Formulation and Drug Delivery

Breakthrough processing for poorly soluble API's

Covaris®

Covaris Process Technology

AFA for Formulation and Drug Delivery

Today, the majority (> 80%) of new chemical entities (NCE) discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds; as are about 40% of existing drugs in the market. Consequently, this creates major challenges in drug development due to poor solubility, short biological half life, poor bioavailablity, prominent adverse affects, and stability of NCE.

AFA provides the ability to process a number of different constructs to help overcome solubility difficulties. Using AFA-based systems, both Liposomes and Emulsions are prepared at low processing temperatures without the use of organic solvents. This allows for the encapsulation of temperature or solvent sensitive API's such as peptides or proteins, which would otherwise be destroyed or inactivated during the preparatory processing. Thus, API's previously considered not feasible, can now be considered for development.

What is AFA Technology?

Adaptive Focused Acoustics® (AFA®) is an advanced acoustic technology, which enables mechanical processing of samples by Covaris Focused-ultrasonicators. AFA employs highly controlled bursts of focused high-frequency acoustic energy to efficiently and reproducibly process samples in a temperature-controlled and non-contact environment.

- Focuses the acoustic energy into a discrete focal zone within a sample vessel
- Requires minimal energy input, avoiding the adverse effects of excess energy such as damaging heat, experimental variability, and sample over-processing typical of ordinary sonicators

Covaris Consumable

Focal Zone

Water bath

Focused-ultrasonicator Transducer
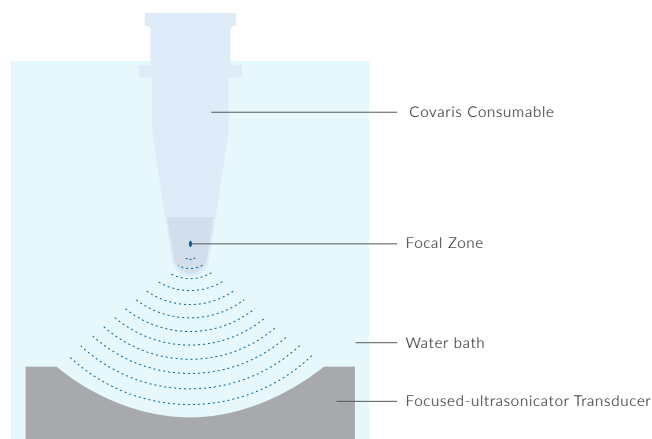
Sample processing with AFA ultrasonic energy is accomplished by controlling the creation and collapse of millions of cavitation bubbles within the sample vessel. Acoustic waves pass through a solution creating localized pressure fluctuations which in turn cause dissolved gasses to form hundreds of thousands of microscopic cavitation bubbles. The bubbles then grow, oscillate, and collapse. Covaris AFA-energetics enables precise control of the generated shear forces.

Applications

AFA Application Advantage: AFA can be tuned to process samples in a variety of applications, from low-power gentle mixing of solutions to higher-power applications such as liposome formation and milling nanosuspensions.

- **Compound dissolution for HTS:** AFA offers an automated platform to drive compounds that may have precipitated or settled back into solution before screening dispense. This ensures accurate and uniform dispensing.
- **PK studies:** Homogenize and extract for PK analysis, from a wide range of tissue types including brain, muscle, and cornea to name a few.

- **Animal study formulation preparation:** Automated preparation of suspensions/formulations for animal dosing. Eliminate operator variation between sites. Dramatically lower CV's (from 10% to 15%, to less than 0.5% dose to dose CV).

- **Accelerate mixing:** Drive formulation to equilibrium in minutes or seconds. Dramatically shorten mixing needed for complex inclusions, such as cyclodextrins, from days to minutes.

- **Early TOX:** Create small scale (100 µL to 18 mL) nanosuspensions by direct milling. Enable early Dose Response studies on very limited material, in a very short timeline.

- **Create nanoparticles:** Small molecule nanoparticles via milling or controlled crystallization. Liposome, PLGA particle, and nanoemulsion formation.
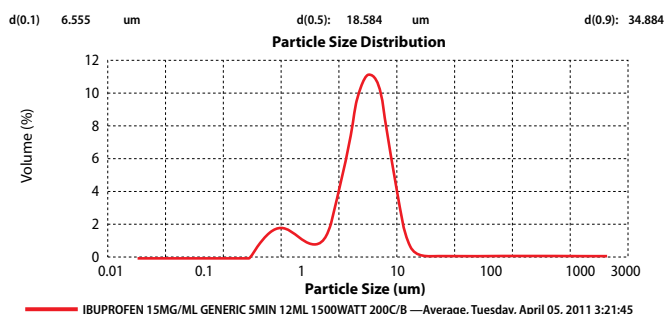
AFA Benefits

- **Reproducible product specification**
  - Automated, computer controlled processing
- **100% Recovery**
  - Formulate with limited material with no waste
- **Non-contact**
  - Eliminates risk of contamination

