PAT Conference 2008

Exercising Real Control Over API & Excipient Isolation

The Power of Sonocrystallization!

30 October 2008, Heidelburg, Germany

Christian Jones, Business Development Manager, Prosonix Ltd.

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Agenda

- Company Overview
- The Critical Importance of Controlled Crystallization in Manufacture
- Sonocrystallization and Ultrasonic Particle Engineering
  - The Key to Controlled Crystallization of Bulk API and Excipient

    #1 Theory and Examples
    #2 Commercial scale solutions
- Advanced Ultrasonic Particle Engineering of Difficult to Manufacture products, such as those for Inhalation

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Prosonix Ltd

- Based in Oxford, UK
- Focused on patented ultrasonic particle engineering technology using proprietary sonocrystallization techniques to make better medicines
- Income stream from partner funded collaborations, licensing, and product supply
- Development collaborations with 8 of top 10 pharmaceutical companies
- *NEW* recent Milestone success with Pfizer

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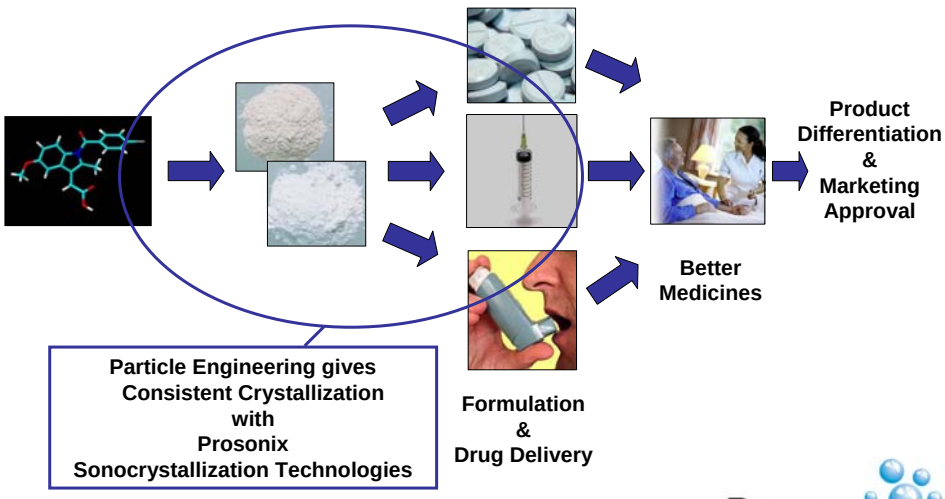
Prosonix Vision

"Making Better Medicines More Efficiently"



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The Critical Importance of Controlled Crystallization in Manufacture

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Pharmaceutical Manufacturing & QbD

- **Selection Criteria for NCE's are:**
  - Clinical Efficacy
  - Bioavailability
  - Stability
  - Processability
- **Manufacturing and ultimate product success is dictated by:**
  - Product physical form
    - *polymorphism, crystal habit etc.*
  - Process scale-up and manufacturing problems
    - *raw material variations*
    - *synthetic complexity*
- Improved understanding of manufacture and design space could also lead to better asset utilisation, quality and lower failure rates
- Sonocrystallization approaches can transform productivity at the same time as improving flexibility and manufacturing compliance

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Importance of Controlled Crystallization

- Crystallization is a ubiquitous and critical manufacturing unit operation
- Almost every chemical process that produces solid form involves at least one crystallization step, either for intermediate separation, final product purification, or for the removal of key impurities
- Crystallization processes are poorly understood and are difficult to control
- Control of the nucleation difficult but is the key to process control
- Process robustness governs process productivity and economics
- Physical form dictates drug product quality and effectiveness

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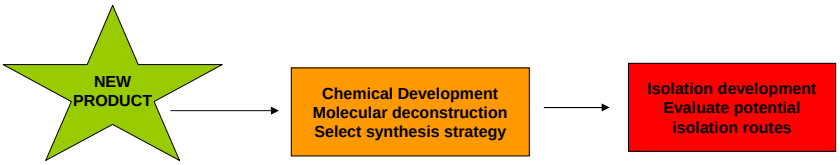
Importance of Materials Science

A lack of understanding in early development stores up future problems



- Classic series based approach to isolation and development brings problems

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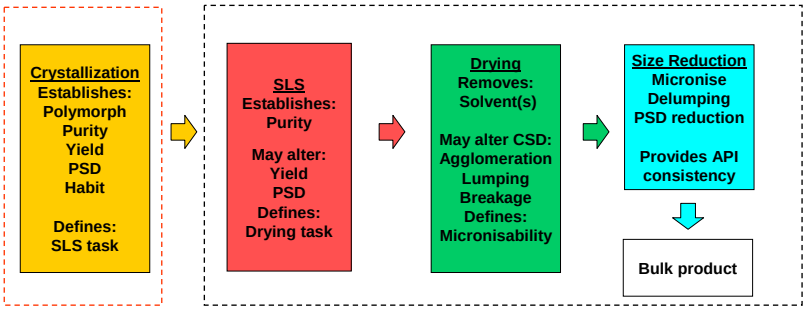
Importance of Controlled Crystallization

