Ultrasound assisted Crystallization: A novel way for performance enhancement

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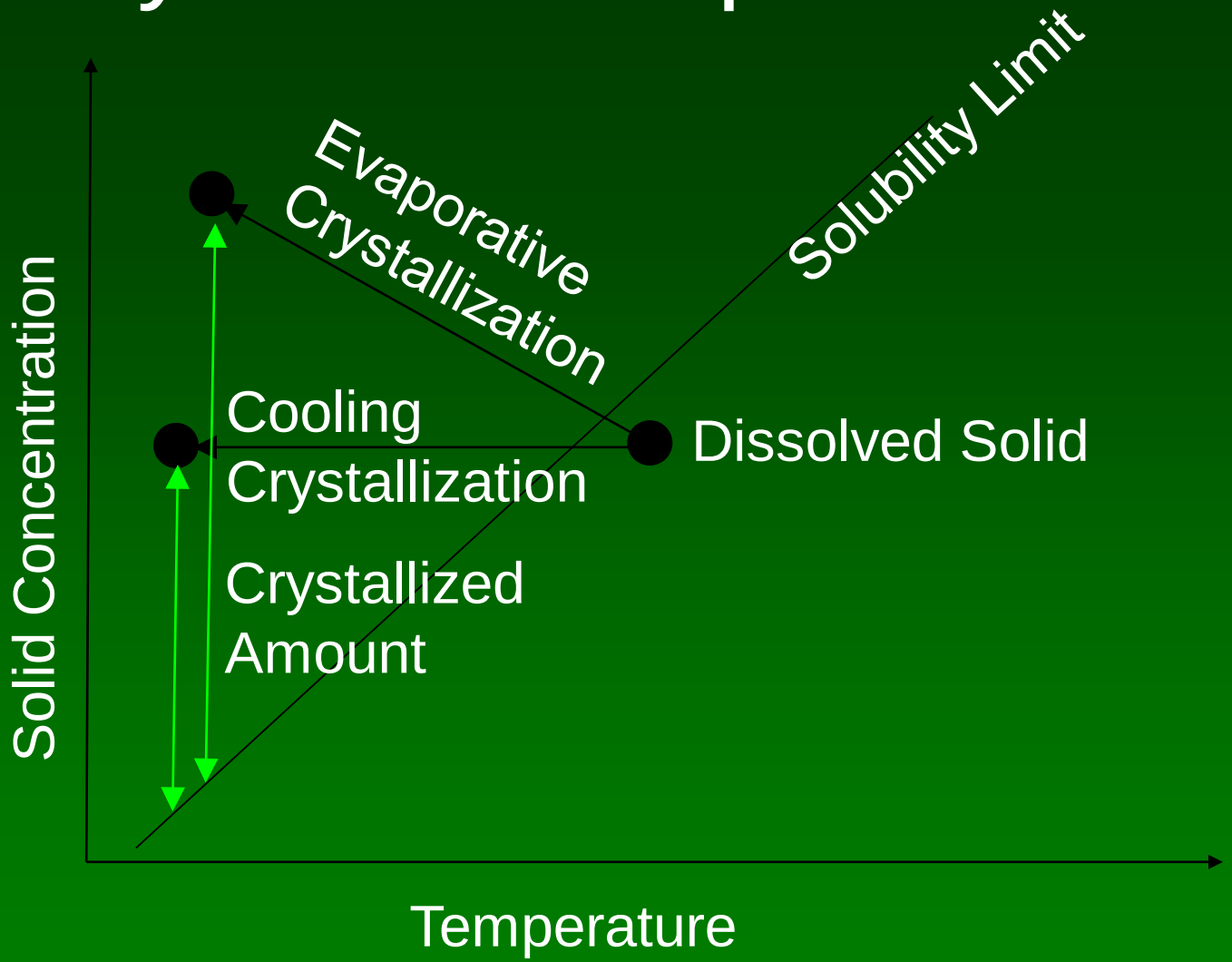
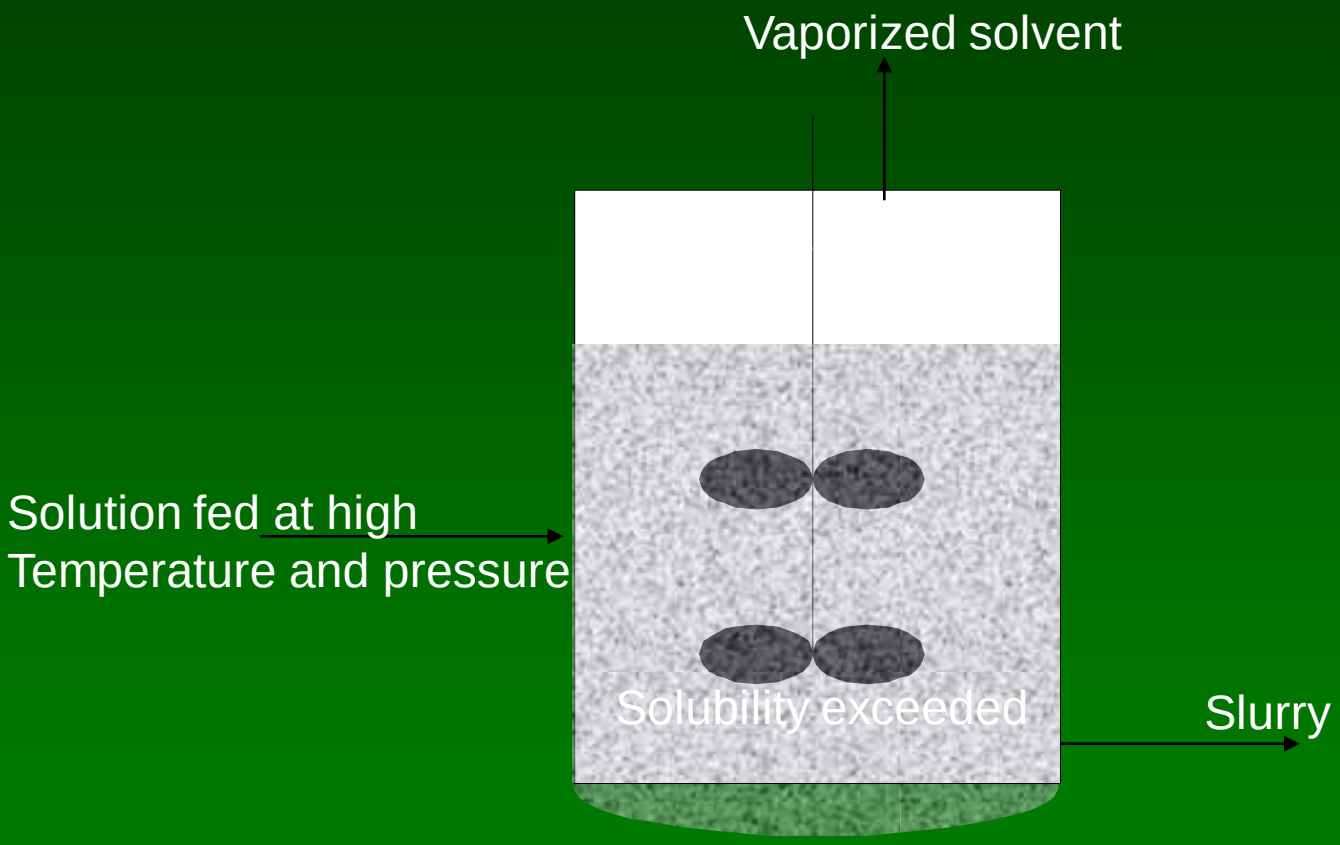
Crystallization processes



Antisolvent Crystallization is also an option

Crystallizer Operation



Fundamental Issues

- Solid suspension and agitation mechanism design
- Near the walls solid particles can accumulate
- Uneven Vaporization of solvent/Cooling/Heat Transfer
- Particle Size Distribution

The Need for Crystallization Control

- Almost every chemical process that produces a solid product involves at least one crystallization step, either for intermediate separation, final product purification, or for the removal of key impurities.
- Products are made to increasingly stringent physical specifications.
- Crystallization processes can be difficult to control *per se.*
- Control of the nucleation event is often difficult but is key to process control.
- Some products such as fats, triglycerides, oligomers, proteins, oligonucleotides, newer complex drug compounds are extremely hard to nucleate and can have extreme habit.

Sonocrystallization – what is it?

- The application of high-intensity (100 W/L), low-frequency (20 – 60 kHz) ultrasound to promote and control crystallization.
- The main effect of ultrasound is to promote nucleation via transient cavitation.

Sonocrystallization Origins

- The first application of ultrasound to crystallization in 1927 predates by decades any serious application to chemistry[1].
- There is a considerable literature from the former Soviet Union in the 1950s to the 1970s, albeit dealing with small-scale applications[2].

1. Richards, W. T.; Loomis, A. I. *J. Am. Chem. Soc.* 49 3086 (1927).
2. Kapustin, A. P. 'The Effects of Ultrasound on the Kinetics of Crystallisation'. USS Academy of Sciences Press. Engl. Trans. Consultants Bureau, New York, 1963; Martynovskaya, N. V. *Akust. Ul'trazvuk. Tekh.* 1970 *(6)*, 14; Reshetnyak, I. I. *Akust. Zh.* 21 99 (1975); Khamskii, E.V.; Crystallization from Solutions. Consultants Bureau, New York, 1969.

Ultrasonic Processing

Power ultrasound is already proven to have significant effects on the rate of various processes such as:

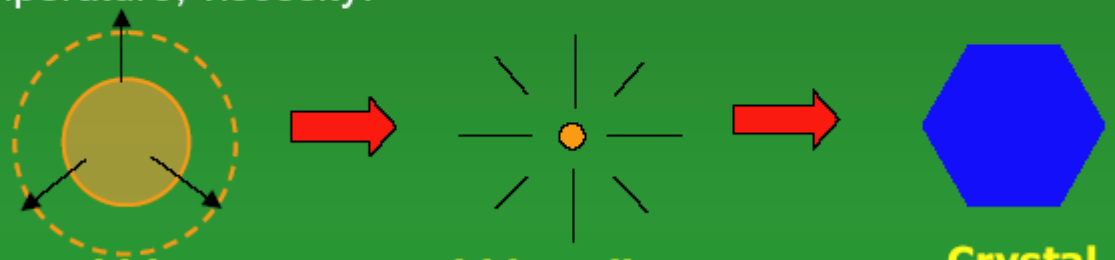
Mixing and Homogenisation
Reaction Rate Enhancement
Emulsification
High Shear
Decontamination
Solid / Liquid Separation
Biological Cell Disruption
Anaerobic digestion (environment)
Secondary metabolism rate increase
Size Reduction

Crystallization
Hydrogenation
Filtration
Extraction
Degassing, Defoaming
Wax Dispersion
De-agglomeration
Particle Disruption
Sieving

But what about scale-up?

Key Principles of Cavitation

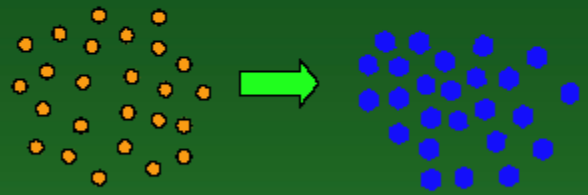
- Application of ultrasound to a liquid produces Cavitation (microscopic gas/vapour bubbles) caused by successive compression and rarefaction (just a few acoustic cycles).
- Transient cavitation bubble collapse produces regions of extreme excitation, temperature (5000K) and pressure (~10^5 bar) to create surface and energy for nuclei to form - but why?
  - Local temperature increase effects?
  - Pressure changes leads to rapid local cooling rates of 10^7-10^{10} $K.s^{-1}$?
  - Concomitant shockwaves?
  - Overcome energy barriers to nucleation?
- Intensity of cavitation depends on factors such as frequency, power, temperature, viscosity.



