Mixing and Crystallisation

December 2, 2015
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Mettler Toledo

Technobis Crystallization Systems
Agenda

- Mixing basics
- Mixing and scale down
- Crystallisation introduction
- Crystallisation
- Case study
- Flow Crystallisation
Mixing Basics

- Solutions and slurries need to be stirred to allow good mixing of the various components in the mixture and for good heat transfer.
- The type of stirrer / agitator and the shape of the vessel will affect the motion of the solution and / or slurry and so the mixing taking place.
- Lab equipment tends to be spherical – round-bottomed flasks.
- Plant equipment is usually cylindrical.
- Plant vessels are usually baffled.
Flow Pattern in an Unbaffled Tank

Vortex

Swirl
Flow Pattern in a Baffled Tank
Mass Transfer and Agitation

- Type of agitation affects motion in solution and effectiveness of mass transfer
- Design of agitator may be important
  - Impeller, Anchor, Turbine?
  - Number of blades
  - Diameter
  - Pitch angle
  - Distance from bottom
  - Width of baffle(s)
Suspending Solids

Scientific Update course: *Physicochemical Concepts in Process Development*, presented by Dr N. Powles and Dr M. Stirling (University of Huddersfield).
HCl Neutralisation with KOH: Unbaffled

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HCl Neutralisation with KOH: Baffled
Mixing Varies Across the Vessel

- The very best mixing takes place right by the tip of the agitator.
- Poor mixing zones can be found at the bottom of the vessel and on the surface of the liquid.
- Addition point for chemical reactions, salt formations, and anti-solvent crystallisations can be critical.
- Sub-surface via a dip pipe is often the best option if mixing is critical.
- Addition on to the surface can be improved by using a spray nozzle.
Mixing and Agitators

- The motion of the liquid / slurry in the vessel will affect the mixing.
- The motion of the liquid / slurry is directly affected by the agitator / stirrer being used.
- How much radial mixing (sideways) and axial mixing (up and down) takes place in the vessel will depend on the position and design of the agitator.
Impeller

- 3 radial and curved blades
- Assembled axially with 1-2 baffles
- Axial suction and radial flow
- Application range peripheral speed 0.5-10 m/s - turbine flow
- Service
  - homogenization
  - suspension of solids
  - liquid-liquid & solid-liquid dispersion
  - heat transfer
  - chemical reaction
Anchor

- Anchor agitator
- Assembled axially without baffle or with one thermopocket
- Axial suction and radial flow with rotation of product
- Application range peripheral speed 0.5-5 m/s - transitory or laminar flow
- Service
  - homogenization
  - heat transfer
  - chemical reaction
Radial Turbine

- Flat parallel blade to give high radial flow and obtain high mix shear
Uniflow Axial Turbine

- Pitched blades to give high axial flow & low shear
- Tapered blade to minimize radial flow and maintain constant mix velocity at blade tip
- Shear mix minimized
- 3 blades give ease of installation through centre opening
- Assembled with or without baffles
- Application range: per. speed 2-5 m/s
- Service
  - homogenization
  - suspension of solids
  - liquid-solid & gas-liquid dispersion
  - heat transfer
  - chemical reaction
Twin Agitator

- Several 2-bladed wheels 90° rotated
- Assembled with or without baffle
- Prevailing flow axial
- Application range peripheral speed 0.5-12 m/s - laminar or turbulent flow
- Service
  - homogenization
  - liquid-liquid & solid-liquid dispersion
  - heat transfer
Pitched Turbine

- 4 or 6-bladed propeller
- Assembled axially with 1-4 beaver-tail baffles or eccentrically without baffle
- Prevailing flow axial
- Application range peripheral speed 3-20 m/s - turbulent flow
- Service
  - homogenization
  - suspension of solids
  - liquid-liquid, solid-liquid & gas-liquid dispersion
  - heat transfer
Disc Turbine

- Turbine wheel with 6 radial blades
- Assembled axially with or without 1-4 beaver-tail baffles.
- Axial suction and radial flow
- Application range peripheral speed 3-10 m/s – transitory or turbulent flow
- Service
  - homogenization
  - suspension of solids
  - liquid-liquid, solid-liquid & gas-liquid dispersion
  - emulsion
  - chemical reaction
  - heat transfer
Loop Agitator

