Innovation Through Microfluidizer™ Processor Technology
The Microfluidics Processor User Guide is intended to be a brief tutorial or reference document for a better understanding of the basics of the Microfluidizer® processor, its chambers, the process conditions, and many of the applications where our technology is utilized.

Introduction

The Microfluidizer high shear fluid processor relies upon the forces of shear, impact, and occasionally cavitation to emulsify a liquid-liquid system (physically disperse one immiscible liquid into another) or to de-agglomerate and disperse a solid into a liquid. The process takes place at high energy intensity levels within an interaction chamber.

- The Microfluidizer processor excels at:
  - Particle size reduction
  - Cell disruption
  - Emulsions, liposomes, and encapsulation
  - Reaction technology: PureNano™ (formerly known as MRT)

The entire product volume experiences identical processing conditions in a uniform, continuous, and repeatable manner with the following results:

- Small particle or globule size (often sub-micron)
- Uniform particle or globule size (small poly-dispersity index)
- Completely scalable process to liters/minute flow rates
- Continuous processing

Interaction Chamber (IXC)

Description

The IXC for the Microfluidizer processor is essentially a continuous flow micro reactor that can use turbulent mixing, localized energy dissipation, impinging jets, and a fixed geometry to create a uniform pressure profile for accurate and repeatable particle size distributions. Inside these IXCs formulations experience high flow velocities and shear. The micro channels are as small as 50 µm and this small height creates micro volumes that collectively experience a consistent pressure profile (up to 275 MPa/2750 bar/40,000 psi) and thus a uniform application of shear.

There are two types of chambers: the “Z” type (Figure 1) and the “Y” type (Figure 2). However, there are multiple heights available for each type (Dimensions available in Appendix A), ranging from high shear to low shear.

These IXCs can be used in conjunction with an auxiliary processing module (APM). An APM can be placed downstream of the Y chamber to add backpressure; this configuration enhances the effectiveness of the Y chamber, stabilizes the flow rate, and helps increase the lifetime of the chamber. The APM can also be placed upstream to assist in pre-dispersion of formulations containing solids or crystals prior to the high shear step of the Z chamber.
The APM placed upstream is much like an in-line mixer or preprocessor that is used to prepare the material for the smaller passages and higher energy dissipation of the chamber. The APM is always a Z type chamber and always has a larger height than the high shear and downstream IXC.

Single slotted IXCs have a single micro channel and are used for small batches or for lab-scale testing/processing. Multi-slotted IXCs (Figures 3 – 4) are comprised of multiple micro channels in parallel to increase the volumetric flow rate through the IXC. The increase in flow rate allows for larger volumes of product to be continuously processed in an efficient amount of time.

The IXCs’ exterior is made of stainless steel and the interior is made of either polycrystalline diamond (PCD) or aluminum oxide ceramic (AOC).

**Operation and Shear Rates**

Microfluidizer processors are the gold standard in the industry for applications that require high shear. Fluids inside the chambers can travel at velocities up to 500 m/s, faster than the speed of sound (343 m/s). The minimum dimension of the inside of the chamber can be as small as 50 µm (0.002 inches).
In addition to the high shear forces, impact forces from collisions with the micro channel walls and with the fluid itself are the other main forces that assist in particle/globule size reduction. A change of velocity in magnitude or direction exposes the fluid to a high shear field. High turbulence inside the microliter volumes is also responsible for mixing on the nano scale.

Factors contributing to abnormal chamber wear:
- Gas mixed in with the formulation (through cavitation)
- Improper priming of the pump
- Undersized feed pump for large machines
- Entrained foam from the product
- Air trapped inside the product
- Allowing the product reservoir (hopper) to empty completely
- No APM downstream of a Y-chamber

**Processing very abrasive materials**

One measure of the chamber wear is an increased flow rate of a chamber at a specific pressure on a processor. Small variations in the micro channel dimensions may result in large variations in flow rates. An APM and increase the flow rate of the Y-chambers up to 30% by suppressing cavitation; however, the APM may only decrease the flow rate of the Z-chambers < 3%.

**Microfluidizer Processor**

The Microfluidizer processor acts as a large pump that forces a formulation through a very small orifice (i.e. micro channels). The pressures can be as low as 3.4 MPa/500 psi and go as high as 275 MPa/40,000 psi. The process pressure will vary with each different application to achieve the desired processing goals.
The formulation is initially poured into the inlet reservoir. The intensifier pump has two motions: a suction stroke and a compression stroke. During the suction stroke, a portion of the sample is drawn into the processor through a one-way (check) valve. The compression stroke follows and will push this portion of the sample past the pressure gauge (when present), through the IXC (and APM if required) and then to the jacketed cooling coil or heat exchanger for heat removal (depending on the model). The sample exits via the heat exchanger or cooling coil outlet and is collected, recirculated, or poured back into the reservoir.

