Microfluidizer® Processors:
Technology and Applications

Presented by:
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Microfluidics at a Glance

Headquartered in Boston, MA and Germany with localized sales and support in 47 countries

25 years serving customers worldwide with over 3,000 machines for 1,700 customers

Microfluidizer® high shear fluid processors
  Top-down particle size reduction
  Bottom-up nanoparticle creation

Process development by research engineers in the Microfluidics Technology Center
Microfluidics manufactures high shear fluid processors that are used for:

- “Top-down” particle size reduction of suspensions, emulsions or liposomes
- Cell disruption
- “Bottom-up” creation of nanoparticles

(Microfluidics Reaction Technology)
Microfluidics serves a variety of industries:

**Pharmaceutical**
- Injectables, inhalables, parenterals

**Biotech**
- Cell disruption, vaccines

**Chemical**
- Inks, ceramics, polymers, carbon nanotubes

**Cosmetic**

**Nutraceutical**
- omega-3, plant sterols, vitamins

**Food**
- Soy milk, food colorings, flavorings
**Microfluidizer Processors**
- Effective particle size reduction
- Narrow distribution
- Suitable for many applications
- Scaleup with repeatable results

**Microfluidics Reaction Technology**
- Creates smallest particles
- Precise control of particle structure (polymorph, etc.)
- Low energy requirements

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**Top-down**

**Bottom-up**

Species A

Microfluidizer Processors

Species B

MRT
Technology
Microfluidizer Processor Configuration (Top-down)

Inlet Reservoir

Intensifier Pump

Cooling Jacket

Interaction Chamber

Outlet

Pressures up to 276 MPa (40,000 psi)

Product
A. Interaction Chamber:
The heart of Microfluidizer® technology
Z-Type Interaction Chamber

**“Z” Single-slotted**

- High Pressure Inlet $P_1$
- High Shear Zone
- High Impact Zone
- Low Pressure Outlet $P_2$

**“Z” Multi-slotted**

- High Pressure Inlet $P_1$
- High Shear Zones
- High Impact Zone
- Low Pressure Outlet $P_2$

- Channel velocities over 400 m/s
- Channel minimum dimensions typically 50-300 microns
- Shear rates up to $10^7$ s$^{-1}$; controllable mixing in the 25-50 nm scale
- Constant mixing conditions for entire batch
- Demonstrated scalability to tens of liters per minute
Y-Type Interaction Chamber

• Channel velocities over 400 m/s
• Channel minimum dimensions typically 50-300 microns
• Shear rates up to $10^7$ s$^{-1}$; controllable mixing in the 25-50 nm scale
• Constant mixing conditions for entire batch
• Demonstrated scalability to tens of liters per minute
Primary Forces

Shear: The deformation of fluids caused by inducing a differential velocity.

Impact: The force of a collision.

- Average velocities in microchannels may reach 500 m/s
- Change of velocity magnitude or direction exposes the fluid to a fairly uniform high shear field.
- High turbulence inside a microliter volume is responsible for mixing in the nanometer level.
If Velocity Maximum ($V_{\text{max}}$) = 8000 IN/SEC
Velocity at Wall ($V_{\text{wall}}$) = 0

Then Average Shear = $8000 \frac{\text{IN}}{\text{SEC}} \cdot \frac{0.002}{0.004}$

= $4,000,000 \times \frac{1}{\text{SEC}}$

OR 4,000,000 SEC$^{-1}$ (inverse seconds)
Nominal Shear Rates as a Function of Pressure & Chamber

Internal diameters vary from 75 µm – 300 µm
Shear Rates For Various Technologies

Shear 1/sec

10,000,000

1,000,000

100,000

Agitator

Sawtooth-blade

Closed-rotor

Rotor-stator

Colloid Mill

Homogenizer

Microfluidizer® Processor

From Chemical Engineering, August 1998
Bio-Pharmaceutical Applications

**Particle Size Reduction**
- Emulsions
- Suspensions
- Liposomes

**Nanoencapsulation**
- Polymers, Liposomes, Emulsions

**Cell Disruption**
- E-coli
- Yeast

**Reaction Technology**
- Crystallization
Pharmaceutical Emulsions
Particle size reduction
applications
Particle Size Reduction
Drug Nanoemulsion (cancer drug)

- Median particle size (D50) **AFTER**: 45 nm
Scaling up – Particle Size Reduction
Drug Nanosuspension (epilepsy drug)

- Median particle size with **Lab machine** (D50): **773 nm**
- Median particle size with **Large scale CP machine** (D50): **614 nm**
Micro/Nano encapsulation: tiny particles or droplets surrounded by a coating or wall

- Protection of active material
  Fish oil and vitamin protected from oxidation

- Control delivery of drugs, pesticides, nutrients, etc.
  Cancer drugs, vaccines, anti-corrosion agents

- Masking of taste or odor
  Flavor microcapsules for drugs, fish oil

Microfluidics offers three platforms for nanoencapsulation
Nano-emulsions - Liposomes – Polymers
Drug Encapsulation in a Liposome

• 5 passes at 18,000 psi with the F20Y (75 μm) Chamber

BEFORE

AFTER

Particle Size Distribution

Unloaded 58 nm

Loaded – 10 mg/mL 84 nm
DNA Encapsulation in a Liposome

- 0.1% plasmid DNA solution was encapsulated inside a Palmitoyl oleoyl phosphatidyl choline liposome
- DNA intact after processing
Fish Oil Encapsulation

Fish oil contains Omega 3 fatty acid, which is an essential nutrient. By encapsulating the fish oil, the undesirable taste can be reduced substantially and the oil is protected from oxidation.