- Tubular gate agitator
- Assembled axially without baffle or with one thermopocket
- Centripetal and centrifugal radial flow
- Application range peripheral speed 3-5 m/s - transitory or laminar flow
- Service
  - homogenization of viscous products
  - heat transfer
  - chemical reaction
Less Common Impeller Types

- Stabilized Flat-Blade Turbine
- Perforated Propeller
- Saw-Toothed Propeller
- Studded Cage Beater

SpinChem Rotating Flow Cell
SpinChem Rotating Flow Cell

SpinChem Video
Impeller Diameters

- Ratio of impeller diameter to vessel diameter is an important factor in scale-up
  - To disperse a gas in a liquid, optimum ratio is approximately 0.25
  - To disperse 2 immiscible liquids, optimum ratio is approximately 0.40
  - To blend 2 miscible liquids, optimum ratio is > 0.60
- Where a gas is introduced to a solid-liquid dispersion a complex situation arises.
  - Gas bubbling may lead to poor mass transfer, whereas in absence of gas, mixing was good with the same agitator.
- On scale-up, KEEP GEOMETRIC SIMILARITY!

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Laminar or Turbulent Flow?

- Osborne Reynolds (1883) distinguished between two types of flow
  - laminar - pressure drop proportional to $v$
  - turbulent - pressure drop proportional to $v^2$
- The feature of turbulence is formation of lots of eddies of varying sizes, vital for good mixing
- Degree of turbulence can be characterized by a quantity called the “Reynolds number” $N_{Re}$
- For scale-up, if pilot vessel designed so that $N_{Re}$ is the same as in the lab, then equivalent mixing is likely
Reynolds Number $N_{Re}$

- For agitated vessel
  \[ N_{Re} = ND^2 \frac{\rho}{\mu} \]
  - $D = \text{diameter of impeller (m)}$
  - $N = \text{rotation speed of impeller (s}^{-1})$
  - $\rho = \text{density (kg.m}^{-3})$
  - $\mu = \text{viscosity (kg.m}^{-1}.\text{s}^{-1})$

- $N_{Re}$ has NO dimensions

- Change from laminar to turbulent flow usually occurs around same values of $N_{Re}$
  - $N_{Re} < 4,000$ \quad \text{laminar}$
  - $N_{Re} > 10,000$ \quad \text{turbulent}$
Viscosity and Mass Transfer

- For high viscosity applications (\(N_{Re}\) up to 5000)
  - Large scale diameter agitator
  - Low speed
  - i.e. anchor stirrer

- For low viscosity fluids
  - Diameter of agitator may be as low as one third vessel diameter
  - High speed

- Propeller type agitators induce axial flow
  Turbines induce radial flow

- Axial flow component increased by angling turbine blades
Macromixing (Bulk Mixing)

- Achieves a uniform blend on a large scale
- Bulk mixing times:
  - 500 ml flask (500 rpm) 2 - 3 seconds
  - 40 m³ vessel (25 rpm) 30 - 60 seconds
- Before complete mixing occurs there may be
  - “local” excesses of reagent
  - pH differences across mixture
- This may cause formation of by-products
  - particularly if rate of by-product formation is comparable to that of main reaction
- Therefore, selectivity may change with scale
Micromixing

- Mechanical agitation will not give a completely homogeneous blend
- For 2 homogenous fluids, there will be a residual eddy size below which no further blending takes place
- This is a function of
  - power input via agitator
  - viscosity of medium
- For aqueous solutions, eddy size range is $10^{-2} - 10^{-3}$ cm.
- Timescale for homogenization (by molecular diffusion) is of the order of 0.1 - 1 sec
  - Micromixing time can be reduced to a few milliseconds using specially designed static mixers
$E_i$: Mixing Energy Dissipation

- A measure of power/unit mass put into mixing fluid (dissipation of turbulent kinetic energy)
- Values range from 0 to $\sim 3.5$ W/kg

$$E_i = \frac{N_P N^3 d^5}{V}$$

- Perhaps most useful parameter for “scale-down” experiments

Where: $d =$ impeller diameter (m), $N = $ rotational speed (sec$^{-1}$), $N_P = $ power number, $V =$ volume (m$^3$)
$E_i$ Mixing Energy Dissipation

$$Ei = \frac{Power}{mass} = \frac{N_P N^3 d^5}{V} = \frac{N_P \rho N^3 d^5}{m} = \frac{w}{kg}$$

