diseases

1928 | 1936 | 1952 | 1972 | 1980s | 1990s | 2004 | 2006 | 2008-2010 | 2016 | Today

Chemical Group → **Primary Care Pharma** → **Specialty Bio-pharma**

Engineering Sciences @ UCB – workflow

Experiments and model predictions and verification

Solid-Liquid separation: Crystallisation

By Selim Douieb

Solid-Liquid separation: Crystallisation

- Critical unit operation for control of the final product quality

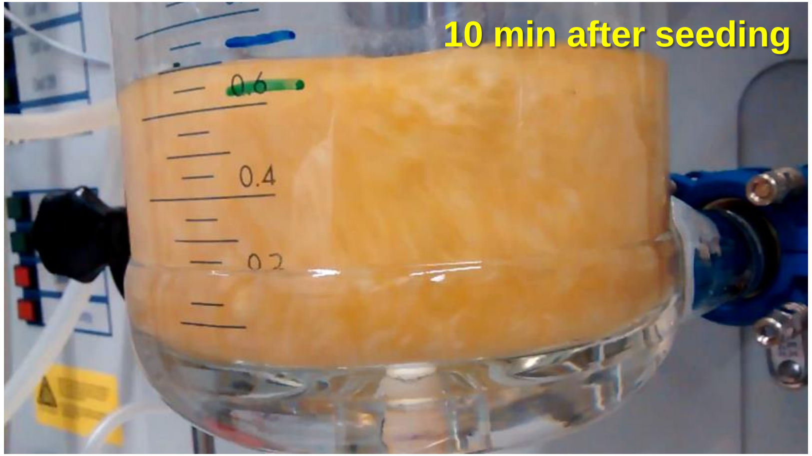
- Workhorse of the chemical purification processes to achieve purity, desired form and chemical physical properties of the powder suitable for formulation

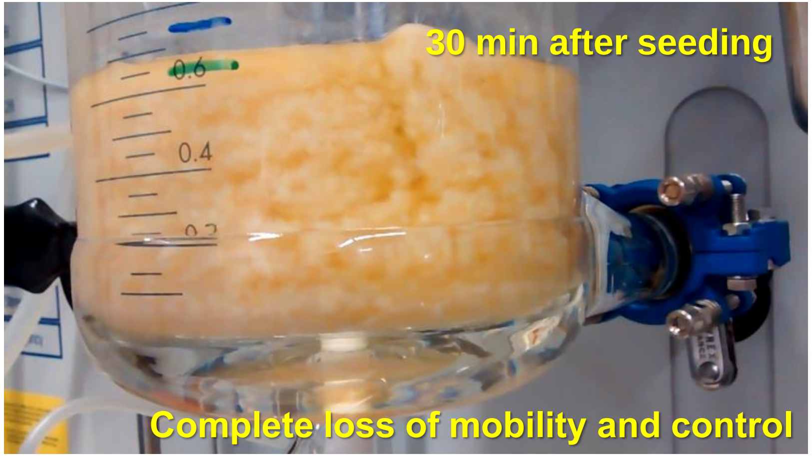
- To make sure consistency is always delivered at whatever scale the crystallisation is performed, we need to know not only what are the process parameters controlling quality of a process but also understand its physical interactions with equipment = > and this is ever more true for multiphases processes

Solid-Liquid Separation: Crystallisation

Context: (1) Seeded Antisolvent Addition Cooling Crystallisation

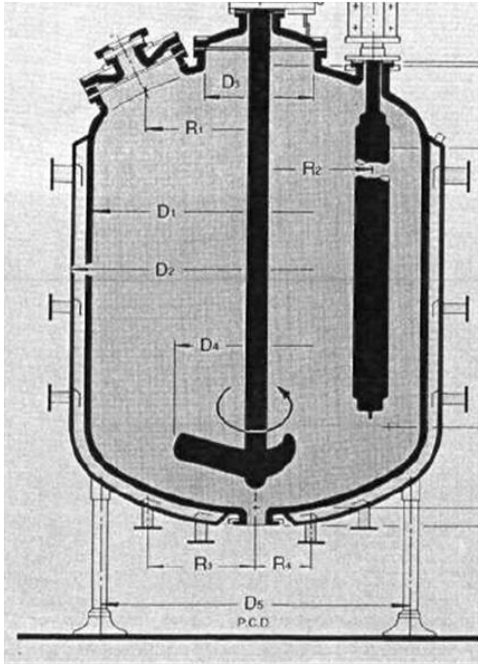
- Late stage crystallisation development of an highly soluble intermediate;
- Primary control point for impurities generated by previous RXN steps;
- Rapid thickening of the suspension upon seeding leading to a complete loss of mobility and control