But by fixing things early by design enhances productivity and control



- Controlled crystallisation eliminates downstream problems
- Sonocrystallization potentially “best available technology” for API manufacture

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QbD Manufacture: A Cultural Change

Acknowledgement to Prof. Kevin Roberts, University of Leeds

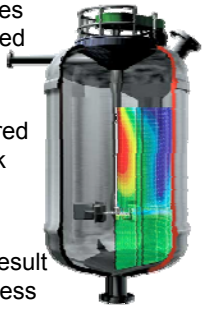
Historic Approach

“Process Down”

Processes discovered

Engineered to work

Products result from process



Improvements incremental

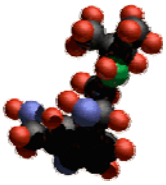
Poor product enhancement potential

Future QbD

“Molecule Up”

Step change in capability

Dynamic control of properties



Products built from molecules

Molecular design of product property

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Sonocrystallization

The Key to Controlled Crystallization of Bulk API's and Excipients

#1 Theory and Examples

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Key Benefits of Sonocrystallization

- Control particle size, shape, crystallinity, polymorphism
- Improve batch consistency, filtration, isolation and drying
- Improve formulation consistency, stability and performance
- Enhance dissolution of poorly soluble drugs
- Replace problem physical seeding
- Increase cGMP compliance

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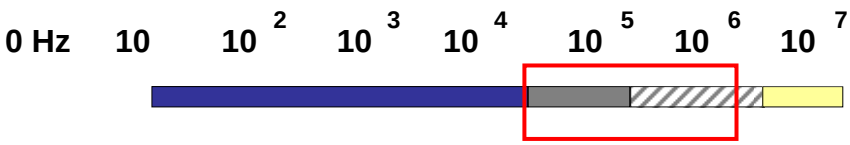
Frequency Ranges of Sound



Human hearing	**16Hz - 20kHz**
Conventional power ultrasound	**20kHz - 100kHz**
Extended range for sonochemistry	**20kHz - 2MHz**
Diagnostic ultrasound	**3MHz - 10MHz**

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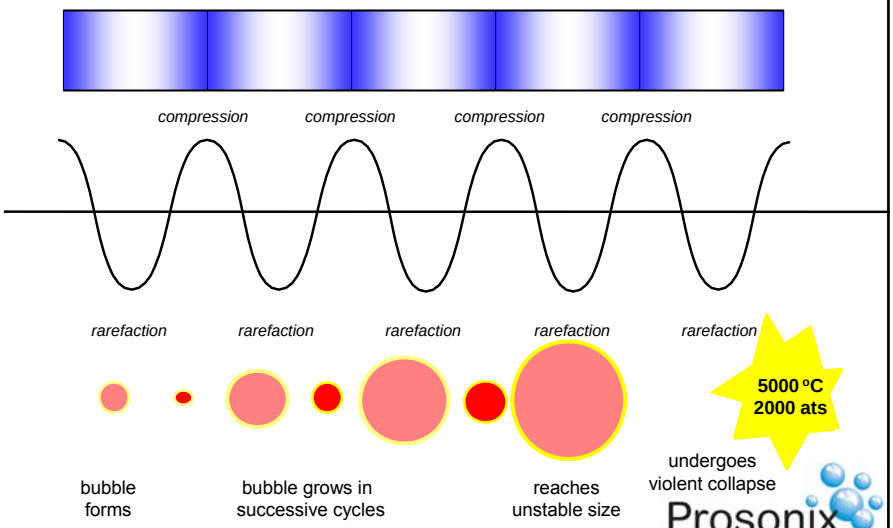
Acoustic Cavitation: Generation of the Bubble

Acknowledgement to Prof. Tim Mason, Coventry, UK



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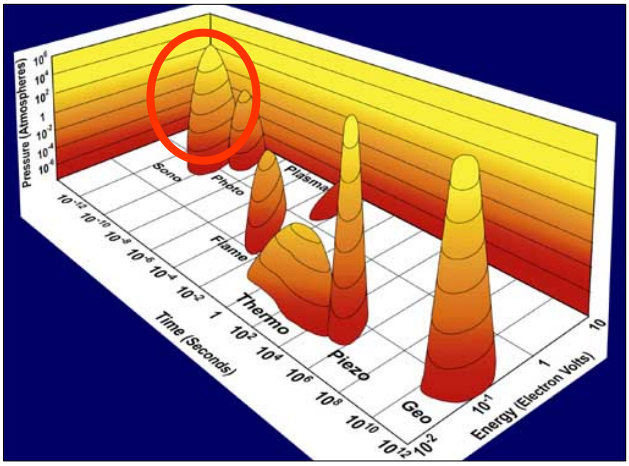
Comparison of Acoustical Energy to Other Sources



