Role of mixing in crystallization processes

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Crystallization process

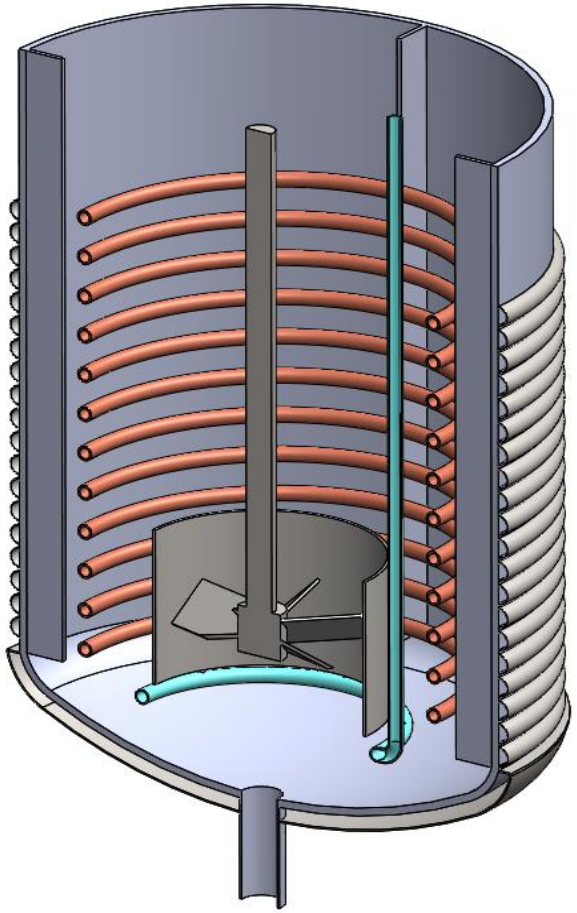
- **Methods:**
- Cooling crystallization
- Evaporative crystallization
- Anti-solvent crystallization

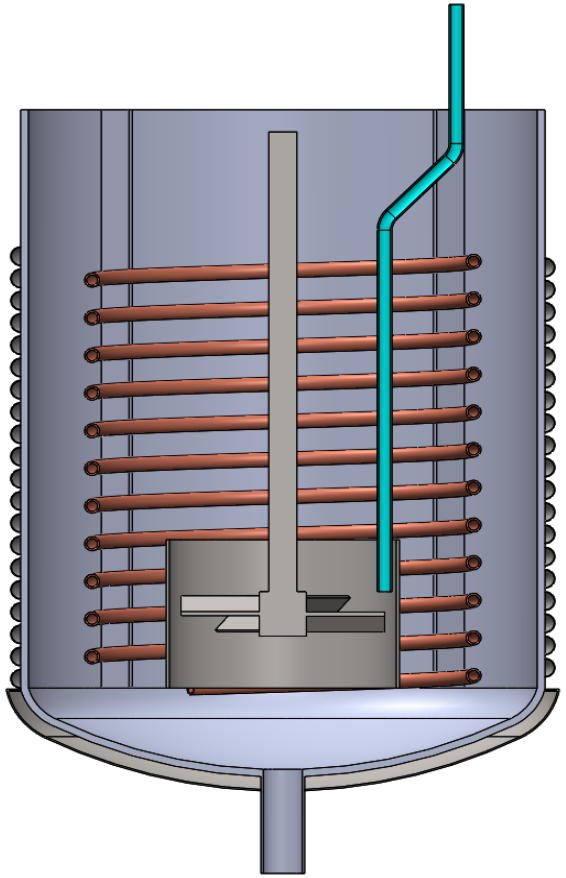
- **Stages:**
- Nucleation
- Crystal growth
- Crystal aggregation and break-up based on local hydrodynamics

Mixing aspects in crystallization

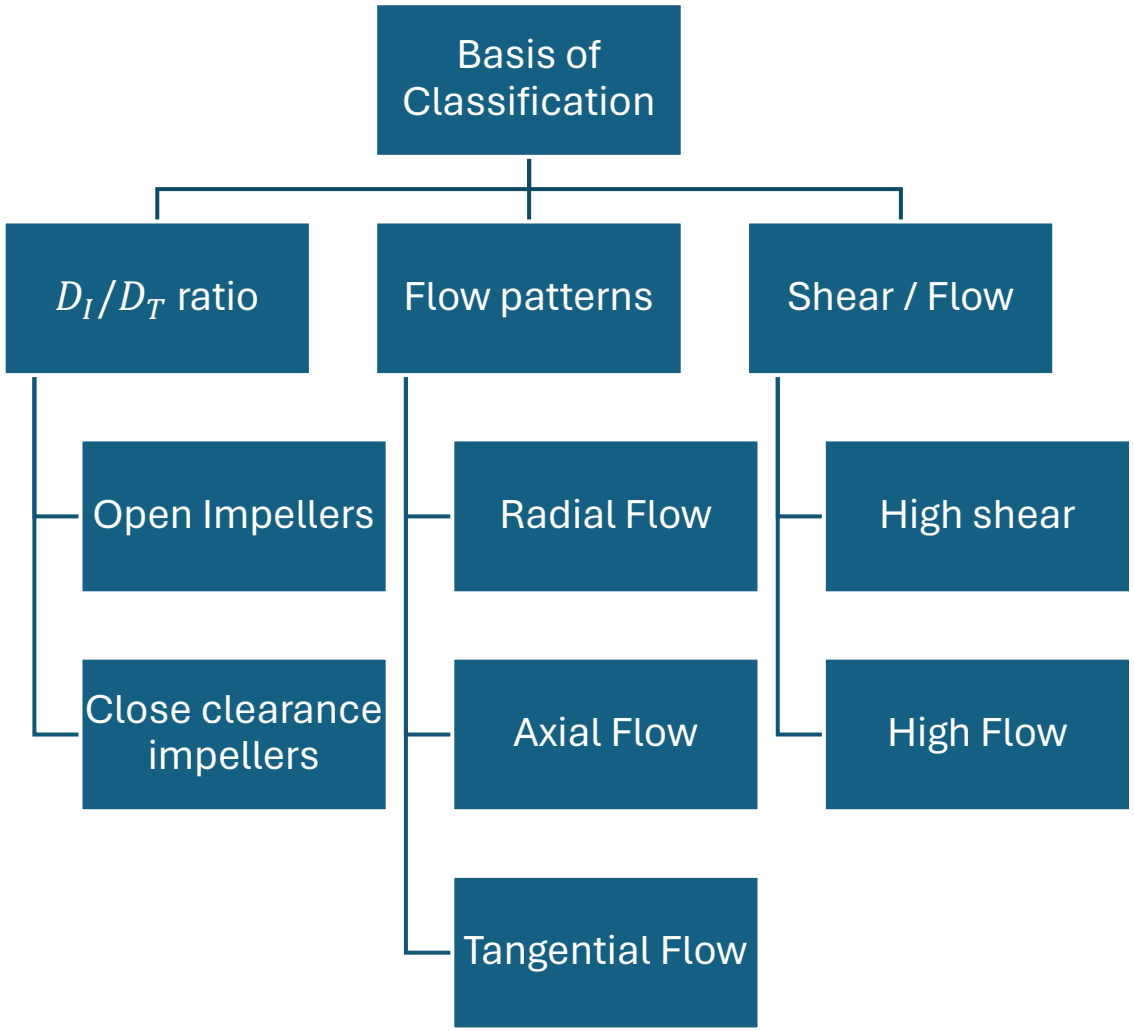
- All crystals need to be suspended
- Crystals may have tendency to agglomerate", "stick" to walls
- Adequate turbulence needed to ensure good mass transfer rate for crystal growth
- Local shear rate: crystal break-up
- Cooling rate, degree of supersaturation and mixing will govern crystal morphology as well as crystal size distribution.

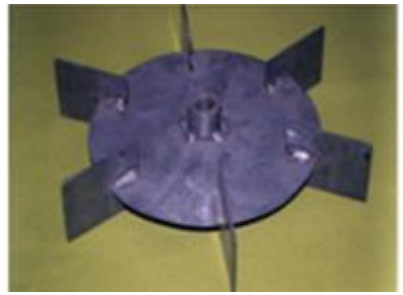
Stirred tanks : Internals





Impeller Classification





Important design parameters

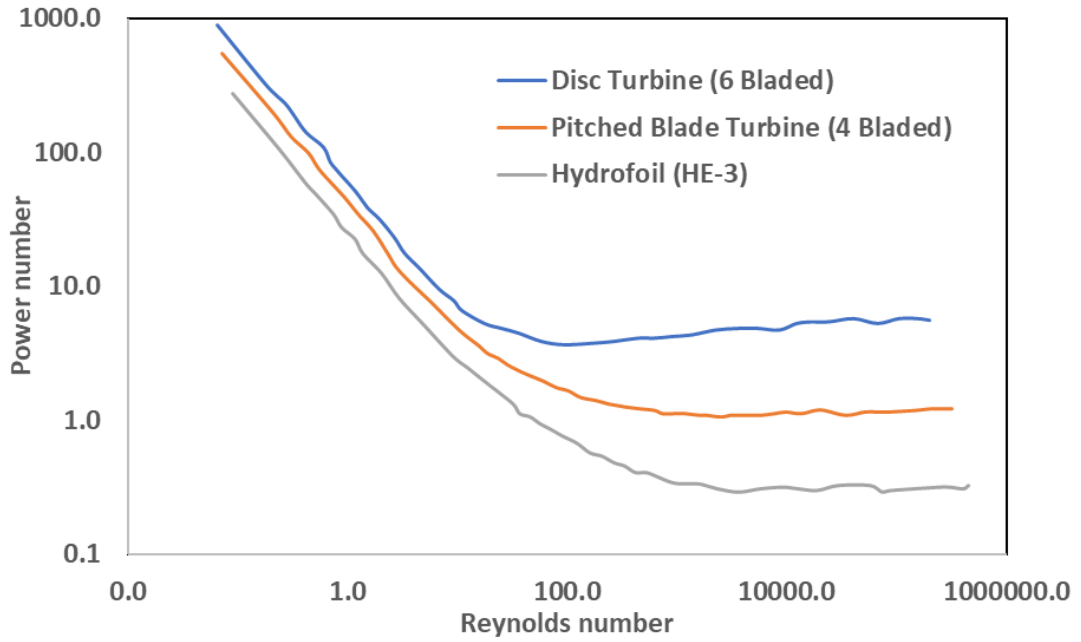
- **Reynolds number**
- Power number
- Flow number
- Power per unit volume
- Max. energy dissipation rate
- Tip Speed

- $N_{Re} = \frac{N D_I^2 \rho}{\mu}$
- The system is considered fully turbulent when N_{RE} >10,000
- Scale-up criterion to ensure similar flow patterns in the system
- Process side heat transfer coefficient correlates well with the Reynolds number

Important design parameters

- Reynolds number
- **Power number**
- Flow number
- Power per unit volume
- Max. energy dissipation rate
- Tip Speed

- $P = N_p \times \rho \times N^3 \times D_I^5$
- Power number is function of Reynolds number and it is constant under fully turbulent conditions
- It is a measure of energy delivered to the process fluid



Important design parameters

- Reynolds number
- Power number
- **Flow number**
- Power per unit volume
- Max. energy dissipation rate
- Tip Speed

- $Q = N_Q \times N \times D_I^3$
- It is a measure of pumping action of impeller.

