Particle Size Analysis for Homogenization Process Development

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Horiba Seminar
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Outline

- Background
- Study Objective
- Equipment Operating Principles
- Emulsion Preparation Process
- Instrument for Evaluation
- Laboratory Study Results
- Summary
Pulmonary Drug Delivery Product Life Cycle

Formulation
- Dose
- Chemical/Physical Stability
- Solid-state properties
- Excipients

Particle Engineering
- Aerodynamics
- Dispersability
- Process control
- Scale up

User Technology Synthesis

Aerosol Delivery
- Patient’s needs
- Reproducible
- Easy to use & reliable

Fine powders
- Low mass, tight RSD
- Remain dispersable
- Billions/year

Filling & Packaging

Powder Processing

Synthesis
Methods to Produce Fine Particles for Pharmaceutical Applications

**Molecule**

- Spray Drying
- SCF
- Lyophilization
- Crystallization
- Attrition / Jet Milling

**Emulsion Based**

- Solution Based

**Fine Particles (MMAD ~ 1-5 mm)**

*PulmoSphere® Technology*
Novartis PulmoSphere Technology

- Manufacture of a Fluorocarbon-in-Water Emulsion
- Excipients primarily composed of phospholipids
  - Perfluorocarbons added as a processing aid
  - Removed in the process
Manufacture of *PulmoSphere* Particles

- **Atomization**
  - Homogeneous droplet

- **Drying**
  - Hot air drying

- **Collection**
  - Cyclone or filter collection

**Stage I**
- Water loss & particle formation

**Stage II**
- Blowing agent removal
- Blowing agent

**Emulsion**
- Homogeneous droplet

**Drop radius**

**Suspension**

**Solution**

**Components**
- FC
- Water + Drug
- Heat
- H₂O
PulmoSphere Particle Characteristics

- **Particle Physical Properties**
  - Hollow and porous
  - Surface roughness
  - Low density

- **Particle Performance Attributes**
  - Flowability
  - Dispersibility
  - Aerodynamic
The objective of this study is to develop a robust homogenization process for making pharmaceutical emulsions by evaluating droplet size distribution.

Homogenization is a fluid mechanical process that involves the subdivision of droplets or particles into nanometer or micron sizes to create a stable emulsion or dispersion for further processing. This technology is one of most efficient means for size reduction.
Criteria for Evaluating High-Pressure Homogenizers

- Mean Particle Size
- Particle Size Distribution
- Emulsion Stability
- Cycle Time
- CIP/SIP Capability
- Scale Up Capability
- Routine Operation
- Maintenance
High-Pressure Homogenizer Systems

- High-pressure homogenizers generally consist of a high-pressure pump, mostly in the form of a one- to three-piston plunger pump which can be electrically or pneumatically actuated, an interaction assembly, and a cooling unit. High-pressure interaction assembly can be subdivided into three different types:

<table>
<thead>
<tr>
<th>Types</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial Diffusers/Valves</td>
<td>Avestin, APV, Niro…</td>
</tr>
<tr>
<td>Nozzle Aggregates</td>
<td>BEE, Kombi-Blende…</td>
</tr>
<tr>
<td>Counter-jet Dispergators</td>
<td>Microfluidics, Bayer, Nanoject…</td>
</tr>
</tbody>
</table>
Homogenization Principles

- High-pressure processing equipment for reducing droplet or suspension particle size primarily involves four mechanisms:
  - Shear - is caused by elongation and subsequent breakup of droplets, due to acceleration of a liquid
  - Turbulence - is caused by high velocity fluid resulting in chaotic motion to tear apart the globules
  - Impact - is caused by impinging of pressurized fluid on a hard surface breaking globules into smaller droplets
  - Cavitation - is caused by an intense pressure drop, leading to formation of vapor bubbles in the liquid, which implode causing shock waves in the fluid

_Homogenizers, available from different manufacturers operate based on combination of these mechanical forces_
Process and Product Parameters

- **Processes**
  - Configuration (gap, length, shape, and size)
  - Pressure drop
  - Residence time
  - Cooling efficiency (temperature control)

- **Product**
  - Concentration
  - Viscosity (ratio and individual)
  - Interfacial tension (surfactant amount and adsorption rate)
  - Coalescence rate (Gibbs elasticity)
  - Temperature sensitivity
Equipment for Evaluation - Microfluidics

- **Microfluidics: M-110EH**
  - Microfluidics combines high flow with high-pressure, scalable fixed-geometry interaction chambers that impart high shear rates to product formulations
  - The entire product experiences identical processing conditions, producing the desired results, including: uniform particle and efficient droplet size reduction
Emulsion Preparation Process

- Aqueous phase prepared with lipid surfactant
- Addition of modifier
- Pre-mix: Oil phase is slowly added to aqueous phase while mixing with a high-speed rotor/stator mixer
- High pressure homogenization
Process Parameters Evaluated