- Utilisation of ultrasound is a process intensification method in comparison to other energy applications
- Enables delivery of large quantities of energy in short timeframes on microscales, but for controlled macro process effect

Suslick, K. S.; Didenko, Y.; Fang, M. M.; Hyeon, T.; Kolbeck, K. J.; McNamara, W. B. III; Mdleleni, M. M.; Wong, M. "Acoustic Cavitation and Its Chemical Consequences" Phil. Trans. Roy. Soc. London A, 1999, 357, 335-353.

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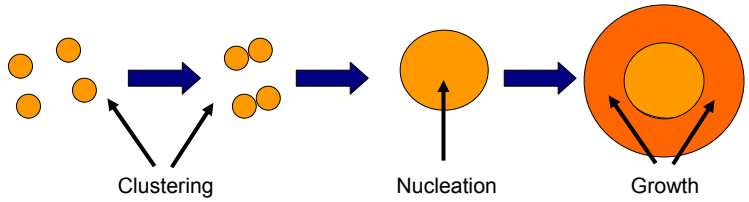
Sonocrystallization

Consistent crystallization for API and Excipients

- Classically Nucleation is random, and resultant crystallization processes are uncontrolled, leading to poorly performing API, and drug formulations
- Molecules of product assemble in clusters. The clusters will progressively increase in size to become viable crystals



- Controlled nucleation is fundamental to crystallization control
- Power ultrasound via cavitation allows controlled nucleation, *i.e. Sonocrystallization*
- Increasingly recognised and used for manufacturing improvement by *Merck* (Aaron Moment, Jan 2008, Leeds RSC SonoChemistry Conference), *AZ* (Literature), *Pfizer* (Material Science Presentation, Ivan Marziano APS meeting 2007)

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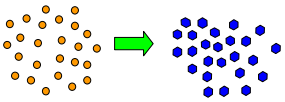
Control of Crystal Size

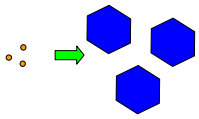
General Rules on the Effects of Cavitation on a Saturated Solution

ULTRASONIC TREATMENT OF SUPERSATURATED SOLUTION

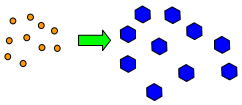
1. Continuous insonation produces many nuclei resulting in small crystals



2. Initial insonation produces finite nuclei which can be grown into large crystals

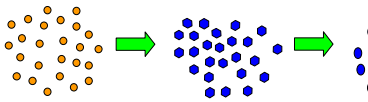


3. Pulsed insonation gives tailored crystal size



ULTRASONIC TREATMENT BEFORE & AFTER CRYSTALLIZATION

4. Continuous insonation throughout supersaturation produces many nuclei resulting in small crystals. Application of ultrasound thereafter can condition the crystals produced



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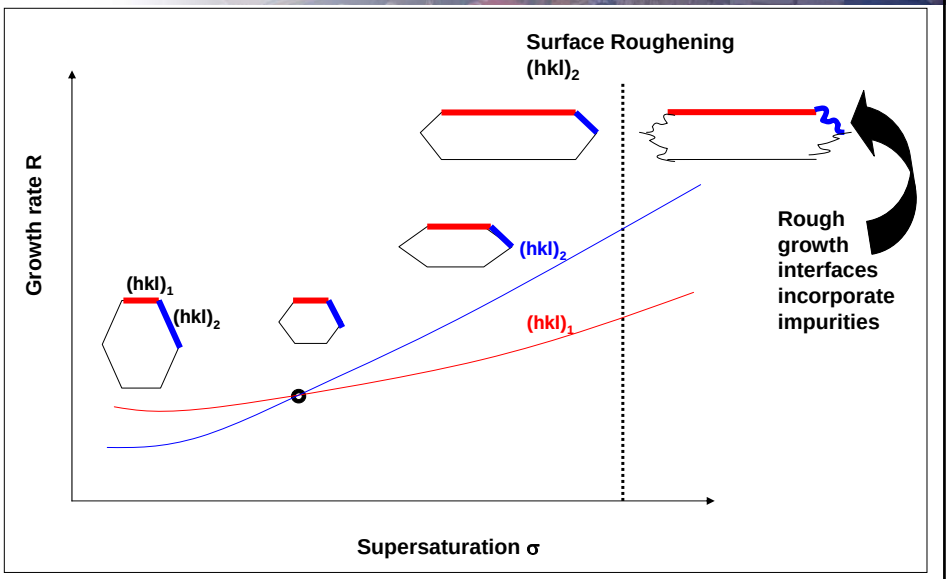
In-situ Ultrasonic Seeding: Aspect & Purity Control