Impeller	N_Q
Disc Turbine	0.7-0.85
45° Pitched-Blade Turbine (4 blades)	0.7-0.8
45° Pitched-Blade Turbine (6 blades)	0.9
Marine Propeller	0.4-0.55
Chemineer HE-3	0.48

HE-3 with 500 mm diameter with rotation speed of 60 rpm will generate ~ 200 m^3/hr circulation flow

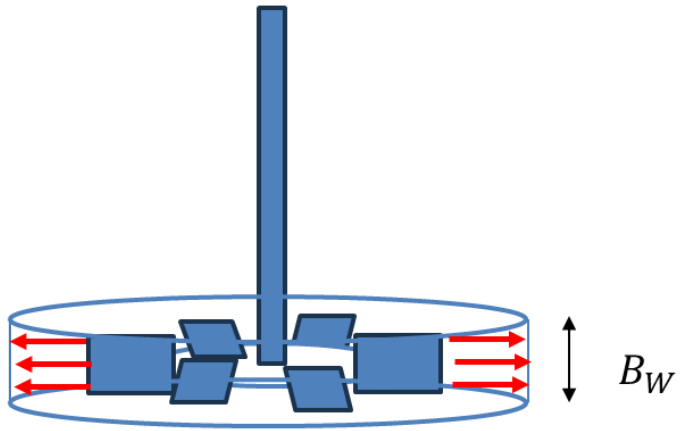
Important design parameters

- Reynolds number
- Power number
- **Flow number**
- Power per unit volume
- Max. energy dissipation rate
- Tip Speed

Radial Flow Impeller

integral of radial velocity leaving the surface surrounding the impeller

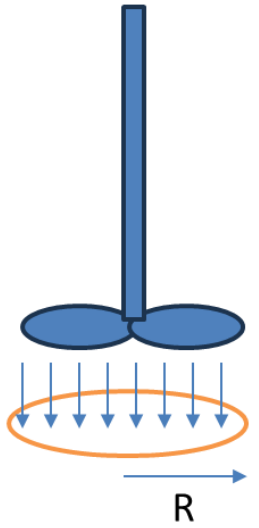
$$N_Q = \frac{\int_{-B_W/2}^{+B_W/2} 2\pi\, r\, u_r\, dz}{ND^3}$$



Axial Flow Impeller

integral of axial downward velocity from the impeller

$$N_Q = \frac{\int_0^R 2\pi\, r\, u_Z\, dr}{ND^3}$$



Important design parameters

- Reynolds number
- Power number
- Flow number
- **Power per unit volume**
- Max. energy dissipation rate
- Tip Speed

- $\left(\frac{P}{V}\right)_{Avg} = \left(\frac{N_P \rho D_I^5 N^3}{V}\right)$
- This is used as a scale-criterion in multiphase mass transfer-controlled applications.

APPLICATION	POWER CONSUMPTION PER UNIT MASS (kW/m^3)
BLENDING	0.1 to 0.8
HEAT TRANSFER	0.2 to 1.5
SOLID SUSPENSION	0.4 to 2.0
GAS-LIQUID DISPERSION	0.7 to 10.0
LIQUID-LIQUID DISPERSION	1.0 to 5.0
GAS-LIQUID-LIQUID	5.0 to 100.0
GAS-LIQUID-SOLID	1.0 to 7.0

Important design parameters

- Reynolds number
- Power number
- Flow number
- Power per unit volume
- **Max. energy dissipation rate**
- Tip Speed

- $\epsilon_{Imp,zone} = \dfrac{Impeller\ power}{impeller\ blade\ swept\ volume}$
- $\epsilon_{Imp,zone} = \left(N_p d_I^5 N^3\right) / \left(\dfrac{\pi D_I^2 h_I}{4}\right)$
- The maximum energy dissipation rate often is derived from the total power consumed by an impeller in relation to the volume swept by its blades.
- Turbulence or shearing action in the impeller zone

Important design parameters

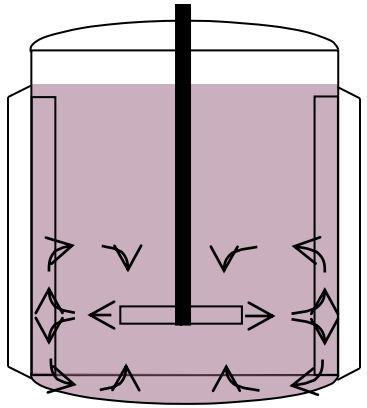
- Reynolds number
- Power number
- Flow number
- Power per unit volume
- Max. energy dissipation rate
- **Tip Speed**

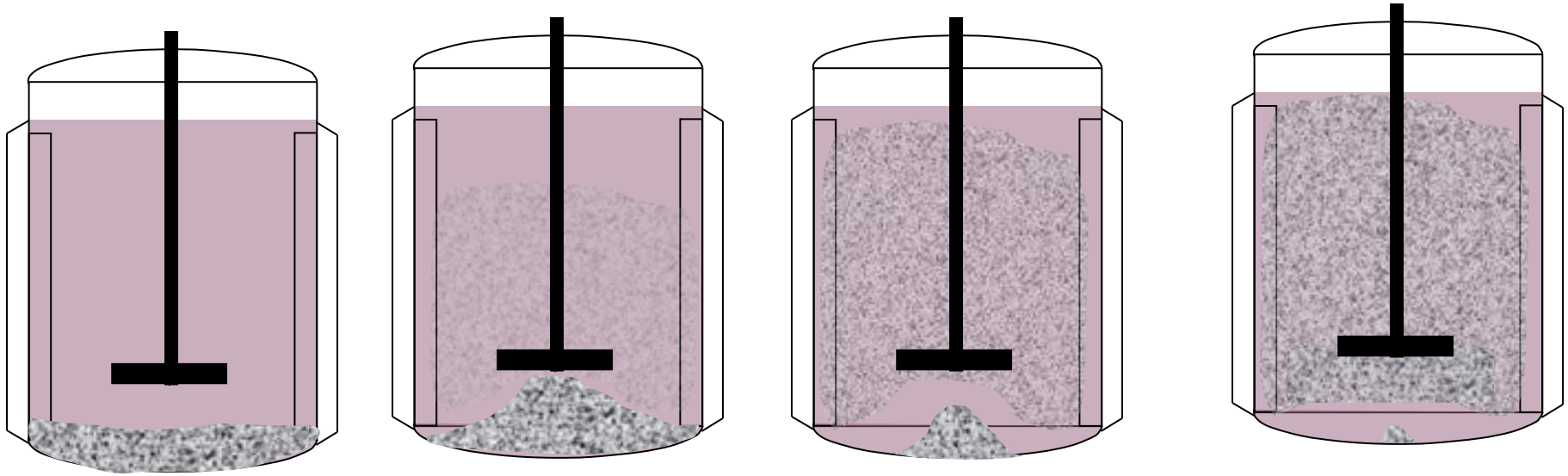
- $v_{Imp,tip} = \pi D_I N$
- Highest fluid velocity is observed at the tip of the impeller blade
- Correlated with crystal breakage characteristics
- One of the scale-up criterion used in crystallization and bioprocessing

Shear in agitated vessels

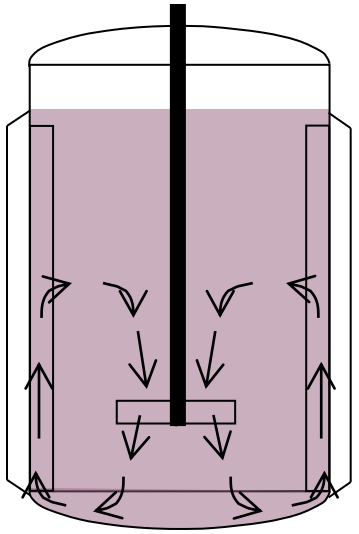
- Shear is a force acting due to velocity gradients in the systems.
- Shear rate is proportional to agitation speed raised to 1 in laminar flows and raised to (3/2) for turbulent conditions
- Average shear rate: $\gamma = (P/V)\mu^{0.5}$
- Tip speed is just an indicator of maximum shear under turbulent conditions. If shear is important, then one should carry out experiments/simulations to get the reliable estimations in the domain

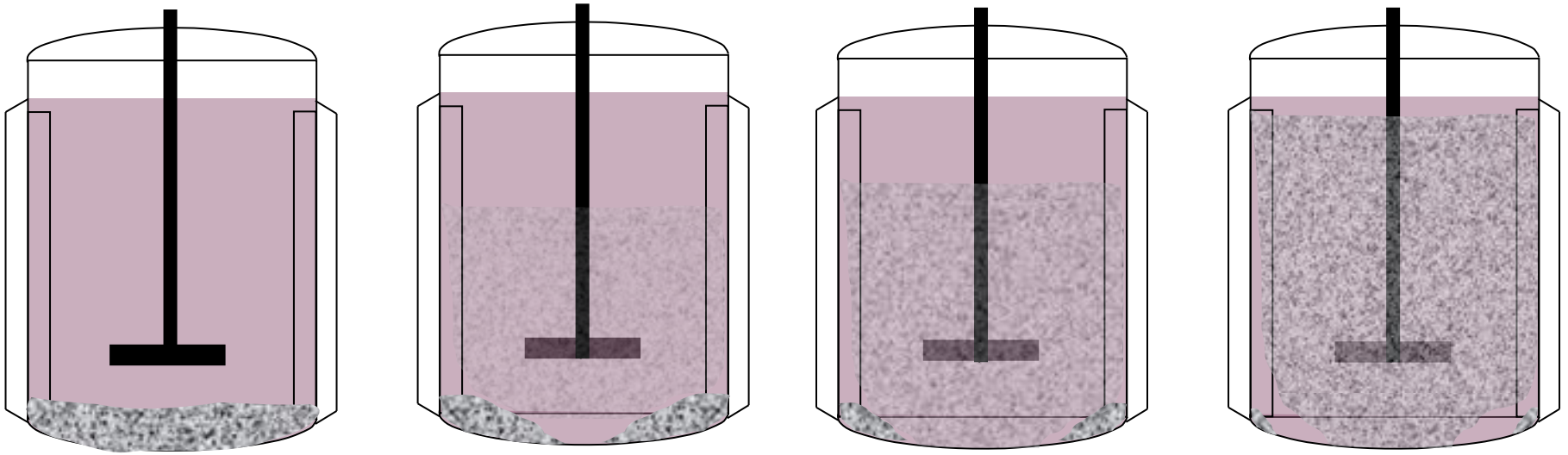
Solid Suspension (Radial flow impellers)





Solid Suspension (Axial flow impellers)