- **Maintain critical quality attributes**
- **Scalable**
  - 100 µl to continuous process flow with PAT feedback
- **"Temperature-tunable" process**
  - Low temperature processing (4 °C)

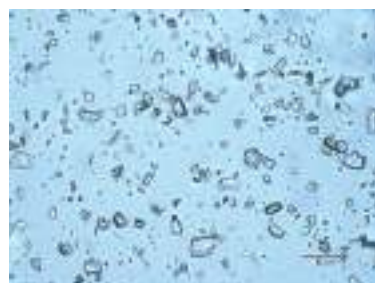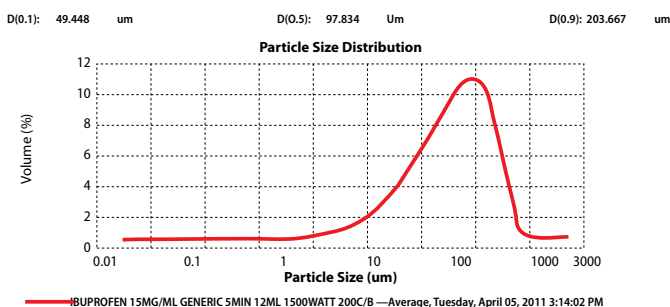# Formulation and Drug Delivery Applications

Micronization

- Enhanced bio-availability

- Dramatic reduction in API degradation during solubility screening

- Standardize and automate repeatable protocols

12 ml of ibuprofen before and after 5 minutes

d(0.1) 6.555 um   d(0.5): 18.584 um   d(0.9): 34.884

Particle Size Distribution

IBUPROFEN 15MG/ML GENERIC 5MIN 12ML 1500WATT 200C/B —Average, Tuesday, April 05, 2011 3:21:45

D(90) > 200 µm before

D(0.1): 49.448 um   D(0.5): 97.834 Um   D(0.9): 203.667 um

Particle Size Distribution

IBUPROFEN 15MG/ML GENERIC 5MIN 12ML 1500WATT 200C/B —Average, Tuesday, April 05, 2011 3:14:02 PM

D(90) < 35 µm after

AFA Enables Fast to First-in-Human

Liposomes

- Emulsions
- AFA-nanoparticle
- Co-solvent free
  - Formulate lipids or hydrophobic compounds without organic solvents
- **No thermal damage**
  - Formulate at low temperature, such as 4 °C
- **No contamination**
  - Formulate in self-contained, sterile, single-use vessels
- **Non-contact**
  - Full recovery of rare and expensive materials
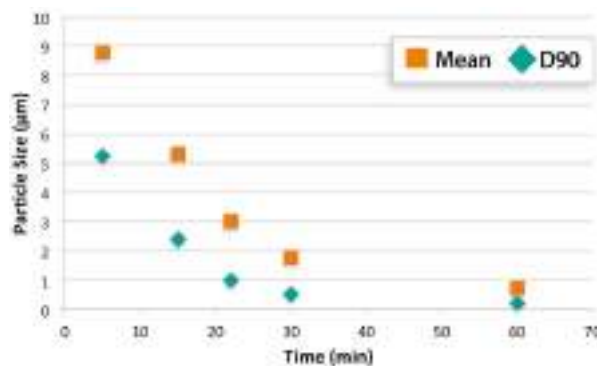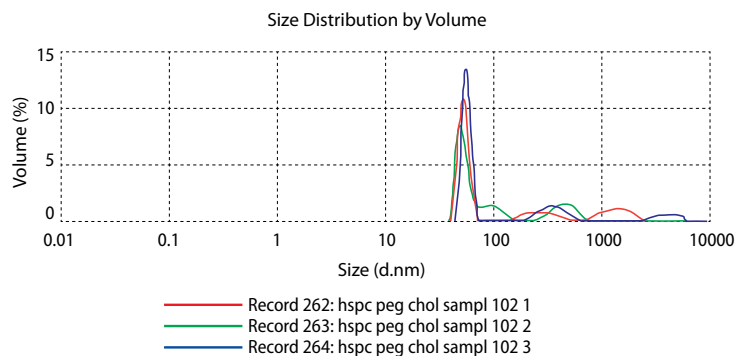
Nanosuspensions

Milling "Tops Down"

Crystallization "Bottoms Up"

- **Enables early stage toxicology studies with limited material**
  - 100% Material recovery
  - In sterile, uncontaminated vessels
- **Best in class particle size**
  - No bead contamination
- **Accelerates dose range finding studies**
  - Reduce both time and material for complex formulation development

Unique Constructs and Intravenous Preparations

Size Distribution by Volume

Record 262: hspc peg chol sampl 102 1
Record 263: hspc peg chol sampl 102 2
Record 264: hspc peg chol sampl 102 3

Dissolution

- Resuspend formulations that have settled
- Enhance solvent/solvate interactions at molecular boundary layer
- Dramatically accelerate dissolution rates
- Automate compound re-suspension in high-throughput screening

Crystallization Comparison

- Accelerate nucleation and reduce induction time
- Maintain morphology
- Control particle size

Without AFA   With AFA

4

Focused-ultrasonicators

AFA Focused-ultrasonicators deliver highly efficient, targeted ultrasonic acoustic energy in a highly tunable manner, enabling programmable control of the energy density of the acoustic burst delivered to a sample. The ability to tune these acoustic characteristics controls the particle size/shape formation. Focused-ultrasonicators are extremely robust platforms providing reproducible formulation preparation.