Another commonly used quantity:

$$P = \frac{Power}{volume} = \frac{N_P \rho N^3 d^5}{V} = \frac{w}{m^3}$$

Where: $d =$ impeller diameter (m) \hspace{1cm} N = rotational speed (sec$^{-1}$)

$N_P = $ power number \hspace{1cm} V = $ volume (m$^3$)

$\rho = $ density (kg/m$^3$)
Mixing Configuration:
Semi-Batch Reactors
Crystallisation
Solubility Curve and Metastable Zone

Labile, supersaturated region where spontaneous crystallisation is probable, but not inevitable.

Stable, undersaturated region where crystal growth is impossible.

ΔC = C₁ - C₂ supersaturation
Cooling Profiles

a. Natural cooling
\[ \theta - \theta_f = \exp\left(-\frac{t}{\tau}\right) \]

b. Linear cooling
\[ T = T_o - \left( T_o - T_f \right) \left(\frac{t}{\Delta t}\right)^3 \]

c. Controlled cooling

G Steele (AZ), presentation at Process Analytical Technology Conference, Clearwater FL, November 2007
During Crystallisation

- Nucleation rate affected by
  - Agitation rate
  - Supersaturation level
  - Seeding
  - Trace impurities
  - Temperature

- Rate of crystal growth affected by
  - Agitation rate
  - Density and viscosity of solvent
  - Temperature
  - Trace impurities

- Optimum temperature for nucleation may not be the optimum for crystal growth

Nucleation

- Spontaneous appearance of tiny “embryos” of solid phase
  - < 1 μm; too small for visual detection
- Classical nucleation theory (CNT)

\[
B_0 = A \exp \left( \frac{-16\pi^3 \gamma^3 \varpi^2}{3R^3T^3(\ln S)^2} \right)
\]

- \( B_0 \) - nucleation rate (m\(^{-3}\)s\(^{-1}\))
- \( A \) - pre-exponential factor
- \( \gamma \) - interfacial tension (dn m\(^{-2}\))
- \( \varpi \) - molecular volume (m\(^3\))
- \( R \) - Gas constant
- \( T \) - Temperature (K)
- \( S \) - Relative supersaturation (C/C\(_{eq}\))

- R. Davey & J. Garside; *From Molecules to Crystallizers*, OUP 2000, pp 17 – 18

- Measurement of Induction Time \( t_{\text{ind}} \)
  \( t_{\text{ind}} = 1 / B_0 \)
  - Delay between creation of supersaturation and appearance of detectable particles
  - \( t_{\text{ind}} \) decreases exponentially with increasing \( S \)
Two-Step Nucleation Mechanism

- Nucleation occurs inside pre-formed metastable clusters (several hundred nanometers)
- Concentration is higher than in the bulk solution, but still no order to the molecules (spinodal phase)
- Accounts better for observed rates of nucleation, which are about $10^{10}$ time lower than CNT would predict
Primary Nucleation

- **Homogeneous**
  - Spontaneous appearance of solid phase from solution
  - Requires very high degree of supersaturation

- **Heterogeneous**
  - Induced by foreign particles at moderate supersaturation levels
  - Lab solutions contain $>10^6$ foreign particles per cm$^3$ below 1 micron
  - Filtration removes foreign particles (to below $10^3$ / cm$^3$), thus making primary nucleation more difficult
Primary Nucleation

- This paper reports detection of both mechanisms.
- The plot induction time against the reciprocal of the square of supersaturation.
- Homogeneous
  - Early part of the curve where supersaturation is high.
  - Induction time is short.
- Heterogeneous
  - As supersaturation decreases, induction time extends.
  - At some point, induction time falls and this is thought due to heterogeneous nucleation.