Summary of experimental work for N_{CS}

References	Impeller type	Design parameter		Particle details		
		T (m)	D (m)	d_P(μm)	ρ_S(kg/m^3)	x (wt. %)
Zwietering (1958)	6-DT 2-Paddle	0.154 - 0.6	0.06 – 0.2	125-850	510-1810	0.5-20
Nienow (1968)	6-DT	0.14	0.0364 0.049 0.073	153-9000	530-1660	0.1-1.0
Chapman et al.(1983)	4, 6-PTD	1.83	0.79	80-2800	50-1900	0-3.0
	6-DT	0.56	0.14 - 0.28	80-2800	50-1900	0-3.0
Barresi & Baldi (1987)	A310, 4, 6-PBTD, 6-DT	0.39	0.33T	100-500	2600-2670	0.5- 5.19
Raghav Rao et al. (1988)	6-PTD	1.5	0.1-0.5	100-2000	1520	0.7-50
	6-PTU	0.57, 1	0.19	100-2000	1520	0.7-50
	6-DT	0.3, 0.4	0.19 0.285	100-2000	1520	0.7-50
Ibrahim & Nienow (1996)	HE3, A310, RT, 6PTD	0.29	0.10 - 0.12	500-710	2950-8450	0.5
Armenante & Nagamine (1998)	6-DT, 6-FBT, 6-PTD, HE-3	0.188 - 0.584	0.0635 -0.203	60-300	2500	0.5
Bujalski et al. (1999)	A310, A315	0.29	0.10 - 0.12	100-1000	1350-2500	0-40

Critical speed for off-bottom suspension

- No crystal should spend more than couple of seconds at the reactor bottom (visual and qualitative criterion)
- As the impeller speed is increased beyond the critical speed, the solid concentration becomes more uniform.
- **Zwietering correlation**

(Tank diameter=0.154-0.6 m, Impeller diameter=0.06-0.2 m)

$$N_{CS} = \frac{s\upsilon^{0.1} dp^{0.2} \left(g\Delta\rho/\rho_L\right)^{0.45} X^{0.13}}{D^{0.85}}$$

Rewatkar and Joshi correlation

$$N_{CS} = 1.15 \frac{V_{S\infty}^{0.28} X^{0.1}}{D^{0.85}} (T/D)^{0.8}$$

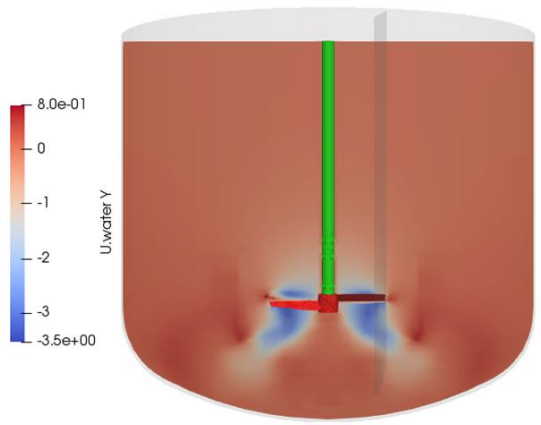
Solid suspension correlations: Limitations

- Very specific to impeller shape, dimensions, relative sizing of impeller and vessel
- Spherical shape particles
- Limited to laboratory or pilot scale systems, for industrial applications, extrapolation is needed
- May not be applicable to multi-impeller systems