Solid-Liquid Separation: Crystallisation

Context: (2) Development and Scale-up constrains



- Solvent matrix fixed (Solvent 1/Solvent2), product recovery yield critical (Cost), concentrated solution with low fill level, dilution limited by impact on impurity purging
- Industrial reactor geometry fixed – thousand glass lined vessel mounting a standard Retreat Curved Impeller (RCI) with single beavertail baffle
- Impeller rotational speed fixed at high rpm (not variable);
- Industrial batch size fixed (poor mixing expected due to low fill level and poor baffling);

Solid-Liquid Separation: Crystallisation

Objective

- Ensure mobility of the crystallisation suspension throughout the entire crystallisation at industrial scale
- Reproducible yield and crystallisation performance throughout different scales
- Met target quality – purging of impurities

Solid-Liquid Separation: Crystallisation

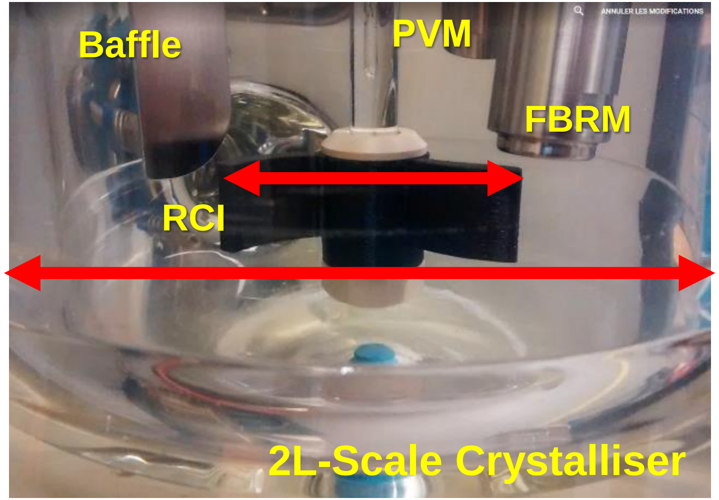
Methodology

- **Lab scale crystallisation experiments – up to 2L scale**
  - Process parameters investigated : Dilution – Solvent/antisolvent ratio – Rotational speed (mixing)
- **Mixing characterization and comparison study – up to 30L scale**
  - Selection of process conditions (Dilution and Solvent/antisolvent ratio) that should ensure a satisfactory mobility of the crystallisation suspension throughout the entire crystallisation at industrial scale
- **Industrial scale validation on a thousand L scale crystallizer**
  - Process validation on manufactory scale equipment

Solid-Liquid Separation: Crystallisation

2L-scale crystallisation experiments

- Scale down laboratory 2L vessel mounting a 3 blade retreat curve impeller with torispherical shaped bottom providing good mixing capability
- Focused Beam Reflectance Measurement (FBRM) and a Particle Vision and Measurement (PVM) probes providing good baffling of the slurry



Solid-Liquid Separation: Crystallisation

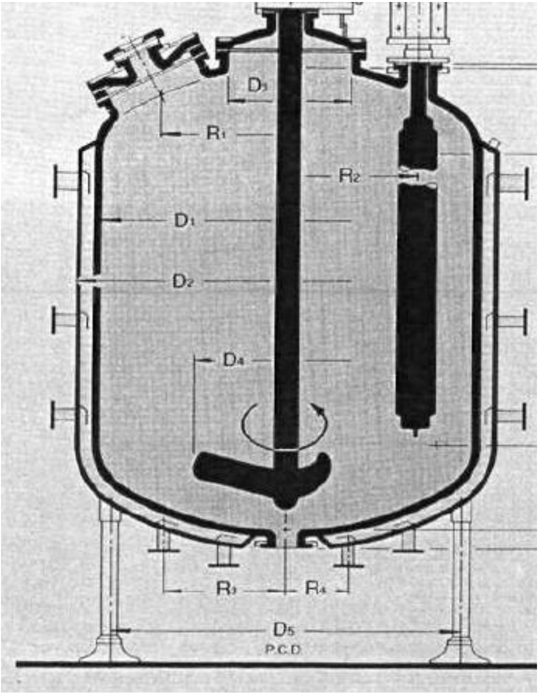
2L-scale crystallisation experiments: results