Growth Kinetics of L-Arginine Trifluoroacetate Crystals
Liu,*, Xu, Ren, Zhang, Wei, and Wang
Late Appearance of a Hydrate

- 4 Solvates and 1 anhydrate known
- 10 Batches of anhydrate produced in a seeded crystallisation
  - Slurry seeds for 1-2 hours, followed by stirring at room temperature
  - Gives needles
- New seed preparation
  - Sonicate the seeds for 20 minutes, followed by stirring at room temperature

DOI:10.1021/acs.oprd.5b00030, published online on June 26, 2015.
Seeds and Final Cake

- Morphology – rods not needles
- Faster filtration, lower solubility

DOI:10.1021/acs.oprd.5b00030, published online on June 26, 2015.
Thermal Analysis

DOI:10.1021/acs.oprd.5b00030, published online on June 26, 2015.
Analysis of the New Form

- Anhydrite shows no weight loss
- New form shows weight loss of 2.6% on heating from room temperature to 130°C
- KF on new form gives 2.3 wt% water
- This corresponds to a hemi-hydrate
- The hemi-hydrate loses water at 77.6°C and then crystallises as a new anhydrous form at 145.1°C
- This melts at 184.2°C and is a new polymorph
- This is confirmed by variable temperature XRPD

Variable Temperature XRPD

DOI:10.1021/acs.oprd.5b00030, published online on June 26, 2015.
Increasing the Dissolution Rate

1. Unmilled hydrate
2. Pin-milled x 1
3. Pin-milled x 4
4. Jet-milled x 1

Surface area (m²/g)
1. 0.5
2. 0.8
3. 3.3
4. 3.3
5. 6.9 (anhydrate)

Metastable Zone Width

- Varies with
  - Cooling rate
  - Agitation rate
  - Vessel size
  - Impurities
  - Presence of particles
  - Thermal history of the solution

- Width of metastable zone is independent of crystallisation technique
  - Comparable values for evaporative and cooling crystallisations
Effect of Cooling Rate

- Crystallisation of L-Glutamic Acid in an oscillatory baffled crystalliser
- MSZW wider at higher cooling rates

Variation in MSZW

- 198 experiments at 1 ml scale on solubility of paracetamol at 0.015g/ml
- MSZ width varies from 7.2°C to 33.8°C
- Statistically the MSZ width does not change after 150 experiments at 1 ml scale

Effect of Vessel Size

- Emphasises that nucleation is a random process
- In 1 mL volume, the chance of observing nucleation at 7 degrees is very low, perhaps 0.1%
- But in 1 litre, the number of molecules is a thousand fold greater, so the chance of observing nucleation is also multiplied a thousand fold to around 100%
- For the MSZW, you really need a larger reactor

Probability distribution of the MSZW $\Delta T$ for a paracetamol concentration of 0.015 g/mL in water at a cooling rate of 0.5 C/min: squares, 1mL experiments; circles, 1 L experiments.

Agitation Rate

- Most agitated solutions nucleate spontaneously at lower degrees of supersaturation than quiescent ones (i.e. width of metastable zone is reduced!)
- Increased agitation USUALLY causes additional secondary nucleation by seed proliferation and attrition
- Faster agitation may enhance growth kinetics, particularly in viscous media
- Large crystals (e.g. for XRD) normally require quiescent conditions
Influence of Addition Rate and Stirring Rate

- Investigation of an API Crystallisation
- Zone width decreases slightly at higher agitation rate
- Zone width increases at higher addition rate

Importance of Point of Addition

Addition close to impeller

Addition close to vessel wall

Importance of Point of Addition

Computational fluid dynamics calculations indicated the difference was due to differing levels of turbulence.

Anti-Solvent Crystallisation

Concentration of the solution for crystallisation

Keep Temp fixed while adding anti-solvent
Anti-Solvent Crystallisation

Concentration of the solution for crystallisation

Keep Temp fixed while adding anti-solvent
Anti-Solvent Crystallisation

Concentration of the solution for crystallisation

Keep Temp fixed while adding anti-solvent
Crystallisation by Anti-Solvent Addition

- Less control over crystallisation
- Manual addition of anti-solvent – operator variation
- Mixing dependent
- Changing volume during the crystallisation

- Uncontrolled crystallisation at the addition point
- Particle size dependent on reactor size
- Solvent recovery more difficult
- Cooling crystallisation preferred
Crystallisation by Anti-Solvent Addition

- Add anti-solvent slowly at the start
- Faster towards the end
- Or add anti-solvent in portions with intermediate seeding

Problem / difficulty:

- Knowledge of the change in solubility relative to solvent : anti-solvent composition
- Mixing of solvent and anti-solvent
- Changing volume in the crystallisation vessel
Two Alternatives

