Accentus C^3 Technology

Harwell, Oxfordshire, U.K.

Crystallization Control using Power Ultrasound - Process Development and Scale-up

Graham Ruecroft PhD
graham.ruecroft@accentus.co.uk
www.sonochemistry.co.uk

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New Technologies for Scale-Up

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Agenda

- Crystallization – key issues, problems
- Ultrasound in crystallization - sonocrystallization
- Application of ultrasound – R&D equipment
- Nucleation, polymorphism, crystal size distribution- pertinent examples
- Equipment for large scale
- Benefits of Sonocrystallization
- Future of Sonocrystallization

The Need for Crystallization Control

It's a fact…..

- 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.

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Key Issues of Crystallization

Generation of Supersaturation (unstructured solution)

- **Prepare saturated solution at at T1 then cool to T2**
- **Evaporation**
- **Anti-solvent addition**

Nucleation

- **Define solubility curve and metastable zone width**
- **Define metastable supersaturation**
- **Primary homogeneous, heterogeneous**
- **Secondary heterogeneous (shear, contact, fracture, attrition, needle)**

Crystal growth

- **Complex process**
- **Supersaturated solution composed of variety of units (atoms, molecules, ions, hydrates, dimers, trimers, clusters, polymers)**
- **Driving forces is supersaturation – units transported by diffusion then built into surface of crystal**

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Problem Areas

Solvation

Size distribution

Agglomeration

Attrition

Purity

Solids handling

Habit

Yield

Nucleation

Polymorphism

Encrustation

Growth

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Ultrasonic Processing

The concept of ultrasonic processing is not new…
…but perhaps the ability to use it on industrial scale is.

- 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

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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).

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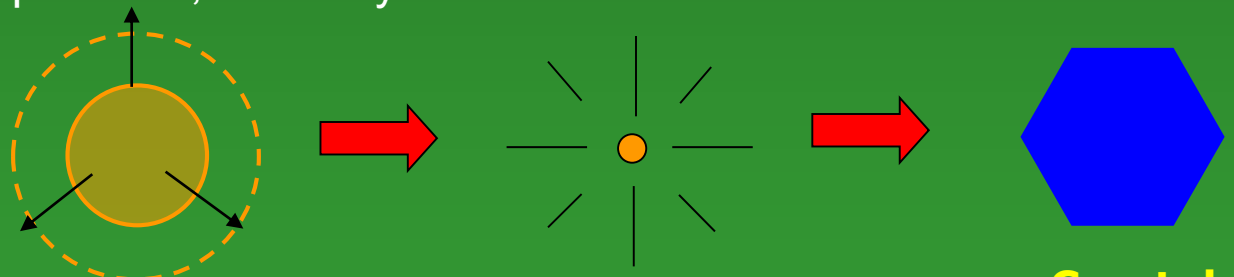
Key Principles of Cavitation

- 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 (2000 atm) to create surface and energy for nuclei to form - but why?
  - Local temperature increase effects?
  - Concomitant shockwaves?
  - Rapid local cooling rates of 10^{7}-10^{10} $K.s^{-1}$?
  - Overcome energy barriers to nucleation?
- Intensity of cavitation depends on factors such as frequency, power, temperature, viscosity.



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Solvent Cavitation Parameters

- I_{max} Maximum intensity relative to water = 100
- T_{max} Temperature for maximum intensity
- T_1/T_2 Range for >70% of I_{max}

Solvent	I_{max}	T_{imax} (°C) (T_1/T_2)
Water	100	35 (20/50)
Toluene	71	29 (10/40)
2-Propanol	38	16 (0/30)
Ethanol	46	21 (15/27)
Methanol	52	19 (4/23)
Dichloromethane	38	-40 (-60/–25)
Ethyl acetate	45	9 (-15/16)
Acetone	44	-36 (-50/-20)

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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

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Application of Ultrasound – R&D

Ultrasonic Probe / Horn

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Application of Ultrasound

Process R&D Ultrasonic Micro-Reactor

- 1 – 2 ml capacity for use when material is very limited
- Ultrasound probe on back, glass front for viewing
- Can be used as batch reactor or flow-cell

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Recent Literature

Particle Engineering using Ultrasound

Dennehy, R. D., "Particle Engineering Using Power Ultrasound", Proc. 4th Sci. Update Int. Symp.: 'Aspects of Polymorphism and Crystallization – Chemical Development Issues', Chester, UK, April 2003 and Org. Pro. Res. Dev. 2003, 7, 1002 (GSK)

Kim, S.; Wei, C.; Kiang, S. "Crystallization Process Dev. and Particle Engineering", Org. Pro. Res. Dev. 2003, 7, 997 (BMS)

- Crystallization of various drug compounds using batch and anti-solvent addition processes using probe-based flow-cells.
- Particle size control to avoid of milling.
- Consistent Particle size distribution

❑ Sonocrystallization in the Process Chemist's toolkit.

❑ Some probe erosion issues – the challenge for scale-up.