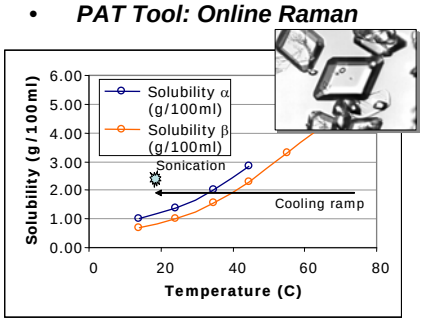
Acknowledgement to Prof. Kevin Roberts, Leeds, UK

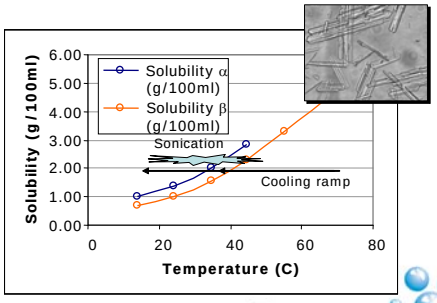


Polymorph Control with Ultrasound #1

L-Glutamic Acid

- L-glutamic acid has two polymorphic forms: α & β
- Metastable α-form: produced under kinetic control
- The transformation of form α to β is solution mediated
- The metastable a form is difficult to obtain
- Use power ultrasound to reproducibly prepare the α or β form
- Sononucleation at different supersaturation
- ***PAT Tool: Online Raman***





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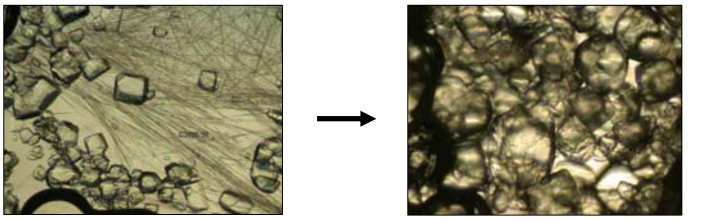
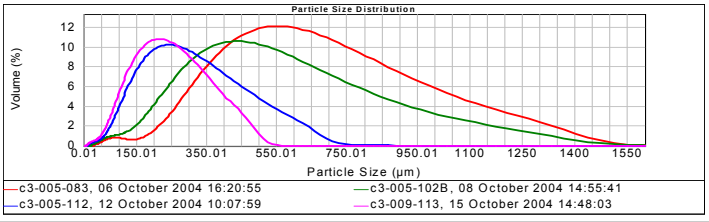
Polymorph Control with Ultrasound #2

Advanced small molecule API





Key results: reduced median crystal size, tighter CSD, polymorph control
PAT Tools: Online Raman and Lasentec

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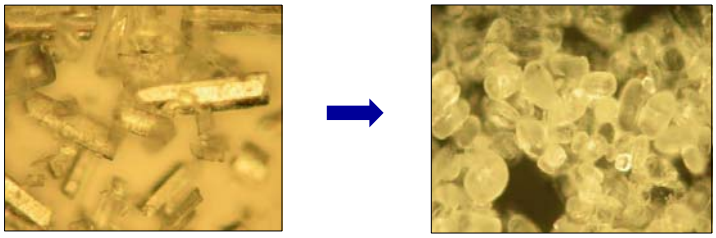
APIs – PRT Improves flowability

Diltiazem Hypertension Product



Raw powder **Rounded powder**

- Improved uniform packing density of powders
- Enhanced flow of powders
- Reduced electro-static charges
- Manufacturing by direct compression without granulation
- Higher filler loading in composite pastes
- Bypass patents on particle size/shape
- Significantly enhanced flowability
- Improved stability on storage (no agglomeration)

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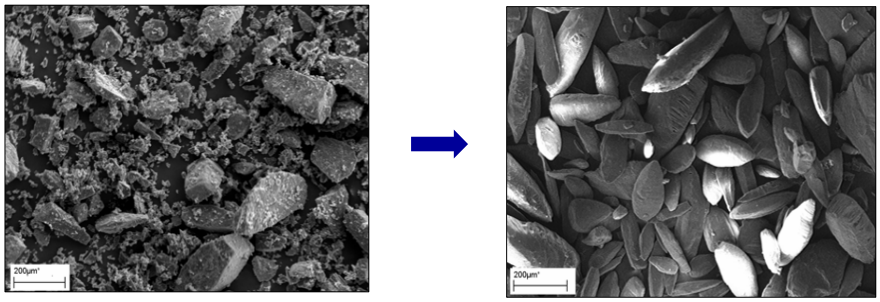
Excipients – PRT applied to Lactose