- Add anti-solvent at ambient temperature
- Stir and cool to complete crystallisation
- Seeding best carried out after a small portion of the anti-solvent has been added

- Add anti-solvent at elevated temperature
- Carry out a standard cooling crystallisation
Oratinib

- API, coloured, light sensitive
- Crystallisation process not robust
- Variable amounts of IPA, often exceeding the ICH limit of 5,000 ppm
- Variable particle size distribution

DoE Study of Crystallisation

- 8 Factors studied in a quarter factorial design, with 2 centre point
- Amount of solvent: 16.4, 21.4, 26.4 vols
- Solvent ratio: 31, 41, 51: IPA/H₂O
- Temperature: 40, 50, 60°C
- Agitation speed: 80, 160, 240 rpm
- HCl concentration: 7, 12, 17%
- Duration of HCl addition: 1, 2, 3 hours
- Final pH: 1, 3, 5
- Additional agitation: 0.25, 1, 1.75 hours

Variation in Particle Size

- 16.4 vols, 31% IPA/H₂O, 40°C, 80 rpm, 17% HCl, 3 hour addition, to pH 5, 0.25 hour stir out

- 26.4 vols, 51% IPA/H₂O, 60°C, 80 rpm, 7% HCl, 3 hour addition to pH 1, 0.25 hour stir out

Key Factors for Residual IPA

- Temperature > Amount of solvent > Agitation speed > Duration of HCl addition > Solvent ratio
- The high setting of each factor is preferred

Key Factors for PSD

- Solvent ratio ≈ Temperature > Duration of HCl addition

Further Optimisation

- Unimportant factors omitted in next design
  - HCl concentration, final pH, and stir out time
- A further 16 experiments plus 2 centre points were carried out to upgrade to a response surface analysis
  - Temperature, solvent volume, solvent ratio, agitation speed, duration of HCl addition
- Aim to reduce residual IPA levels and obtain a PSD similar to original API

## Ranges Expanded

<table>
<thead>
<tr>
<th>Factor</th>
<th>Original range</th>
<th>Expanded range</th>
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<tbody>
<tr>
<td>Temperature</td>
<td>40-60°C</td>
<td>40-80°C</td>
</tr>
<tr>
<td>Solvent ratio</td>
<td>31-51%</td>
<td>11-51%</td>
</tr>
<tr>
<td>Duration of HCl addition</td>
<td>1-3 hours</td>
<td>0.25-3 hours</td>
</tr>
<tr>
<td>Amount of solvent</td>
<td>16.4-26.4 volumes</td>
<td>16.4-36.4 volumes</td>
</tr>
<tr>
<td>Agitation speed</td>
<td>80-240 rpm</td>
<td>40-280 rpm</td>
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</tbody>
</table>

- Higher temperature gives less IPA, but larger particles
- Lower solvent ratio gives smaller particles
- Shorter HCl addition gives smaller particles
- Larger solvent volume gives less IPA
- Although agitation has no specific effect it was expanded at both ends

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Residual IPA

(b) Residual IPA (ppm)

6171.944 ± 1441.5388

(a) Temperature (°C)(40, 60)
Amount of solvent (v/w)(16.4, 26.4)
Agitation speed (rpm)(80, 240)
Duration of HCl addition (h)(1, 3)
Ratio of solvent (vol % IPA/H2O)(31, 51)

Particle Size

(a) Ratio of solvent (vol % IPA/H2O) (31, 51)
Temperature (°C) (40, 60)
Duration of HCl addition (h) (1, 3)

(b) D50 (μm)
4.877778 ± 0.452183

Results

- Impurity levels increase at higher temperature, 80°C or lower solvent ratio (11% IPA/H₂O)

- Optimum conditions calculated to be:
  - Temperature: 67°C
  - Solvent ratio: 22% IPA/H₂O
  - Duration of HCl addition: 2 hours
  - Volumes of solvent: 36 volumes
  - Agitation speed: 200 rpm

- Predicted to give:
  - Residual IPA: 2223 ± 1210 ppm
  - PSD: $D_{10} 3.2 \pm 0.8 \mu m$
    $D_{50} 4.9 \pm 1.2 \mu m$
    $D_{90} 7.4 \pm 2.0 \mu m$