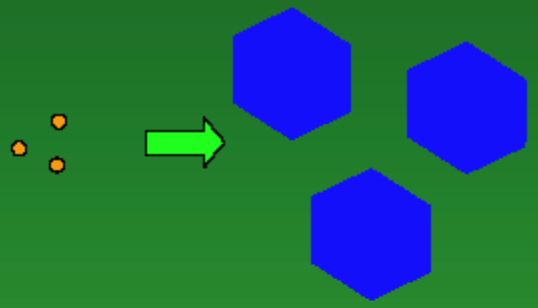
Control of Crystal Size

Very General Rules on the Effects of Cavitation

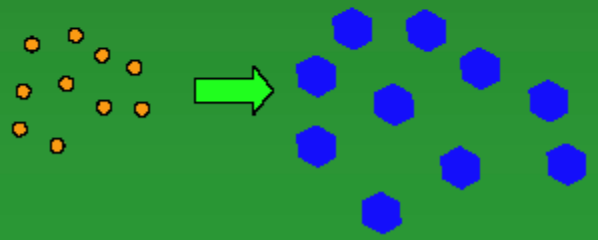
Continuous insonation produces many nuclei resulting in small crystals



Using insonation to only initiate nucleation allows larger crystals to grow



Pulsed insonation gives a combination effect



Why use Sonocrystallization?

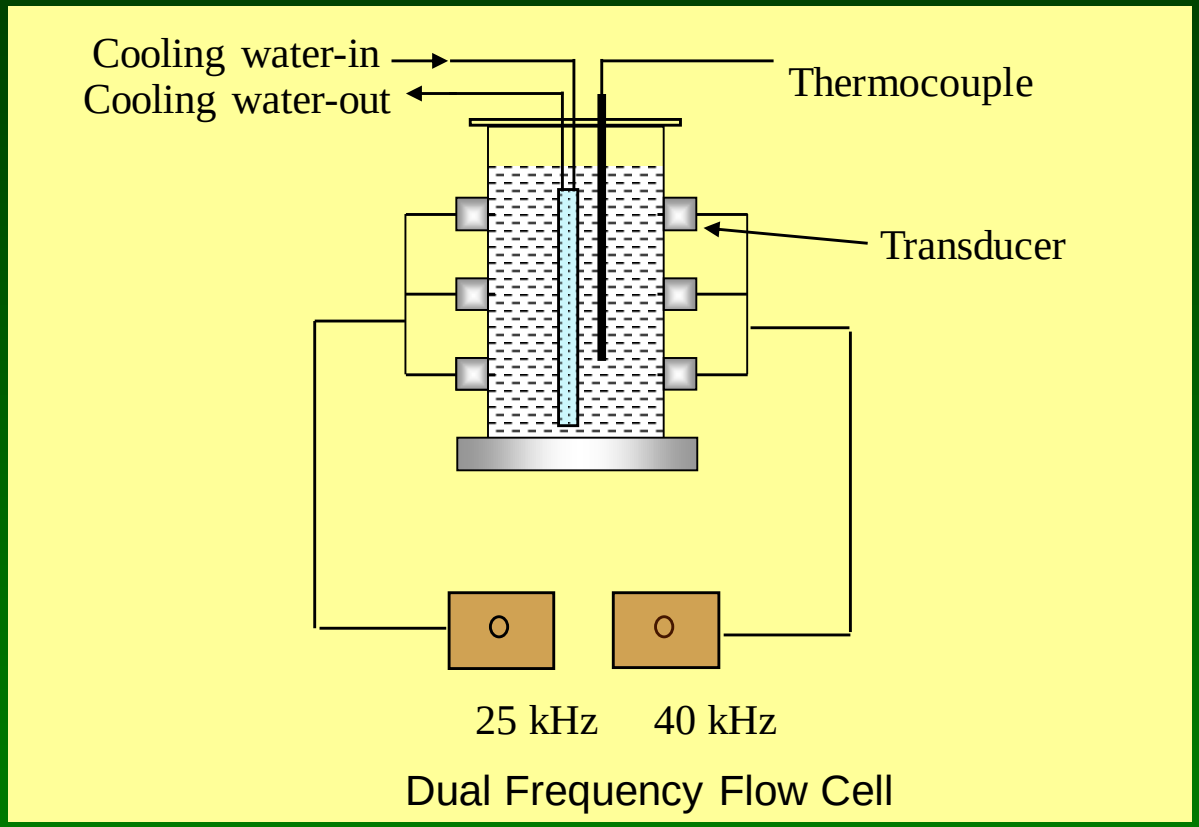
- The use of ultrasound provides a non-invasive way of improving crystal properties and process control
- Non-invasive means no added chemicals or additional mechanical treatment – maintain a sterile closed loop in seeded processes
- By controlling the nucleation event and therefore the crystal size and crystal size distribution, yield, purity, habit and product handling (including filtration) may be improved
- Avoidance of encrustation
- Manufacture better quality products and improved productivity

Application of Ultrasound – R&D

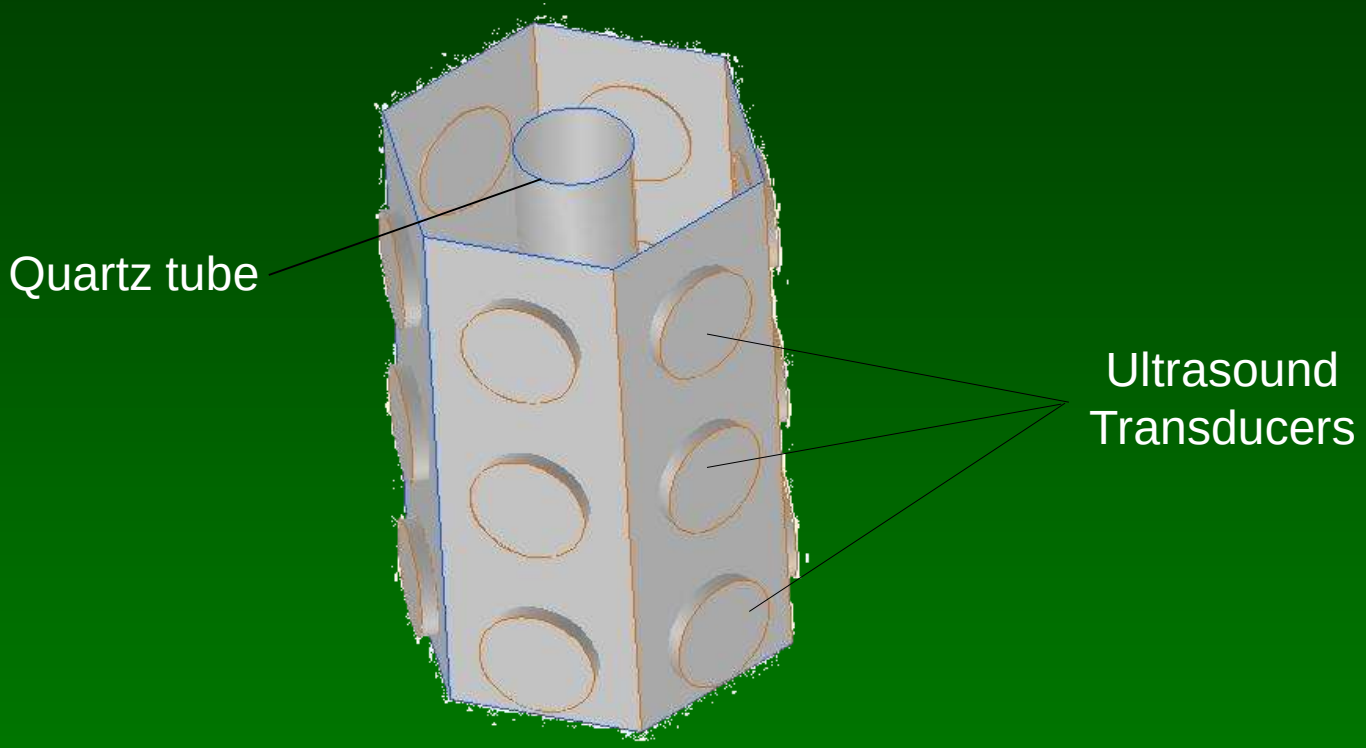
Ultrasonic Probe / Horn

Small scale (100 mL) Sonocrystallizer

- 100 mL jacketed vessel with external transducer
- Fully automated temperature control, feeds and stirring
- Measurement of temperature, turbidity, pH etc
- Integration of Lasentec® FBRM
- Modify to a flow-cell with external transducer



Rectangular flow cell with opposite faces housing Multiple frequency multiple transducers

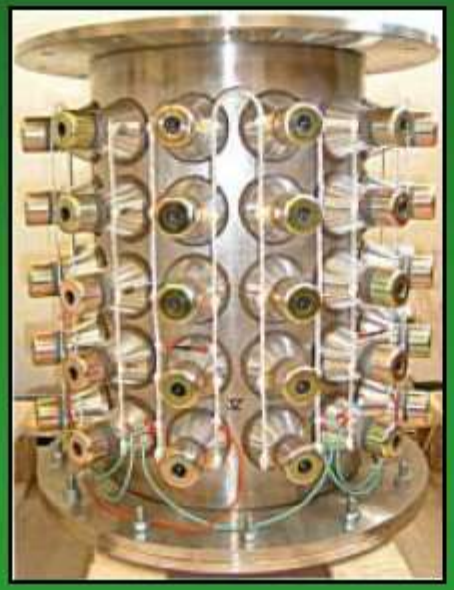


- Hexagonal Reactor with 10 cm sides
- Quartz tube for photolytic studies
- Transducers attached to the side of tank for sonication

Scale-Out Philosophy

Generator module

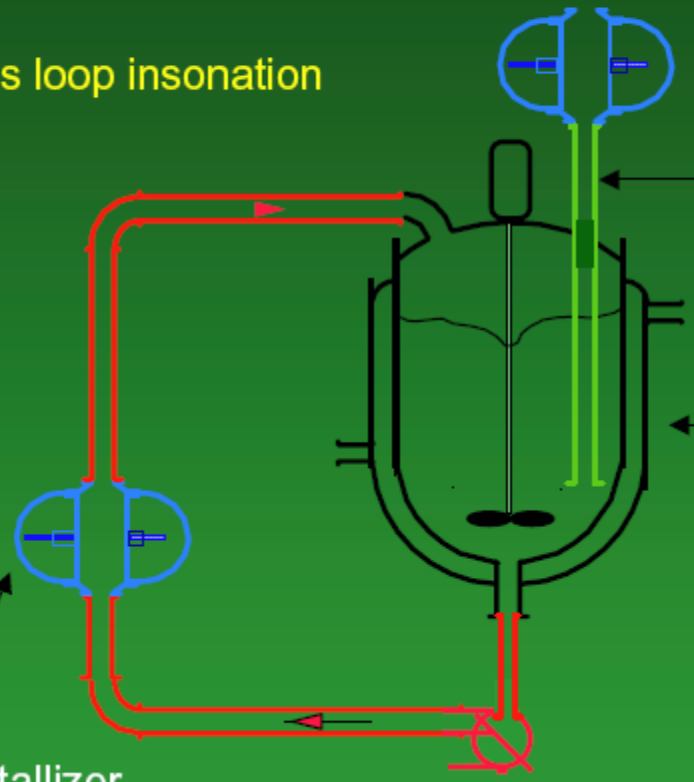
37 litre cell module
5 rows, each with 12 transducers



n x modules
stacked to give desired residence time

Sonocrystallization at Scale

Mode 2 :
Continuous loop insonation



Mode 1:
Batch insonation (*in situ* seed generation)
Nucleation aliquot raised into insonator by vacuum or pressure

Existing crystallizer typically up to 4,500 litres

Sonocrystallizer

Benefits of Sonocrystallization

The controlled delivery of power ultrasound facilitates:

- Nucleation of troublesome systems, narrow the metastable zone and make nucleation predictable
- Crystallization without using external seeds in difficult-to-nucleate systems
- Formation of the desired polymorph
- Increased productivity - from pharma to bulk inorganic materials
- Improved crystal purity and physical properties
- Removal of secondary unit operations (milling etc)
- Generation of new intellectual property

Case Study 1

‘Sonocrystallization’ of Reconstituted lactose solutions in presence of ‘Anti-solvent’

Sonocrystallization set-up

Specifications of ultrasound bath Assembly

Make:	Supersonics
Frequency:	22KHz
Rated output power:	120W
Dimensions of Bath:	15 cm× 15 cm × 14 cm

Surface area of ultrasound : 225 cm^2

irradiated face

Parameters investigated

Lactose Recovery (carried out at RT, 30 °C)

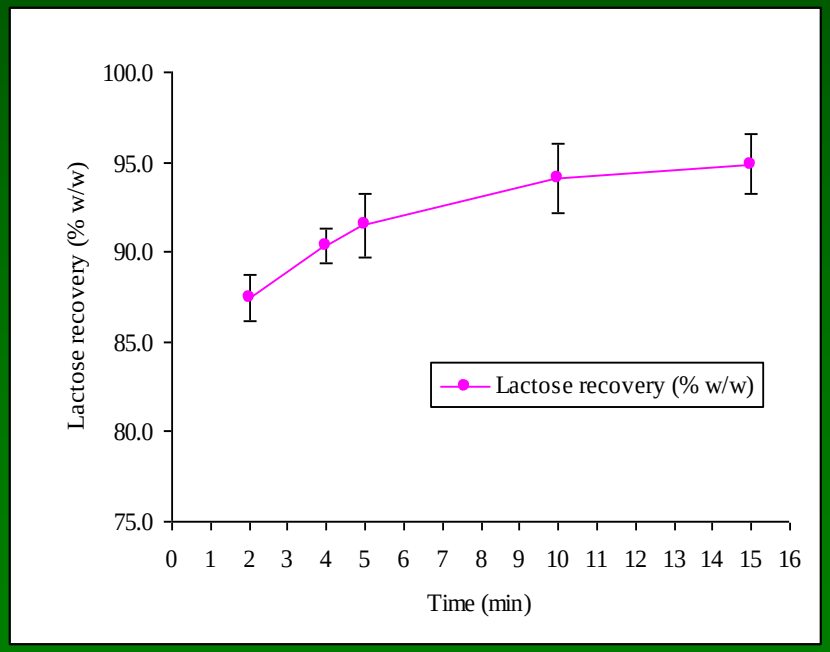
- Effect of Time (0-15 min)
- Effect of lactose concentration (0-20 % w/v)
- Effect of pH (2.7, 4.2)
- Effect of protein content (0-0.8 % w/v)

Lactose recovery

Sample: Reconstituted lactose solutions (11.5-17.5 % w/v) Sample size: 10 ml

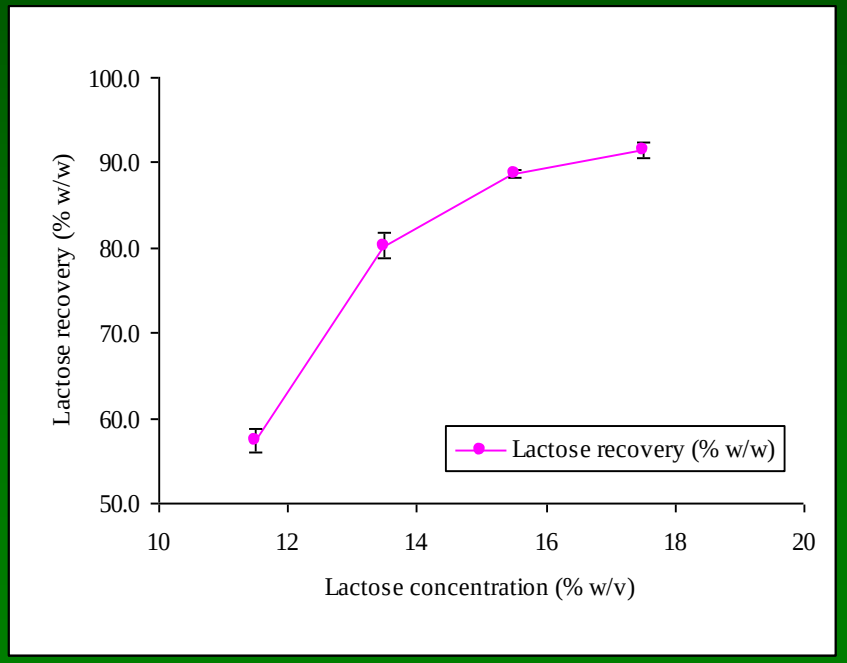
Time: 0-15 min Ethanol conc.: 85 % v/v Temperature: RT (30 ± 2°C)

Effect of time



In 2 min >85 % lactose recovery

Effect of lactose concentration



Increase in recovery with increase in lactose concentration

Lactose recovery continued…

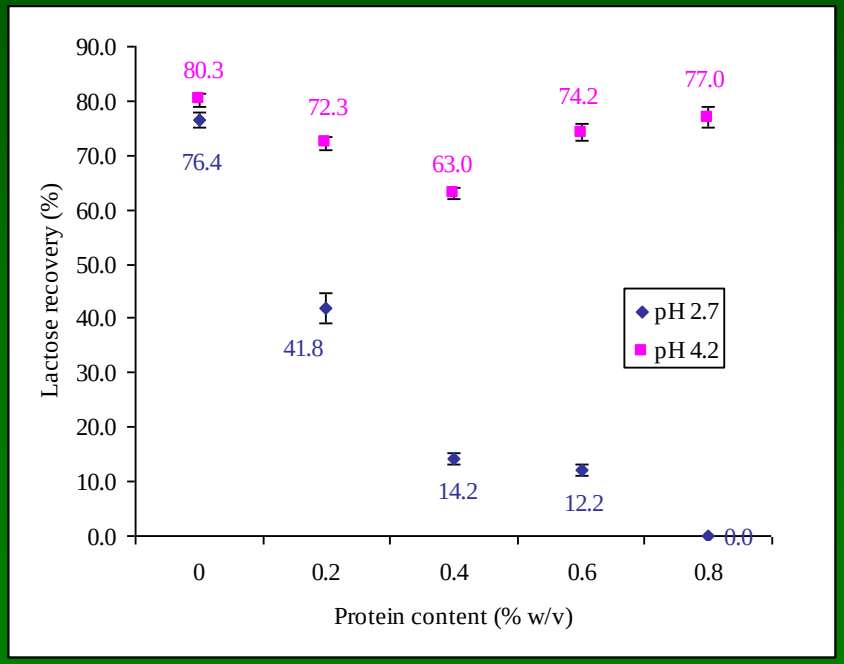
Effect of pH and protein content

Sample: Reconstituted lactose solutions (13.5 &17.5 % w/v) Sample size: 10 ml

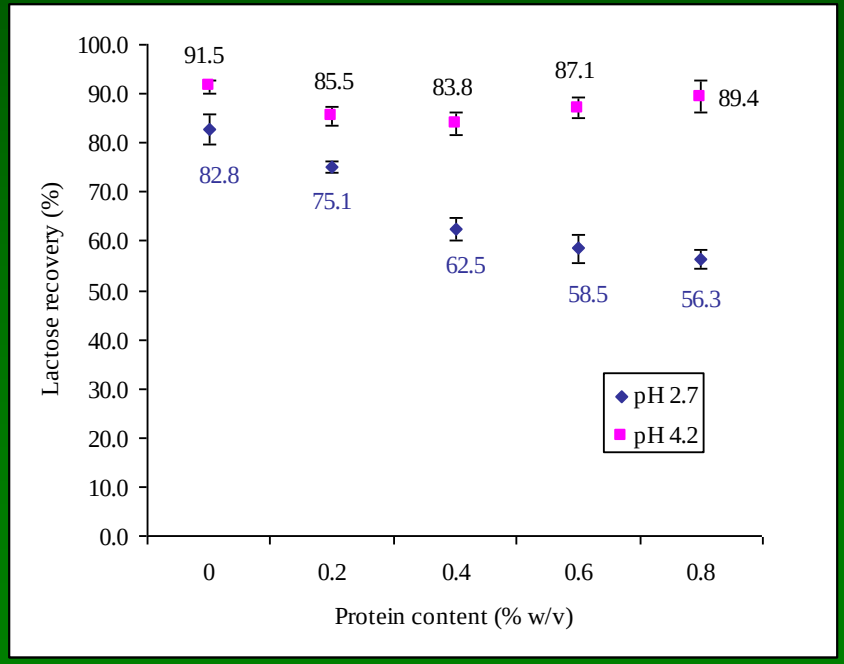
Time: 5 min Ethanol conc.: 85 % v/v Temperature: RT (30 ± 2°C)

Protein content: 0-0.8 % w/v pH: 2.7 & 4.2

Lactose 13.5 % w/v



Lactose 17.5 % w/v



Effect of inhibition in crystallization due to protein > in solution with low lactose concentration

Pictorial depiction of the effect of protein content

Lactose 15.8%,
Protein content 0%
pH of 2.7,
Time: 75 sec

Lactose 15.8%,
Protein content 0.2%
pH of 2.7,
Time: 75 sec

Lactose 15.8%,
Protein content 0.6%
pH of 2.7 ,
Time: 240 sec

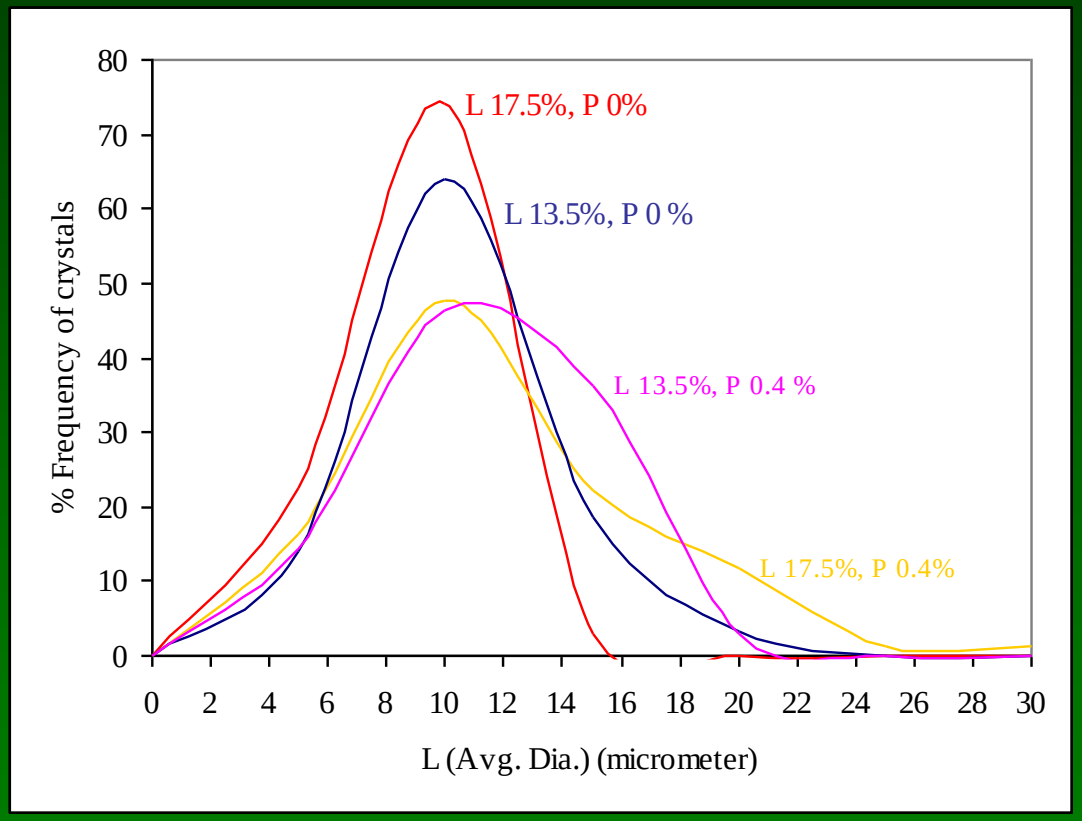
Pictorial depiction of the effect of pH

Lactose 15.8%,
Protein content 0.6%
pH of 2.7,
Time: 240 sec

Lactose 15.8%,
Protein content 0.6%
pH of 4.2 ,
Time: 70 sec

Crystal size distribution (CSD)

