MIXING IMPACT ON ANTISOLVENT CRYSTALLIZATIONS

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Agitator Parameters

$$Q = N_Q ND^3 \times 7.48 \, (\text{in gpm})$$

where N is rotational speed in revolutions per minute and D is impeller diameter in feet, and

$$P = \left(N_P N^3 D^5 sg\right) \Big/ 1.523 \times 10^{13} \quad (\text{in hp})$$

where D is impeller diameter in inches and SG is specific gravity
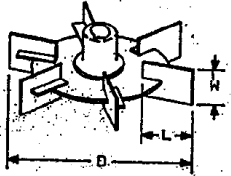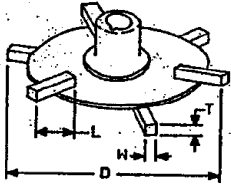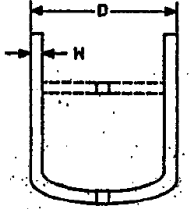
Table 1. Agitator Parameters
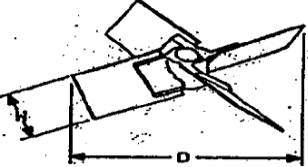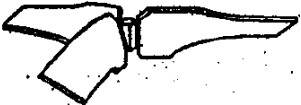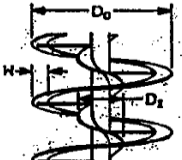
Agitator Type	N_P	N_Q	$(Q/P)_R$
PBT	1.27	0.79	1.00
Hydrofoil	0.30	0.56	1.51
Rushton	5.20	0.72	0.18
GL Retreat Blade*	0.35	0.24	0.10
GL Curved Blade Turbine**	1.44	0.54	0.23

$(Q/P)_R$ = ratio of (Q/P) to that with a PBT at constant flow (Q) and diameter (D)
* 2000 gallon glass lined vessel, diameter @ 44" and $N_{Re}>2.4 \times 10^6$
**2000 gallon glass lined vessel, diameter @ 33" and $N_{Re}>2.4 \times 10^6$

Description of Seven Basic Impellers

Number	Name	Description	
R-1	Flat Blade	Vertical blades bolted to support disk	L=1/4D W=1/5D DISC DIA.=2/3D
R-2	Bar Turbine	6-blades bolted/welded to top and bottom of support disk	L=1/4D W=1/20D T=1/20D DISC DIA.=2/3D
R-3	Anchor	Two blades with or without cross arm	W=1/10D
A-1	Propeller 3-blades	Constant pitch/skewed back blades	1:5 PITCH RATIO
A-2	Axial Flow 4-blades	Constant angle at 45 degrees	W=1/5D X=45°
A-3	Axial Flow 3-blades	Variable blade angle, near constant pitch	BLADE ANGLE AND WIDTH DECREASES HUB TO TIP
A-4	Double Spiral	Two helical flights; $\text{pitch} = \frac{1}{2}D_0$	D_0=(OUTER) D_1=1/3D_0 W=1/6D_0

Power and Flow Numbers

		N_P	N_Q	Twist	$(Q/P)_R$	
Axial	A6000	0.23	0.59	16°	2.30	
axial	A310	0.30	0.56	16°	1.51	FLOW
	A200	1.27	0.79	00°	(1.00)	
	A210	0.53	0.55	45°	0.81	
	C 100	0.29	0.46		0.87	R~
Curvature	C100	0.25	0.64	13.3°	2.70	4.0
.8	C102	0.23	0.56	13.3°	1.97	.8
	A315	0.75	0.73	10°	1.34	2.0
	C104F	0.60	0.52	18°	0.60	PRESSURE
Radial	C104	0.50	0.50		0.65	
	R100	5.20	0.72		0.18	
	R510	0.65				SHEAR
	R500	0.45				