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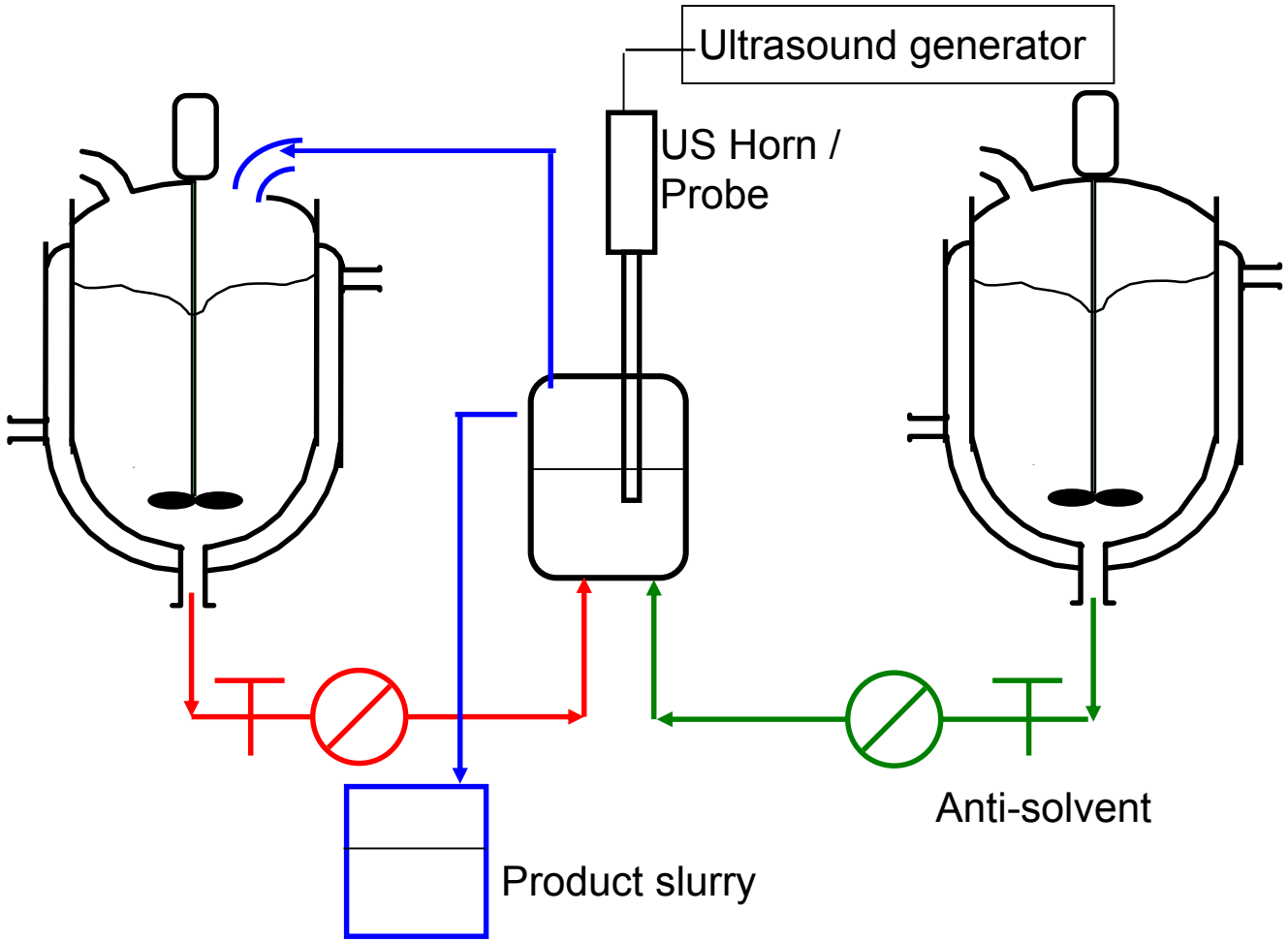
Particle engineering using ultrasound



Vessel and flow-cell not in proportion

Process Research and Development:

Simple laboratory set-up

Nucleation

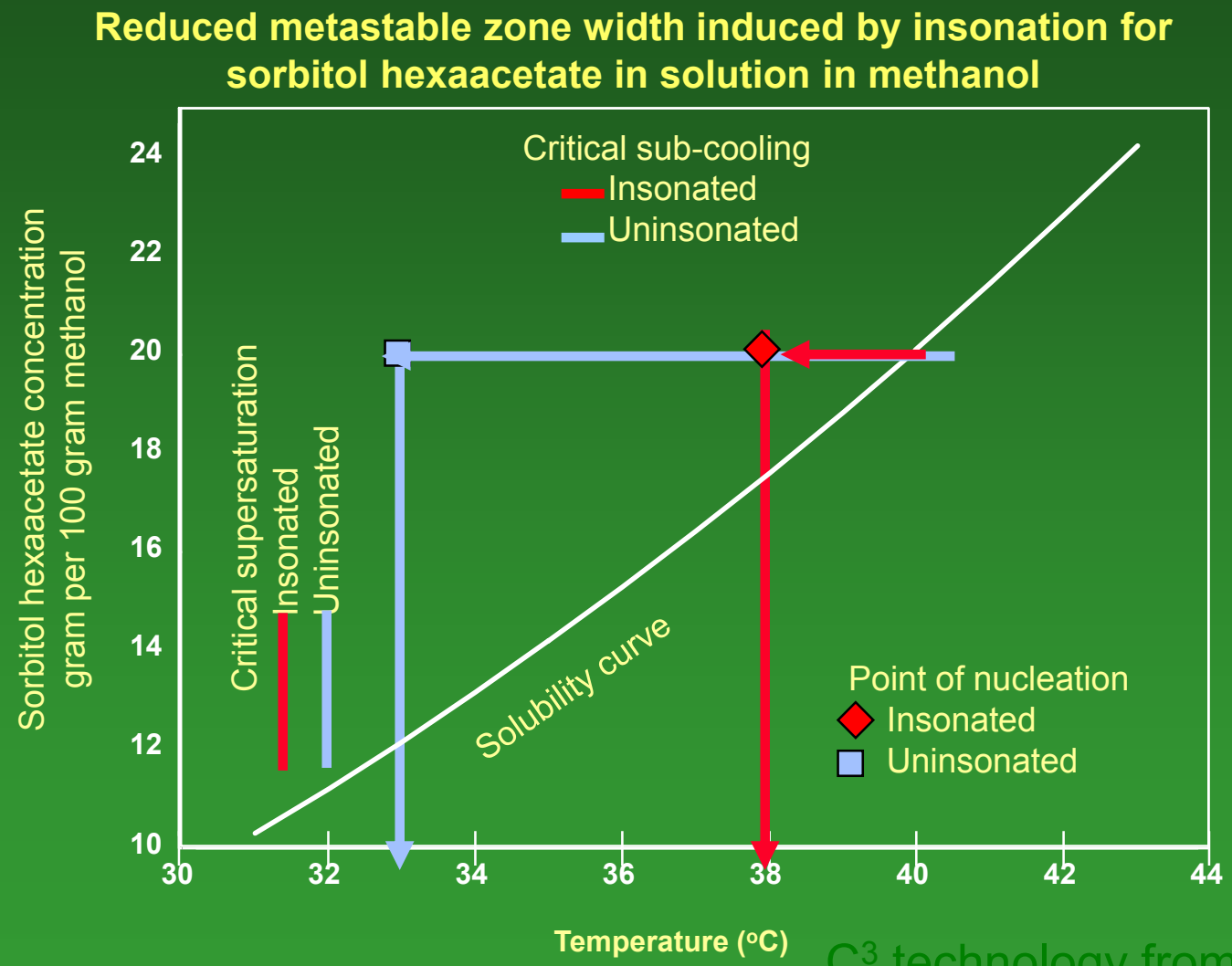
Define solubility curve

Define metastable supersaturation (first appearance of nuclei / crystals):