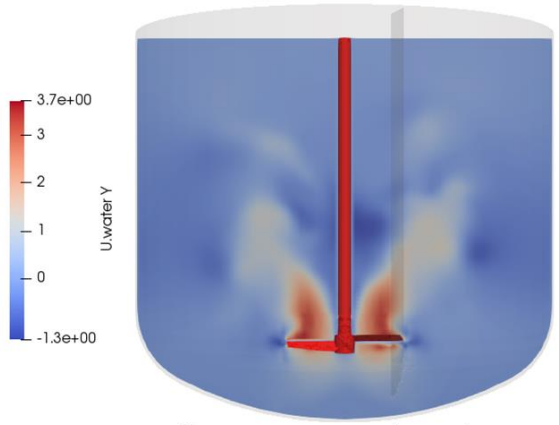
CFD – Solid suspension

Agitation: 244 rpm

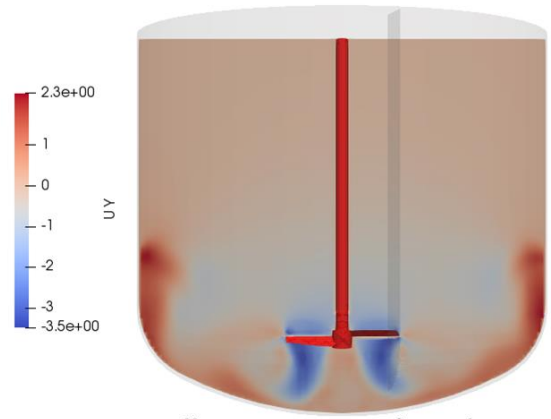
Axial velocity



Impeller at Tan Line
Downflow

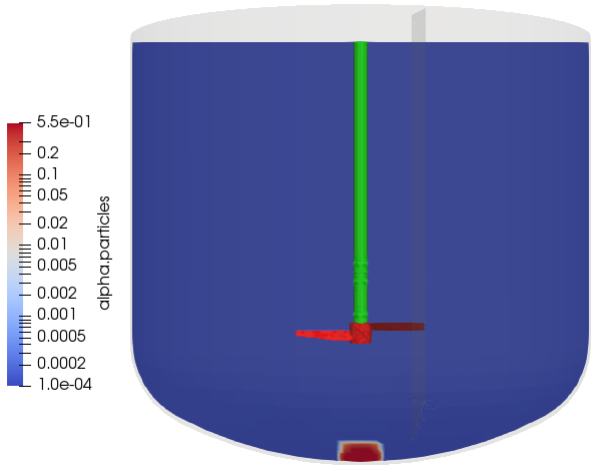


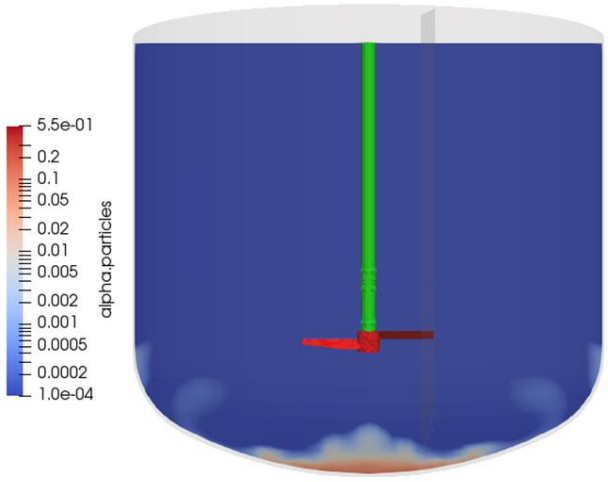
Impeller at 375 mm from bottom
Upflow



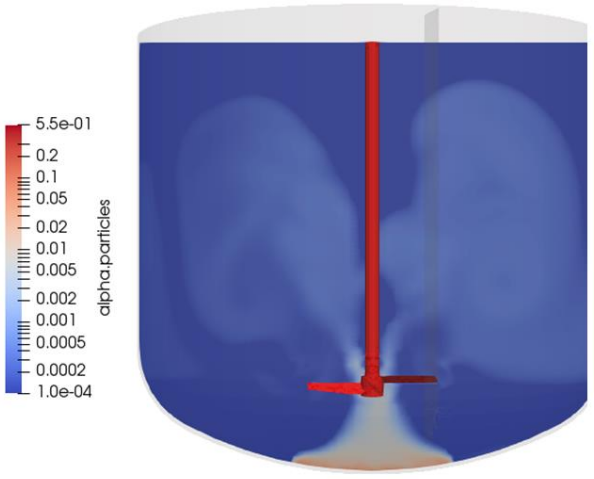
Impeller at 375 mm from bottom
Downflow

Suspension Quality

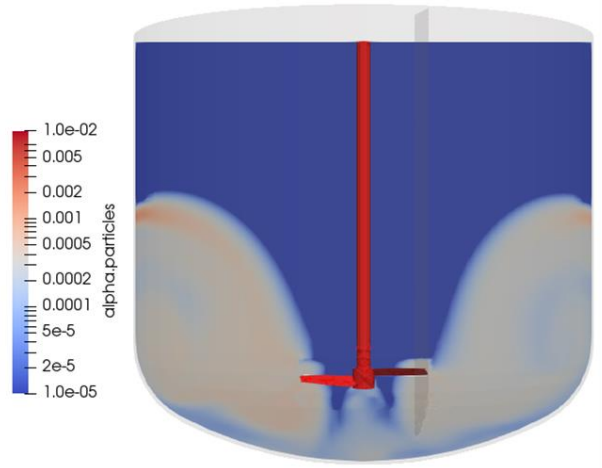




Impeller at Tan Line
Downflow



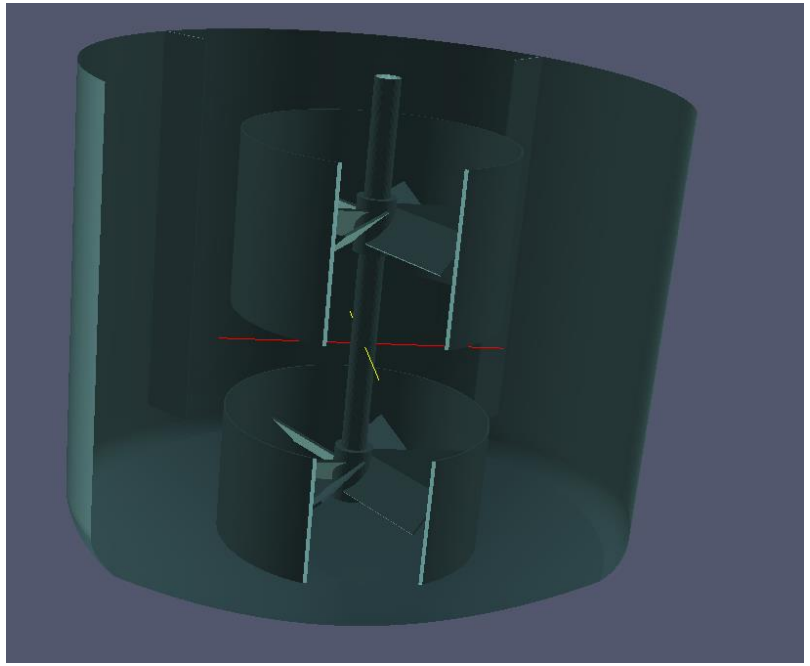
Impeller at 375 mm from bottom
Upflow

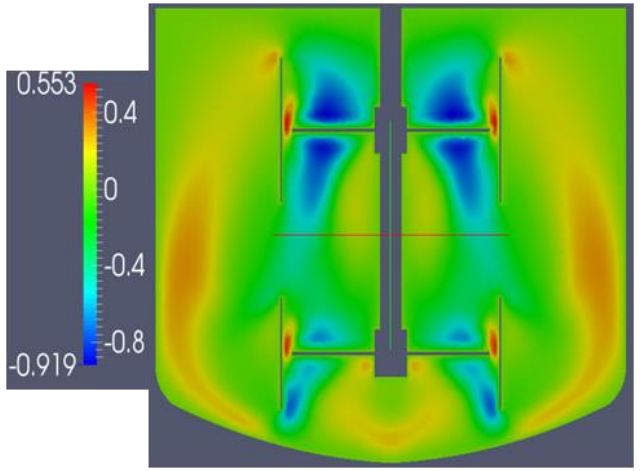


Impeller at 375 mm from bottom
Downflow

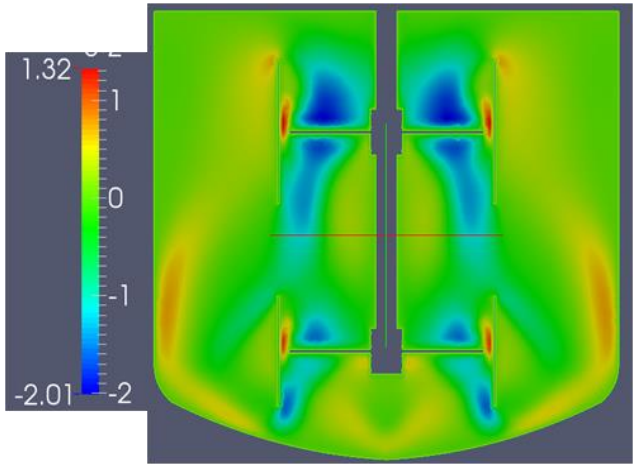
CFD - OpenFOAM

Draft Tube





45 rpm



90 rpm

Heat Transfer

- Rate of cooling depends on the overall heat transfer rate from the system
- Heat transfer area to volume ratio reduces in scale-up.
- If overall U is constant during scale-up, the cooling rate need to be maintained by changing the temperature driving force ($\Delta T = T_{process} - T_{utility}$)
- Overall U is also a function of % occupancy in the crystallizer
- Overall U should be measured based on heating/cooling experiment with same solvent or by matching fluid rheology

$$MC_P \frac{dT}{dt} = UA\left(T_{process} - T_U\right) \Rightarrow \frac{dT}{T_{process} - T_U} = \frac{UA}{MC_P} dt$$

$$\Rightarrow \ln\left(\frac{T_{process,final} - T_U}{T_{process,initial} - T_U}\right) = \frac{UA}{MC_P} t$$

Scale-up

$$Scale\ ratio = s = \frac{D_{I,1}}{D_{I,2}} = \frac{D_{T,1}}{D_{T,2}}$$ (Geometric scale-up)

$$Reynolds\ number = Re = \frac{ND_I^2\rho}{\mu}$$ (Reynolds number)

$$Power\ per\ unit\ volume = P/V = \frac{N_P\rho N^3 D_I^5}{V}$$ (Power per unit volume)

$$Tip\ speed = u_{tip} = \pi N D_I$$ (Tip speed)

Scale Up Example

- Given the product particle size distributions for a crystallization process evaluated at lab scale in figure, what is the optimal agitation speed ?
- What are the likely explanations for the other two size distributions?
- These results were with an impeller of 70 mm in diameter and process is to be scaled to a plant vessel with a 700 mm diameter. What agitation rate should be employed to maintain optimum conditions

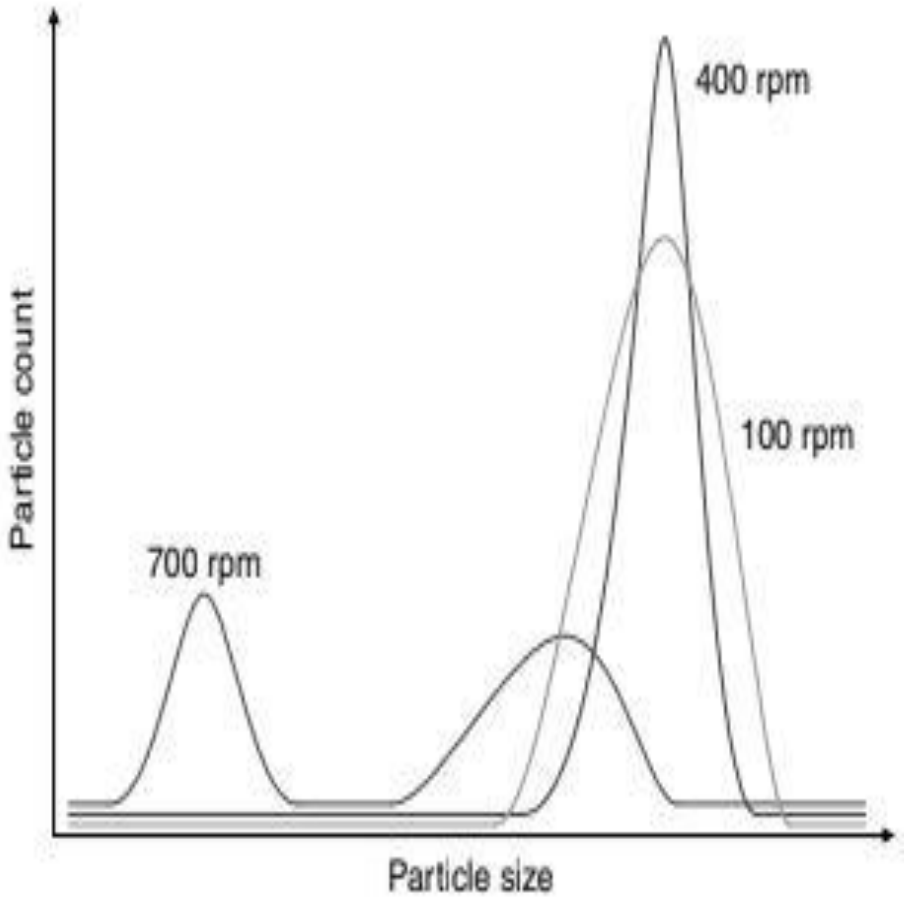


Fig a: Lab Scale Particle size distribution

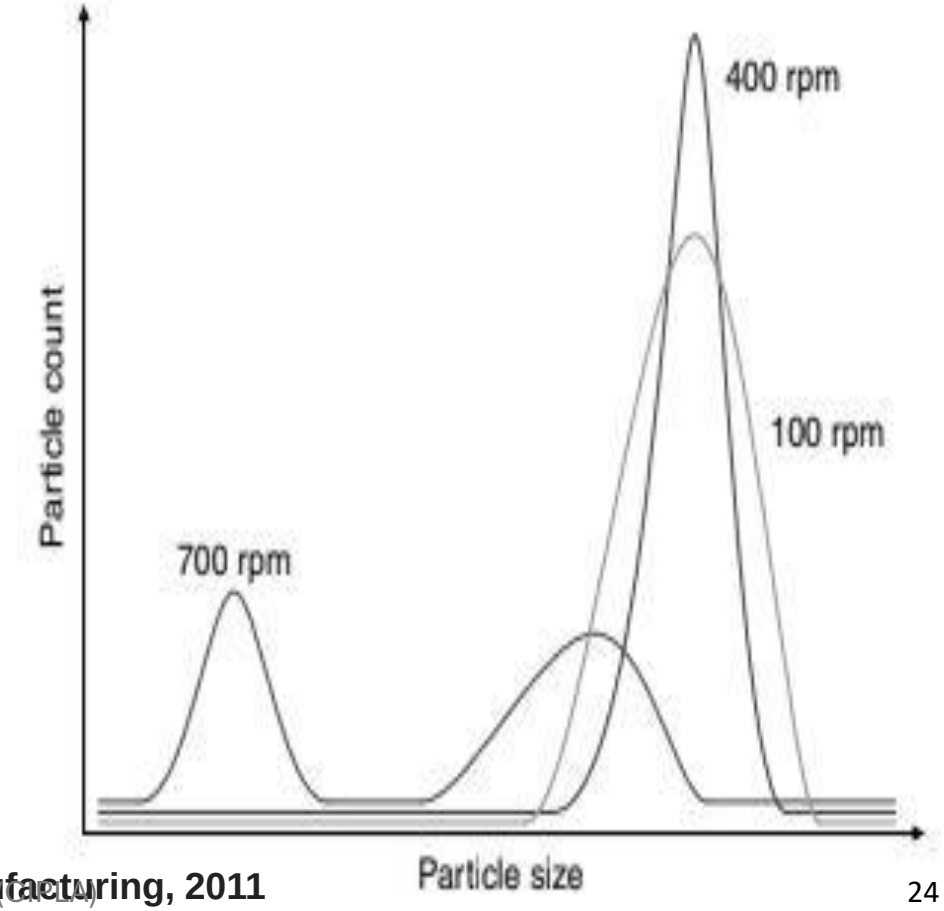
Source: chemical engineering in the pharmaceutical industry: R&D to manufacturing, 2011

Scale Up Example

The lower agitation rate, 100 rpm, did not have sufficient suspension of the particles, leading to stratification and growth dispersion, evidenced by a broader distribution. The higher agitation rate, 700 rpm, led to attrition and breakage of the particles, evidenced by a bimodal distribution. The narrowest particle size distribution was observed at 400 rpm, making that the most desirable of the three agitation rates.

$$s = \frac{H_{lab}}{H_{plant}} = \frac{T_{lab}}{T_{Plant}} = \frac{D_{lab}}{D_{Plant}} = \frac{70\ mm}{700\ mm} = 0.1$$

$$V \approx \frac{\pi}{4} T^2 H = \frac{V_{lab}}{V_{Plant}} \approx s^3$$



Source: chemical engineering in the pharmaceutical industry: R&D to manufacturing, 2011

Scale Up Example

A) Maintaining constant energy dissipation rate

$$\left(\frac{P}{V}\right)_{lab} = \left(\frac{P}{V}\right)_{Plant}$$

$$\frac{P_{op} N_{lab}^3 D_{lab}^5}{V_{lab}} = \frac{P_{op} N_{Plant}^3 D_{Plant}^5}{V_{Plant}}$$

$$N_{Plant}^3 = N_{lab}^3 . \frac{D_{lab}^5}{D_{Plant}^5} . \frac{V_{Plant}}{V_{lab}}$$

$$N_{Plant} = N_{lab} \left(s^5 . \frac{1}{s^3} \right)^{\frac{1}{3}}$$

$$N_{Plant} = N_{lab} . s^{\frac{2}{3}} = 400 \times 0.1^{\frac{2}{3}} = 86\, rpm$$

B) Maintaining constant specific flow

$$\left(\frac{Q}{V}\right)_{lab} = \left(\frac{Q}{V}\right)_{Plant}$$

$$\frac{N_Q\, N_{lab} D_{lab}^3}{V_{lab}} = \frac{N_Q\, N_{Plant} D_{Plant}^3}{V_{Plant}}$$

$$N_{Plant} = N_{lab} . \frac{D_{lab}^3}{D_{Plant}^3} . \frac{V_{Plant}}{V_{lab}}$$

$$N_{Plant} = N_{lab} \left(s^3 . \frac{1}{s^3} \right)$$

$$N_{Plant} = N_{lab} = 400\, rpm$$

Source: chemical engineering in the pharmaceutical industry: R&D to manufacturing, 2011