RATIO (Q/P)/ (Q/P) max AT CONST. Q.D =
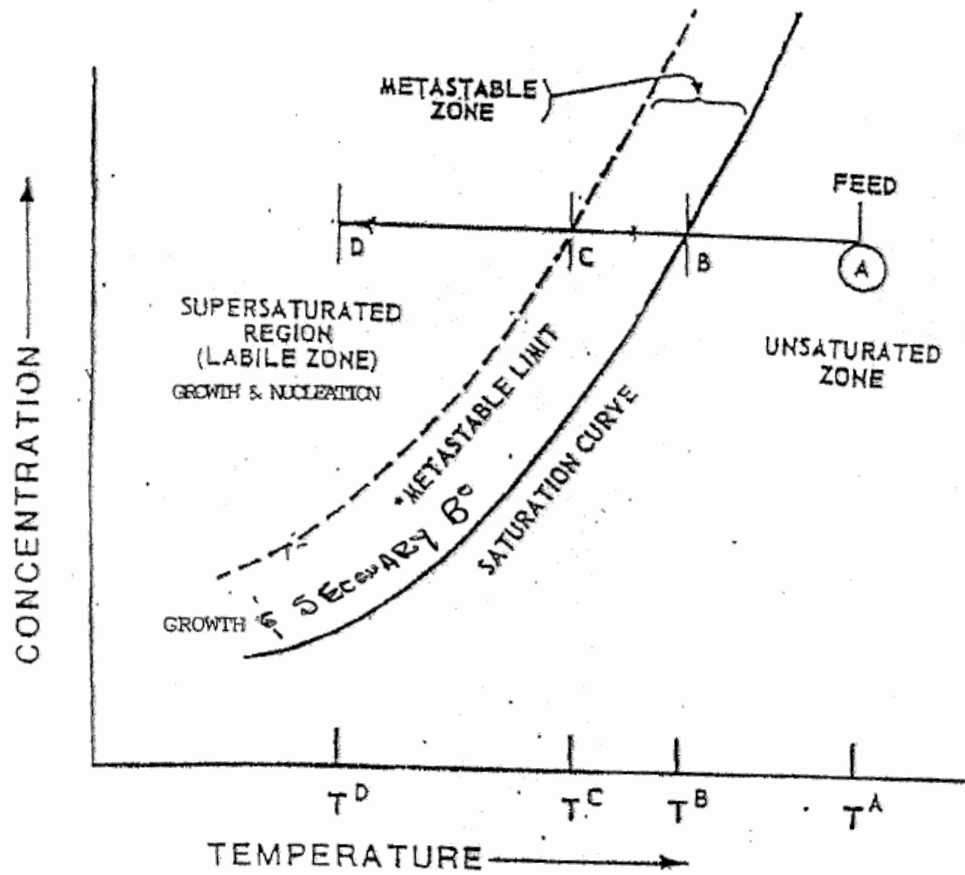
FIG. 1 - Concept of Supersaturation

$$S = T^B - T^D = \text{SUBCOOLING}$$

Supersaturation

Difference between system conditions and equilibrium; driving force for nucleation and growth.

Methods of Generation
•Cooling
•Evaporation
•Evaporative cooling
•Chemical reaction
•Antisolvent addition

•Direct-contact cooling
•Other

Nucleation Mechanisms

<u>Primary</u> – Does not involve participation of product crystals
- Homogeneous
- Heterogeneous

<u>Secondary</u> – Product crystals are involved in nucleation
- Contact
- Shear
- Fracture
- Attrition
- Initial Breeding

Primary Heterogeneous Nucleation

Circulation must be adequate to yield a supersaturation which will suppress primary heterogeneous nucleation by keeping all areas within the metastable zone and avoiding the critical limit will result in highly undesired primary nucleation.

$$S_{max} \: \alpha \: 1/Q_c$$

Where S_{max} is the supersaturation and the Q_c is the rate of circulation. The supersaturation must be kept below S_{max} to avoid primary nucleation.

Secondary Nucleation

Crystal-Impeller contacts have been shown to be the dominant mechanism for low slurry densities and small vessels. It has been shown that the number of secondary nuclei produced is proportional to the energy of impact. For this case, a qualitative model is

$$B_{ci} \; \alpha \; M_T \, N^4 \, D^5/V \; \alpha \; M_T \, N(P/V)$$

For a crystallizer with constant S_{max}, Q is constant. Therefore, ND^3 is constant or $N \sim D^{-3}$. Thus, $B_{ci} \sim D^{-7}$.