Hence metastable zone width

Aim to control and induce nucleation by judicious application of power ultrasound

Induction of Nucleation [1]



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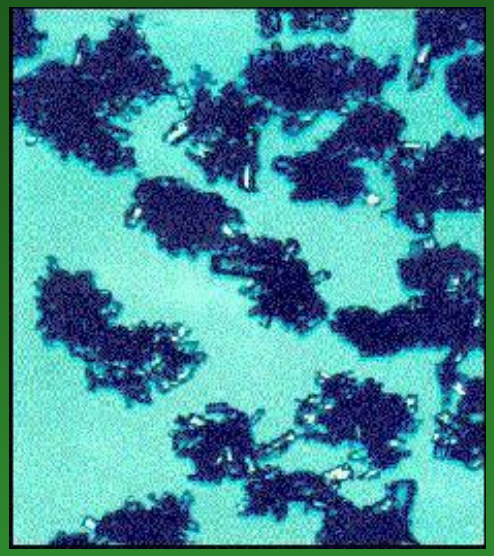
Control of Crystal Size

Sorbitol hexaacetate



Cooling crystallization

No Ultrasound

Cooling crystallization

Ultrasound to initiate nucleation

Same magnification

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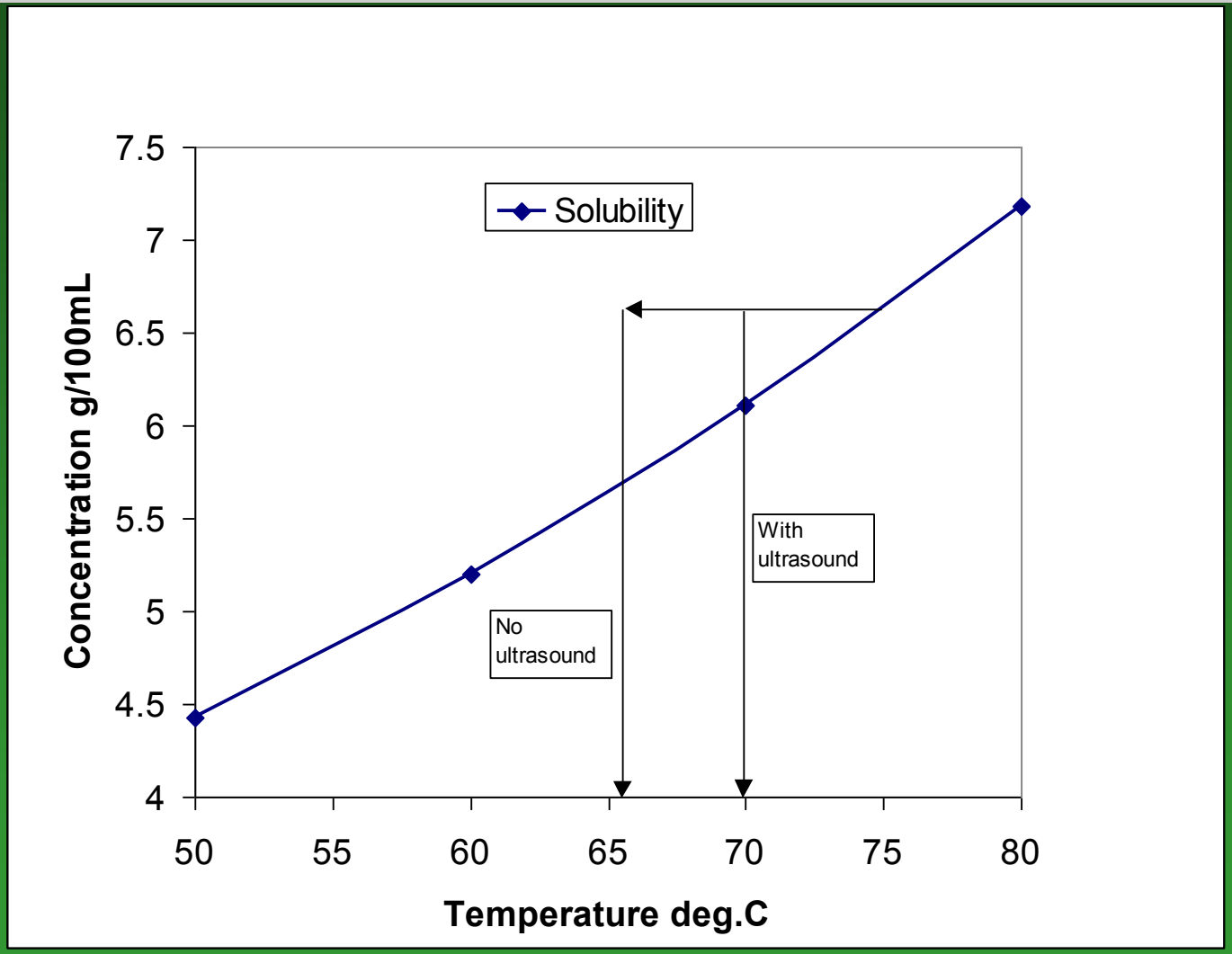
Induction of Nucleation [2]

Phenylalanine in water



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Crystal Size Distribution (CSD)

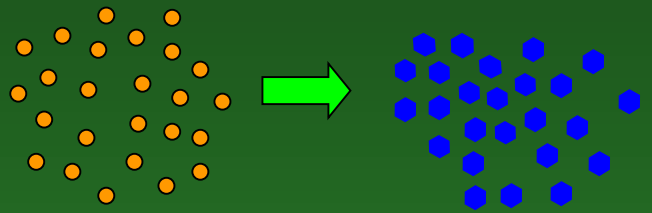
- The CSD is determined by:
  - The operation of the crystallizer throughout the supersaturation time profile
  - The use of seeds ……or ultrasound
  - The agitation conditions etc

  and is defined by Growth and Nucleation rates, which depend in turn on supersaturation history
- The size distribution which is generated will affect the performance of both the immediate downstream processing operations and also the subsequent performance of the material during storage, formulation and use.
- Expect problems with fines and wide CSD.

