Utilizing Adaptive Focused Acoustics™ (AFA) Technology to Control Nucleation and Crystal Distribution During API Crystallization

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Covaris, Inc
Adaptive Focused Acoustics™ (AFA)

- Control API “bottom up” nucleation and crystal growth in a batch vessel or continuous process stream
- Control NUMBER of nucleated particles
  - Control particle size by controlling growth dynamics from fixed number of seed particles
- Reduce induction time: accelerate kinetic energy reactions with extreme mixing velocities in isothermal conditions with a non-contact process
- Integrate PAT for automated, real time feedback, and Quality Control

- Potentially improve Permeability and Solubility
- Increase overall productivity
- Reduce losses associated with milling and micronization
- Improve downstream flowability and handling characteristics
- Shorten production process times
- More readily adapted to handling highly potent compounds
AFA Technology

Inducing nucleation

Batch processing

Continuous flow processing
AFA Technology

Inducing nucleation

Batch processing

Continuous flow processing
AFA: “Controlled” Cavitation

- Under appropriate conditions, acoustic waves traveling through a liquid medium may cause the dissolved gasses to come out of solution as microscopic bubbles that then collapse generating shearing forces as the fluids rush back in to fill the void.

- Covaris technology controls cavitation which enables control over shear forces

- Cumulative effect of hundred of thousands of cavitation bubbles
Technology overview

Acoustic frequency spectrum
AFA Technology

High frequency >
Short wavelength >
Allows focusing >
High energy density >
Highly controllable

- Non contact
- Isothermal
- Repeatable
- Efficient
Pressure and temperature profiles of comparable processes

**Covaris AFA**
- focused transducer
- non-contact

**Bath Sonicator**
- unfocused transducer
- non-contact

**Probe Sonicator**
- focused waveguide
- sample contact

**Pressure Profile**
- Covaris AFA: 0.8 Watt
- Bath Sonicator: 130 Watt
- Probe Sonicator: 4.6 Watt

**Thermal Profile**
- Covaris microTUBE
- Microcentrifuge Tube

To create cavitation ~1 MPa

~150X Energy

~5X Energy

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A few of the locations of the > 4,500 systems placed worldwide
System Hardware Overview

• Flow Module
  – Bath
  – Transducer
  – Acoustic Window
  – Flow Cell
  – Pressure Sensor

• Cabinet
  – Control Electronics
  – Chiller
  – Filters (Particle, UV)
  – Degas System
  – Sensors (Flow, O₂)
Flow Module Features

• Passivated 316 stainless steel construction
• Simple, polished/smooth surfaces with no micro-passages
• Explosion proof design
• No contact between the sample and transducer
• Thermal control of the sample
• M16x1 fittings and triple insulated hoses
AFA Technology

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Paracetamol solubility reference

AFA dramatically reduces meta stable zone width (MSZW)
Without AFA it stays in solution
Multipass 100mL batch testing in EasyMax 102

Formulation
200mg/mL paracetamol
100% Ethanol
100mL solution

EasyMax reactor
300rpm stir
30C

Pump
Watson Marlow 120U
10mL/min
PharMed -16 tubing

AFA:
Chiller 20C
Sample 24-28C
150 PIP
50% Duty Factor
1000 Cycles/burst
Batch setup

ParticleView
(Real time imaging)

AFA module

Particle Track
(Real time crystal distribution and trends)

EasyMax
(Automated reactor with temperature control)
Inducing Nucleation using AFA

Upon heating to 65 ºC complete dissolution; No crystals observed cooling down to 30 ºC

Exposure to AFA 150 PIP induced nucleation after ~ 6 min (30 ºC)

Paracetamol slurry after exposed to multiple AFA cycle

Crystals @ steady state

<10 micron counts from ParticleTrack

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AFA Technology

Inducing nucleation

Batch processing

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Impact of AFA PIP on Induction Time
Multipass batch testing in EasyMax 102

Formulation
- 200mg/mL paracetamol
- 100% Ethanol
- 100mL solution

EasyMax reactor
- 300rpm stir
- 30°C

Pump
- Watson Marlow 120U
- 10mL/min
- PharMed -16 tubing

AFA:
- Chiller 20°C
- Sample 24-28°C
- 0, 75, 150, 300 PIP
- 50% Duty Factor
- 1000 Cycles/burst
Experiment 2  75 PIP – A Closer Look (AFA Start : 00:50:16)
Experiment 2  75 PIP – A Closer Look (AFA Start : 00:50:16)