CSD for lactose recovered at end of 5 min

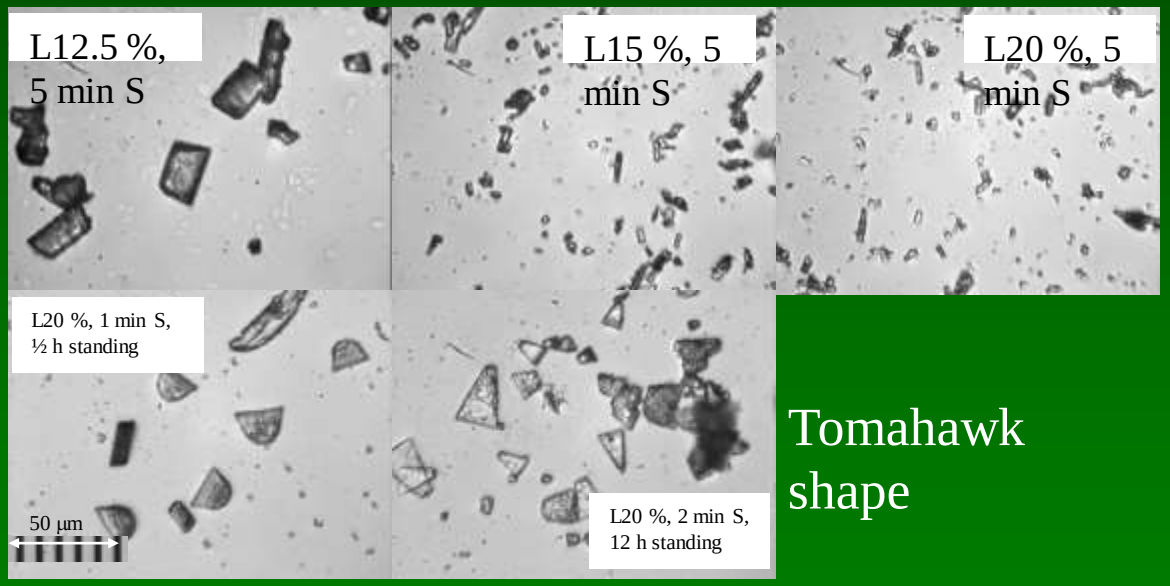


- Maxima of % Frequency decreases as protein is added
- Maxima of % Frequency increases as lactose concentration increases, indicating more uniformity

Different shapes of lactose crystals

Shape changing : change in supersaturation

time of crystallization



Needle shape

Standing samples

Tomahawk shape

Crystals observed under Leica Gallen microscope (40 X objective)

Conclusions

- More than 85 % lactose recovery in just 2 min at RT, by sonocrystallization with ethanol as anti-solvent, which is very fast as compared to 60% recovery in 72 hours by the conventional approach
- Lactose recovery decreases on decrease of pH from 4.2 to 2.7
- Lactose recovery inhibited greatly by increase in protein content of lactose solution
- Effect of inhibition more pronounced, in solutions with lesser lactose concentration
- More uniform CSD in absence of protein and at higher concentration of lactose
- Opposite trend of log n vs. L observed in sonocrystallized lactose samples (protein 0%) at both 13.5% and 17.5 % concentration.

Case Study II

Sonocrystallization in paneer whey

Optimization of parameters for lactose recovery by sonocrystallization in paneer whey

- Statistical design approach using MINITAB software
- Taguchi Design
  - L12 (2^7) orthogonal array design
- ‘Identification of crucial factors’ and ‘optimum levels’ for lactose recovery
- Analysis of data in terms of delta values, S/N ratios and mean values

Parameters (factors and levels)

	Levels	
Parameters	1	2
Deproteination step (A)	W/O $CaCl_2$	W $CaCl_2$, 2 mM
Crystallization time (B)	10 min	20 min
Crystallization temperature (C)	5-10°C	RT (30 ± 2°C)
Initial pH (D)	2.7	4.2
End pH (E)	2.7	4.2
Stirring (F)	N	Y (250-300 rpm)
Seeding (G)	N	Y (1 % w/w)

L 12 (2^7) design for selected parameters

	Parameters for Taguchi L12 design (2^7)						
Expt. No.	A	B	C	D	E	F	G
1	1	1	1	1	1	1	1
2	1	1	1	1	1	2	2
3	1	1	2	2	2	1	1
4	1	2	1	2	2	1	2
5	1	2	2	1	2	2	1
6	1	2	2	2	1	2	2
7	2	1	2	2	1	1	2
8	2	1	2	1	2	2	2
9	2	1	1	2	2	2	1
10	2	2	2	1	1	1	1
11	2	2	1	2	1	2	1
12	2	2	1	1	2	1	2

Sample: 10 ml, deproteinated and concentrated paneer whey

Antisolvent: Ethanol (effective concentration 85 % v/v)

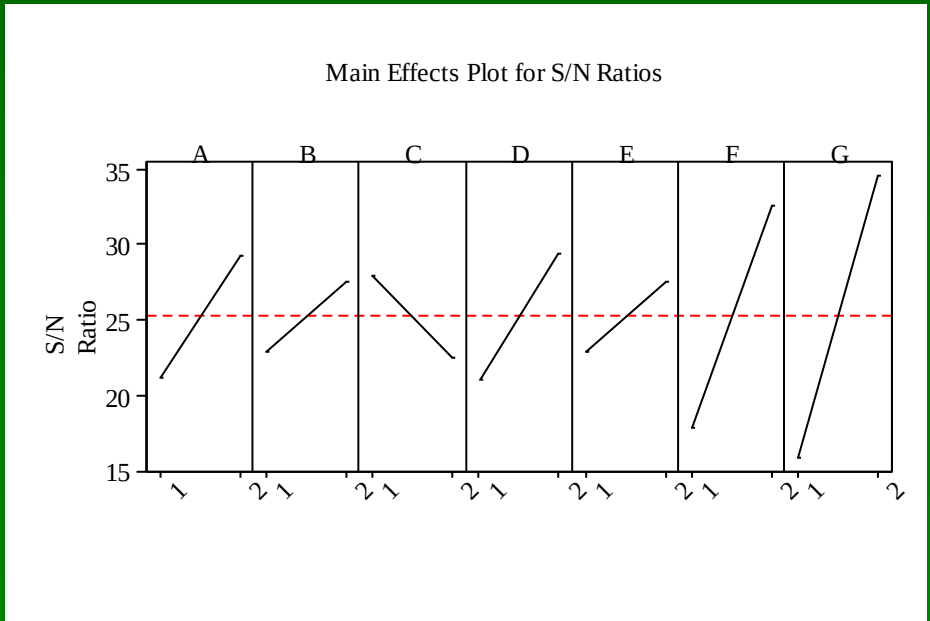
Responses for experiments

Expt. No.	Responses			
	Recovery (%)	Lactose content (% w/w)	Protein content (% w/w)	Ash content (% w/w)
1	0.8	100	0.010	0.001
2	39.8	98	2.150	0.001
3	1.9	94	2.440	2.000
4	35.0	96	2.590	0.990
5	15.8	98	2.200	0.001
6	65.7	98	2.100	0.001
7	58.8	98	2.118	0.001
8	54.5	98	2.091	0.001
9	39.2	94	3.060	1.980
10	0.9	100	0.010	0.001
11	66.7	98	2.130	0.001
12	81.1	98	2.040	0.001

Analysis for lactose recovery
(Recovery larger is better)

Response table for S/N ratio

	Parameters (Factors)						
Level	A	B	C	D	E	F	G
1	21.14	22.94	27.91	21.00	22.89	17.86	15.84
2	29.29	27.49	22.52	29.42	27.53	32.57	34.59
Delta	8.15	4.56	5.39	8.42	4.64	14.70	18.75
Rank	4	7	5	3	6	2	1



Optimized parameters suggested by Taguchi method

Parameter	Symbol	Level	condition
Deproteination step	A	2	W $CaCl_2$ (2 mM)
Crystallization time	B	2	20 min
Crystallization temperature	C	1	5-10°C
Initial pH	D	2	4.2
End pH	E	2	4.2
Stirring	F	2	Y (250-300 rpm)
Seeding	G	2	Y (1 % w/w)

The predicted lactose recovery, 10 ml sample: 93.3 %

Experimental recovery 10 ml sample : 89.6 %

Recovery, 75 ml sample (directly in bath, RT): 84 %

Lactose recovered from paneer whey using sonocrystallization

Analytical grade lactose

Lactose recovered from paneer whey using sonocrystallization and ethanol as anti-solvent

Conclusions

- Statistical design and analysis by Taguchi method proved to be a vital tool for final optimization of parameters and levels for improving lactose recovery using sonocrystallization
- Seeding, stirring and initial pH of whey were identified as the top 3 influential factors, in sonocrystallization from paneer whey
- The predicted recovery (93.3 %) matched well with the experimental recovery (89.6 %) on final optimization of parameters and respective levels
- In bigger trial (75 ml), 84 % recovery was obtained in just 20 min at RT (30°C)

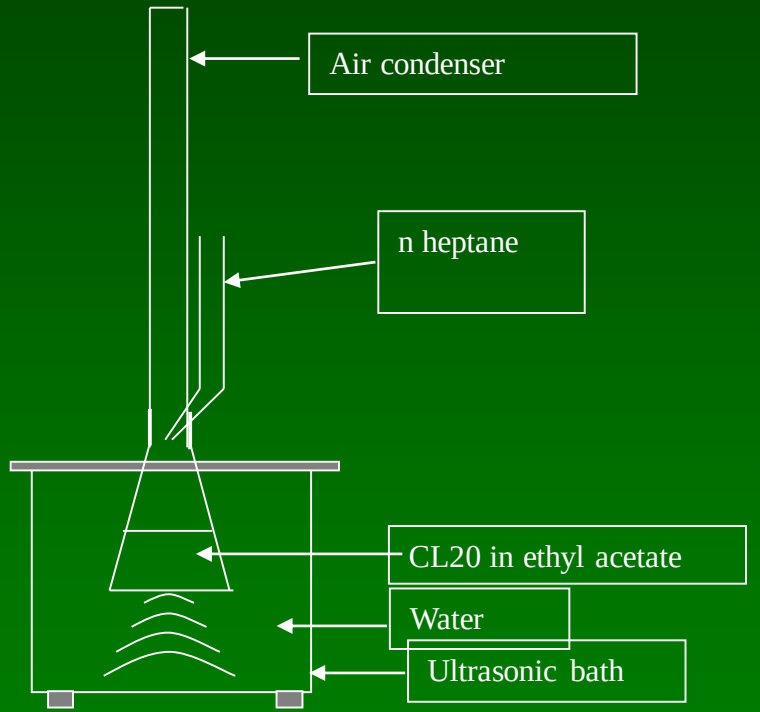
Case Study III

Sonocrystallization in High Energy Materials

Precipitation of explosive materials to obtain required size and morphology

Solute- CL20 (0.2 grams)
Solvent- Ethyl acetate (2 grams)
Antisolvent- n-heptane (8 grams)

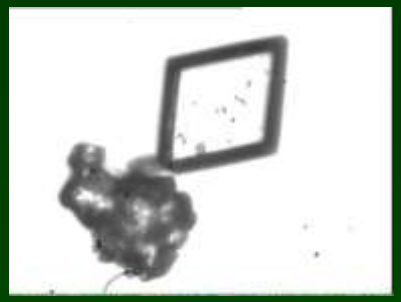
Scale up studies also done for
5 grams of the compound with similar proportion of solvent and anti-solvent