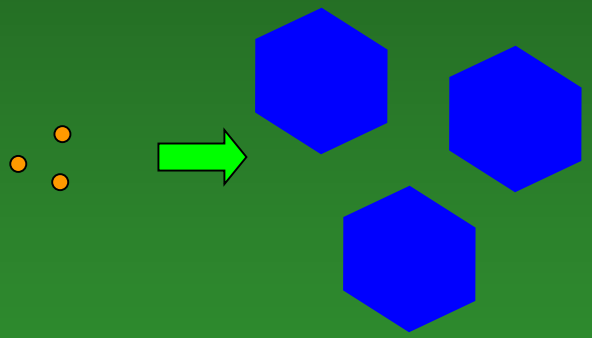
Control of Crystal Size

General Rules on the Effects of Cavitation

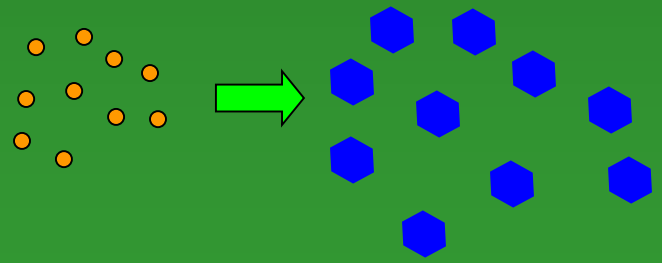
Continuous insonation produces many nuclei resulting in small crystals



Using insonation to only initiate reaction allows larger crystals to grow



Pulsed insonation gives a combination effect



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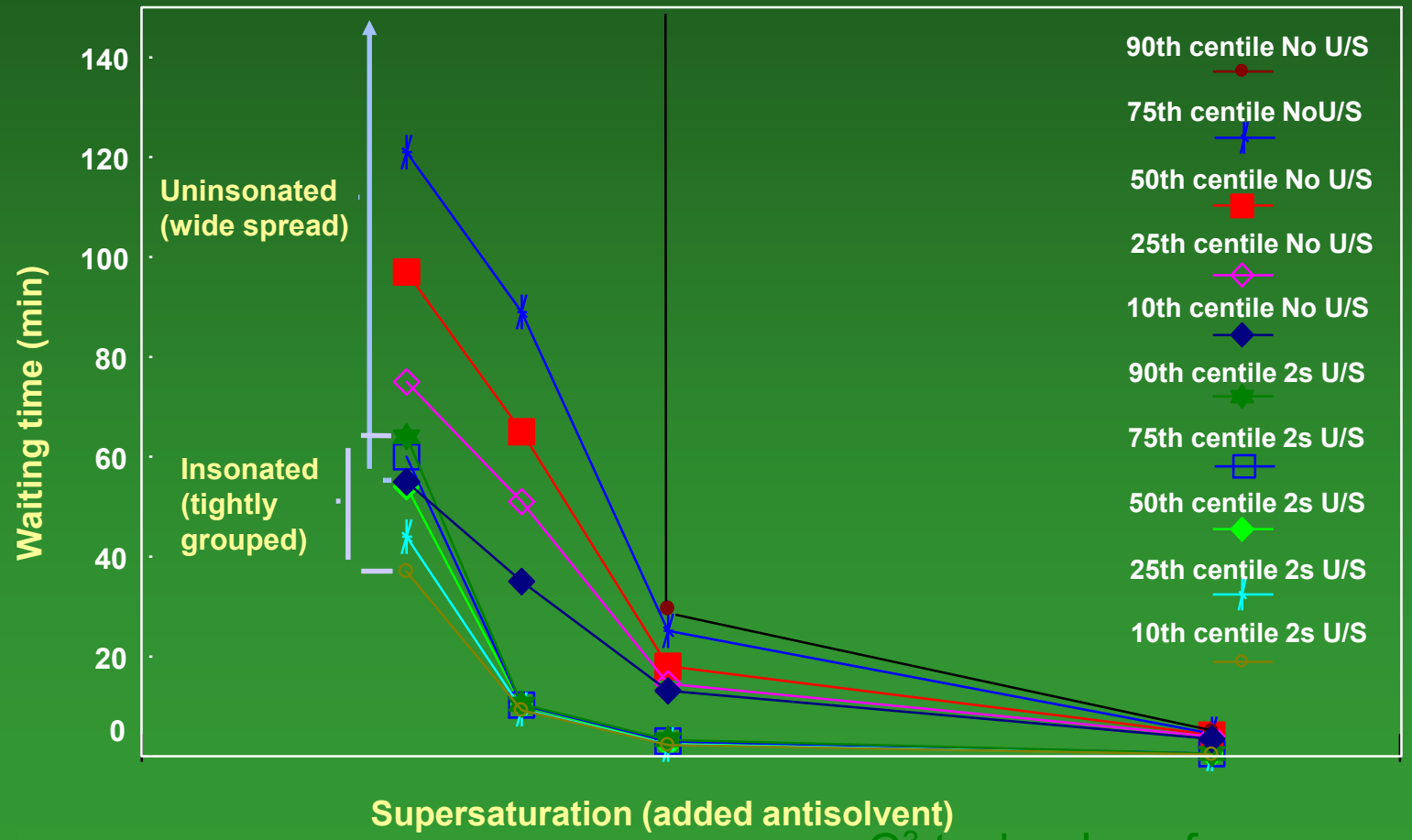
Induction Times for Nucleation

Data for a pharmaceutical product (amino acid derivative) driven out of solution (Aq) by addition of an acetone anti-solvent (drowning out crystallization)