Verification Experiments

- **Lab scale**
  - Residual IPA: Actual 2138 ppm, Predicted 1013-3433 ppm
  - $D_{10}$: Actual 1.6 $\mu$m, Predicted 2.4-4.0 $\mu$m
  - $D_{50}$: Actual 2.7 $\mu$m, Predicted 3.7-6.1 $\mu$m
  - $D_{90}$: Actual 4.2 $\mu$m, Predicted 5.4-9.4 $\mu$m

- **Model improved by adding this data gave new conditions:**
  - Temperature: 67°C changed to 70°C
  - Solvent ratio: 22% changed to 25% IPA/H$_2$O
  - Duration of HCl addition: 2 hours no change
  - Volumes of solvent: 36 volumes no change
  - Agitation speed: 200 rpm no change

## Second Verification Experiments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Predicted</th>
<th>Actual 1</th>
<th>Actual 2</th>
</tr>
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<tbody>
<tr>
<td>Residual IPA</td>
<td>1386-3252 ppm</td>
<td>2622 ppm</td>
<td>2297 ppm</td>
</tr>
<tr>
<td>D$_{10}$</td>
<td>2.5-4.1 μm</td>
<td>3.5 μm</td>
<td>3.4 μm</td>
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<tr>
<td>D$_{50}$</td>
<td>3.9-6.1 μm</td>
<td>5.6 μm</td>
<td>6.0 μm</td>
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<tr>
<td>D$_{90}$</td>
<td>5.7-9.3 μm</td>
<td>8.6 μm</td>
<td>9.7 μm</td>
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<tr>
<td>Yield</td>
<td>94.7%</td>
<td>95.2%</td>
<td></td>
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</tbody>
</table>

- Process successfully scaled up to produce 3kg of API

Scale Down Then Scale Up

- Typical lab crystallisation:
- Everything sets solid
- The lab chemist “cranks up” the stirrer to get the slurry moving again
- Operating at much too high supersaturation
- Look at mixing parameters comparing 2000 gal reactor with 1 litre lab reactor

Scientific Update course: Secrets of Batch Process Scale Up, given by F. McConville (FXM Engineering).
Matching Power per Unit Mass

Before and After

ORIGINAL PROCESS

(Fine, “bridging” needles)

IMPROVED PROCESS

(Large, regular needles)

Scientific Update course: Secrets of Batch Process Scale Up, given by F. McConville (FXM Engineering).
Continuous Crystallisation

Critical parameters

- Solid loading
- Solid density relative to solvent density
- Particle size
- Flow rate / residence time
- Choice of reactor type
- Choice of pump
- Choice of connections
- Choice of back pressure regulator (if required)
Oscillatory Baffled Reactor (OBR)

Mixing in an OBR

- Mixing is controlled by oscillations
- The baffles oscillate back and forth or
- The fluid pulsates

Continuous OBR Reactor

- Mixing is controlled by oscillations, not the net flow as in the case of turbulent flows.

- Plug flow characteristics are obtained in laminar flows.

- This allows significantly shorter length of reactor and a much more compact reactor setup than conventional systems.
Genzyme Plant

- Increase in demand for API
- Predicted to need 18 tankers per day of acetonitrile for recrystallisation
- Only extra space available for expansion / new building was the staff car park
- 2 Years from first discussions to manufacturing
Commercial API Crystallisation
Continuous API Crystallisation

- World’s largest continuous API plant
- Genzyme, Haverhill, UK
- In production since April 2007
- Reactor volume reduced by >99%
Lilly Asymmetric Hydrogenation

1. Rh(COD)$_2$OTf, L, Zn(OTf)$_2$, MeOH, EtOAc, 70$^\circ$C, 70 bar
2. Aqueous work up
3. Solvent swap to PhCH$_3$
4. IPA, seed, crystallise 86%, >99% ee

H$_2$ - Pd/C, LiBr
THF - EtOH (EtO)$_3$CH, Ac$_2$O 80%

L = (t-Bu)$_2$P$_{(0-Tol)}$ Fe

S/C = 2,000:1

LY500307

**Continuous Crystallisation**

MSMPR = Mixed Suspension Mixed Product Removal

- Longest continuous run: 91.5 hr
- No problems with fouling or plugging
- Product 99.6% ee
- Thermodynamic crystallisation (after aging) gives ~95% ee