- Median particle size of 12% fish oil emulsion after processing: 0.163 µm
- Median particle size of 14% fish oil emulsion after processing: 0.119 µm
**Process:** Solvent/Anti-Solvent recrystallization

As a drug solution interacts with an anti-solvent, the drug precipitates in the form of nano-crystals

**Reactants:** (a) NFN-DMSO, and (b) water – reactant streams are miscible

**Product:** Drug nanosuspension

Median particle size: **204 nm**
Microfluidizer® processors are routinely used for cell disruption applications.

When compared to other cell disruption methods they provide:

• Higher *disruption efficiencies* (yeast, e-coli)
• Higher *protein activity* due to effective cooling and minimum of # of passes
• Easier *downstream processing* (separation of the cell fragments from the protein)
• Greater *repeatability*
• *Scalability*
Cell Disruption
E-Coli

**Before**

![Before Image]

**After**

![After Image]

**Process pressure:** 18,000 psi (1241 bar)

**Chamber:** H10Z (100 microns)
Yeast Lysis (S Cerevisiae)

Un lysed

1 pass G10Z 30,000 psi ~75% lysis

5 passes G10Z 30,000 psi ~95% lysis

10 passes G10Z 30,000 psi >99% lysis
Yeast Lysis (S Pombe)

Un lysed

1 pass G10Z 30,000 psi ~60% lysis

5 passes G10Z 30,000 psi ~95% lysis

10 passes G10Z 30,000 psi >99% lysis
Lysis of haploid S. pombe on 110EH - 30K PSI

- At 5 passes, the maximum recovery of soluble protein is achieved.
## Chemical Applications

<table>
<thead>
<tr>
<th>Samples</th>
<th>PSI</th>
<th>Passes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% Ag, 25% Pd powder in D.I. water</td>
<td>8800</td>
<td>10</td>
<td>Particle size from 20 to &lt; 1µ</td>
</tr>
<tr>
<td>Wax dispersion, lumber preservative</td>
<td>12100</td>
<td>2</td>
<td>Preheat sample to 60°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Particle size 0.136µ +/- 20%</td>
</tr>
<tr>
<td>Red ink, water based</td>
<td>10200</td>
<td>1</td>
<td>1-7µ originally, reduced to 0.11µ. Intensified color.</td>
</tr>
<tr>
<td>Green ink, water based</td>
<td>10200</td>
<td>1</td>
<td>1-10µ originally, reduced to 0.10µ. Intensified color.</td>
</tr>
<tr>
<td>Black ink (iron oxide)</td>
<td>10000</td>
<td>1</td>
<td>1-6µ originally, agglomerates reduced to mostly submicron.</td>
</tr>
<tr>
<td>10% Cobalt aluminate (pigment)</td>
<td>5000</td>
<td>1</td>
<td>Original size 0.95µ</td>
</tr>
<tr>
<td></td>
<td>10000</td>
<td>1</td>
<td>0.641µ ± 26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.553µ ± 17%</td>
</tr>
</tbody>
</table>
## Chemical Applications

<table>
<thead>
<tr>
<th></th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Original size 5.48µ</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% Ultramarine (pigment)</td>
<td>5100</td>
<td>10500</td>
<td>1</td>
<td>1.07µ +/- 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.872µ +/- 51%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pigment aggreg. &lt; 5µ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TiO2 particles 1-2µ</td>
</tr>
<tr>
<td>63% TiO2 w/blue pigment</td>
<td>10000</td>
<td>15000</td>
<td>2</td>
<td>Uniform pigment aggreg.&lt; 3µ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viscosity increase noted.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mostly primary particles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 1% were aggregates &gt; 10µ</td>
</tr>
<tr>
<td>25% phthalocyanine blue</td>
<td>15000</td>
<td>15000</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>pigment in aqueous w/1% surf</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Disperse Carbon Nanotubes and Control Conductivity of Polymer Composites

<table>
<thead>
<tr>
<th>Magnification 20,000x</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unprocessed</strong></td>
</tr>
<tr>
<td>1 μm</td>
</tr>
<tr>
<td><strong>1 Pass H30Z-G10Z @ 158 MPa</strong></td>
</tr>
<tr>
<td>1 μm</td>
</tr>
<tr>
<td><strong>10 Passes H30Z-G10Z @ 158 MPa</strong></td>
</tr>
<tr>
<td>1 μm</td>
</tr>
<tr>
<td><strong>20 Passes H30Z-G10Z @ 158 MPa</strong></td>
</tr>
<tr>
<td>1 μm</td>
</tr>
</tbody>
</table>
Why Microfluidizer® technology?

- Smaller Particles
- Tighter PS distribution
- Greater Repeatability
- Guaranteed Scalability

Fixed Geometry (Chamber)

Uniform Pressure Profile
Microfluidizer Processors: from Lab to Production
Laboratory Equipment

M-110S

M-110Y

M-110L

HC-2000

HC-5000

HC-8000
Laboratory Equipment

M-110P Microfluidizer® Processor
Laboratory Equipment

M-110EH Microfluidizer® Processor
Production Equipment

- Feed Pressure Transducer
- TC 1
- Flow Meter
- TC 3
- Motor Starter Panel
- Heat Exchanger
- Product Temperature Controller
- Cooling Water Control Valve
- Feed Pump
- TC 2
- Process Pressure Transducer (Inside)
Microfluidizer® Processors:

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