The use of a large, slow speed impellers with a high N_Q relative to its N_P, such as a hydrofoil, can greatly reduce nucleation.

- P/V Constant

$$B_{ci} \propto D^{-0.67}$$

- Tip Speed Constant

$$B_{ci} \propto D^{-2}$$

N constant = S_{max} constant

$$B_{ci} \propto D^{+2}$$

The impact of impeller contacts can be reduced by employing impellers made of softer, elastomeric materials. The problem is maintaining the integrity of the coating.

Crystal-crystal impacts become controlling at high slurry densities and large scales. In this case, it can be qualitatively show that:

$$B_{cc} \, \alpha \, M_T^2 \, (P/V)^{1.5} \, d_p^6$$

Attrition/Breakage

This phenomena occurs without the need for supersaturation. Two general modes apply, being

- collisional breakup
- fluid mechanical breakup

The efficiency of the breakage process is dictated by the 2 opposing factors:

- mechanical strength of the crystals
- applied breaking forces

Antisolvent Crystallization
Normal Addition

- Growth vs. nucleation ----- PSD?

    - Controlled and slow antisolvent addition – linear profile often used but has problems

    - Seeding/powder or slurry in antisolvent

    - Feed point location

    - Feed pipe/sparger configuration and size

    - Figure #1
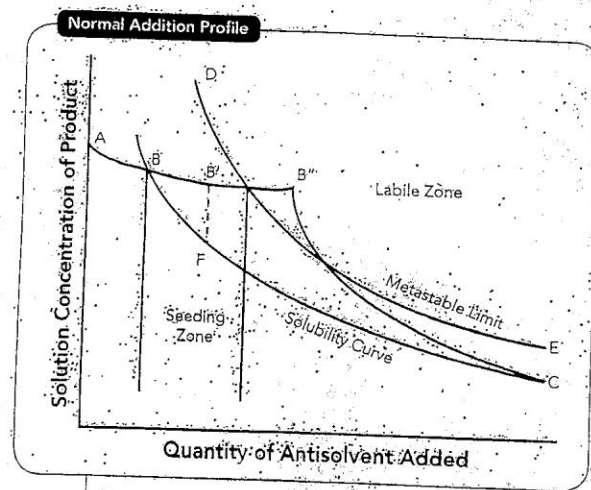
Figure 1. Enough seed and a slow addition rate may keep concentration in the metastable zone.

Antisolvent Crystallization
Reverse Addition

- Small particles/large deviation from equilibrium

  - Potential for undesirable waxes/particles

  - High levels of supersaturation at feed point

  - Potential for nucleation prior to mixing at molecular level

  - Potential for encrustation on vessel and agitator

  - Figure #2

Reverse Addition Profile

Solution Concentration of Product

Labile Zone

F

Metastable Limit

D

B

C

Solubility Curve

A

E

Quantity of Product Solution Added
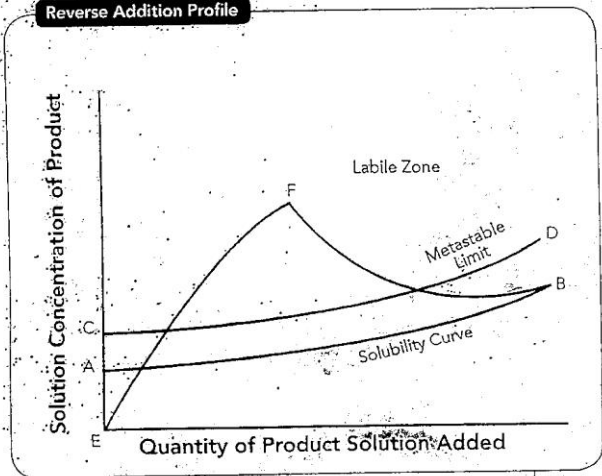
Figure 2. Adding product solution to the antisolvent often leads to production of small particles.

ANTISOLVENT CRYSTALLIZATIONS/PRECIPITATION

- Potential for:

    - Small PSD/CSD
    - Oily particles/agglomerates
    - Amorphous entities
    - Large drops of coalesced oil – gum/wax
    - Agitation difficulties/wax
    - Occlusion of impurities and solvents in gum/wax
    - Poor lattice quality
    - Transformation of forms
    - Problems with downstream recovery and washing.