The piston of the intensifier pump will oscillate between suction strokes and compression strokes. It is driven by either compressed air or by an electro-hydraulic mechanism.

Lab scale machines are equipped with a single intensifier piston and deliver a pressure profile (Figure 9) that utilizes cyclical suction and compression strokes. Synchronous mode on the production machines uses a pressure profile similar to that of lab scale machines, except using one or two intensifier pistons; having two pistons minimizes the cycle lag.

The constant pressure settings on the two piston scale up processors also incorporate multi-intensifier pumps and use a linear variable differential transformer (LVDT) to provide continuous electronic control of the pumps for a constant pressure profile (Figure 10).

Figure 8: Schematic of the Microfluidizer processor

![Figure 8: Schematic of the Microfluidizer processor](image)

Figure 9: Single Intensifier Pumping Profile

![Figure 9: Single Intensifier Pumping Profile](image)

Figure 10: Multi-Intensifier Pump Constant Pressure Profile

![Figure 10: Multi-Intensifier Pump Constant Pressure Profile](image)

Figure 11: Two Intensifier Piston Microfluidizer

![Figure 11: Two Intensifier Piston Microfluidizer](image)

Figure 12: Single Intensifier Piston Microfluidizer

![Figure 12: Single Intensifier Piston Microfluidizer](image)
Process Controls

There are five major process control variables to control/optimize:

1. Type of chamber
2. Size of the chamber
3. Process pressure
4. Number of cycles the material will pass through the processor
5. The inlet/outlet temperatures (i.e. the thermal history)

IXCs

The Y chamber is typically used for liquid-liquid emulsions, encapsulation, and creating liposomes. The Z chamber is typically used for cell disruption and for dispersions. Dispersion encompasses many topics: de-agglomeration of carbon nanotubes, reducing particle aggregation, and particle size reduction. The correct IXC will be selected based on the starting particle size, the application, and the amount of required shear and impact.

Pressure

Once a Microfluidizer processor (with a chamber and if needed an APM) has been selected for the specific application, the processing pressure is the next variable. The applied pressure is the mechanism that accelerates the sample through the chamber and achieves the particle size reduction (shear), the encapsulation, the de-agglomeration, etc. The pressure is the main driving force for the shear and the volumetric flow rate. Increasing the pressure will increase the rate of shear and increase the amount of sample that can be processed in a given time. Not all material responds the same to shear; some applications (i.e., food products) require lower shear for optimal processing.

Number of passes

Microfluidizer processors have been designed with continuous processing capabilities in mind, which is helpful during scale up.

The processors can be used to process both batch-style operations and continuous operations. An entire volume of a sample can be processed for “discrete passes” through the IXC or continuously for multiple passes for further processing. Additional passes through the chamber will increase exposure time to the energy of the system. If the desired particle size has not been achieved after the initial pass, subsequent passes may achieve the desired results.

Temperature

In addition, the pressure also raises the temperature of the sample. It is estimated that for every 1000 psi of pressure applied to water, the temperature will rise by 1.0ºC-1.7ºC. The specific temperature increase will vary depending on the material and it will occur nearly instantaneously, but can be reduced at nearly the same rate (if needed). The residence time inside the chamber is 1-5 milliseconds).

(6.9 MPa = 1000 psi) => 1.7ºC

Pre-heating/cooling of some samples may assist in particle size reduction and in making emulsions. There is either a cooling coil or a shell and tube heat exchanger that can return the sample back to ambient temperature before it exits the system. It is very important to understand the material’s thermal history for each application. Applications will respond differently based purely on the cooling profile established during processing.

Summary

Microfluidizer processors utilize a fixed geometry micro-channel design inside of the IXC and produce a uniform pressure profile to provide unparalleled results. The results are smaller particles and a tighter particle size distribution. Microfluidics’ customers have greater repeatability with Microfluidizers than other high shear technologies.
Pressure and Chamber Selection for Individual Applications

Cell Disruption

- Mammalian cells
  - 13.8 – 34.5 MPa (2000 – 5000 psi)
  - L30Z (300 µm)
- Bacteria cells (i.e., *E. coli*)
  - 82.7 – 124 MPa (12,000 – 18,000 psi)
  - H10Z (100 µm) or G10Z (87 µm)
- Yeast cells
  - 138 – 207 MPa (20,000 – 30,000 psi)
  - H10Z (100 µm) or G10Z (87 µm)
- Algae cells
  - 69 – 207 MPa (10,000 – 30,000 psi)
  - H10Z (100 µm) or G10Z (87 µm)

