Microfluidics™

User Guide

Microfluidizer® Technology Interaction Chambers™

INTRODUCTION

This 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 Interaction Chamber™, the process conditions, and many of the applications where our technology is utilized.

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:

- Emulsions, liposomes, and encapsulation
- Cell disruption
- Particle de-agglomeration & size reduction

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 polydispersity index)
- Completely scalable process
- Continuous processing

Microfluidizer® Technology

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 207 MPa/30,000 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 cooling coil or heat exchanger for temperature control (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 (figure 1).

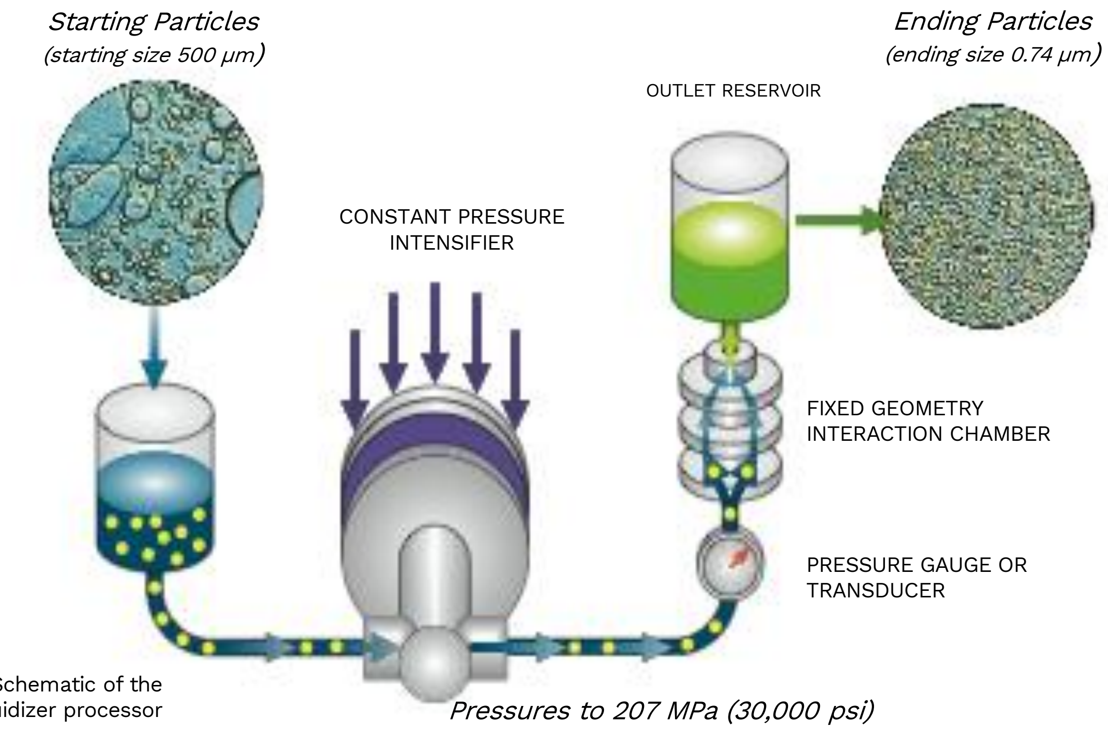

Figure 1: Schematic of the Microfluidizer processor

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Operation and Shear Rates

Microfluidizer processors are the gold standard in the industry for applications that require high shear.

Fluids inside the Interaction Chambers™ can travel at velocities up to 500 m/s, faster than the speed of sound (343 m/s). The high velocities along with constant high pressure and the use of a small fixed geometry microchannels ensures Microfluidizer processors can achieve much higher and constant shear rates than other technologies as shown in Figure 2.