Types of Mixing

- **Macro –** overall mixing in vessel/blending

- **RTD –** residence time distribution of entering fluid
  element – decaying exponential fn with wide range of possible RT's

  $$t_c = V/Q_c$$

- **Micro –** turbulent mixing on the molecular level – smallest scale of motion – (Kolmogorov scale) and final scales of molecular diffusivity (Batchelor's scale)

  $$t_{micro} = 17.3(\upsilon/\text{\euro}_{loc})^{1/2}$$

  - **Viscous – convection deformation of fluid elements**

  - **Inverse – fn of diffusional mass transfer coefficient**

  - **For ppts – important only at high concentrations with resulting low values of time constants vs. time constants for mixing**

  -- **υ= kinematic viscosity,** m^2 /sec

  - **$\text{\euro}_{loc.}$ = local energy dissipation rate, W/kg**

  -- For S_c **less than 4,000**

Types of Mixing

Meso – **interaction of feed plumes and bulk/blending – only at rct. zone – intermediate mixing time scale – Turbulent Diffusion – feed stream spreads transverse to its streamline**

$$t_D = Q_{feed} / UD_t$$

Q = volumetric flow rate of antisolvent, m^3/sec

U = velocity magnitude in region of feed pipe, m/sec.
D_t = turbulent diffusivity = 0.1 k^2/€

k = turbulent kinetic energy
€ = turbulent kinetic energy dissipation rate, W/kg.

Types of Mixing

- Meso – Inertial Convective Disintegration of large Eddies

$$t_s = A(Q_{feed} / \pi \, U \text{€})^{1/3}$$

Where the length scale of the feed stream, L_c, is smaller than the length scale of the big Eddies, L_v. A is usually 2.

ANTISOLVENT CRYSTALLIZATION AND MIXING IN STIRRED TANKS

- Macro – bulk blending
- Micro –
    - Time of blending to molecular level
    - Induction time for nucleation
    - Times vary throughout the vessel
    - Local energy dissipation rates easily vary by 100X throughout the vessel
    - Shear rates vary throughout the vessel with max value at impeller discharge
    - Addition rate
    - Feed location
    - Design/diameter of feed point and agitator design plus rpms

ANTISOLVENT CRYSTALLIZATION AND MIXING IN STIRRED TANKS

- Mesomixing – dispersion of plume of antisolvent in bulk solution/slurry

  – A change in the PSD with different feed locations confirms sensitivity to mixing
  – Subsurface addition may be beneficial – reverse flow for large pipe and small flow rate may occur
  – Addition rate
  – Feed location
  – Design/diameter of feed point and agitator design plus rpms

ANTISOLVENT CRYSTALLIZATION AND MIXING IN STIRRED

- Macromixing impact – normally not controlling – addition time much longer than macromixing time.

- As the feed rate increases:
  - MZ increases
  - t_D increases
  - t_{micro} decreases due to local kinetic energy

  - At low feed rates micromixing dominates
  - Large pipes and small flows can allow unfavorable backmixing with pluggage
  - In line mixing via impinging jets or rotor-stator configurations.

Industrial Case

- Fully baffled SS crystallizer
- 5.5' ID, 7.15' height
- 26.5" A310/510
- 2cP
- sg = 1.0
- API in IPA @ 500 gallons
- 100% IPAc antisolvent added at 500 gallons

Industrial Case – Initial Conditions

- No seeding
- IPAc added linearly over 1 hour
- 3" feed pipe near baffle
- 20 C addition
- Evidence of gum/oil formation
- Feed point pluggage
- Small particles with difficult filtration
- Amorphous content