Raw powder **Rounded powder**

PAT Tool: Online Lasentec

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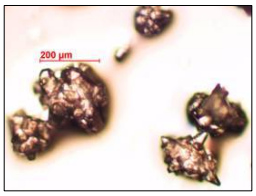
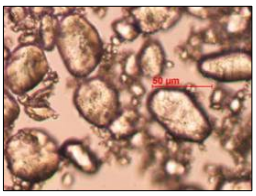
Sonocrystallization, Sonomilling, Particle rounding

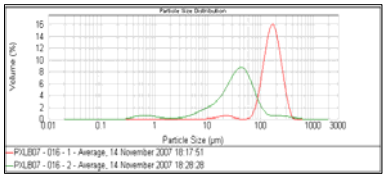
Specific angiotensin II type 1 antagonist - Hypertension

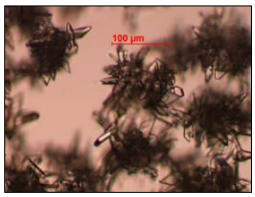


Cooling crystallisation

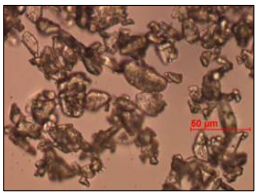


Sonomilling and rounding

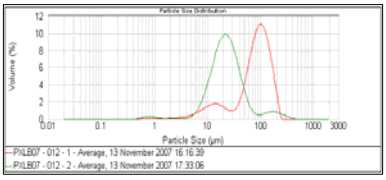




Sonocrystallisation



Sonocrystallization, Sonomilling and rounding



- Agglomeration and solvent inclusion is avoided
- Circumvent micronisation

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Sonocrystallization

The Key to Controlled Crystallization of Bulk API's and Excipients

#2 Commercial Scale Solutions

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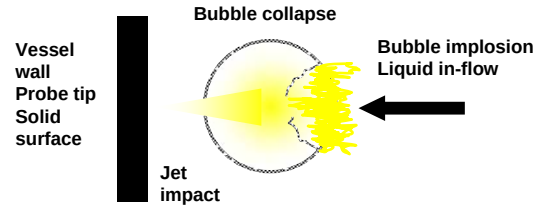
Probe Problems:

Cavitational surface erosion hitherto prohibited commercial use

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



Probes **can not** be used for commercial scale production

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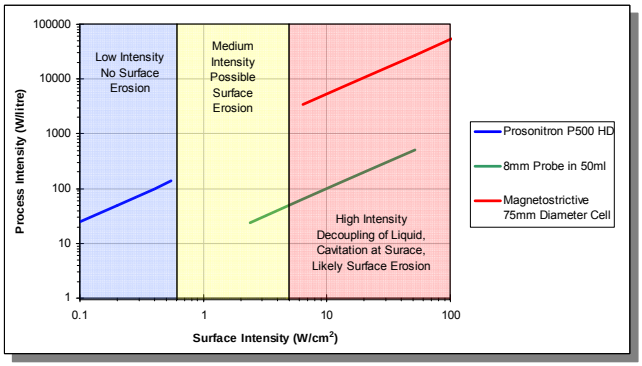
Prosonitron™ processing

Surface erosion compared with other ultrasonic devices



- Spreading of ultrasonic input over the whole surface of the cell allows significant specific power input to the fluid without demanding high surface intensity

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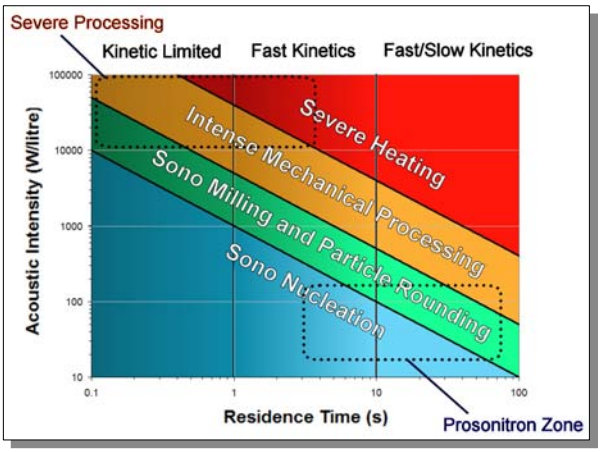
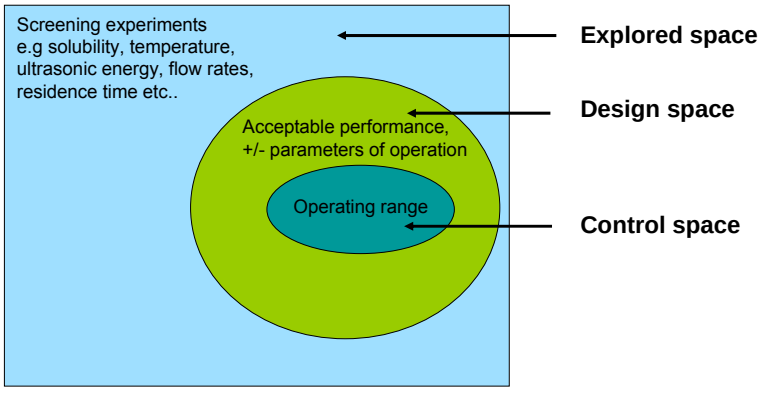
Consideration of Ultrasonic Design Space