Suspension mobility		→ Total dilution → [v] LOW	MID	HIGH
↓ V_{rot} ↓ [rpm]	250	KO	KO	KO
	400	OK	-	-
	600	-	-	OK*,1

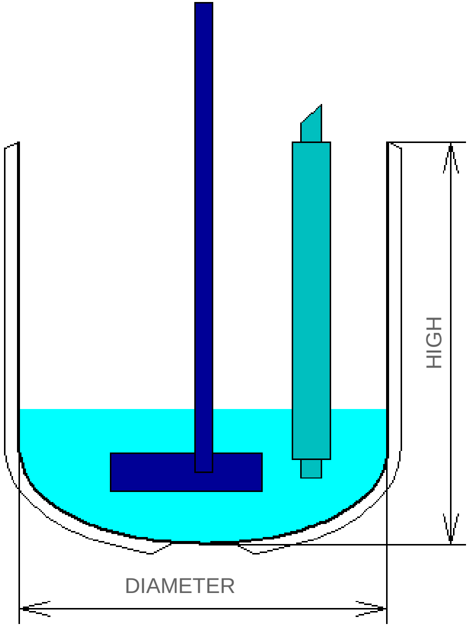
Suspension mobility		→ Total dilution → [v] LOW	MID	HIGH
↓ Solvent 1/ Solvent 2 [v/v] ↓	5/4	-	OK	OK
	5/2	OK*	OK	-
	5/0	OK	-	-