Visimix Modeling for Antisolvent Addition

	500 Gallons 50 RPMS	1000 Gallons 50 RPMS	500 Gallons 80 RPMS	1000 Gallons 80 RPMS
Hydrodynamics				
Mixing power, hp	0.03	0.031	0.11	0.13
N_{re} Flow	75,500	55,900	1.21e+05	89,000
Avg. Tangential Velocity, m/s	0.136	0.078	0.218	0.125
Wall Tangential Velocity, m/s	0.095	0.054	0.152	0.087
Max. Tangential Velocity, m/s	0.260	0.160	0.412	0.158
Avg. Circ. Vel., m/s	0.118	0.119	0.190	0.173
Mean. Time of Circ., s	10.9	23.8	6.81	14.8
Tip speed, m/sec.	1.78	1.78	2.81	2.81
Macromixing time, s	30.1	79.1	18.8	48.1
Power number	0.26	0.29	0.26	0.29
Turbulence				
Energy dis. Avg. W/kg	0.0108	0.006	0.044	0.025
Energy dis Max. W/kg	4.56	5.10	18.7	20.9
Energy dis. near baffle, W/kg	0.0043	0.0023	0.0175	0.0095
Characteristic micromixing time, s	34.0	58.8	21.1	29.0
Shear Rate near blade, 1/s	1,510	1,600	3,060	3,240
Shear rate in bulk, 1/s	46.3	34.2	93.8	69.2
Shear rate near baffle, l/s	46.3	34.2	93.8	69.2
Microscale of turb. near impeller, m	3.64e-05	3.54e-05	2.56e-05	2.49e-05
Microscale of turb. near baffle, m	2.08e-04	2.42e-04	1.46e-04	1.70e-04
Microscale of turb. in bulk, m	2.08e-04	2.42e-04	1.46e-04	1.70e-04

Radial Distribution of Tangential Velocity
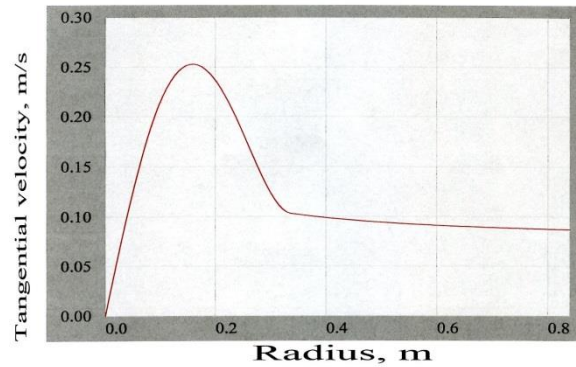

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1000 gal
80 RPM

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RADIAL DISTRIBUTION OF TANGENTIAL VELOCITY

Dissipation of Energy Around the Impeller

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1000 gallons / 80 RPM's

DISSIPATION OF ENERGY AROUND THE IMPELLER
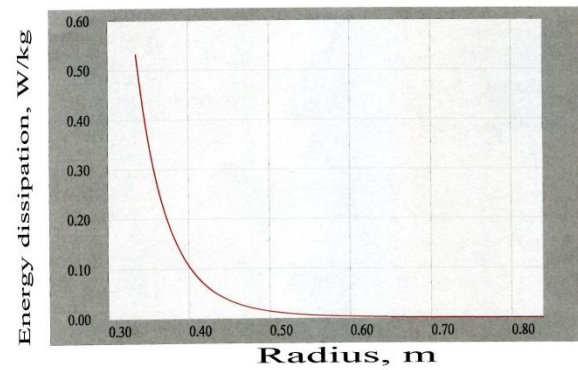
Industrial Case – Modified Conditions

- Seeds added with IPAc
- IPAc added in non-linear profile over 2 hours
- 1" feed pipe near impeller
- 35 C addition
- No evidence of gum/oil formation
- No feed point pluggage
- Larger particles much easier to filter
- Highly crystalline product

Conclusion

Visimix has proven to be an excellent aid in the design, scale up and troubleshooting of crystallization systems

Table 2. EFFECT OF VARIOUS SCALE UP STRATEGIES

| Parameter | Normalized Pilot-Plant | Scale Up Strategy | | | |
		P/V Constant	Q/V Constant	ND Constant	N_{Re} Constant
Power (P)	1.0	125	3,125	25	0.2
P/V	1.0	1.0	25	0.2	0.0016
Speed (N)	1.0	0.34	1.0	0.2	0.04
Impeller Diameter (D)	1.0	5.0	5.0	5.0	5.0
Pumping Capacity (Q)	1.0	42.5	125	25	5.0
Q/V	1.0	0.34	1.0	0.2	0.04
Tip Speed (ND)	1.0	1.7	5.0	1.0	0.2
Reynods No. N_{Re} ($ND^2 \rho/\mu$)	1.0	8.5	25.0	5.0	1.0