Scale Up Example

C) Maintaining constant tip speed

$$v_{lab} = v_{Plant}$$

$$\pi D_{lab} N_{lab} = \pi D_{Plant} N_{Plant}$$

$$N_{Plant} = N_{lab} . \frac{D_{lab}}{D_{Plant}}$$

$$N_{Plant} = N_{lab} . s = 400 \times 0.1 = 40\ rpm$$

D) Maintaining Solids Suspension

$$\frac{N_{js\ Plant}}{N_{js\ lab}} = \frac{D_{Plant}^{-0.85}}{D_{lab}^{-0.85}}$$

$$N_{js\ Plant} = N_{js\ lab} . \left(\frac{1}{s}\right)^{0-0.85}$$

$$N_{js\ Plant} = N_{js\ lab} . s^{0.85} = 400 \times 0.1^{0.85} = 56\ rpm$$

Source: chemical engineering in the pharmaceutical industry: R&D to manufacturing, 2011

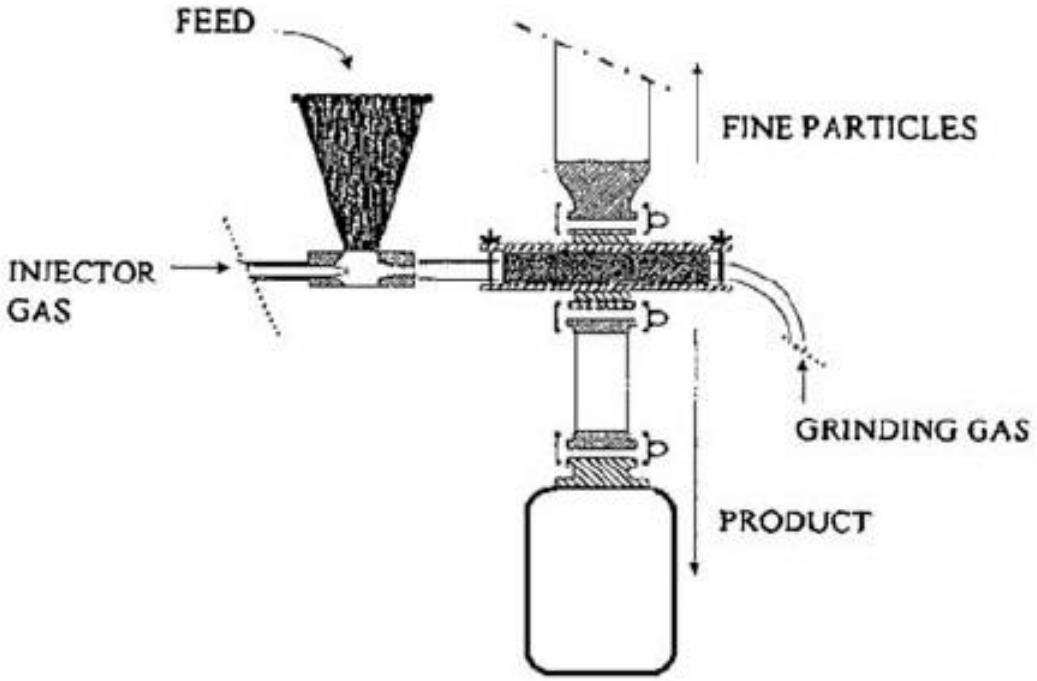
Scale Up Example

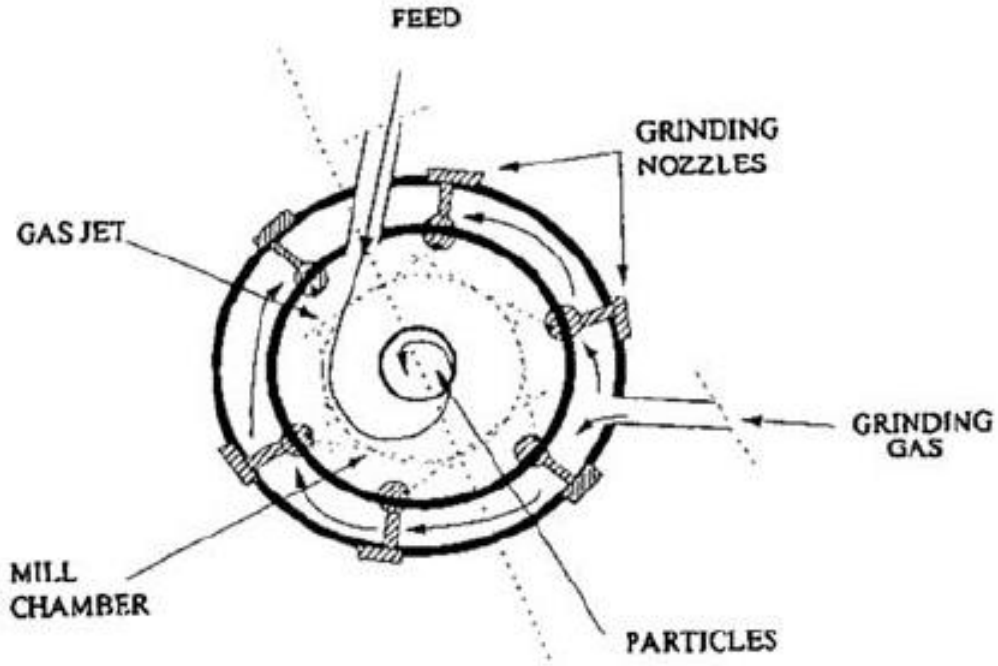
- Goal: scale-up the process and maintain crystal suspension
  - Adequate mixing
  - avoid attrition by excessive shear
- For suspension: agitation rate at least 56 rpm
- This rate may not ensure local homogeneity in the solution
- Constant P/V criterion: 86 rpm (first choice)

Effect of downstream operations

- Filtration
- Drying
- Milling

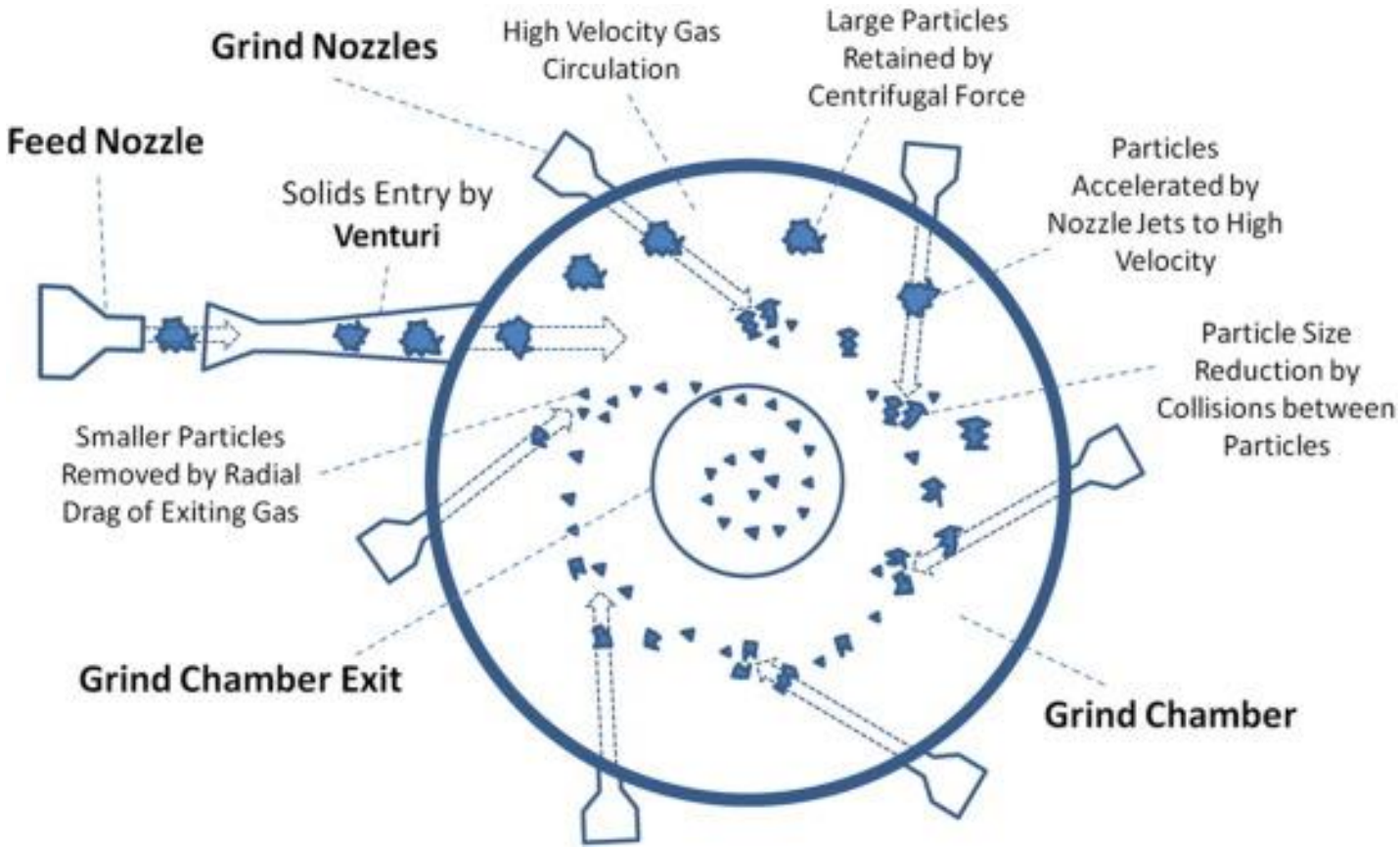
Spiral Jet Mill or Pancake Mill





Spiral Jet Mill

Spiral Jet Mill



Spiral jet mill grind chamber (plan view)

Spiral jet mill grind chamber (side view)

Jet Mill

Spiral Jet Mill

- **Milling agent** :: Air/N_2 gas/Liquid Nitrogen
- **Compressed gas** :: Grinding pressure and Venturi Pressure
- **Feed Inlet** :: Gravimetric Feeder or Volumetric Feeder
- **Feed Flow rate**

- **Spiral Jet Mill Design**

➢ **Grinding chamber size**

➢ **Number of Nozzles**

➢ **Size of Nozzles**

➢ **Angle of Nozzles**

Spiral Jet Mill

- **Milling agent** :: Air/N_2 gas/Liquid Nitrogen
- **Compressed gas** :: Grinding pressure and Venturi Pressure
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- **Feed Flow rate**

To meet target PSD

- **Spiral Jet Mill Design**
  - **Grinding chamber size**
  - **Number of Nozzles**
  - **Size of Nozzles**
  - **Angle of Nozzles**

Prime features affecting Grinding Ratio

- Geometrical parameters which concern the mill design such as diameter of the grinding chamber, shape, number and angle of grinding nozzles.

- Operational conditions e.g., solid feed rate, grinding pressure, injector pressure and, of course, material to grind.