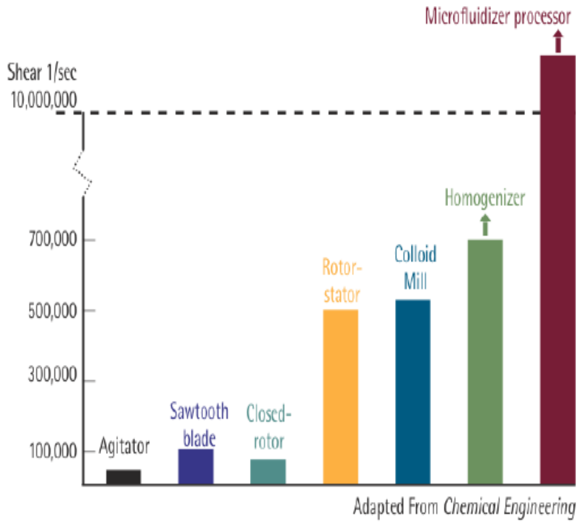

Figure 2: a comparison of shear rates for Microfluidizer processors vs similar technologies

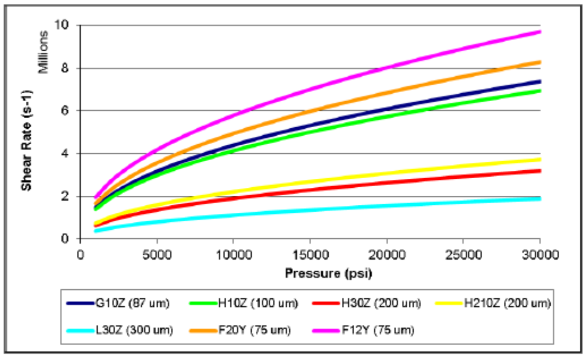

Figure 3: Shear rates as a function of pressure for various Interaction Chamber types

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. Additionally, high turbulence within the product stream generates high levels of micro-mixing.

Microfluidizer® Technology Interaction Chambers™

Microfluidizer Processor

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.

The square pressure profile of the pump ensures that >90% of the product is processed at the same pressure and shear. This enables more uniform processing than the profile of a valve homogenizer where only a very small amount of product is processed at the set pressure.

Lab scale machines are equipped with a single intensifier piston (Figure 4) and deliver a pressure profile (Figure 6) 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 (Figure 5); 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 7). The two pump systems ensure 100% of product is processed at the set pressure.

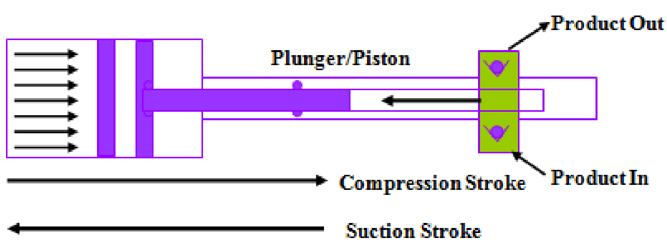

Figure 4: Single intensifier piston Microfluidizer processor

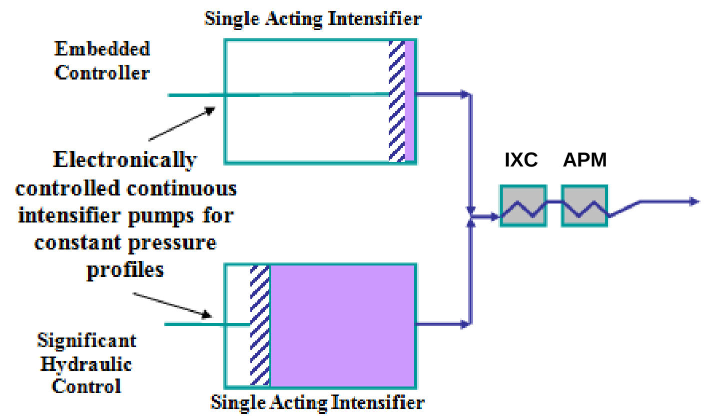

Figure 5: Two intensifier piston Microfluidizer processor

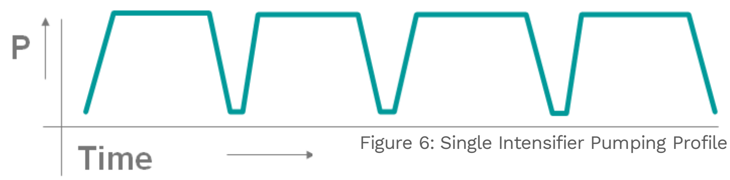

Figure 6: Single Intensifier Pumping Profile

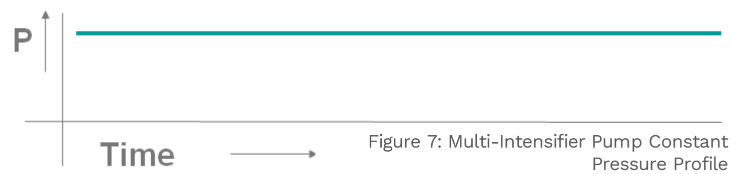

Figure 7: Multi-Intensifier Pump Constant Pressure Profile

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Process Controls

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

1. Type of Interaction Chamber
2. Size of the Interaction Chamber
3. Process pressure
4. Number of cycles the material will pass through the processor
5. The inlet/outlet temperatures