Scale Up Criteria

- **Constant stirrer speed**

  $N_1 = N_2$

  $\Rightarrow$ constant circulation time and macromixing

- **Constant tip speed**

  $N_1 \pi d_1 = N_2 \pi d_2$

  $N_2 = N_1 (V_2 / V_1)^{-1/3}$

  $\Rightarrow$ constant mean impeller shear rate approximates constant mesomixing – but on scale up max shear rate $\uparrow$ and average shear rate $\downarrow$ in impeller zone – therefore distribution changes

- **Constant P/V**

  $N_2 = N_1 (V_2 / V_1)^{-2/9}$

  $\Rightarrow$ constant ε_{avg} and ε_{loc} energy dissipation rates

  $\Rightarrow$ constant micromixing times related to **Kolmogoroff** length scale of mixing

Problems With "Rules of Thumb"

• More than 1 limiting mixing process

• Scale up @ constant micromixing times alters the mesomixing times

• Can have a dramatic influence on the $\mathbf{B^o}$ rates which are influenced by mesomixing times for fast reactions, antisolvent addition/ppts

Visimix Simulation

	50 gal. Pilot plant	6,250 gal. Constant P/V	6,250 gal. Plant Constant tip speed
Hydrodynamics			
Mixing power, hp	0.086	10.73	2.20
N_{Re} for flow	70300	5.75 e +05	3.39 e +05
Avg. circ. vel. m/s	0.311	0.517	0.305
Mean circ. time, s	3.79	12.7	21.6
$N_{Re,}$ impeller	1.3e + 05	1.11 e +06	6.53 e +05
Tip speed, m/s	3.20	5.44	3.21
Turbulence			
Energy dis. Avg. W/kg	0.356	0.319	0.0655
Energy dis. Max. W/kg	110	110	22.4
Vol. Zone max. dis., cub. M	0.000213	0.0268	0.0269
Characteristic micromixing time, s	4.18	4.43	9.79
Energy dis. @ baffles W/kg	0.147	0.130	0.0267
Energy dis. In bulk w/kg	0.147	0.130	0.0267
Microscale of turb. near blade, m	1.24 e-05	1.24 e-05	1.84 e-05
Microscale of turb. near baffle, m	6.46 e-05	6.66 e-05	9.89 e-05
Microscale of turb. in bulk, m	6.46 e-05	6.66 e-05	9.89 e-05
Turb. shear rate near blade, 1/s	8970	8960	4050
Turb. shear rate near baffle, 1/s	327	309	140
Turb. shear rate in bulk, 1/s	327	309	140
Liquid-solid mixing			
Max. degree axial non-uniformity, %	13.8	9.20	15.9
Max. degree radial non-uniformity, %	0.558	0.237	0.236
Max. energy of collisions, J	7.25 e-11	7.24 e-11	2.51 e – 11
Characteristic time between 2 strong collisions, sec.	38.3	42.5	72.0
Energy of collisions in bulk, J	8.77 e-13	8.11 e – 13	2.82 e – 13
Frequency of collisions of max. energy 1/s	0.0261	0.0235	0.0139

- A brief summary of the definitions for the predicted parameters is as follows:

1. Maximum value of energy dissipation – microscale phenomena RE: breakage and nucleation.

2. Local values of energy dissipation.

3. Characteristic time of micromixing – time of microscale degradation of non-homogeneous concentrations.

4. Shear rates – at microscale level governs process of mass transport for growing and dissolving solids.

5. Maximum energy of collisions at zone of maximum turbulence near impeller blades – as the value increases expect an increase in breakage and secondary nucleation.

6. Energy of collisions in bulk – although less than the maximum value, the large number of collisions in the bulk can affect breakage and secondary nucleation.

7. Frequency of collisions of maximum energy – if higher, more breakage and secondary nucleation.

8. Time between 2 strong collisions – average period of uninterrupted crystal growth.