Solid-Liquid Separation: Crystallisation

Industrial scale crystallizer – Characterisation by VISIMIX model

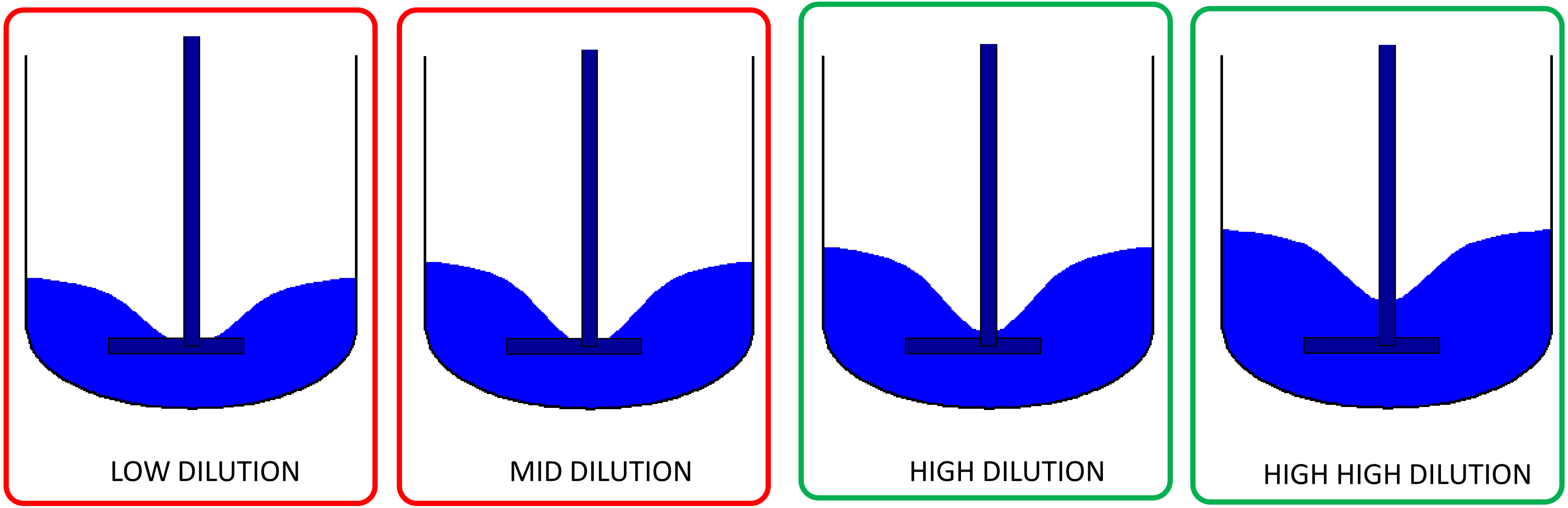


Geometry can be directly implemented in **VISIMIX**



Solid-Liquid Separation: Crystallisation

Industrial crystalliser – Vortex characterization using VISIMIX



Vortex touches impeller: shaft vibration and gas intraining from surface are potential issue

Minimum fill level required to avoid vortex high reaching impeller

Solid-Liquid Separation: Crystallisation

2L-scale crystallisation experiments: results

- For the **seeded cooling crystallisation** in solvent 1 only a certain mixing intensity threshold was required to maintain mobility and control throughout;
- For the **seeded antisolvent addition cooling crystallisation** higher total dilutions did also prevent mobility losses after seeding at critical mixing intensity.

Solid-Liquid Separation: Crystallisation

Mixing characterization and comparison study – VISIMIX

- **For a solid-free crystallisation solution VISIMIX allowed the calculation of two critical mixing parameters:**
  - The average specific power input, $\bar{\varepsilon}$ [W/kg]
  - The turbulent shear rate at impeller tip, $\dot{\gamma}\_tip$ [s-1]
- **What are the relevant scale-up parameters?**
- **How the mixing used so far on small scale equipment will compare with what is achievable at manufactory scale?**
- **Mixing calculations were relatively straight forward with VISIMIX for the manufactory equipment but what about the laboratory equipment?**

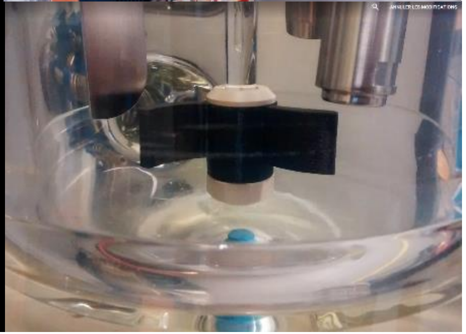
Solid-Liquid Separation: Crystallisation

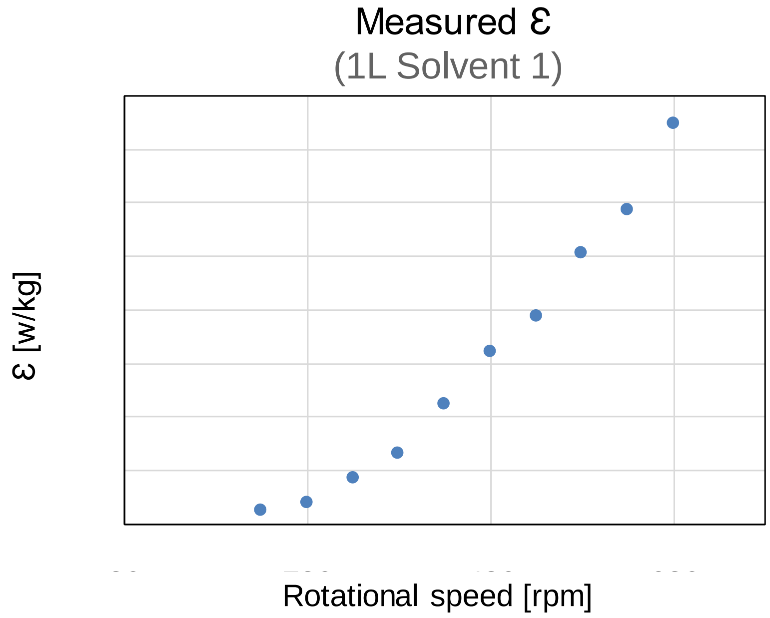
Laboratory scale equipment – building VISIMIX model

- **Need to select an appropriate model for the laboratory equipment in VISIMIX to evaluate the scale-up on manufactory scale;**
  - STEP 1 - Experimental characterization of the effect of Vrot on ε (for a given volume of liquid) in the 2L vessel;
  - STEP 2 – Generate several Visimix models of the 2L reactor with different realistic baffle arrangements;
  - STEP 3 - Select the model enabling to reproduce the experimental characterization results with the highest accuracy.