Type of Milling Medium

The energy in the jet is controlled by the speed of sound, which is inversely proportional to the square root of the molecular weight of the gas used

Most commonly used milling medium is "AIR"

Minimum Ignition Energy (MIE) is the lowest energy required to ignite the flammable material in air or oxygen. **(N_2 gas)**

Cryo Milling (liquid Nitrogen)

Spiral Jet Mill

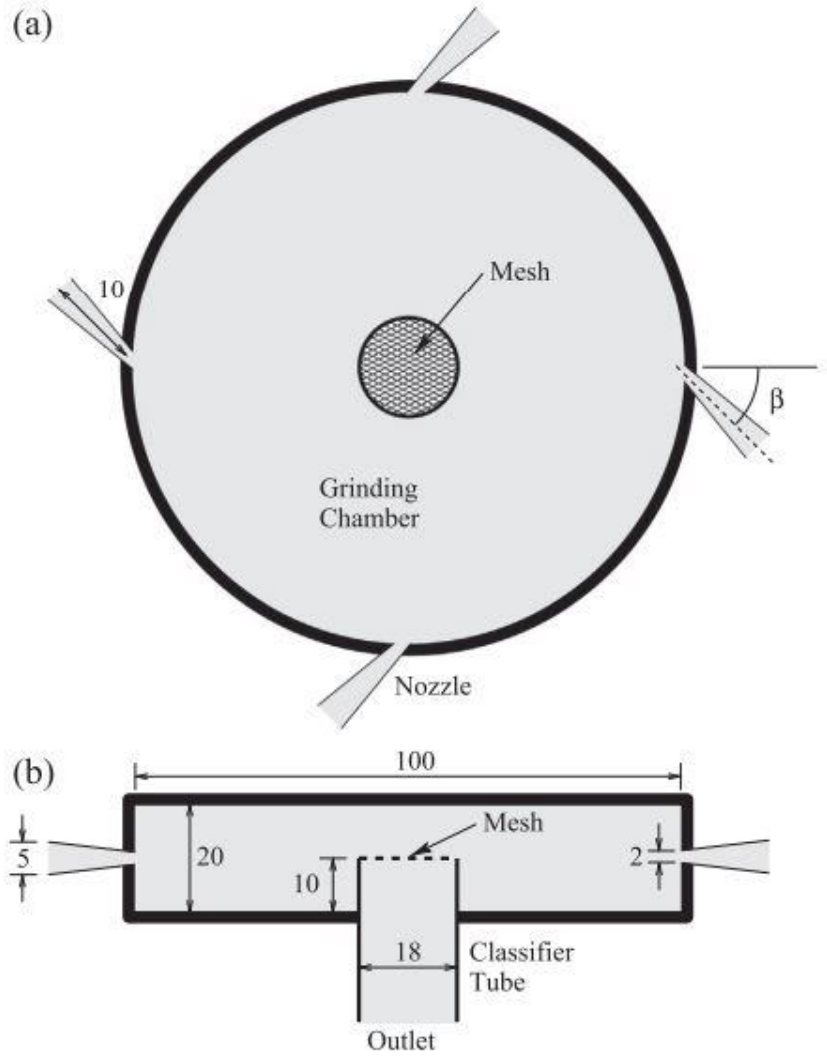
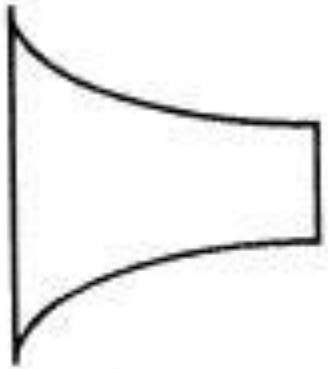


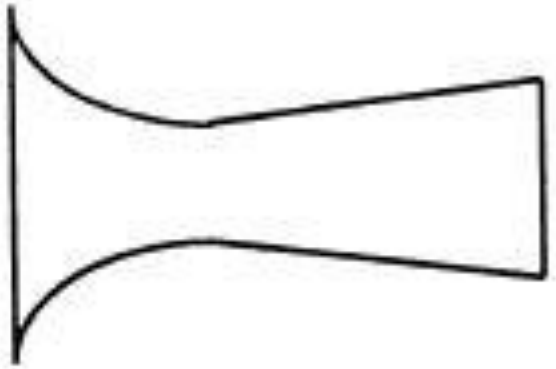
Fig. 1. Schematic view showing the geometry of the air jet mill used in the study. Air enters from the 4 nozzles and exits from the central classifier tube. Dimensions in mm are shown, $\beta = 45°$. (a) Top view. (b) Side view.

Nozzle



1

Abrupt nozzle



2

Laval shaped nozzle

Abrupt Nozzle

- The most common one is the abrupt type which provides sonic velocity at the throat.

- The exit pressure is about 50% of the initial fluid pressure.

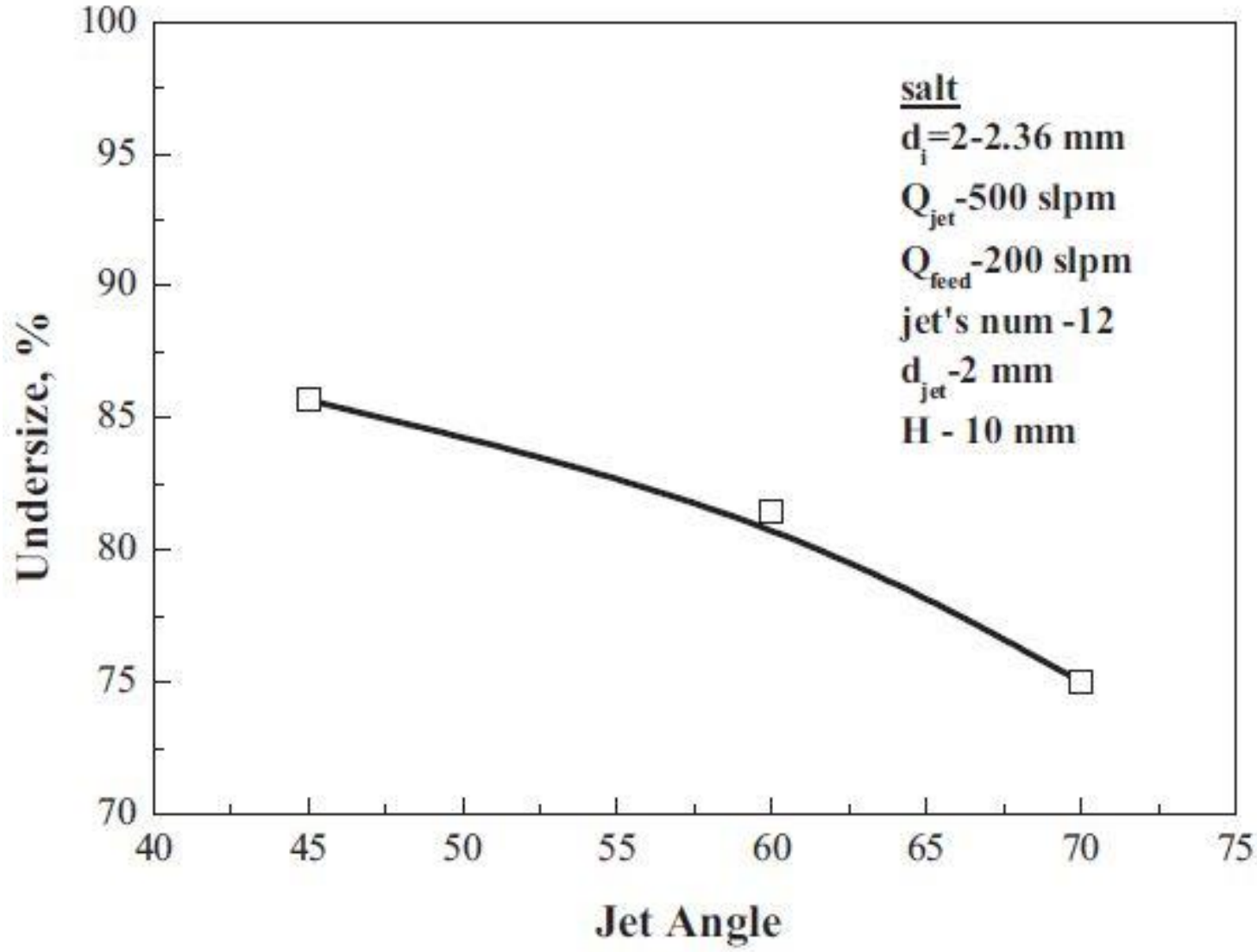
- The final expansion takes place beyond the nozzle throat, creating a suction which entraps particles from the mill, thereby circulating gas and promoting particle collision.

Laval Shaped Nozzle

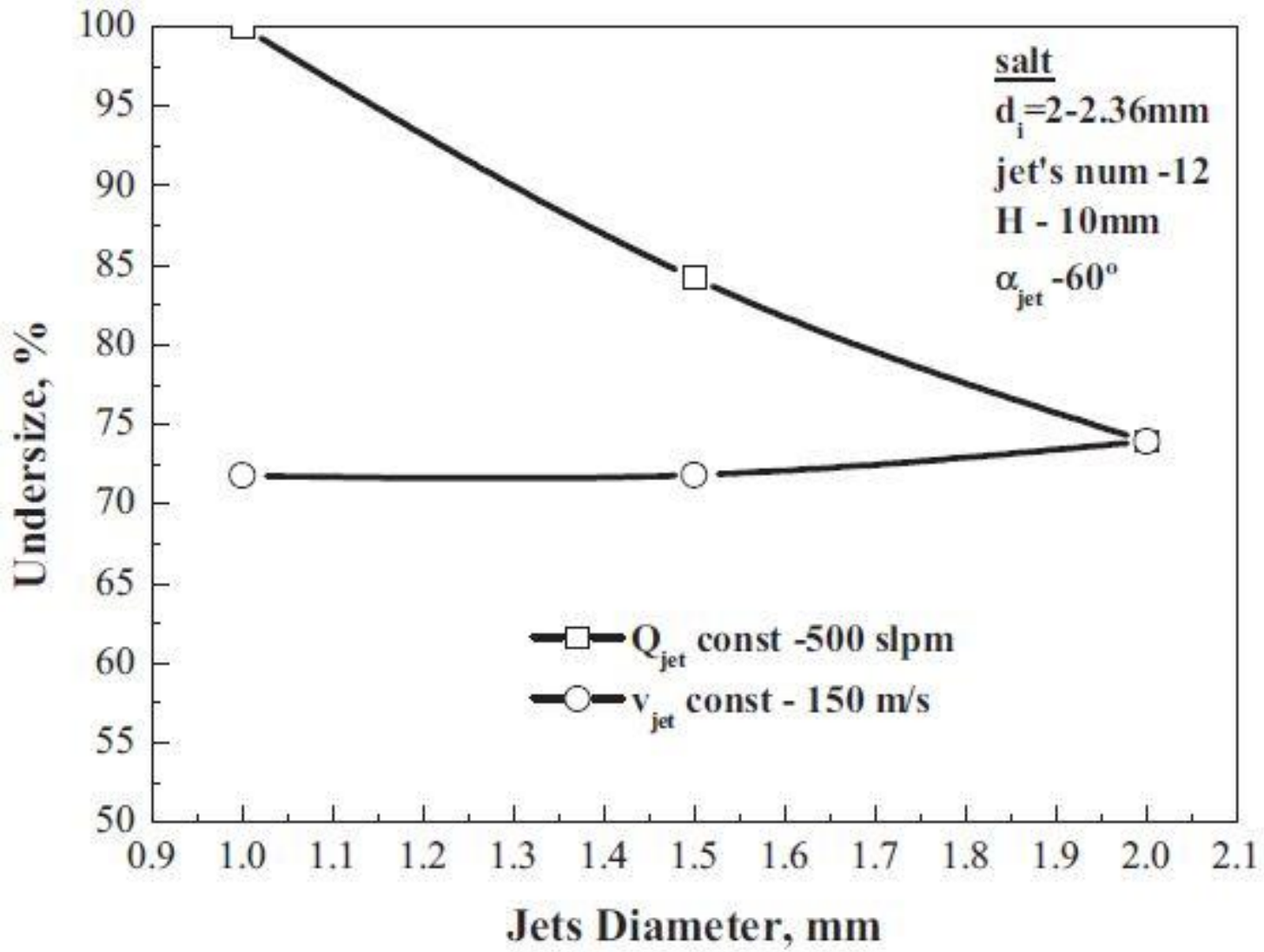
- The gas expands in the divergent section, leading to supersonic velocities which increase the jet's action.