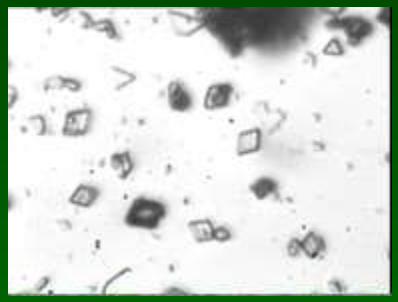
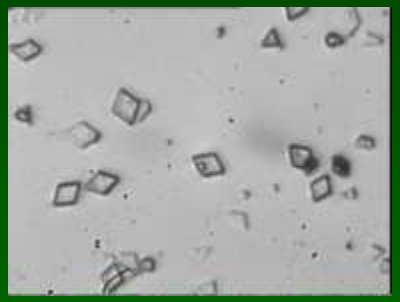
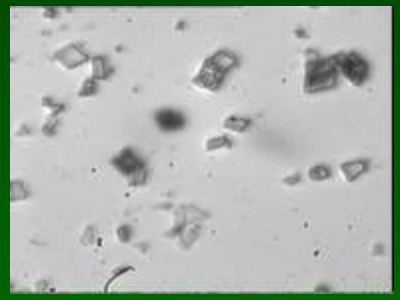
Schematic representation of the Experimental set up

Analysis of crystal size distribution using Image analysis software

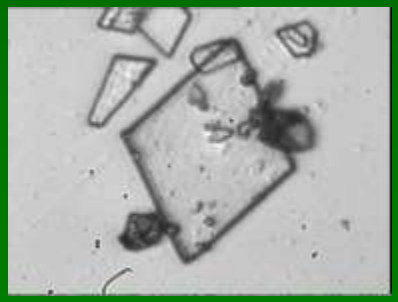
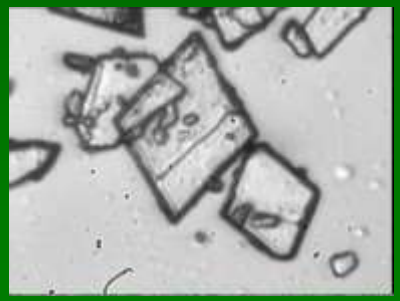
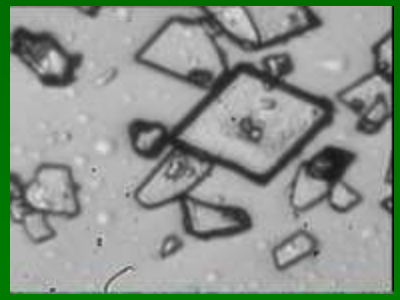




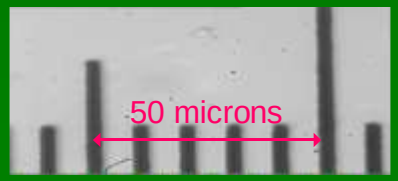
Original sample of CL20 obtained by conventional method

First and second crop obtained using sonocrystallization technique

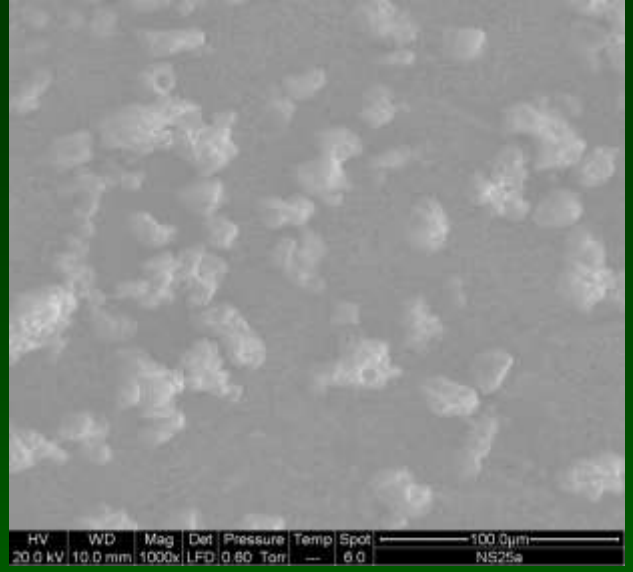




Third crop obtained by evaporation of the solvents

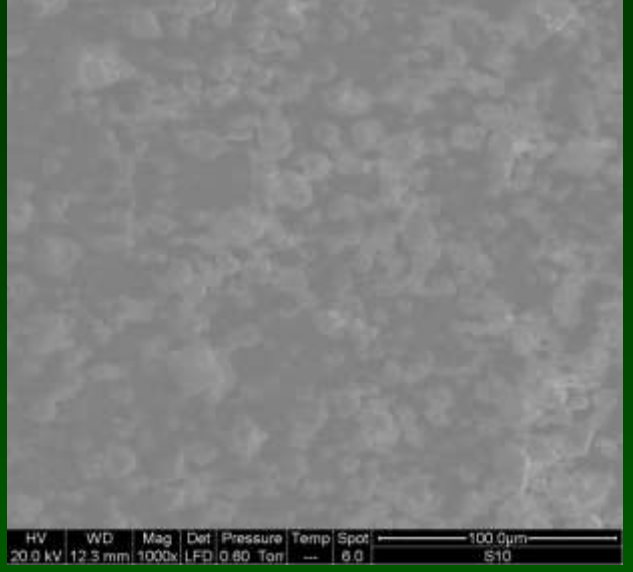


Scale for images

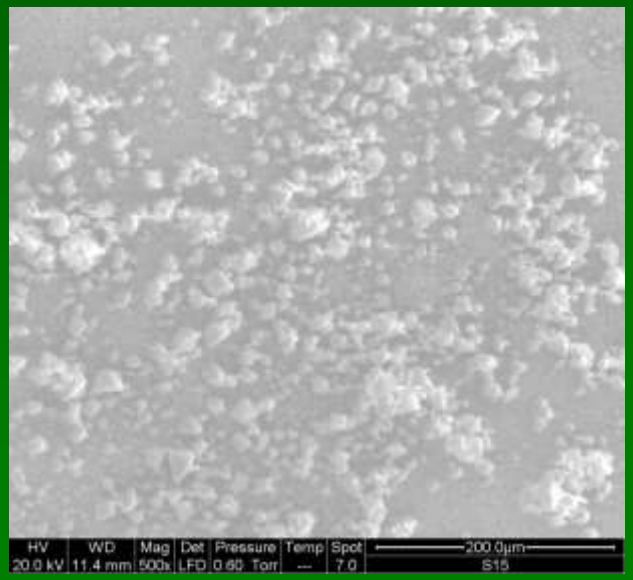
Analysis of crystal size distribution using SEM



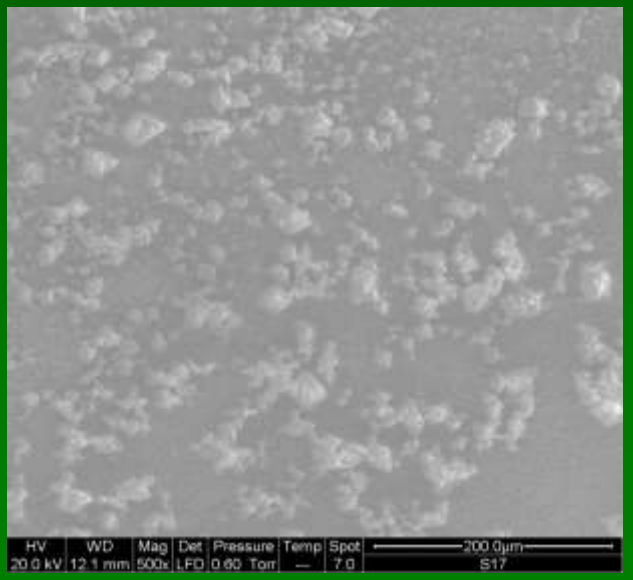
Sample obtained without sonication



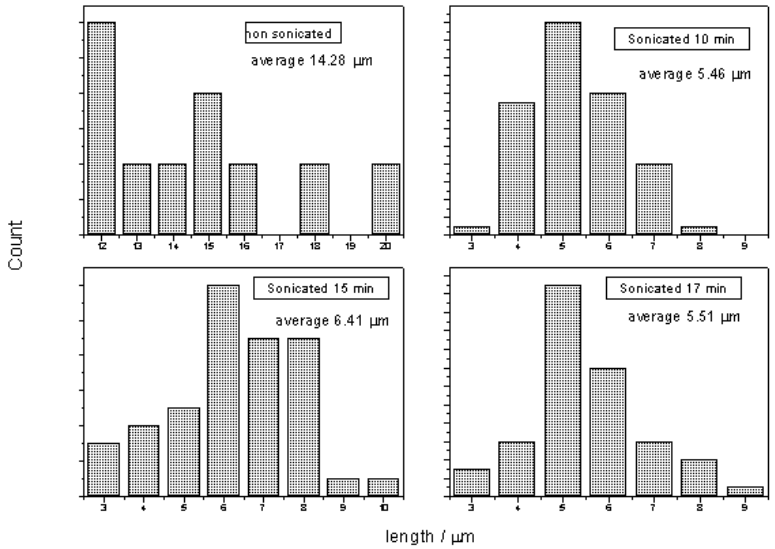
Sample obtained using sonication for 10 min



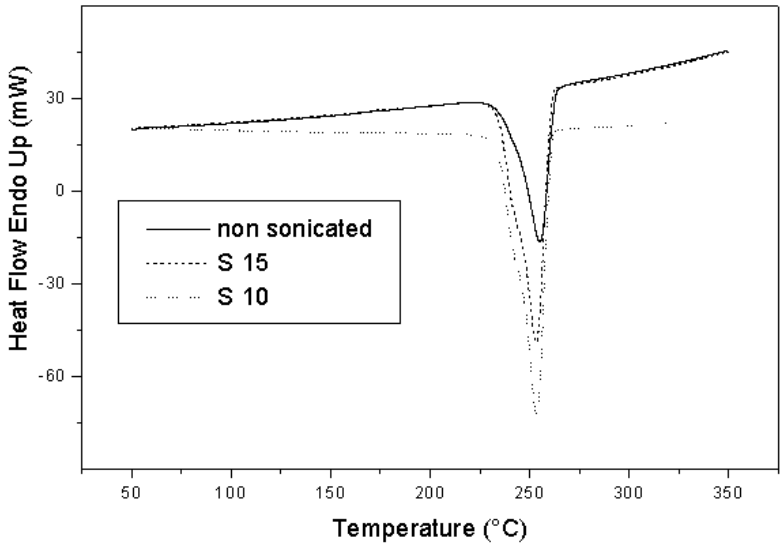
Sample obtained using sonication for 15 min