Interaction Chamber

The Y-Chamber is typically used for liquid-liquid dispersions such as 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 and graphite, 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 the IXC has been selected for the specific application, the processing pressure is the next variable. 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. different cells) require lower shear for optimal processing.

Number of passes

The processors can be used to process both batch-style operations & continuous operations. An entire volume of a sample can be processed via "discrete passes" or continuously via recirculation. 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).

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.

Summary

Microfluidizer processors utilize a fixed geometry micro-channel design inside of the Interaction Chambers and produce a uniform pressure profile to provide unparalleled results. The results are smaller particles and a tighter particle size distribution. Microfluidics' customers achieve greater repeatability with Microfluidizers than is possible with other high shear technologies.

Microfluidizer® Technology Interaction Chambers™

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 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 50μm. This small height creates micro volumes that collectively experience a consistent pressure profile (up to 207 MPa/2068 bar/30,000 psi) and thus a uniform application of shear. The fixed geometry of the Interaction Chambers™ ensures that every microliter of product gets exactly the same treatment.

There are two types of Interaction Chambers™: the Z-Chamber type (Fig 8) and the Y-Chamber type (Fig 9). 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 either upstream or downstream of any IXC. The APM is always a Z type Interaction Chamber™ and always has a larger height than the high shear and downstream IXC.

For the Y-Chamber, the APM is normally placed downstream to add back-pressure; this configuration enhances the effectiveness of the Y-Chamber, stabilizes the flow, and helps increase the lifetime of the chamber.

For the Z-Chamber, the APM is normally 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 pre-processor that is used to prepare the material for the smaller passages and higher energy dissipation of the Interaction Chamber™.

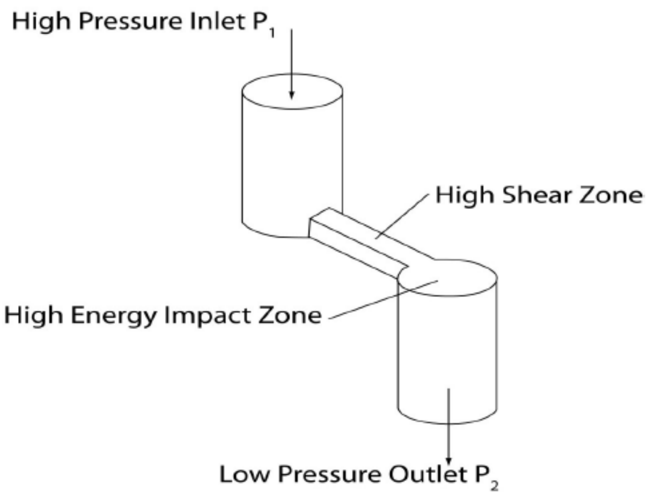


Figure 8: Flow Path Z type Interaction Chambers™

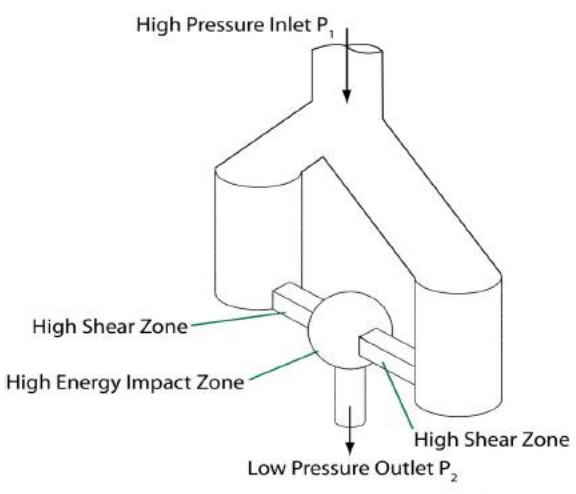


Figure 9: Flow Path Y type Interaction Chambers™

Microfluidizer® Technology Interaction Chambers™

Interaction Chamber™ (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 10 & 11) are comprised of multiple micro channels in parallel to increase the volumetric flow rate through the IXC. This increase in flow rate enables larger volumes to be continuously processed in an efficient amount of time, but at the same shear rate as the single slotted IXCs, with guaranteed scaled up results.