- Pressure Drop
- Configuration
- Number of Passes
- Temperature Control
Desirable Quality Attributes

- **Mean Particle Size**
  - Less than 0.8 micron (fine emulsion)

- **Polydispersity**
  - RSD Less than 10% (narrow distribution)

- **Emulsion Stability**
  - Less than 10-20% change in particle size or particle size distribution over extended period of time (long hold time)
Instrumentation Used For Evaluation

- **Instrument for determining emulsion size**
  - Photo sedimentation – CPS
  - Dynamic light scattering – Malvern Zetasizer
  - Static light scattering – Horiba LA-950

- **Criteria for choosing particle size analyzer**
  - Wide dynamic range
  - Broad applications
  - Accuracy and precision
  - Short cycle times (sample prep, measurement, and cleaning)
  - Ease of operation and maintenance
  - Regulatory compliance
  - At-line/on-line application
Instrument for Particle Size Analysis

- Emulsion Sizing
  - Horiba LA-950
  - Laser light scattering technique
  - Mie theory
  - 0.01 – 3000 micron
  - Good reproducibility
  - Fill, auto-alignment, blank, measurement, and rinse in less than 60 seconds
Microfluidics Study

- Chambers: G10Z and F20Y
- Pressures: 15 and 25 kpsig
- Passes: 1-5

Z-Type

Y-Type
### Microfluidics - G10Z at 15 kpsig

<table>
<thead>
<tr>
<th></th>
<th>x50 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse</td>
<td>8.23</td>
</tr>
<tr>
<td>Pass 1</td>
<td>0.36</td>
</tr>
<tr>
<td>Pass 2</td>
<td>0.27</td>
</tr>
<tr>
<td>Pass 3</td>
<td>0.27</td>
</tr>
<tr>
<td>Pass 4</td>
<td>0.27</td>
</tr>
<tr>
<td>Pass 5</td>
<td>0.27</td>
</tr>
</tbody>
</table>

#### Diameter (µm)

- **Mean q(%)**
  - **Coarse**
  - **Pass 1**
  - **Pass 2**
  - **Pass 3**
  - **Pass 4**
  - **Pass 5**
Microfluidics - G10Z at 25 kpsig

<table>
<thead>
<tr>
<th>Diameter (µm)</th>
<th>x50 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse</td>
<td>8.32</td>
</tr>
<tr>
<td>Pass 1</td>
<td>0.29</td>
</tr>
<tr>
<td>Pass 2</td>
<td>0.26</td>
</tr>
<tr>
<td>Pass 3</td>
<td>0.26</td>
</tr>
<tr>
<td>Pass 4</td>
<td>0.27</td>
</tr>
<tr>
<td>Pass 5</td>
<td>0.27</td>
</tr>
</tbody>
</table>

![Graph showing size distribution of passes and coarse emulsion](image-url)
Microfluidics - F20Y at 15 kpsig

<table>
<thead>
<tr>
<th>x50 (µm)</th>
<th>Coarse</th>
<th>Pass 1</th>
<th>Pass 2</th>
<th>Pass 3</th>
<th>Pass 4</th>
<th>Pass 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse</td>
<td>9.52</td>
<td>0.38</td>
<td>0.26</td>
<td>0.25</td>
<td>0.26</td>
<td>0.25</td>
</tr>
</tbody>
</table>

![Graph showing mean q% vs Diameter (µm)](image)
Microfluidics - F20Y at 25 kpsig

<table>
<thead>
<tr>
<th>x50 (µm)</th>
<th>Coarse</th>
<th>Pass 1</th>
<th>Pass 2</th>
<th>Pass 3</th>
<th>Pass 4</th>
<th>Pass 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse</td>
<td>10.04</td>
<td>0.28</td>
<td>0.28</td>
<td>0.27</td>
<td>0.27</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Mean q(%)
Microfluidics Study – Effects of Temperature Control

Temperature Control Zones
- Interaction Chamber
- Auxiliary Processing Module (APM)
- Cooling Jacket

Inlet Reservoir

Intensifier Pump

Pressure Gauge

Cooling Jacket

Outlet

APM

Interaction Chamber
## Microfluidics Study – Effects of Temperature Control

<table>
<thead>
<tr>
<th></th>
<th>Interaction Chamber</th>
<th>APM</th>
<th>Cooling Jacket</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction Chamber</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>APM</td>
<td>++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Cooling Jacket</td>
<td></td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

Interaction Chamber + Exit Line + Cooling Jacket = ++

*Note: The table and symbols indicate the level of interaction or control, with higher symbols representing greater interaction or control.*
Microfluidics Study – Temperature Control of APM and Cooling Jacket