T = ~6 Min

21 June 2017
Experiment 2  75 PIP – A Closer Look (AFA Start : 00:50:16)

T = ~8 Min

METTLER TOLEDO

21 June 2017
Experiment 2  75 PIP – A Closer Look (AFA Start : 00:50:16)

T = ~20 Min

21 June 2017
Experiment 2  75 PIP – A Closer Look (AFA Start : 00:50:16)

T = ~40 Min

100 µm

142 µm

METTLER TOLEDO
Experiment 2  75 PIP – A Closer Look (AFA Start : 00:50:16*)

Pink Trend (<10 Microns)
Red Trend (100-500 Microns)
Blue Trend (30-90 Microns)

Counts 100-500 Microns
Counts 30-90 Microns
Counts <10 Microns

°C

00:30:00  00:45:00  01:00:00  01:15:00  01:30:00  01:45:00

Relative Time

Images of samples taken at different time points:

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AFA PIP vs. Induction Time

- AFA 150 PIP (~1 min)
- AFA 75 PIP (~3 min)
- AFA 300 PIP (~0.5 min)
- AFA 0 PIP (~18 min)

AFA Started: 21 June 2017
Higher PIP accelerates time to first particle formation

Induction time relationship with AFA PIP

Time to particle formation (min)

PIP (w)
Paracetamol in Ethanol Solubility

![Graph showing the solubility of Paracetamol in Ethanol](image-url)
Crystal Distribution Over Time @ 75 PIP

Statistics

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Counts &lt;10 µm</th>
<th>Counts 100-500 µm</th>
<th>Wt. Mean (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~6 min</td>
<td>3,323</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>~15 min</td>
<td>11,576</td>
<td>297</td>
<td>61</td>
</tr>
<tr>
<td>~60 min</td>
<td>7,942</td>
<td>1,094</td>
<td>84</td>
</tr>
</tbody>
</table>
Crystal Distributions vs. Variable PIP

**Statistics**

<table>
<thead>
<tr>
<th></th>
<th>~15 min @ 75 PIP</th>
<th>~15 min @ 150 PIP</th>
<th>~15 min @ 300 PIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counts &lt;10 µm</td>
<td>11,576</td>
<td>11,038</td>
<td>5,439</td>
</tr>
<tr>
<td>Counts 100-500 µm</td>
<td>297</td>
<td>325</td>
<td>832</td>
</tr>
<tr>
<td>Wt. Mean (µm)</td>
<td>61</td>
<td>63</td>
<td>82</td>
</tr>
</tbody>
</table>

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Conclusion: AFA triggers primary nucleation at conditions that otherwise would not nucleate

Demonstrated:

- Accelerate nucleation/induction times
- Increase yield (mass of solids)
- AFA exposure impacts crystal distribution
AFA Technology

Inducing nucleation

Batch processing

Continuous flow processing
Continuous flow test conditions

Paracetamol: 200mg/mL
Solvent: 100% Ethanol
Stage 1 Feed reactor:
   65C, 300rpm, 1 Liter
AFA module: Sample 35C, 22mL
Stage 2 Crystallization reactor:
   35C, 300rpm, 100mL
Peristaltic transfer pump: 10 to 50ml/min
PharMed -16 tubing

Demonstrated:
• Trigger nucleation below secondary nucleation limit
• Accelerate nucleation/induction time
• Generate specific number of nucleated particles
• Increase yield (mass of solids)
Continuous flow AFA seed nucleation

Real time continuous seed crystal generation using AFA – single pass, recirculation/remelt
Experimental setup

- AFA flow module
- Feed reactor
- Stage 2 reactor with FBRM and PVM Probes
- EasyMax Automated Lab Reactor
Particle count vs PIP

Number of particles below 5 micron showing direct relationship between particle count and AFA PIP setting

Chiller adjusted to maintain constant sample temp
### Statistics

<table>
<thead>
<tr>
<th></th>
<th>200 PIP Steady State</th>
<th>300 PIP Steady State</th>
<th>400 PIP Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counts &lt;5µm</td>
<td>1,240</td>
<td>1,709</td>
<td>2,217</td>
</tr>
<tr>
<td>Unweighted Median (µm)</td>
<td>6.5</td>
<td>6.4</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Particle count nearly linear with PIP

Particle count

<5micron counts from Particle Track

AFA PIP (Watts)
AFA allows more control over nucleation, and subsequent particle size characteristics

Demonstrated:

• Trigger primary nucleation below traditional nucleation limits
• Accelerate nucleation/induction times
• Generate a specific number of nucleated particles
• Real time, computer controlled particle COUNT
• Increase yield (mass of solids)
Thank You