Sample obtained using sonication for 17 min



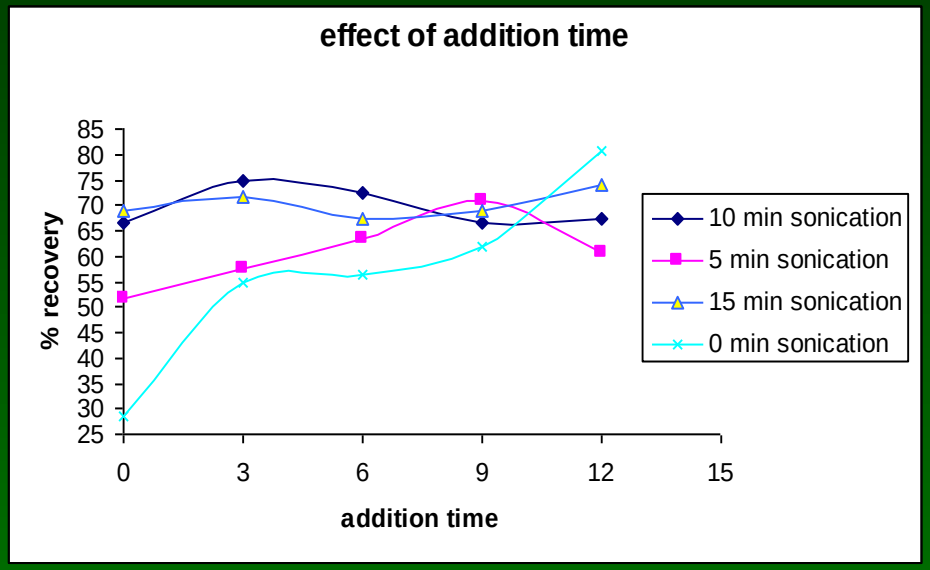
Particle size distributions

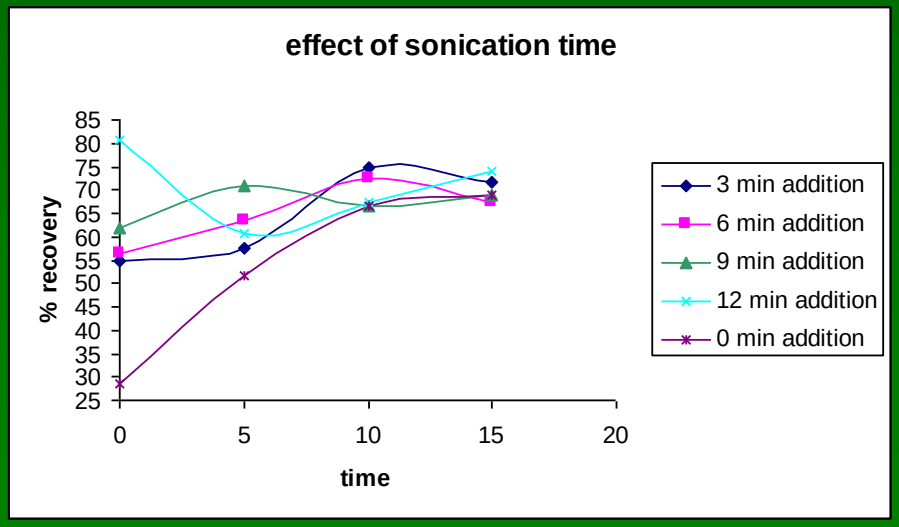


Thermogram

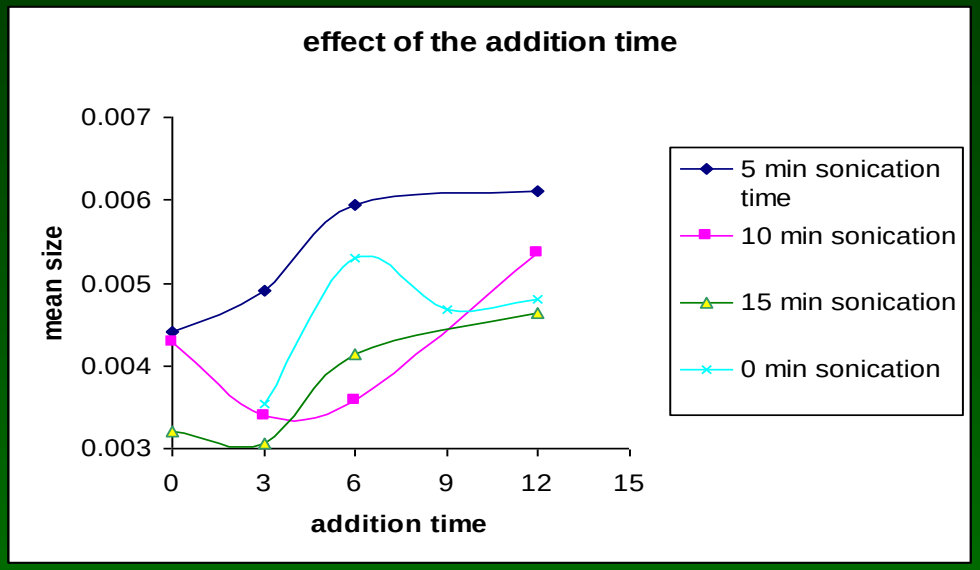
Sample	Impact Sensitivity, 50% explosion height (2kg weight) , cm	Friction Sensitivity, (insensitive up to), kg
CL-20 before sonication	39	14.4
CL-20 after sonication	44	10.8

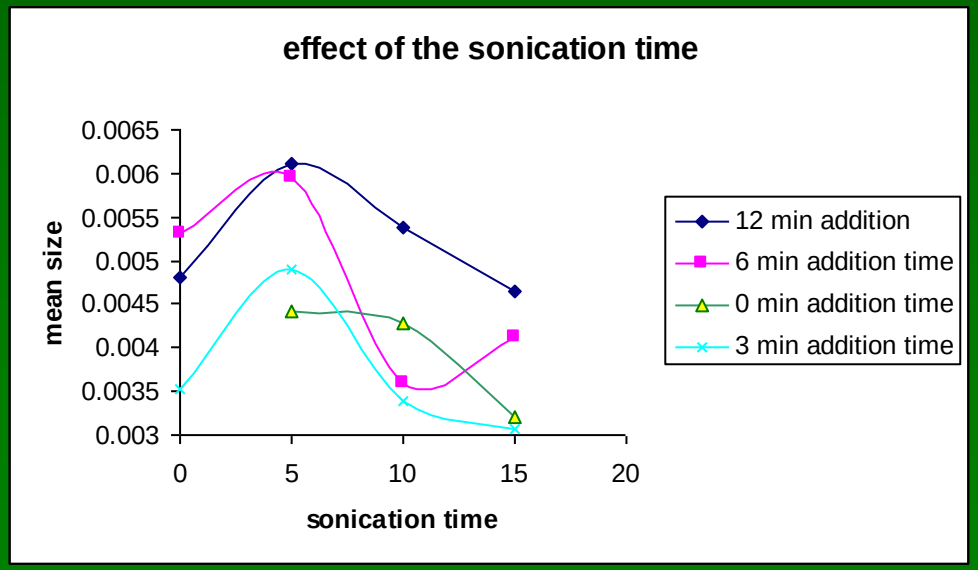
Effect of addition time and sonication time on the recovery





Effect of addition time and sonication time on particle size

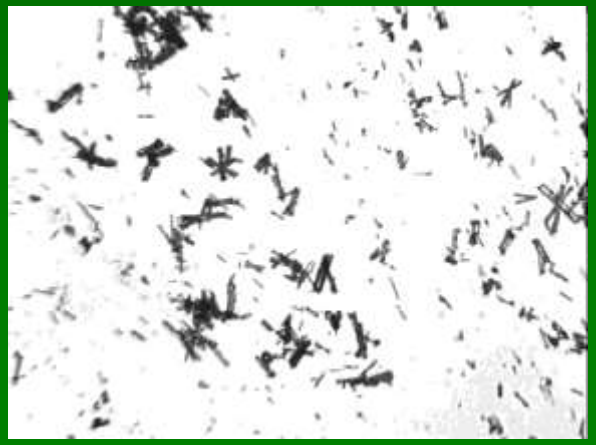


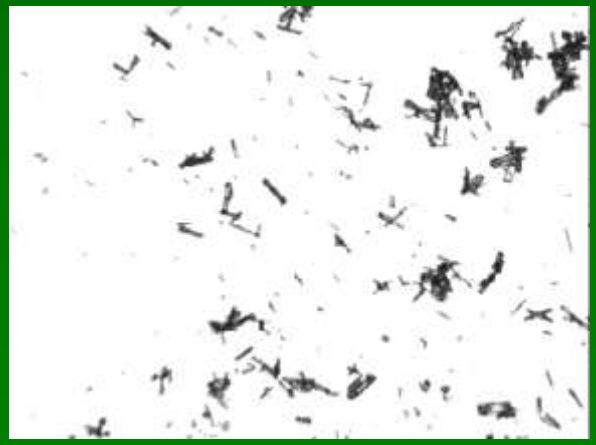


Crystal size distribution patterns for HNF

Before Sonication

After Sonication





Crystallization of dimethyl sulfone

Uses:
High temperature solvent & dietary supplement

Some potential uses in healthcare as well

Main objectives

- Comparison with conventional stirring approach
- Understanding the effect of different operating parameters
- Target parameters in terms of crystal size, metastable zone width and induction time

Experimental methodology

- Method: Cooling crystallization as solubility varies significantly with temperature
- Dimethyl sulfone (40 gm) + methanol (100 ml)
- Reactor: jacketed glass reactor of 300 ml volume
- Cryostat equipment: controlled cooling

Experimental methodology

Stirring: pitched blade impeller

Sonics VC 750 (maximum power is 750 W) ultrasonic processor operating at 20 kHz frequency

Solution heated to 52 ^{0}C to make clean saturated solution and cooled slowly at constant stirring speed

Sample collection: micropipette on four fold tissue

Analysis: images captured by Canon S3iS camera and processed by Image J software.

- Observations: solution turns clear to turbid → nucleation point, induction time, meta stable zone width

- Further sample collected for every 2 ^{0}C drop in temperature → study of the growth of crystal

- Experimental set up:

Results

- Typical shape of dimethyl sulfone crystal: needle like

- Stirring speed: Increase in the stirring speed from 300 to 500 rpm decreases the meta stable zone width from 7 to 3 ^{0}C

- Effect of temperature : Decrease in temperature after nucleation increases the size of crystal due to growth

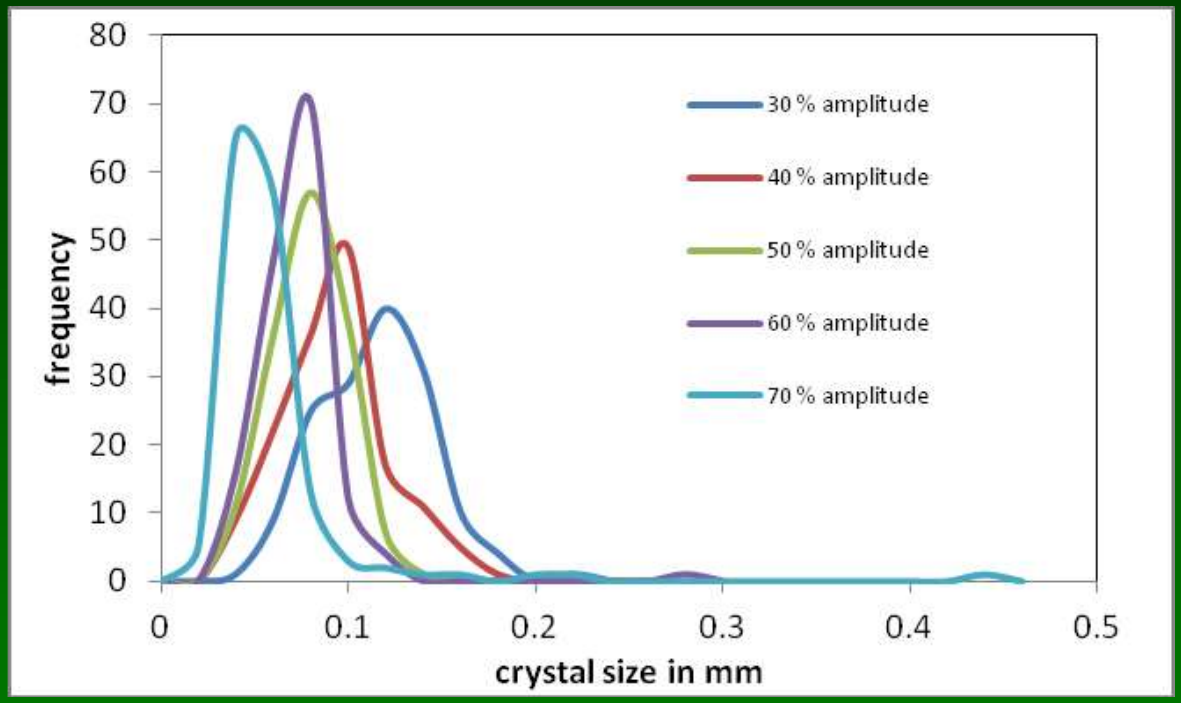
- Variation of crystal size with conventional stirring: generally decreasing trend
- Dimethyl sulfone crystal size range: 0.4-0.8 mm
- Nucleation point reduced with increase in stirring: 300→43^{0}C; 400→ 45^{0}C; 500→ 47^{0}C
- As compared to natural cooling, the crystal size reduced in controlled cooling