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chamber</th>
<th>Pressure kpsig</th>
<th>Particle Size, Micron</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pass 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>x10</td>
</tr>
<tr>
<td>1</td>
<td>G10Z</td>
<td>15</td>
<td>0.26</td>
</tr>
<tr>
<td>2</td>
<td>G10Z</td>
<td>20</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>G10Z</td>
<td>25</td>
<td>0.20</td>
</tr>
<tr>
<td>4</td>
<td>F12Y</td>
<td>15</td>
<td>0.22</td>
</tr>
<tr>
<td>5</td>
<td>F12Y</td>
<td>20</td>
<td>0.19</td>
</tr>
<tr>
<td>6</td>
<td>F12Y</td>
<td>25</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Microfluidics – F12Y at 15 kpsi with Optimized Cooling

<table>
<thead>
<tr>
<th></th>
<th>x10</th>
<th>x50</th>
<th>x90</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pass</td>
<td>0.22</td>
<td>0.31</td>
<td>0.44</td>
</tr>
<tr>
<td>2 Passes</td>
<td>0.19</td>
<td>0.26</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Mean, q%, Diameter, Microns

Two Passes
One Pass
Coarse Emulsion

Diameter, Microns
Microfluidics – F12Y at 25 kpsig with Optimized Cooling

<table>
<thead>
<tr>
<th></th>
<th>x10</th>
<th>x50</th>
<th>x90</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pass</td>
<td>0.19</td>
<td>0.26</td>
<td>0.36</td>
</tr>
<tr>
<td>2 Passes</td>
<td>0.19</td>
<td>0.26</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Two Passes

One Pass

Coarse Emulsion

Diameter, Microns

Mean, q%
# Emulsion Stability Studies

<table>
<thead>
<tr>
<th>Homogenizer</th>
<th>Sample</th>
<th>Time Point</th>
<th>x10</th>
<th>x50</th>
<th>x90</th>
<th>Mean</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avestin C-50</td>
<td>Homogenized Emulsion Pass #3</td>
<td>0</td>
<td>Ave</td>
<td>0.18</td>
<td>0.26</td>
<td>0.38</td>
<td>0.35</td>
</tr>
<tr>
<td>Avestin C-50</td>
<td>Homogenized Emulsion Pass #3</td>
<td>24hrs</td>
<td>Ave</td>
<td>0.19</td>
<td>0.28</td>
<td>0.41</td>
<td>0.35</td>
</tr>
<tr>
<td>Avestin C-50</td>
<td>Homogenized Emulsion Pass #3</td>
<td>96hrs</td>
<td>Ave</td>
<td>0.22</td>
<td>0.32</td>
<td>0.59</td>
<td>0.46</td>
</tr>
<tr>
<td>Microfluidics M-110EH</td>
<td>Homogenized Emulsion Pass #1</td>
<td>0</td>
<td>Ave</td>
<td>0.19</td>
<td>0.27</td>
<td>0.39</td>
<td>0.33</td>
</tr>
<tr>
<td>Microfluidics M-110EH</td>
<td>Homogenized Emulsion Pass #1</td>
<td>24hrs</td>
<td>Ave</td>
<td>0.20</td>
<td>0.29</td>
<td>0.42</td>
<td>0.34</td>
</tr>
<tr>
<td>Microfluidics M-110EH</td>
<td>Homogenized Emulsion Pass #1</td>
<td>96hrs</td>
<td>Ave</td>
<td>0.23</td>
<td>0.32</td>
<td>0.49</td>
<td>0.39</td>
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<tr>
<td>Microfluidics M-110EH</td>
<td>Homogenized Emulsion Pass #2</td>
<td>0</td>
<td>Ave</td>
<td>0.19</td>
<td>0.26</td>
<td>0.35</td>
<td>0.27</td>
</tr>
<tr>
<td>Microfluidics M-110EH</td>
<td>Homogenized Emulsion Pass #2</td>
<td>24hrs</td>
<td>Ave</td>
<td>0.18</td>
<td>0.25</td>
<td>0.35</td>
<td>0.26</td>
</tr>
<tr>
<td>Microfluidics M-110EH</td>
<td>Homogenized Emulsion Pass #2</td>
<td>96hrs</td>
<td>Ave</td>
<td>0.20</td>
<td>0.28</td>
<td>0.38</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Emulsion Study Summary

- High precision and reproducible data from Horiba LA-950 particle size analyzer provide the critical information for evaluating different equipment and processing conditions.

- Both Y and Z types interaction chambers from Microfluidics produce emulsions with fine size and fairly uniform distribution. Y type is slightly more efficient than Z type.

- Cooling study using Microfluidics demonstrates that immediate quench of the processed emulsions is a critical process parameter to control the emulsions stability.

- When employing new cooling strategy, Microfluidics F12Y interaction chamber is able to produce fine and single-mode emulsions in less than two passes.
Acknowledgements

- Jeff Weer*
- Thomas Tarara*
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- Vinh Pham

Novartis Particle Engineering Technology

PulmoSphere

SEDS

PulmSol

Dropmeter