Understand zones of operation to match desired process duty



- Based on Prosonix field experience
- Residence time of several seconds required to allow time for process kinetics, heat transfer and mixing to keep pace
- Particular important consideration in crystallization

Sonocrystallization Design Space for QbD



Process understanding via:

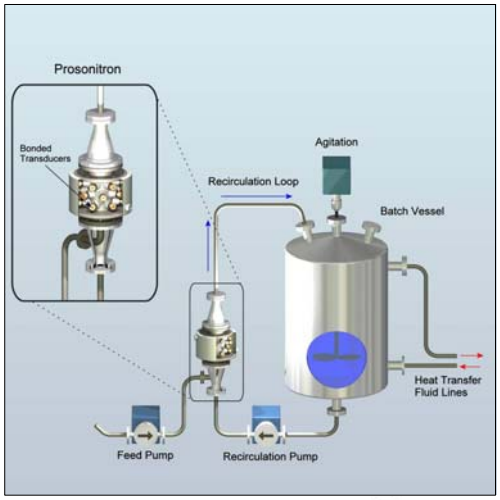
Critical Quality Attributes and Critical Process Parameters

Prosonix Ultrasonic Particle Engineering

'Prosonitron™' Technology for Commerical Scale

SonoLab™ SL-250

5L Prosonitron™



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Scale-Up Factors

Engineering Parameters to Maintain

- **Specific Power Input** – Intensity of acoustic power going into the process liquid (W / litre)
- **Specific Energy Input** – Intensity of acoustic energy used to achieve the process effect (J / litre)
- **Surface Intensity** – Acoustic power per unit area used to supply (W / cm^2)
- **Residence Time** – Required duration inside field to achieve process effect (s)
- **Reynolds Number** – Internal mixing and flow pattern within acoustic field (-)

Prosonitron™ Design Benefits

- Ease of maintaining specific power input to the process liquid and surface intensity at all scales.
- Ability to reproduce flow regime and residence time by configuration choice.
- Result is a system that can deliver consistent processing throughout scale-up from pilot to production.

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PAT & Complete Crystallization Control™

- Use CQA's and CPP's to understand and control manufacturing
- Use ultrasonic technology at scale to provide real time process control
- Need online measurement and feedback to achieve:
  - Control of ultrasonic energy
  - Control of temperature profiles
  - Turbidity / Lasentech for onset of nucleation
  - Particle size distribution
  - Polymorphic forms in solution
  - Supersaturation ?

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Prosonitron™ – Proven at commercial scale

"Best available crystallization technology" potential in pharma production

- Prosonitron™ at Pfizer, UCB & others...
- Pfizer Ireland acquire Prosonitron™ technology for Primary API Manufacture
- 4 year co-development relationship with UCB
- Many new & current trials at major and specialty pharma worldwide
- Primary for oral, but exciting developments in inhalation, nanosuspensions, parenteral, sub Q, and dermatological delivery

Prosonitron™ linked to Lasentec

- Prosonitron™ system in operation in alumina
- Over 3 years continuous service to date
- Follow on global deal with Alcoa

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Advanced Particle Engineering of Difficult to Manufacture products

e.g. Delivery by Inhalation

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Product properties of particulate systems

Its much more than just size control….

Product property = *f*(Dispersity, Chemical Composition)

- Dispersity characterised by:
  - Particle Size
  - Particle Shape
  - Particle Surface Morphology
  - Particle Surface properties

- Aerodynamic Ø 0.5 - 5µm
- Conferred spherical geometry
- Minimise surface free energy – crystals
- Reduce contact area – spherical, rugged surface

- Control of interfacial interactions (adhesion/cohesion) is governed by surface forces
- Geometry, not surface chemistry, is the central design principle in controlling interfaces and their interactions.

Design of particles for end use properties!

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Solution to Particle Technologies

Dr Ivan Marziano, Pfizer Material Science, APS Inhalation meeting 28 March 2007

Micronisation is often not feasible for inhaled medicines!