Solid-Liquid Separation: Crystallisation

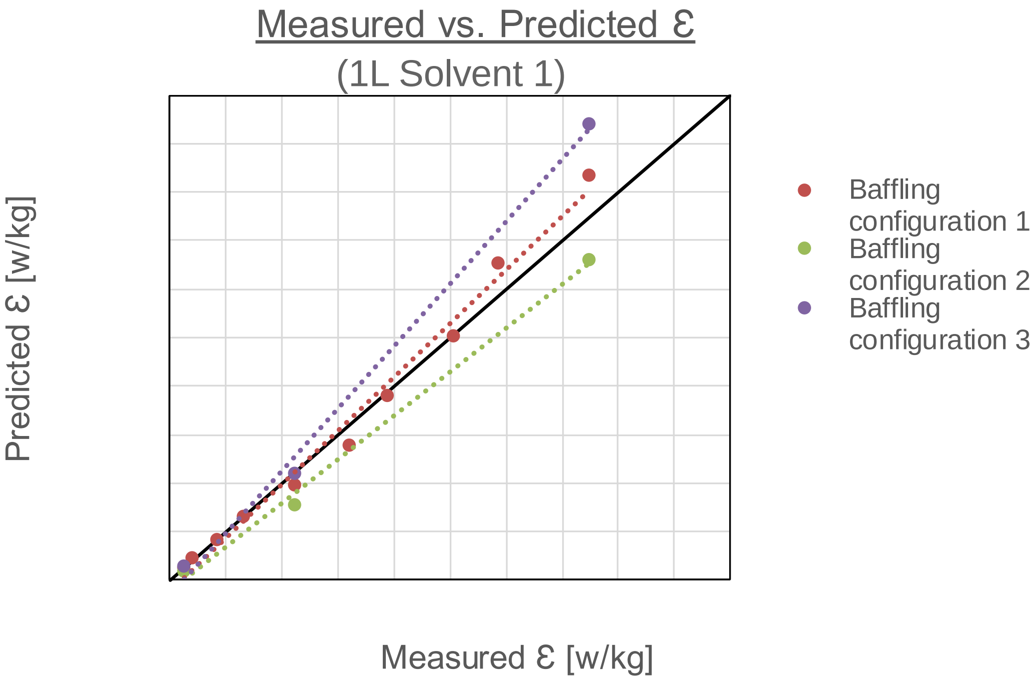
Laboratory scale equipment – measurements





Solid-Liquid Separation: Crystallisation

Laboratory scale equipment – comparison



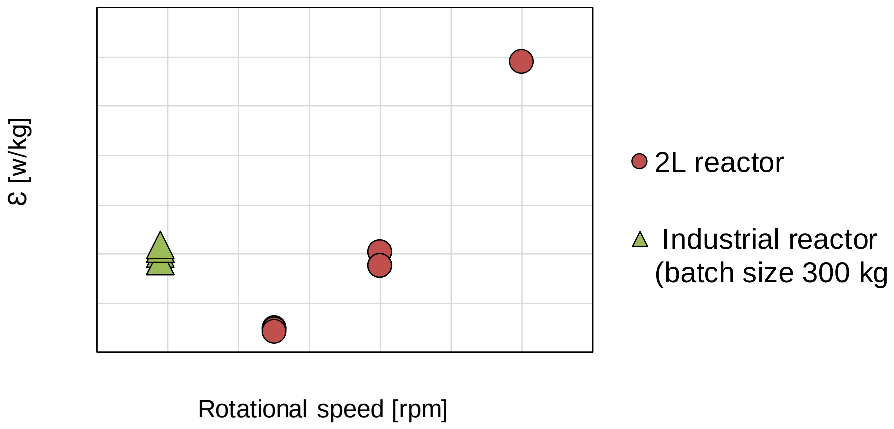
	Baffling configuration 1	Baffling configuration 2	Baffling configuration 3
Baffle type	Beavertail	Beavertail	Beavertail
number	2	1	3
width [mm]	15	15	15
dist. From bottom [	40	40	40
dist. From wall [mm	14	14	14