M-Series Focused-ultrasonicator

✓ Small volume for general purpose lab procedures
✓ 100 µl to 2 mL

S220X Focused-ultrasonicator

✓ Single vessel processing from 300 µl through 18 mL sample volumes
✓ Discovery
✓ Animal dosing
✓ Method development
✓ Optional flow through process vessels for 100 mL to 10 Liter batch processing

E220 Focused-ultrasonicator

✓ High-throughput, automated workflows

Production Focused-ultrasonicator

✓ Passivated 316 stainless steel construction
✓ Explosion proof module design (stainless drip proof cabinet)
✓ 100% sample containment
✓ Outstanding thermal control of the sample
✓ cGMP capability coming soon

AFA Process Vessels

AFA Batch Vessels: Lab Scale

Covaris Consumable

Focal Zone

Water bath

Focused-ultrasonicator Transducer
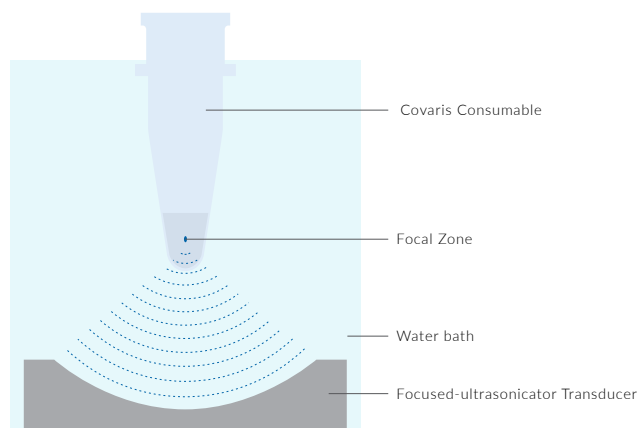
Low Power: AFA Glass

Pharmaceutical grade borosilicate, hardened glass. Specifically designed for use in AFA acoustic circuit.
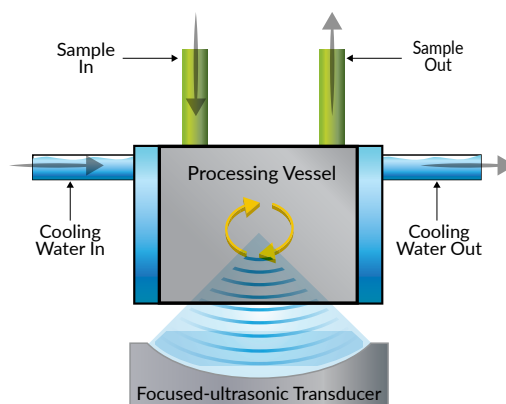
- Engineered and quality controlled for AFA
- Inert materials: Teflon septa, glass (AFA-grade)
- Range of size from 1 to 18 ml

High Power: AFA Stainless Steel

Precision CNC machined exact AFA specifications. Material quality control and traceability. Pharmaceutical grade 316 stainless steel.

- Allows highest AFA processing energy
- Electropolished 316 stainless wetted surfaces
- First step for scalability

AFA Flow Vessels: Continuous Flow Scale

Sample In

Sample Out

Processing Vessel

Cooling Water In

Cooling Water Out

Focused-ultrasonic Transducer

AFA Flow vessels

- Electropolished 316 stainless wetted surfaces
- High heat flux heat exchanger with dean vortex cooling design
- Control sample temperatures from 4 to 40 °C
- Inlet/outlet temperature monitoring
- 316 stainless wetted surfaces

Thermocouple

- In-line temperature measurement for real time sample temperature monitoring

AFA Glass Vessels- bath

- Single use and maximizes mixing
- Size ranges from 1 to 18 ml

AFA Stainless vessels - batch

- 316 stainless steel processing vessels designed to run at maximum power and efficiency
- Volumes as small as 300 µl

AFA Stainless vessels - flow

- Best thermal control for continuous operation
- Flow cell with integrated coding heat exchanger for isothermal temperature control of the sample

AFA Vessel Type	AFA Material	Vessel Volume (ml)	Low Power <150 PIP	High Power <500 PIP	Part Number
Batch	Glass	2	●		520056
Batch	Glass	4	●		520088
Batch	Glass	8	●		520089
Batch	Glass	12	●		520086
Batch	Glass	16	●		520074
Batch	Glass	18	●		520087
Batch	Steel	2	●	●	500350
Flow	Steel	2	●	●	500387
Flow	Steel	22	●	●	500362

Covaris®