Important results for Sonocrystallization

- Increase in crystal size from 70 to 260 microns with an increase in the initial concentration from 10 to 20 gm per 100 ml methanol

- Reduction in crystal size using ultrasound from 400 to 90 microns as compared to conventional stirring

- Further reduction in the crystal size to 60 microns with an increase in ultrasonic amplitude, Based on the desired requirements, optimized power can be selected



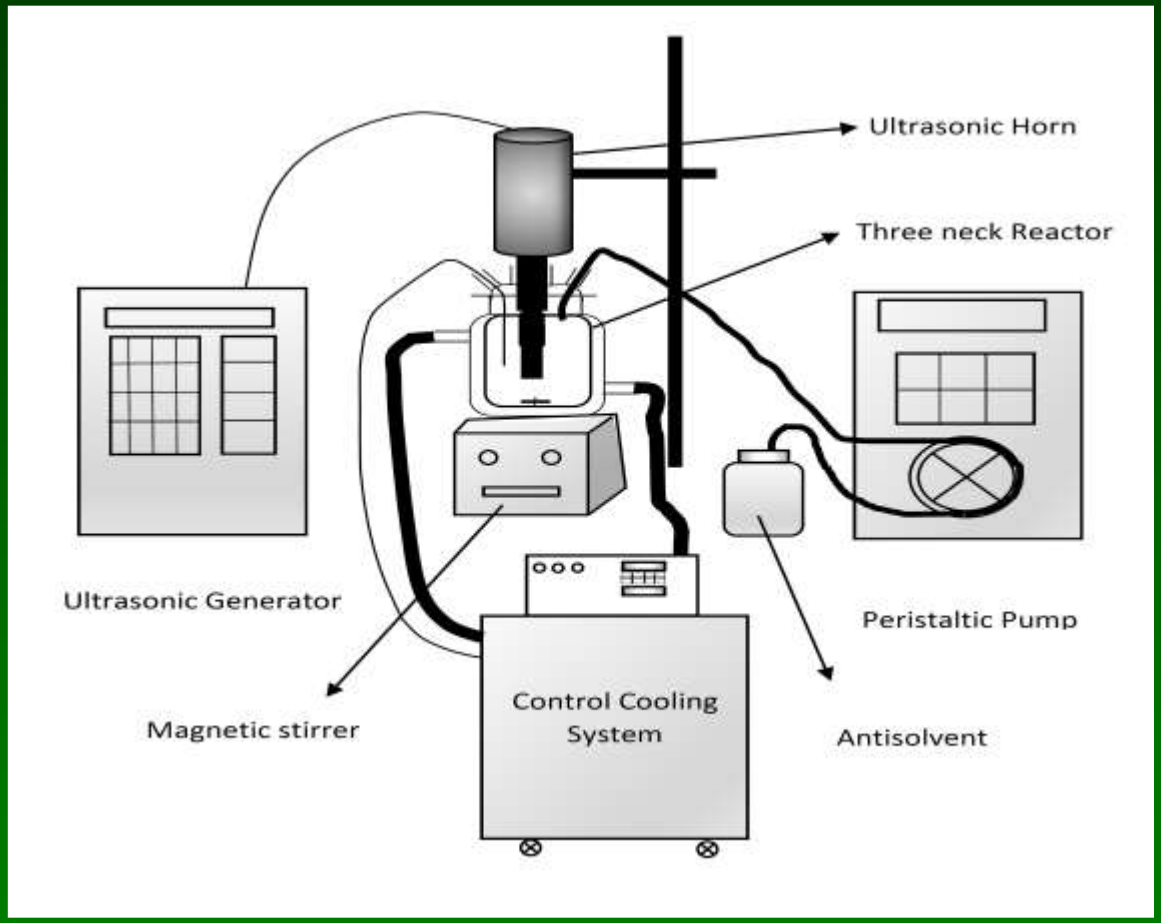
Effect of ultrasonic power on crystal size distribution of dimethyl sulfone

Change in morphology from rod like to rhombic with the use of ultrasound

Also effect of ultrasound on metastable zone width (4 °C for conventional to 1.5 °C for ultrasound), induction time (14 min to 10 min) and nucleation point (4 °C to 1.5 °C)

Crystal size and morphology can be controlled with the parameters such as ultrasonic amplitude and initial concentration

Antisolvent crystallization of benzoic acid


Ultrasonic Horn
Three neck Reactor
Ultrasonic Generator
Peristaltic Pump
Magnetic stirrer
Control Cooling System
Antisolvent

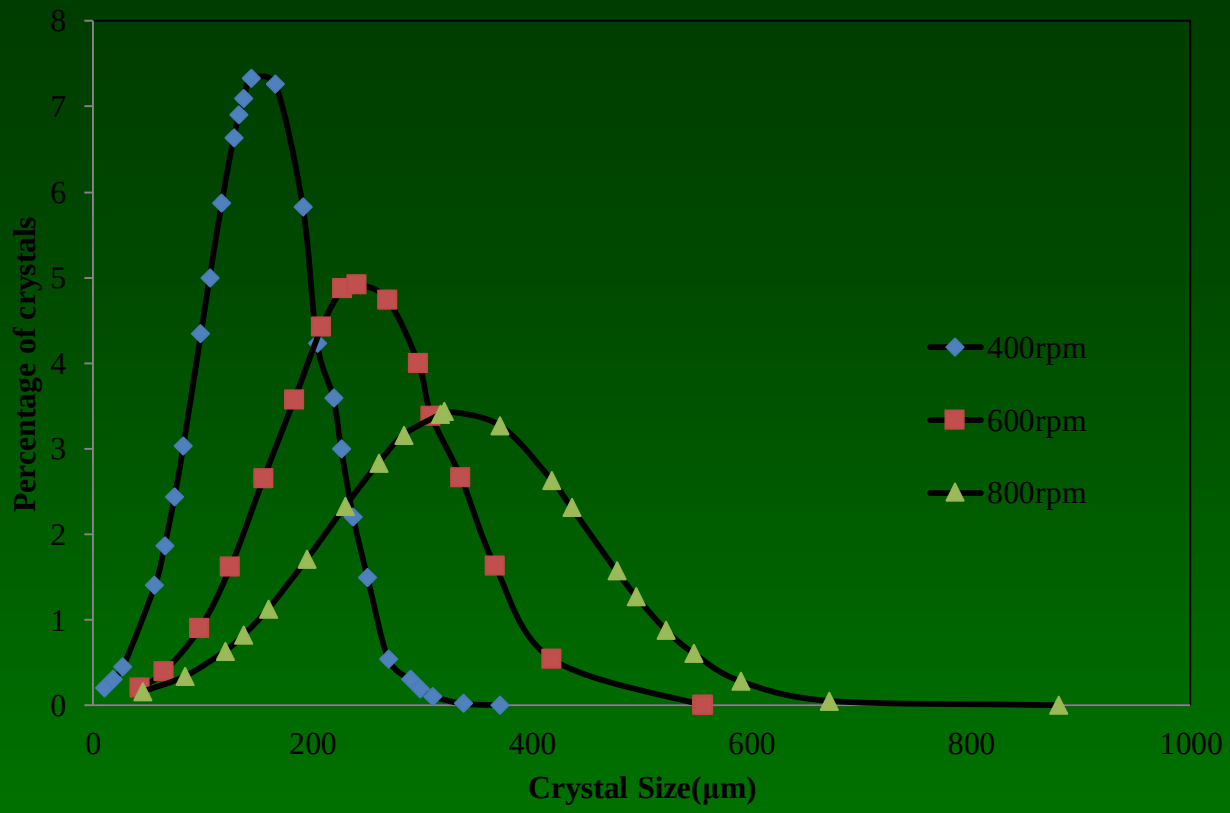
Experimental Details

Sonics VC 750 (maximum power is 750W) ultrasonic processor operating at 20kHz frequency

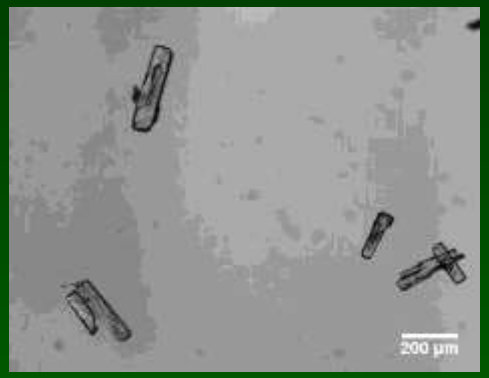
A temperature controlled cooling system has been used with silicon oil as a circulating liquid

For comparing the ultrasonic sonocrystallization with conventional crystallization, pitched blade impeller (REMI Motors Pvt. Ltd., Mumbai).

Samples of crystals and slurry has been collected using micro pipette and placed in micro centrifuge tips for the filtration, drying and analysis of the supernatant solution.



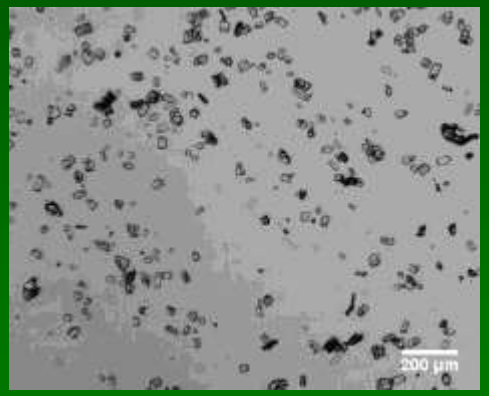
Effect of agitation rate on the crystal size of benzoic acid at flow rate of 0.018ml/s