Solution to Particle technologies are based on the formation of highly supersaturated droplets either through spraying or dispersion in non-miscible media; Particle growth occurs within confined space (= droplet)

- Aerosol flow reactor (VTT)
- SAX™: solution atomisation and crystallization by sonication ***(Prosonix)***
- Emulsion crystallization
- Quasi emulsion/spherical crystallization
- Cryogenic spray freezing/liquid extraction
- Spray freezing into liquids/spray freeze drying
- Spray drying
- EPAS: evaporative precipitation into aqueous solution (Dow)
- Segregated flow tubular reactor ("Bubbletube")

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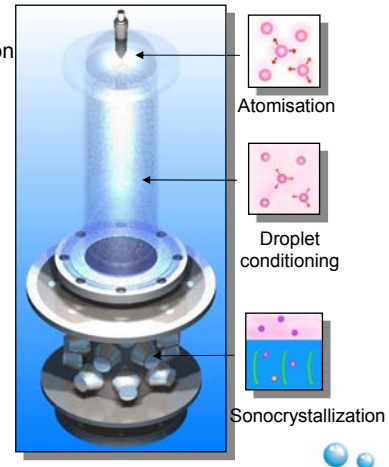
SAX™ – New "Solution to Particle" Technology

The future solution to ultimate particle control ?

- SAX™ builds on the Prosonitron™ IP
- Designed to produce 1 to 5 µm crystalline combination particles tailored uniquely for inhalation
- 20 customer studies completed to date
- Combination of proven unit operations:
  - Solution of API / mixtures of API + excipients
  - Atomization creates spherical droplets
  - Controlled evaporation
  - Controlled crystallization by Sonocrystallization
  - Simple and proven isolation procedure
- Tested on a range of APIs and NCEs
  - Stable crystalline particles
  - Combinations of 2 or 3 drugs possible
  - Improved *in-vitro* performance



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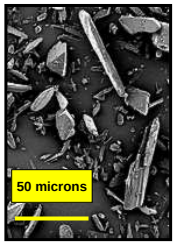
Unprecedented Process & Product Control

Optimal SAX™ drug particles should give better inhalation clinical performance

- Current destructive (i.e. micronisation) production techniques are severely limited
- API particles can be fully engineered from the the “ground up” via controlled SAX crystallization
- Improved SAX™ drug particles gives optimum formulation performance and patient benefit across all inhalation delivery platforms



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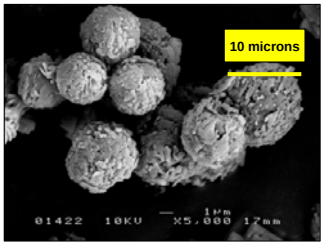
Micronisation

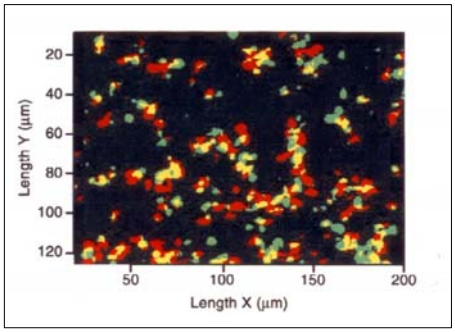


Size	☑
Shape	☑
Surface Morphology	☑
Surface properties	☑
Crystallinity	☑
Stability	☑

SAX™

Seretide Combination: Single *vs* separate inhalers?

Nelson et al J. Allergy Clin. Immunol. Vol 112 (1), 2003, 30



Raman laser analysis of Seretide metered-dose inhaler formulation on stage 4 ACI

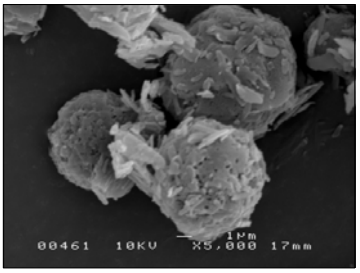
Key:
Fluticasone (green),
Salmeterol (red)
Co-association (yellow)

- 4 Separate clinical studies showed equivalence viz primary efficacy
- Consistent trend in favour of combination therapy
- Increased efficacy over concurrent use of same doses of same 2 drugs
- Co-deposition offers increased opportunity for synergistic interaction

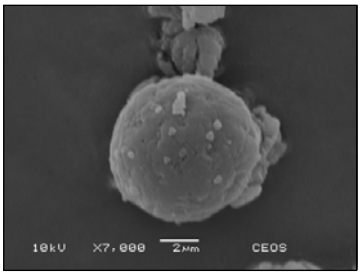
SAX™ - Designed Combination Particles

A new way to treat Asthma/COPD and other disease states?