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Polymorphism

- Polymorphism common amongst organic materials.
  - Small-molecule drugs are very flexible
  - Difficult to predict how a large floppy molecule might behave in the solid state
- Isolation of the “wrong” polymorph brings substantial problems in some applications.
  - i.e Ritonavir (Abbott) – new more stable polymorph produced at various sites
- Polymorphs differ in bioavailability, solubility, dissolution rate, chemical and physical stability, Mpt, colour, filterability, density, flow properties
- Stable polymorphs are thermodynamically favoured (least soluble, most stable but form slowly)
- One problem is the very small energy differences between polymorphs
- Metastable polymorphs are kinetically favoured (fast growth and nucleation)

Polymorphism and Ultrasound

- Ultrasound induced nucleation of potentially polymorphic systems may assist in producing the ground state polymorph or one near the ground state
  - i.e insonate a saturated solution of the most stable polymorph known – check for nucleation and crystal growth; thus more stable polymorph
- Judicious application of US (nucleate when you want to!) at the right level of supersaturation, temperature, concentration can assist in getting polymorph A over polymorph B
- Some caution though: seeds of A might predominantly secondary nucleate to produce A but equally can seed for polymorph B

With ultrasound there are a number of control options i.e:-

- Frequency: Changes size of cavitation event affecting unit cell formation
- Amplitude: Affects ground state selection
- Cavitation Threshold: Acoustic streaming can influence crystal growth whereas Transient cavitation influences nucleation

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Sononucleation – Sugars

- Sugars are very difficult to crystallize
- Seeding used (use seeds suspended in IPA)
- Benefits of ultrasound
  - Autonucleation without the need for seeding
  - Obviates requirement for IPA
  - Control of crystal size
  - Saves steam energy in process plant
- Full Scale Development Program underway

Sononucleation - Sugars

Saturated 50 °C, cooling 0.2K /min. 20kHz u/s, 2-6 s, ~35 W/L

Solute.	Quantity dissolved in 10g water	Temp. (°C) at which solid appeared	
		Without Ultrasound	With ultrasound
D-xylose	25	36	43
D-sucrose	18	<40	47
D-lactose	5.5	41	43
D-maltose	13	<20*	40
D-cellubiose	2.0	<20*	42

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Crystallization of Proteins

Exciting Developments

- In C^3 laboratories ultrasound has been used to induce the separation of DNAse I from aqueous solutions as crystalline particles.
- The objective was to develop a method to produce particles in a narrow size distribution with aerodynamic diameters in the range 3 – 5 μ as a model system for inhalation.
- More-recently one client has demonstrated potential benefits of ultrasound even with a ‘probe-in-a-beaker’ for predictable and rapid crystallization of a protein analogue for diabetes, reducing process time by 50%.

Crystallization of Aspartame from Water

No ultrasound
Amorphous-looking lumpy solid

Ultrasound
Uniform crystalline product

Ref: McCausland, L. J. Accentus plc. Brit. Patent GB 02 12626.6, 5 May 2002.

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Control of CSD for an API

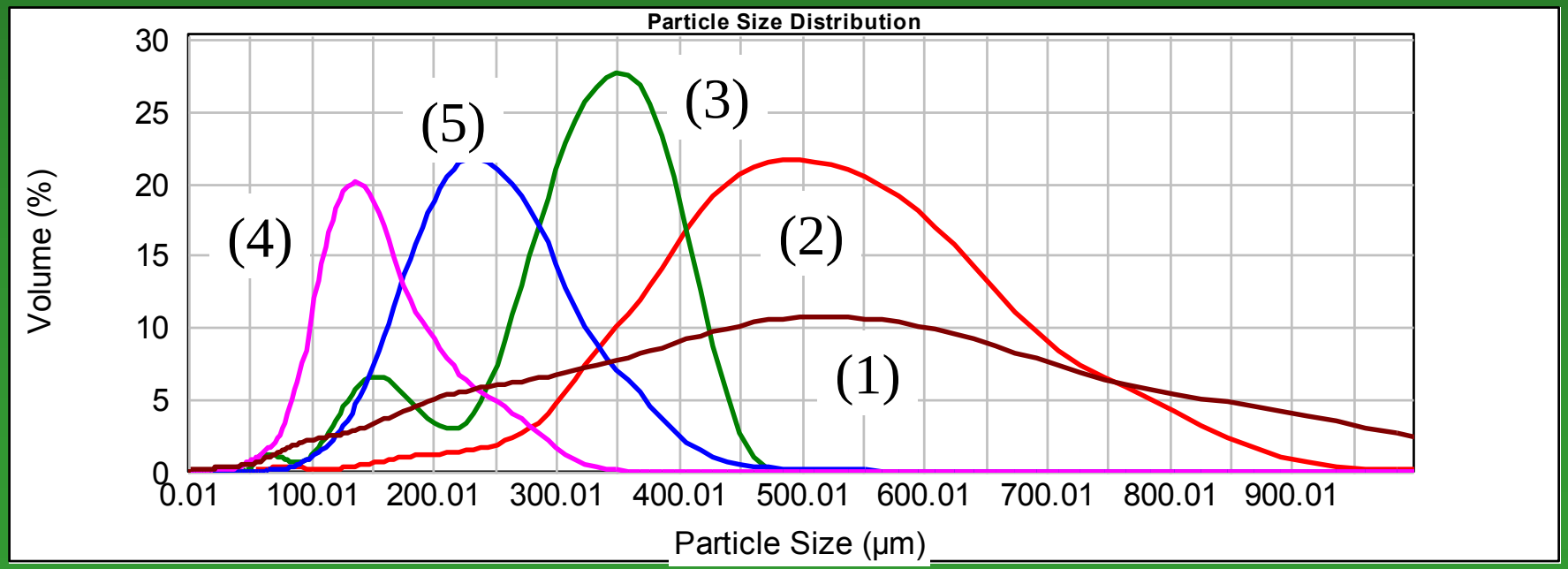
(1) Non ultrasound (US) controlled

(2) Single nucleation (1 W / mL for 30 sec) of aliquot (20 mL) at medium supersaturation (SS) then return to batch

(3) Periodic aliquot insonation every 1 ^{o} from medium to high SS then return each aliquot to batch – cool to ambient