Satisfactory baffle configuration

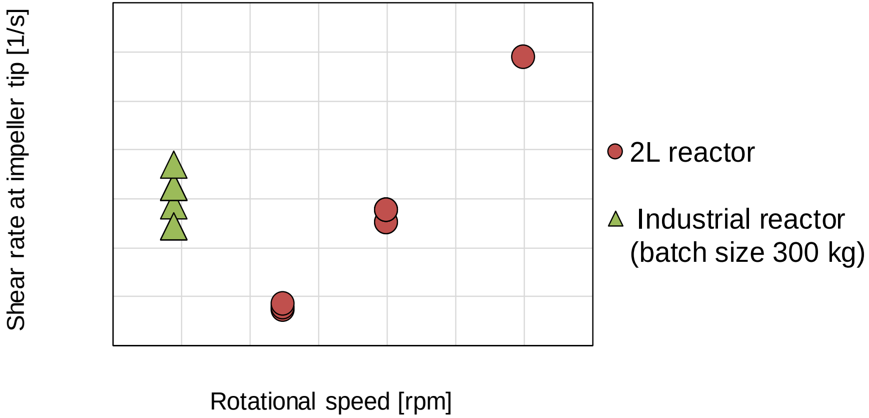
Solid-Liquid Separation: Crystallisation

SCALE-UP calculations and comparison - VISIMIX

Predicted Ɛ for the investigated experimental conditions



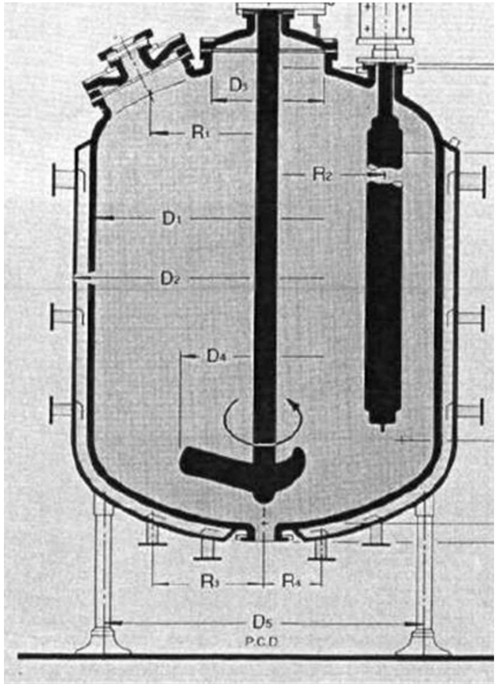
Predicted shear rate at impeller tip for the investigated experimental conditions



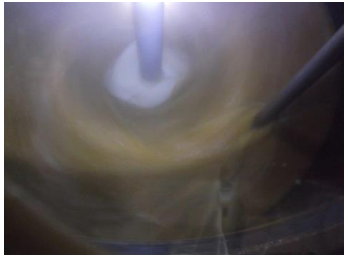
Process conditions leading to a satisfactory mobility/control of the crystallisation throughout the entire crystallisation process @ 2L-scale for a given rotational speed are expected to also give satisfactory results in the industrial scale crystallizer

Solid-Liquid Separation: Crystallisation

Industrial scale validation – thousand L scale crystallizer



- ❑ Dilution HIGH - Solvent/antisolvent ratio HIGH
- ❑ @ batch size of hundreds of kg
- ❑ Good mobility at all time
- ❑ Vortex did not touch impeller
- ❑ Form, yield and purgibility of imps met



Understanding Mixing Strategies

Highlights

- Reliable mixing models are critical support tools for the process engineer in the pharmaceutical industry
- Reliable scale-up is not any longer about appropriate process conditions only but it is about understanding how process interacts with the physical environment – ultimately this will lead to more process flexibility and less chance of failure – to more efficient and economic processes

Questions?

Thanks!