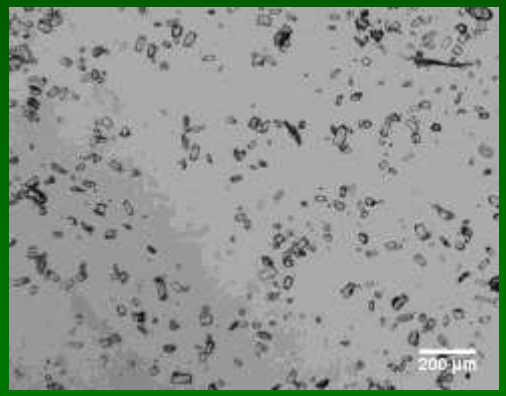
2min

6min

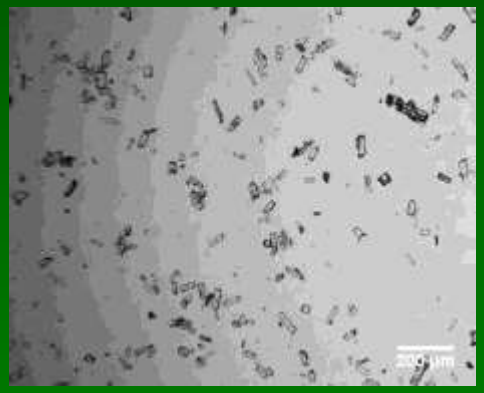
10min



2min



6min

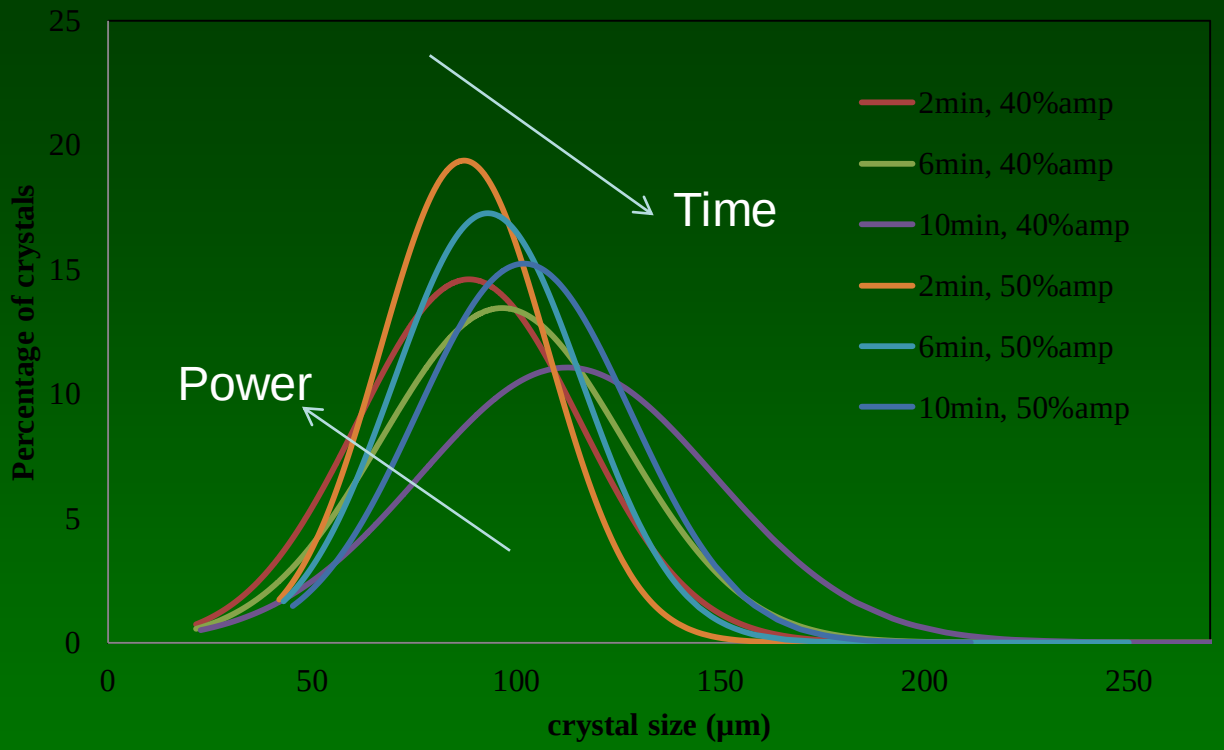


10min

Variation in crystal size with respect to time

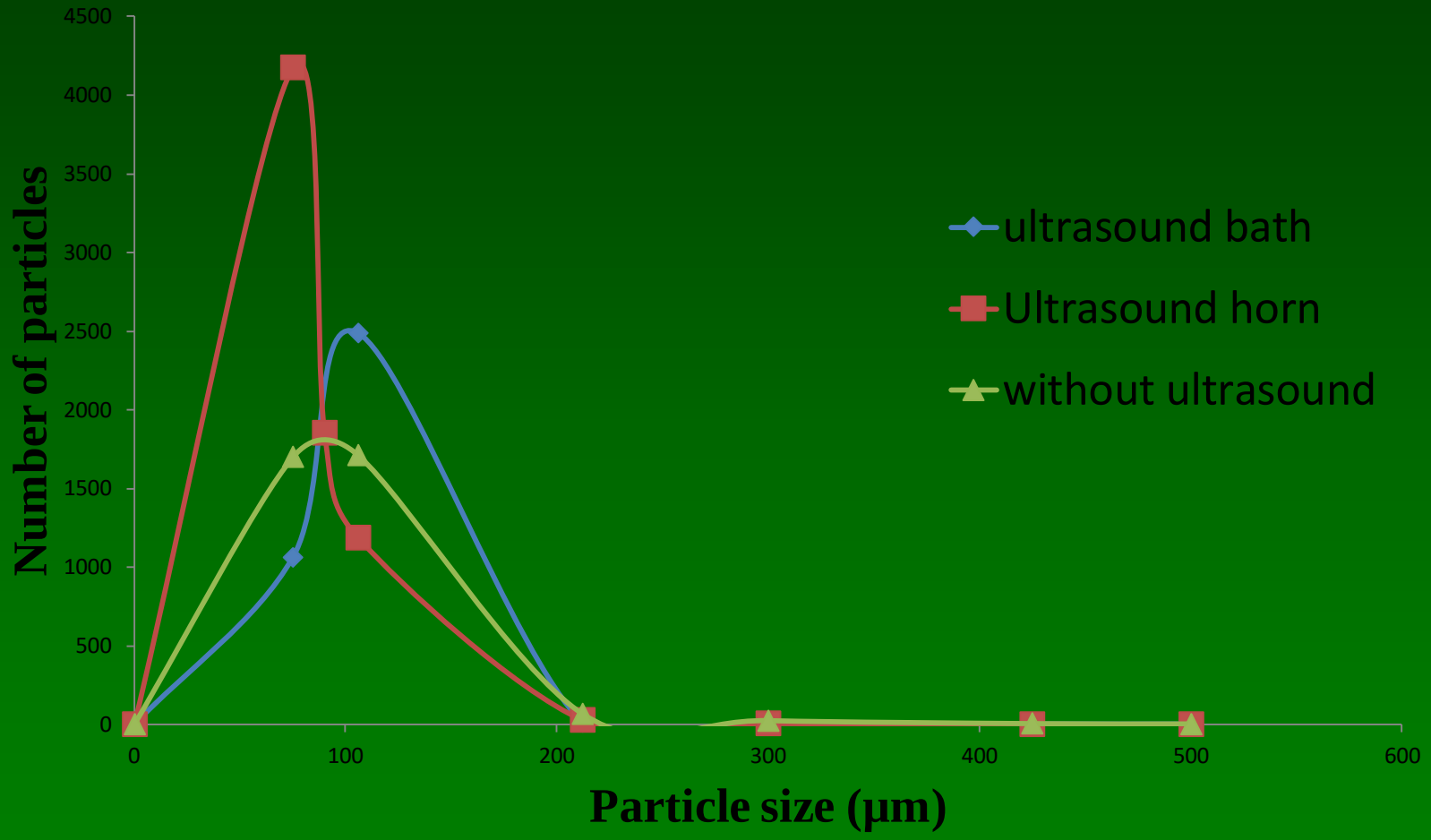
a) at 400rpm of stirring speed

b) b) at 40% amp power of ultrasound

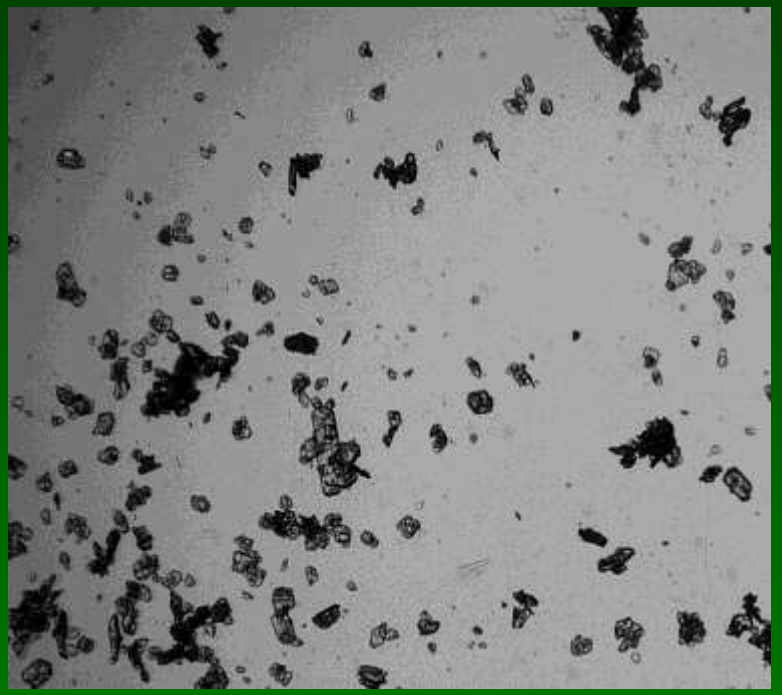


Increase in crystal size with respect to time at 40% and 50% amp of ultrasound at 0.018ml/s of addition rate.

Particle size distribution for oxalic acid under the influence of type of ultrasound.



Mefenamic acid crystallization under the influence of ultrasound.



Microscopic Image of MA Crystals: a) Without Ultrasound (needle like) b) With Ultrasound at P=30W (Plate shaped)

Optimization Methodology for the technology

- Experiments in the presence of ultrasound and using conventional approaches
- Understanding the dependency of crystal size, metastable zone width, induction time and nucleation point on the operating parameters
- Establishing the optimized system for maximum benefits
- Experiments at large Scale operation
- Exploring the design information for other applications

Concluding Remarks

- Improved crystallization of different commercially important products based on the use of ultrasound
- Study of antisolvent crystallization and cooling crystalization; Compounds investigated include dimethyl sulfone, benzoic acid, High energy materials, oxalic acid etc
- Effect of parameters such as initial concentration, rate of supersaturation (cooling rate or the flow rate) and ultrasound amplitude on the crystal size, metastable zone width, induction time and nucleation point has been established
- Ultrasound shows beneficial effect on the metastable zone width, and induction time. Some times seeding can be avoided
- **Crystal size and morphology can be controlled with the application of ultrasound**
- **Comparison with the conventional approach has enabled the quantification of process intensification benefits**

Future of Industrial Sonocrystallization

- Many more applications of Sonocrystallization expected, evolving to become a core platform technology
- It has broad chemical industry applicability for superior particle size control – easy scale-out/up
- An improved autonucleation method for non-invasive seeding in GMP production, potentially becoming the standard seeding method of choice
- Production technology for assisting in the manufacture of new ‘complex’ APIs, proteins, macromolecules
- Emergence of new small scale equipment linked to PC coupled with turbidity measurement, Lasentec etc, scale-out process equipment
- Process intensification and continuous crystallization
- Application in nanotechnology (nucleate nanophases) and biotechnology

Other Applications

- Chemical Synthesis
- Wastewater Treatment
- Biotechnology
- Polymer Chemistry
- Extraction
- Textile Industry

Chemical Synthesis

- Reaction time reduction
- Increase in the yield of reactions
- Switching of the Reaction pathways
- Use of less forcing conditions (mild temperature and pressure) as compared to the conventional routes
- Reduction in the induction period
- Increasing the effectiveness of the catalyst used in the reaction
- Initiation of the chemical reaction by way of generation of the highly reactive free radicals

Wastewater treatment

Oxidation of complex chemicals

- As a supplement to conventional techniques such as biological oxidation or the chemical destruction

Few Examples:

Oxidation of p-Nitrophenol, Phenol, Rhodamine B, CFC 11, CFC 113, potassium iodide, sodium cyanide, carbon tetrachloride, o-dichlorobenzene and dichloromethane, parathion ..

Biotechnology

Cell disruption

- require only about 10-15% energy as compared to the conventional techniques
- Intensity of cavitation has to be controlled for the selective release of the intracellular enzymes

Intensification of Enzymatic reactions

Intensification of bioleaching

Polymer Chemistry:

- Initiation of polymerization due to the formation of free radicals
- Formation of polymer composites and nanocomposites (organic/inorganic)
- Degradation of polymer species in the effluent streams
- De-polymerization reactions

Miscellaneous applications

- Intensification of solid-liquid extraction process
- In petroleum industry for refining fossil fuels, determination of composition of coal extracts, extraction of coal tars
- In textile industry for enhancing the efficacy of dyeing technique
- Synthesis of nanocrystalline materials