- The velocity of the circulating gas stream, thereby allowing greater production rate and fineness of the grind.

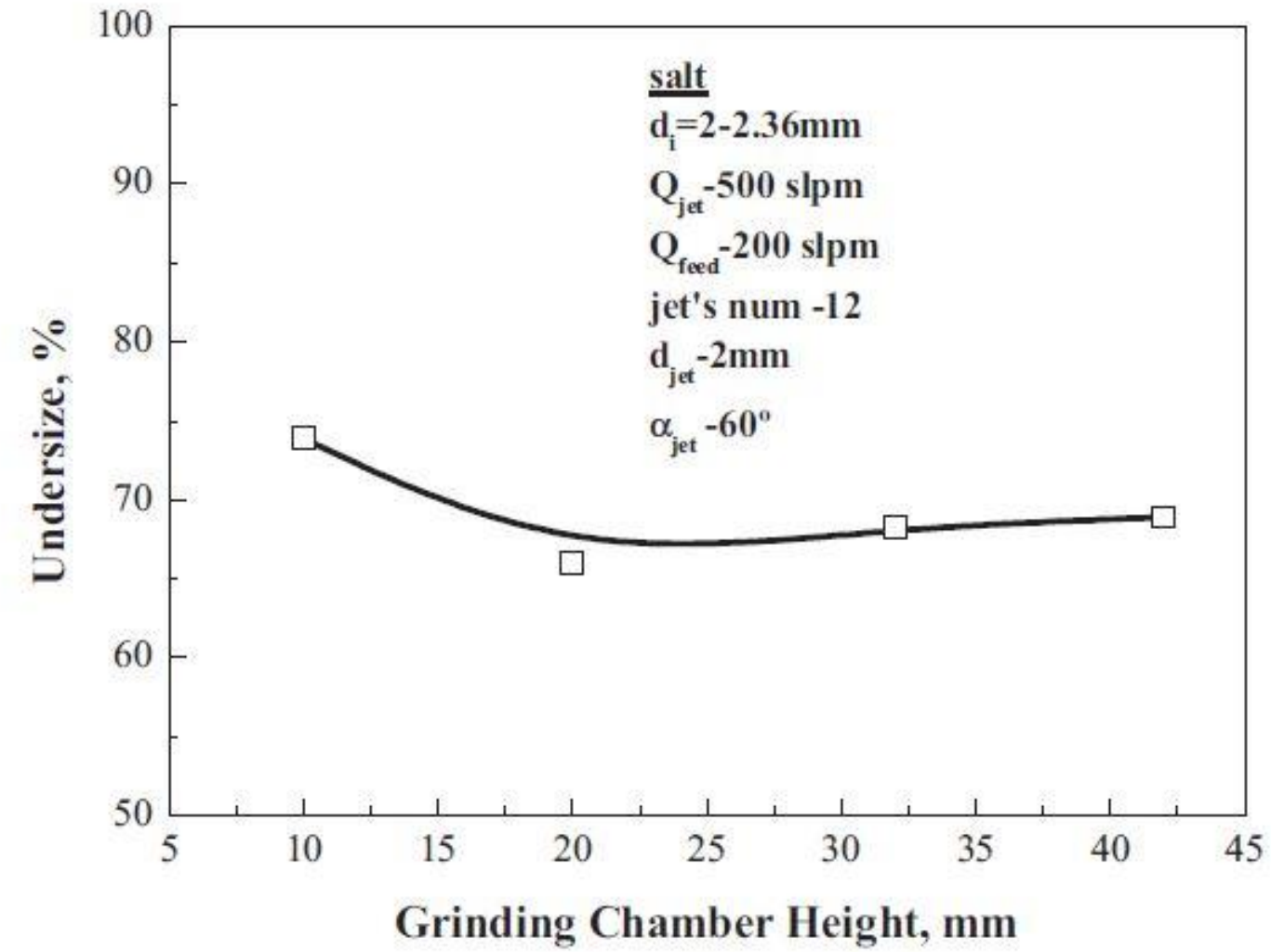
Effect of Nozzle Angle



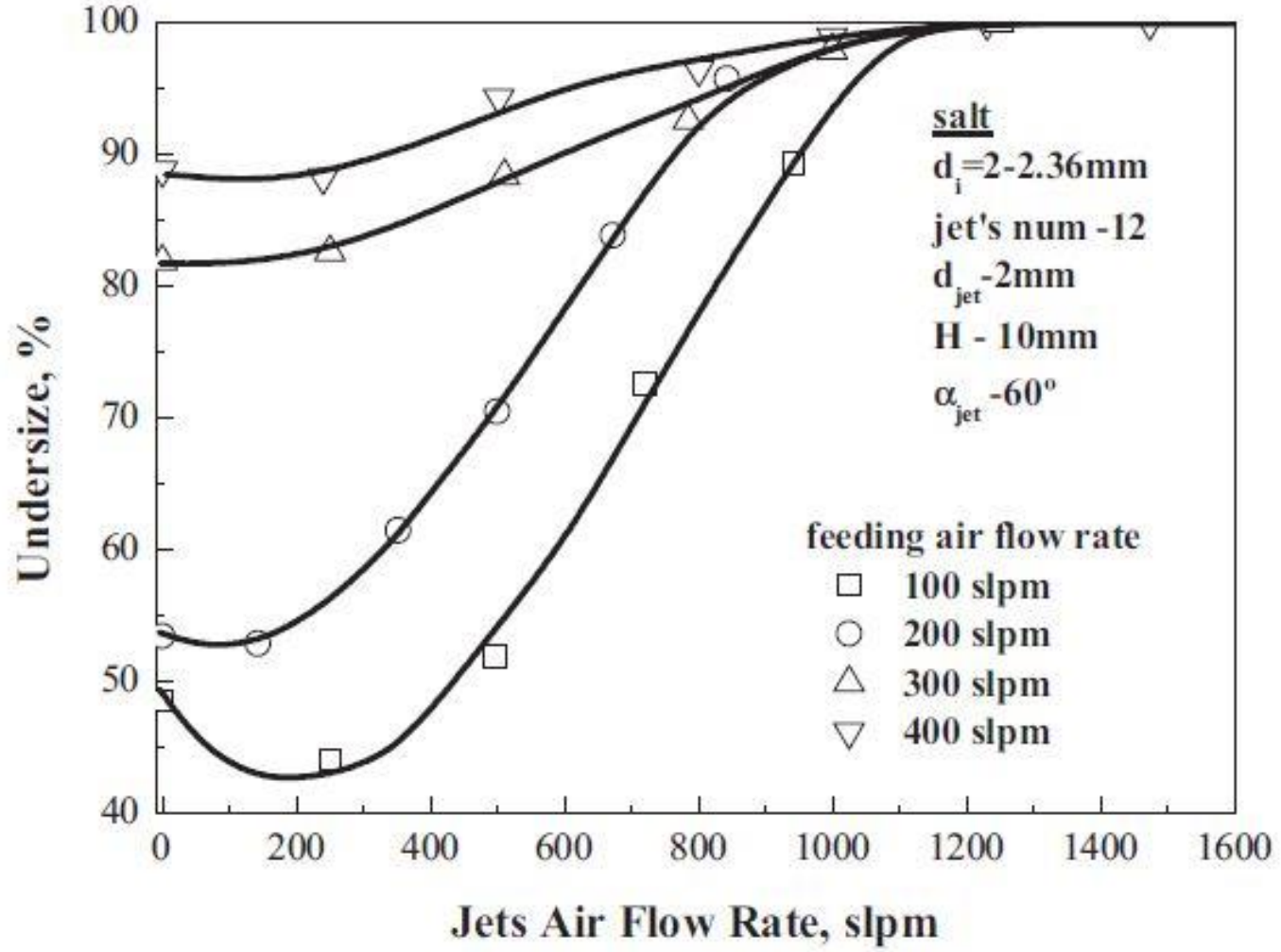
Effect of Nozzle Diameter



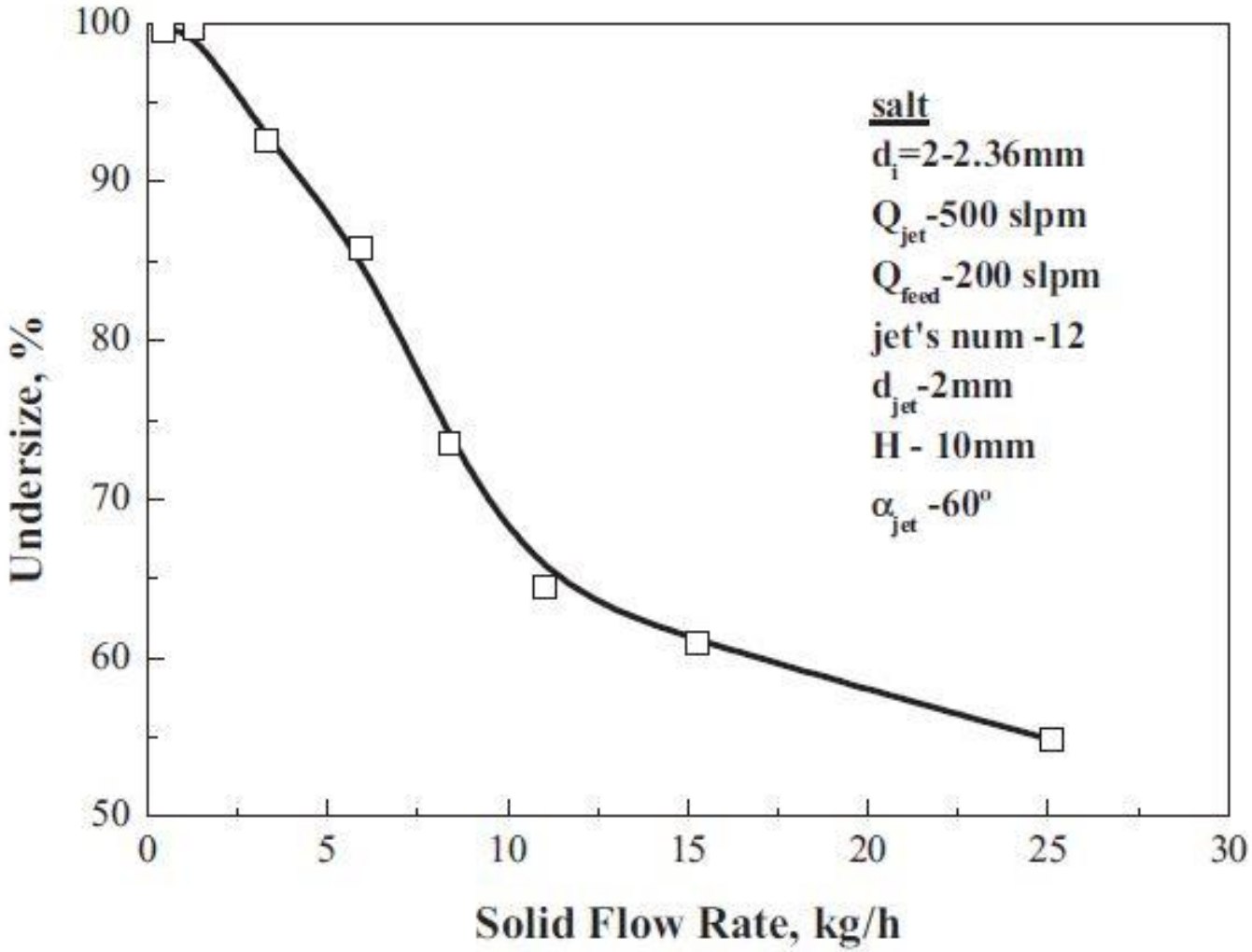
Effect of grinding chamber height



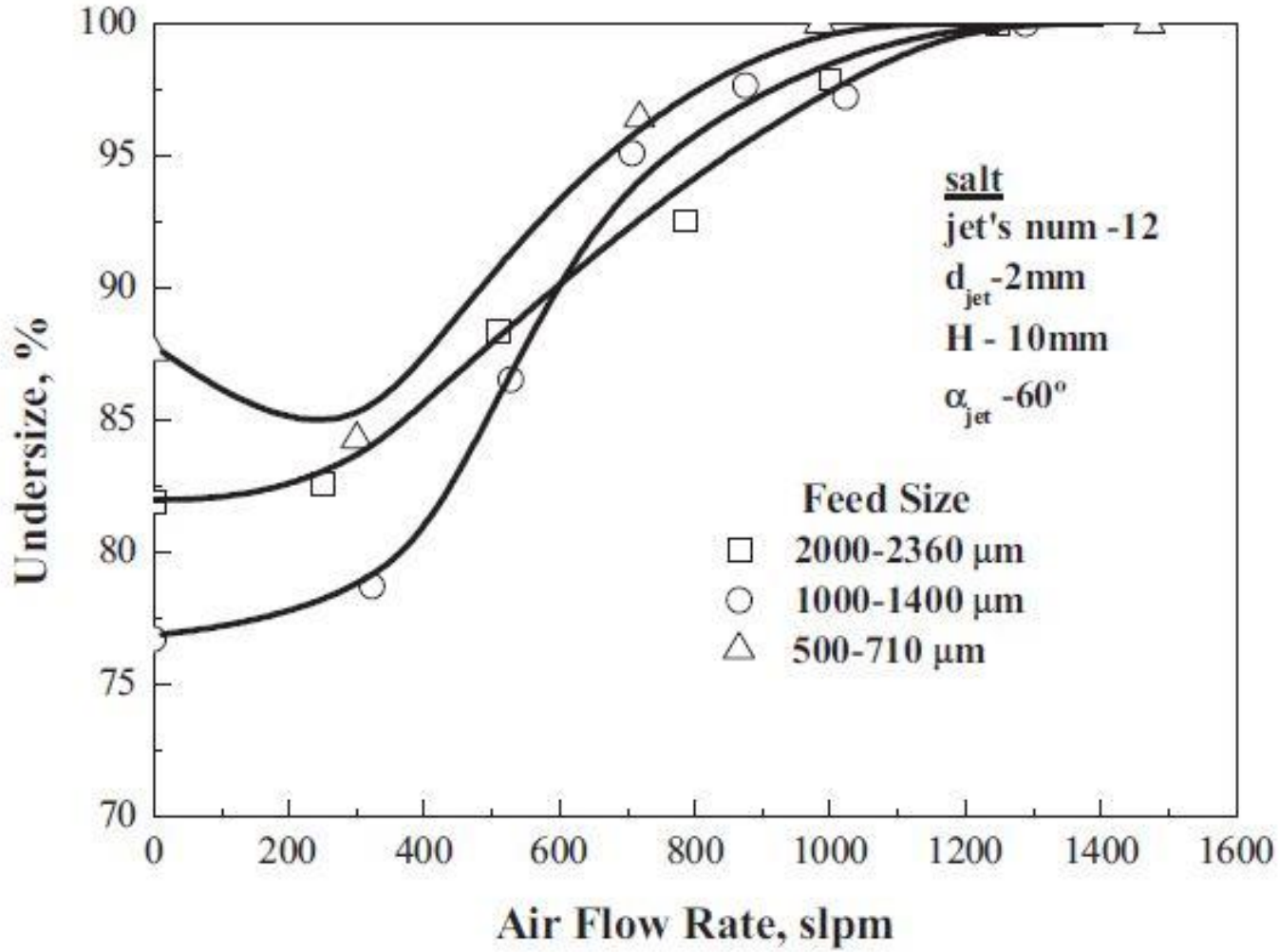
Jet Flow Rate



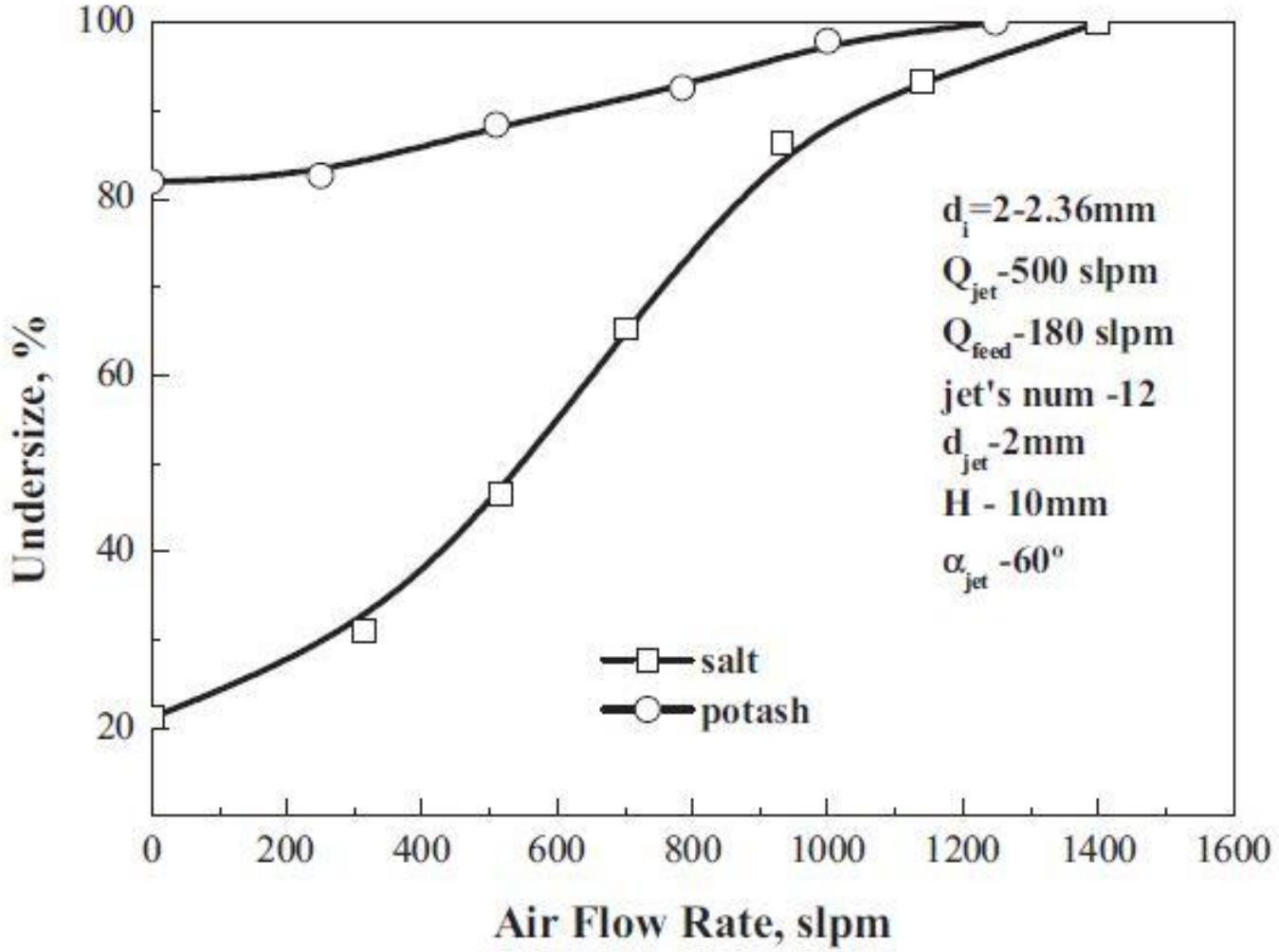
Effect of Feed Rate



Effect of Feed Input Size



Effect of Feed Type



Energy Input

- Design parameters based on minimization of the energy supplied for grinding per unit mass of the product for a specified extent of size reduction.
- The energy per unit mass of material being ground is given by

$$E_W = \mathrm{QP/m}$$

- **P_g is the pressure at the grinding nozzle**
- **Q is the volumetric flow rate of air at the grinding nozzle pressure**
- **m Product mass flux**

Jet Mill Design

Three Parameters must be taken into account

- **The volumetric flow rate *V***
- **The solid feed rate *Q***
- **Diameter of Mill Chamber D**

$$V_n \propto D^2 \qquad Q \propto V_n^{1.4 \pm 0.1} \qquad Q \propto D^{2.8 \pm 0.2}$$

Design and Scale-Up

Objective: To achieve targeted particle size distribution

$D_{50,\ milled}$: Function of [Input feed size, Mill Energy, Residence time]

$$D_{50,\ milled} = K\ (D_{50,\ unmilled})^{a}\ E^{b}\ T^{c}$$

K, a, b and c are constants for a particular system

Conclusion

- Effect of hydrodynamics on final crystal properties is very complex
- Understanding of hydrodynamics can help in reliable scale-up of crystallization operation
- Crystal suspension, heat transfer and shear are critical for crystallization
- Advanced tools such as computational fluid dynamics gives detailed insight about the hydrodynamics in the system and help in optimization of process parameters

Reference Material

- Achyut Pakhare, Channamallikarjun Mathpati, Vishwanath H. Dalvi, Jyeshtharaj Joshi, Raosaheb Patil and Ekambara Kalekudithi, “Effect of crystallizer design and operational parameters on the batch crystallization of ibuprofen I: experimental”, INDIAN CHEMICAL ENGINEER, https://doi.org/10.1080/00194506.2020.1818638

Thank you