(4) Recirculation (20 mL flow-cell) with constant ultrasound 0.5 W / mL from medium to high SS- sampled at ambient

(5) As (4) but sampled at 5^{o} – no further US

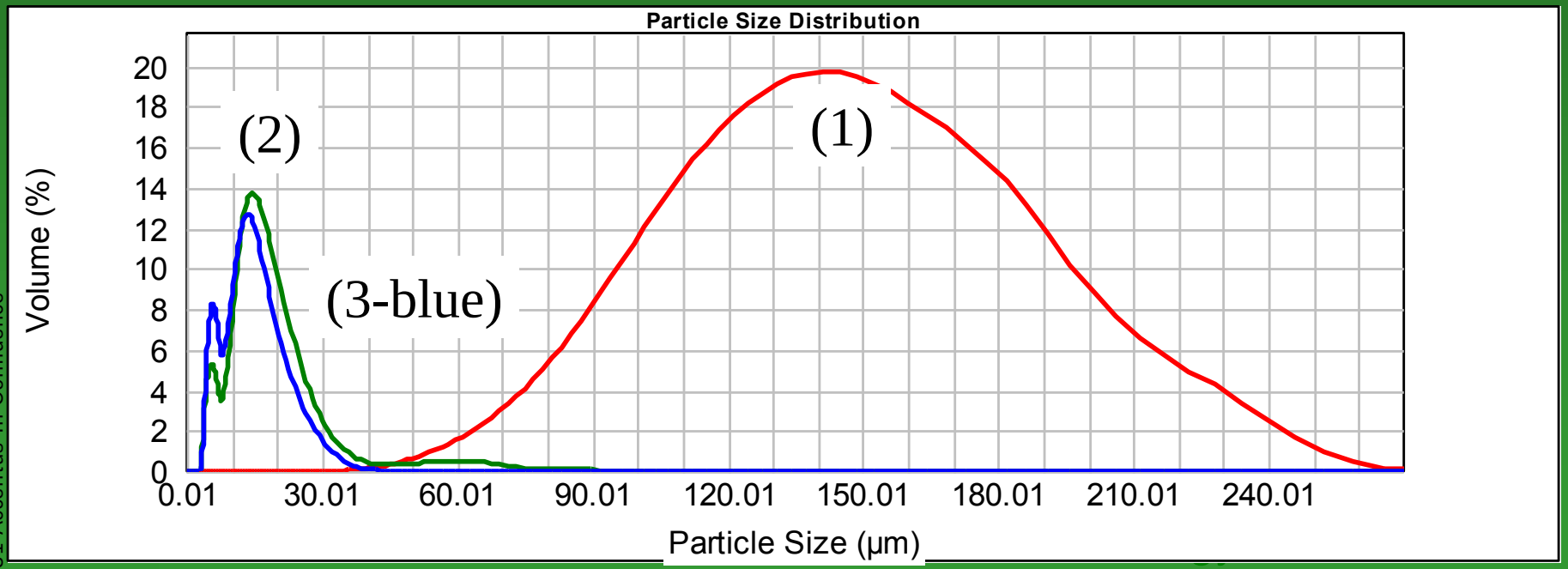


API Formulated for Inhalation

(1) Standard batch cooling crystallization (160 g/L)

(2) Continuous 50 W/L batch insonation (flow-cell in batch mode 160 g/L); sampled at 5°

(3) Continuous 50 W total on probe recirculation insonation 250 g/L; sampled at 5°



Ultrasonic Probe Based Technology

Probe systems have serious disadvantages for scale-up

- 10-150 W cm^{-2} at face (@ 20-60 kHz)
- Creates very high intensity field
- It is not possible to transmit an intense cavitation field more than 5 - 10 cm beyond the end of the probe (geometric losses)
  - Cannot transmit into large process volume, i.e. low W/L and hence precludes scale-up
- Large transducer displacements
  - Increased stress on material, more likely to fail
  - Good for laboratory studies

❑ CAN NOT be used at large commercial scale. Previously cited pilot scale studies (1 L flow-cell) illustrate limit of practicality.

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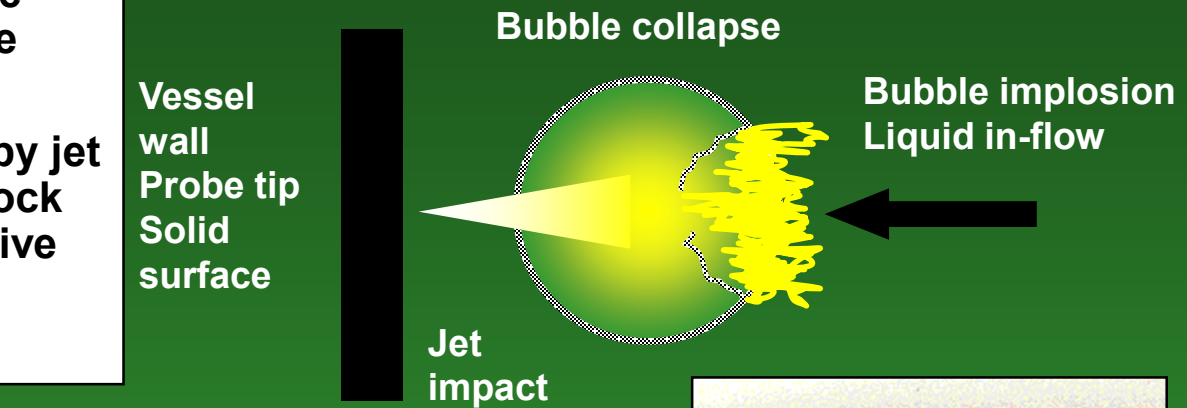
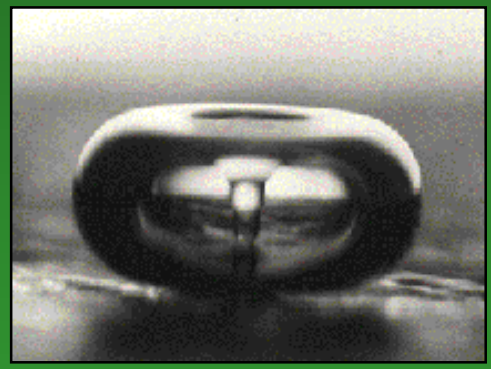
Probe Problems:

Cavitational Erosion

Liquid jet penetrates bubble during asymmetric collapse

Damage to a solid caused by jet impact and emission of shock waves as a result of repetitive bubble implosions





After 30 hrs of non-continuous use

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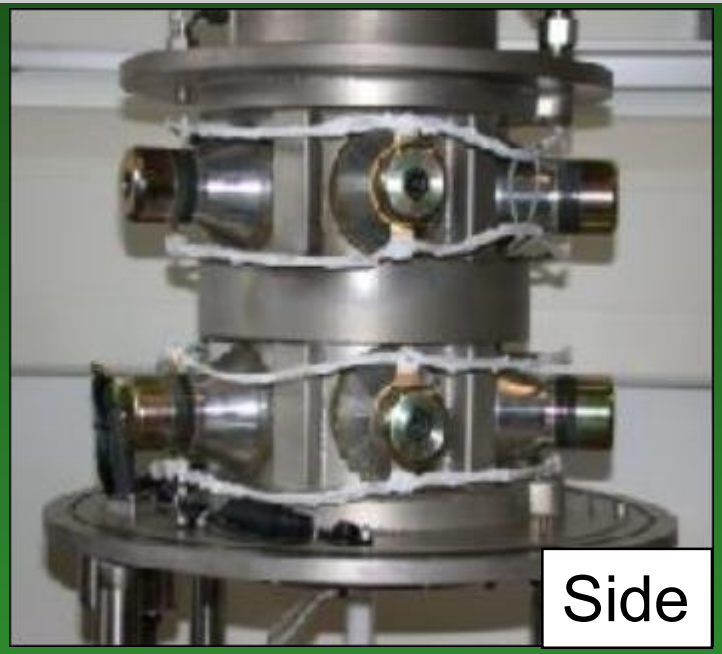
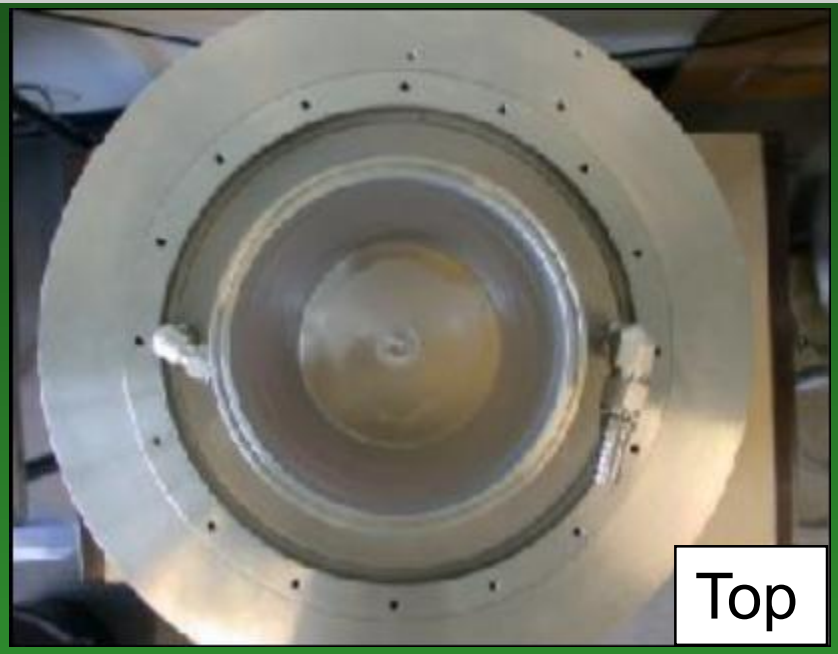
C^3 Ultrasonic Flow Cell

Perkins, J. P. AEA Technology plc. World Patent WO0035579 B1, 22 Jun. 2000





- Modular 5 litre cell, shown in batch mode (with bottom plate)
- Can also operate in continuous mode and units can be combined in a modular fashion for 'scale-out' and increased residence time
- Plurality of low [electrical and acoustic] power (~3 W/cm^2) transducers giving 25 – 150 W/L; ideally 40 – 80 W/L
- Use in continuous and pulsed mode
- Flexible arrangement using non-coherent ultrasound patterns

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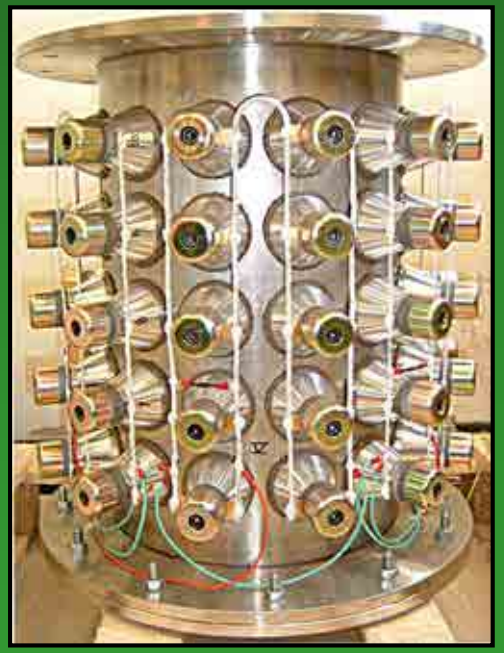
C^3 Scale-Out Philosophy