The exterior of the IXC is constructed from stainless steel and the interior is made of either poly-crystalline diamond (PCD) or aluminum oxide ceramic (AOC).

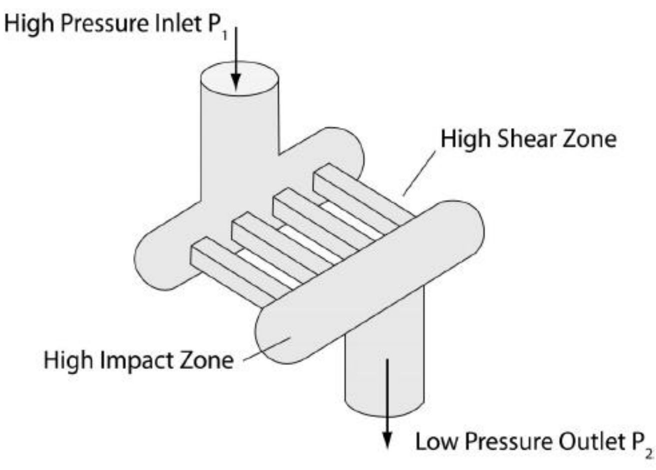


Figure 11: Flow Path multi-slotted Z type Interaction Chamber™

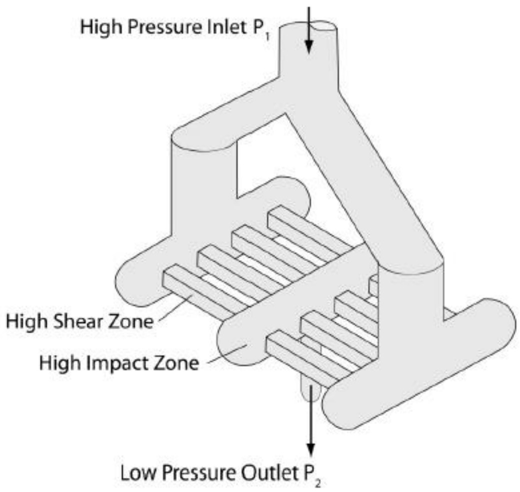


Figure 10: Flow Path multi-slotted Y type Interaction Chamber™

Microfluidizer® Technology Interaction Chambers™

IXC Wear and Flow Rates

Over time, after prolonged use, IXCs will begin to wear; their flow rates will gradually increase, until they are unable to reach the maximum pressure. Microfluidizer processors are designed to compensate for 20% wear before the maximum pressure cannot be maintained. Small variations in the micro channel dimensions may result in large variations in flow rates. One measure of the Interaction Chamber™ wear is an increased flow rate at a specific pressure on a processor.

The poly-crystalline diamond Interaction Chambers™ typically have a lifetime 3-4 times longer than the aluminum oxide ceramic Interaction Chambers™. Material transfer (contamination) from the Interaction Chamber™ to the formulation is not detectable.

Factors contributing to abnormal Interaction Chamber™ wear:

- Improper priming of the pump
- Undersized feed pump for large machines
- Entrained foam/air inside the product
- Allowing the product reservoir (hopper) to empty completely
- No APM downstream of a Y-Chamber

Microfluidizer® Technology Interaction Chambers™

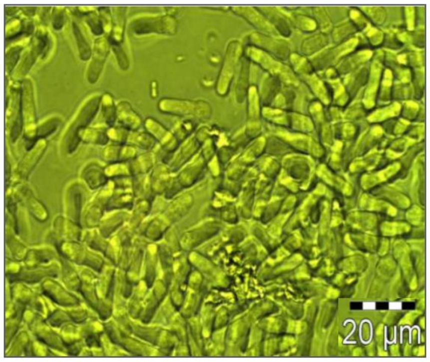
Pressure and Interaction Chamber Selection for Individual Applications