- Eliminate variability associated with blending of 2 or more micronised powders
- Multiple API's in the correct dose ratio can be symbiotically crystallized in a single perfect particle
- Controlled Combination Therapy Delivery



Fluticasone and Salmeterol (1:3.448)



Budesonide and Formoterol (1:17.71)

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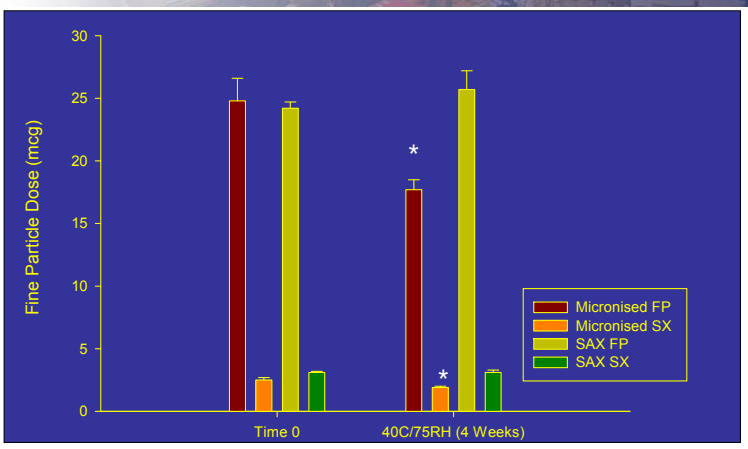
Improved Product Stability with SAX™

Carrier based DPI formulation

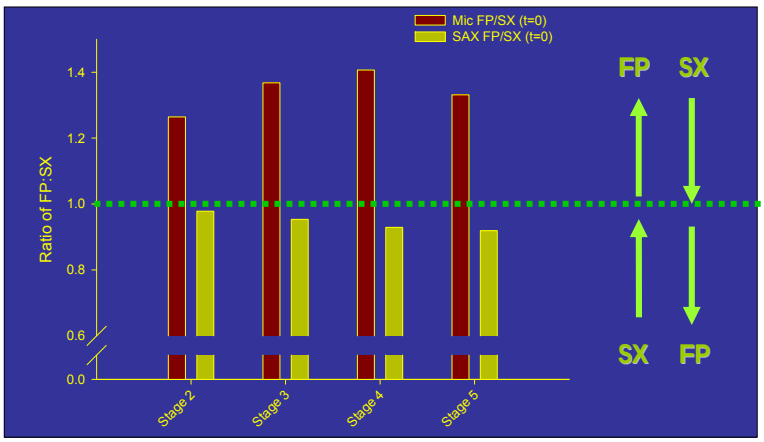


- Carrier based DPI formulations (FP:SX 1:5)
- In vitro apparatus: NGI @ 60 L/min; Monohaler DPI device
- Seamless transition and increased stability

Prosonix
Experts in Sound Science

Improved Dosing Compliance with SAX™

Uniformity of FP-SX doses: lower stages of an NGI

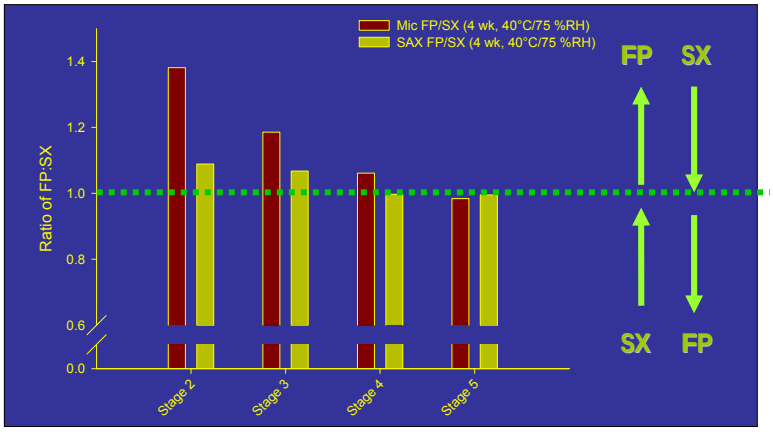


The dose balance of micronised formulations of FP and SX not consistent between stages micronised batches.

Variability in the delivery of FP with respect to SX on the lower stages

Improved Dosing Compliance & Stability

Uniformity of FP-SX upon storage



- Accelerated stability conditions affect the dose balance of micronised formulations
- SAX particles maintain high content uniformity of the actives

Summary

- Now possible to engineer and produce *"Designed for Purpose"* Particles
- QbD provides process understanding
- PAT provides repeatable and robust processes
- Key benefits include
  - Control particle size, shape, crystallinity, polymorphism
  - Improved batch consistency, filtration, isolation and drying
  - Replacement of problem physical seeding
  - Increased cGMP compliance
  - Improved formulation consistency, stability and performance
  - Increased return on investment
  - Reduced time to market
- Ultrasonic Particle Engineering and Sonocrystallization gives levels of control over isolation that current manufacture cannot deliver

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