Encapsulation

- Oil in water emulsions
  - 103 – 207 MPa (15,000 – 30,000 psi)
  - F12Y (75 µm – high shear*) or F20Y (75 µm) with the appropriate APM
- Water in oil emulsions
  - 3.4 – 55.2 MPa (500 – 8,000 psi)
  - H30Z (200 µm)
- Liposomes
  - Drug encapsulation (oil in water)
    - 103 – 207 MPa (15,000 – 30,000 psi)
    - F12Y (75 µm) or F20Y (75 µm – high shear) with the appropriate APM
  - Drug encapsulation (water in oil)
    - 13.8 – 55.2 MPa (5,000 – 8,000 psi)
    - H30Z (200 µm)
- Polymer encapsulation
  - 103 – 207 MPa (15,000 – 30,000 psi)
  - F12Y (75 µm – high shear*) or F20Y (75 µm) with the appropriate APM

* The F12Y chamber produces higher shear than the F20Y chamber because of a smaller internal cross sectional area.
**Dispersions**

- Particle size reduction (solid particles in solution)
  - Pigments (inks and coatings)
    - 138–207+ MPa (20,000-30,000+ psi)
    - Z – chamber (chamber size relative to starting particle size)
  - Pharmaceutical drugs/creams
    - 34.5–207+ MPa (5,000-30,000+ psi)
    - Z – chamber (chamber size relative to starting particle size)

- De-agglomeration
  - Particle aggregation
    - 138–207+ MPa (20,000-30,000+ psi)
    - Z – chamber (chamber size relative to starting particle size)
  - Carbon nanotubes (CNT)
    - 68.9–207+ MPa (10,000–30,000+ psi)
    - H10Z (100 µm)
Z-Type Interaction Chambers (IXC)

The role of the auxiliary processing module (APM) is to act as premixing or preprocessing module that is located upstream of the smaller geometry of the Z-type IXC. The arrow on the image above shows the fluid flow path through the APM then the IXC.

<table>
<thead>
<tr>
<th>Application</th>
<th>Size of Z IXC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Disruption</td>
<td>87 – 300 µm</td>
</tr>
<tr>
<td>Emulsions (Water in Oil)</td>
<td>200 – 500 µm</td>
</tr>
<tr>
<td>Dispersions</td>
<td>87 – 300 µm</td>
</tr>
<tr>
<td>De-agglomeration (Carbon Nanotubes)</td>
<td>87 – 200 µm</td>
</tr>
<tr>
<td>De-agglomeration (Particle Aggregation)</td>
<td>87 – 300 µm</td>
</tr>
<tr>
<td>Liposomes (Water in Oil)</td>
<td>87 – 300 µm</td>
</tr>
</tbody>
</table>

Y-Type Interaction Chambers (IXC)

The role of the auxiliary processing module (APM) is to stabilize the fluid flow by acting as an intermediate pressure relief between the high pressure IXC and the atmosphere. The arrow on the image above shows the fluid flow path through the IXC then the APM.

<table>
<thead>
<tr>
<th>Application</th>
<th>Size of Y IXC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsions (Oil in Water)</td>
<td>75 µm</td>
</tr>
<tr>
<td>Liposomes (Oil in Water)</td>
<td>75 µm</td>
</tr>
<tr>
<td>Polymer Encapsulation</td>
<td>75 µm</td>
</tr>
</tbody>
</table>

*See pages 2 – 3 for more information on APMs.
Appendix A – Commonly used chambers

<table>
<thead>
<tr>
<th>Minimum Internal Dimension</th>
<th>Style of Chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 µm</td>
<td>F12Y</td>
</tr>
<tr>
<td>75 µm</td>
<td>F20Y</td>
</tr>
<tr>
<td>125 µm</td>
<td>J20Y</td>
</tr>
<tr>
<td>125 µm</td>
<td>J30Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimum Internal Dimension</th>
<th>Style of Chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>87 µm</td>
<td>G10Z</td>
</tr>
<tr>
<td>100 µm</td>
<td>H10Z</td>
</tr>
<tr>
<td>150 µm</td>
<td>L10Z</td>
</tr>
<tr>
<td>200 µm</td>
<td>H210Z</td>
</tr>
<tr>
<td>200 µm</td>
<td>H30Z</td>
</tr>
<tr>
<td>250 µm</td>
<td>L210Z</td>
</tr>
<tr>
<td>300 µm</td>
<td>L30Z</td>
</tr>
<tr>
<td>400 µm</td>
<td>H230Z</td>
</tr>
<tr>
<td>425 µm</td>
<td>Q50Z</td>
</tr>
<tr>
<td>550 µm</td>
<td>T50Z</td>
</tr>
<tr>
<td>550 µm</td>
<td>T60Z</td>
</tr>
<tr>
<td>1000 µm</td>
<td>T250Z</td>
</tr>
</tbody>
</table>