Cell Disruption

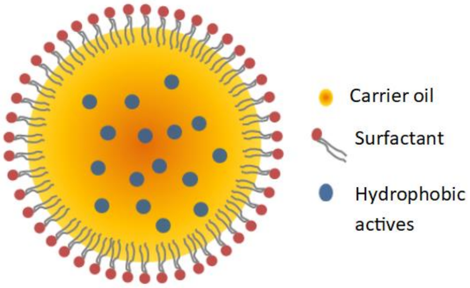
- Mammalian cells
  - 13.8 – 34.5 MPa (2000 – 5000 psi)
  - L30Z (300 µm)
- Bacteria cells (i.e., E. coli)
  - 82.7 – 124 MPa (12,000 – 18,000 psi)
  - H10Z (100 µm) or G10Z (87 µm)
- Yeast cells
  - 138 – 207 MPa (20,000 – 30,000 psi)
  - H10Z (100 µm) or G10Z (87 µm)
- Algae cells
  - 69 – 207 MPa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

Encapsulation

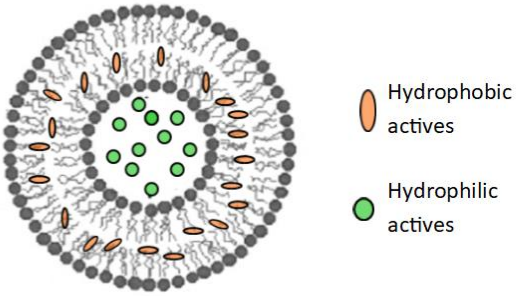
- Oil in water emulsions
  - 103 – 207 MPa (15,000 – 30,000 psi)
  - F12Y (75 µm – high shear*) or F20Y (75 µm) with the appropriate APM
- Water in oil emulsions
  - 3.4 – 55.2 MPa (500 – 8,000 psi)
  - H30Z (200 µm)
- Liposomes
  - 103 – 207 MPa (15,000 – 30,000 psi)
  - F12Y (75 µm – high shear*) or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



Yeast Cells



Oil in Water emulsion



Liposome

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

Microfluidizer® Technology Interaction Chambers™

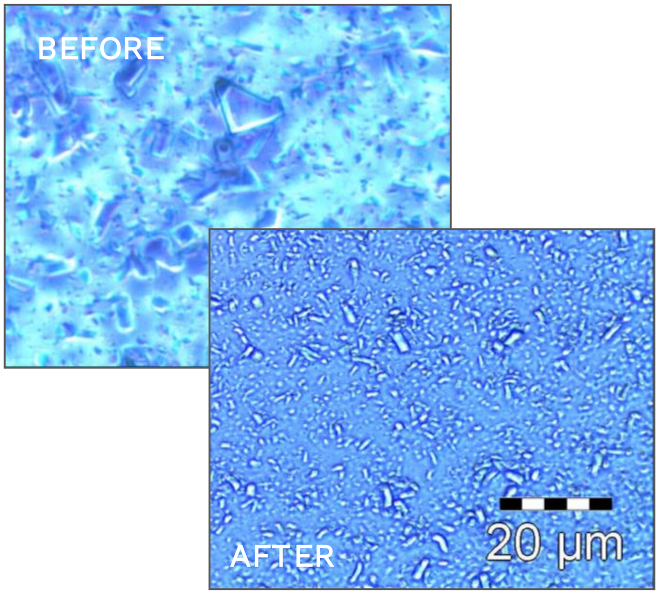
Dispersions

Particle size reduction (solid particles in solution)

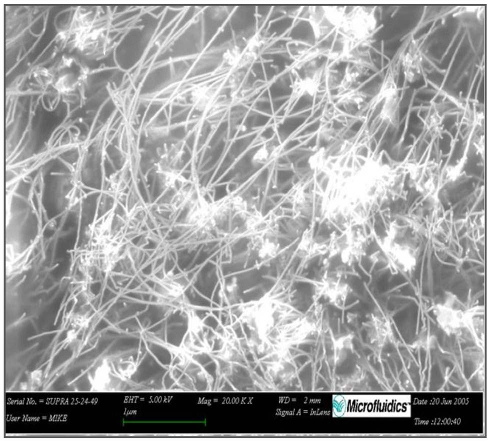
- Pigments (inks and coatings)
    - 138–207 MPa (20,000-30,000 psi)
    - Z–Chamber (IXC size relative to starting particle size)
- Pharmaceutical drugs/creams
    - 34.5–207 MPa (5,000-30,000 psi)
    - Z–Chamber (IXC size relative to starting particle size)

De-agglomeration

- Particle aggregation
    - 138–207 MPa (20,000-30,000 psi)
    - Z–Chamber (IXC size relative to starting particle size)
- Carbon nanotubes (CNT)
    - 68.9–207 MPa (10,000–30,000 psi)
    - H10Z (100 µm)



Example of particle size reduction



De-agglomerated CNT

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Microfluidizer® Technology Interaction Chambers™

Z-Type Interaction Chamber™ (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 below shows the fluid flow path through the APM then the IXC.