Generator module

37 litre cell module
5 rows, each with 12 transducers



n x modules
stacked to give desired residence time

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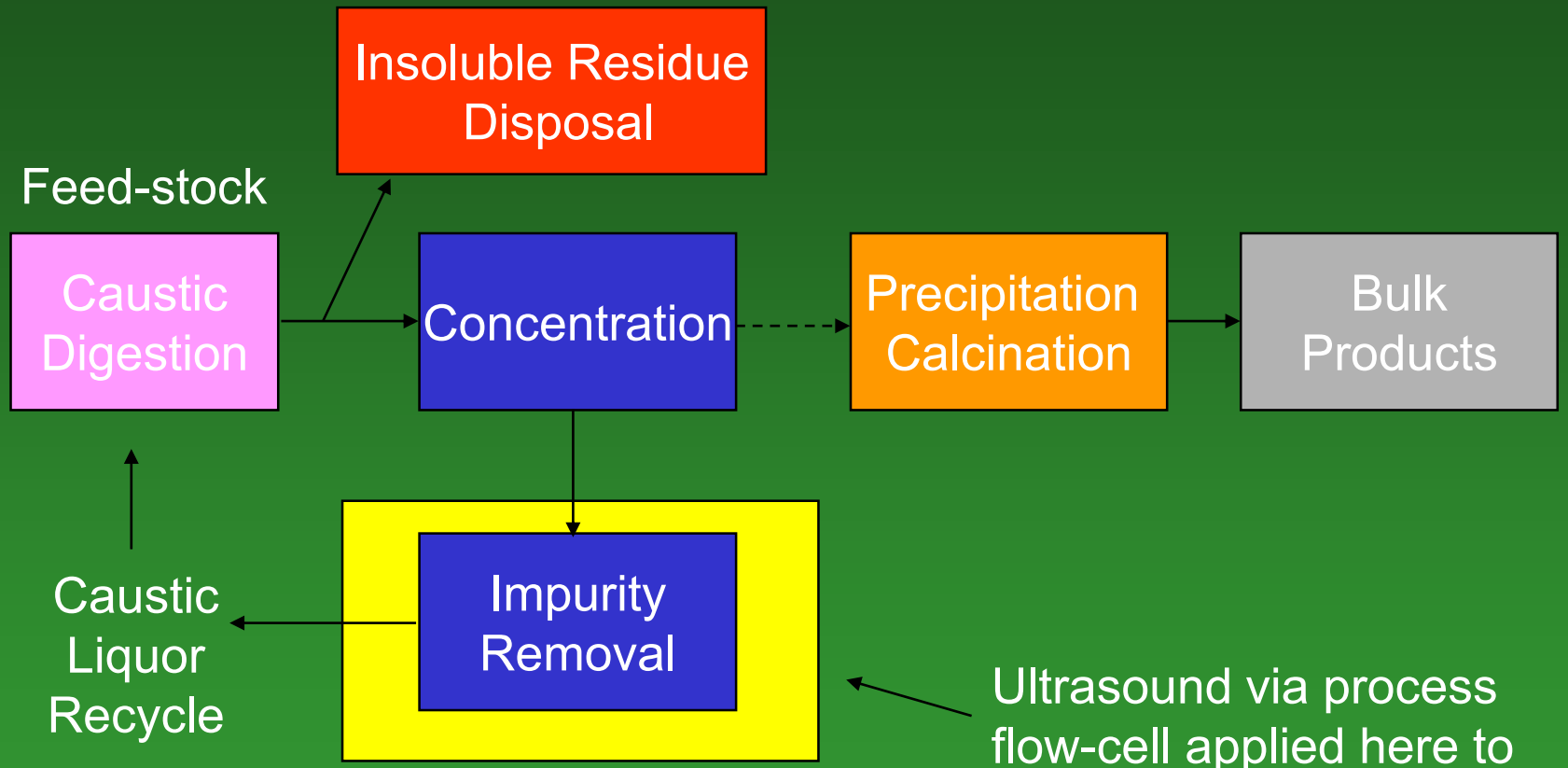
Bulk Inorganic Process > 1000MT pa

Highly simplified and little changed since first operation in late 1800's!



Ultrasound via process flow-cell applied here to remove key salt impurities

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Impurity Removal Benefits

Significant opportunity for Sonocrystallization in ‘old’ inorganic bulk processes

Application of C^3 technology can facilitate:

- Increased liquor productivity
- Lower consumable chemical consumption
- Increased refinery output
- Lower capital cost per tonne of product
- Better energy efficiency from increased concentration
- Fewer residues, lower environmental impact
- Use of lower grade feedstock
- Less degradation of product quality over time
- Increase in profitability of plant

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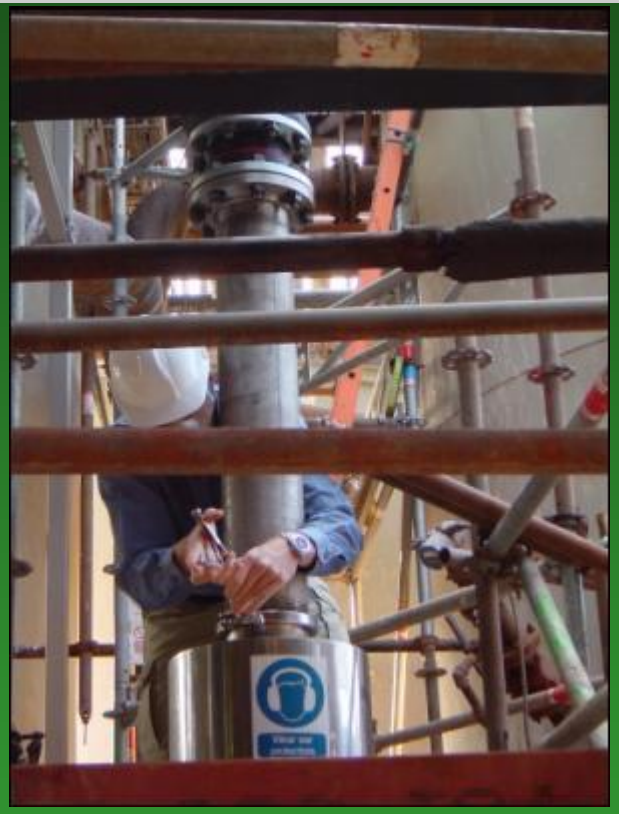
Pilot Flow-cell Installation

Piloted at 1/30th scale over 6 months



- 5-10 m length ultrasonic flow-cell / duct estimated for full scale
- Start up Q1 2005

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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 inorganics
- Improved crystal purity and physical properties
- Removal of secondary unit operations (milling etc)
- Generation of new intellectual property

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Future of 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

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- Rob Perkins (Sonic Systems)
- C^3 Technology customer base

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