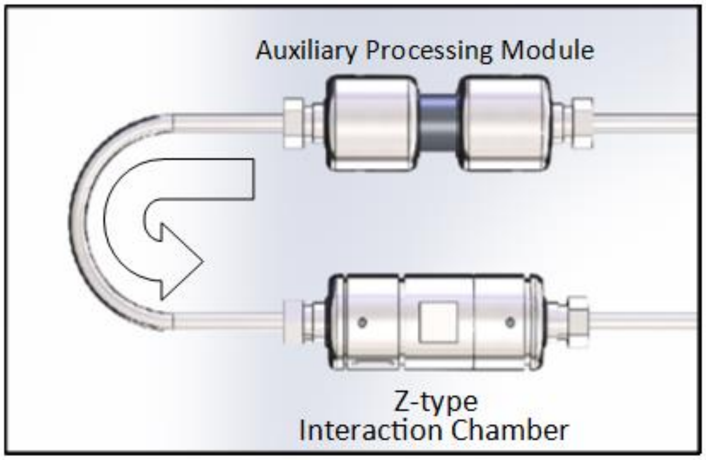
Y-Type Interaction Chamber™ (IXC)

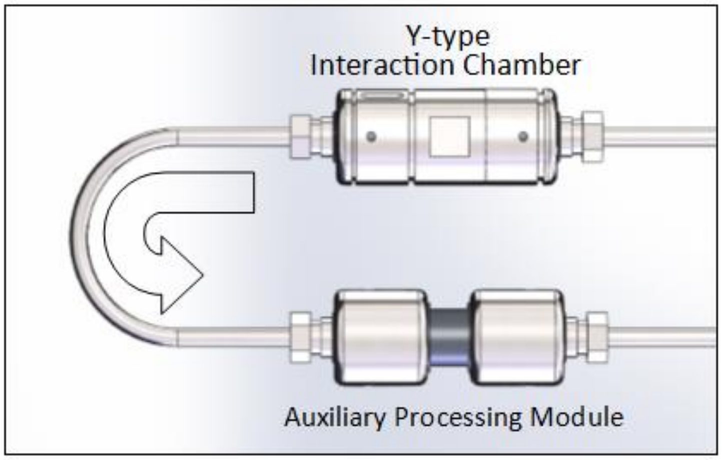
The role of the auxiliary processing module (APM) is to stabilize the fluid flow by acting as an intermediate pressure relief between the high pressure IXC and the atmosphere.

The arrow on the image below shows the fluid flow path through the IXC then the APM.

Application	Size of Z-IXC
Cell Disruption	87 – 300 µm
Emulsions (Water in Oil)	200 – 500 µm
Dispersions	87 – 300 µm
De-agglomeration (Carbon Nanotubes)	87 – 200 µm
De-agglomeration (Particle Aggregation)	87 – 300 µm

Application	Size of Y-IXC
Emulsions (Oil in Water)	75 µm
Liposomes (Oil in Water)	75 µm
Polymer Encapsulation	75 µm





Microfluidizer® Technology Interaction Chambers™

APPENDIX A – Commonly used Interaction Chambers™

Y-Type Interaction Chambers	
Minimum Internal Dimension	Style of Interaction Chamber
75 µm	F12Y
75 µm	F20Y
125 µm	J20Y
125 µm	J30Y

Z-Type Interaction Chambers	
Minimum Internal Dimension	Style of Interaction Chamber
87 µm	G10Z
100 µm	H10Z
150 µm	L10Z
200 µm	H210Z
200 µm	H30Z
250 µm	L210Z
300 µm	L30Z
400 µm	H230Z
425 µm	Q50Z
550 µm	T50Z
550 µm	T60Z
1000 µm	T250Z