Optimizing Drug Delivery – Formulation Development and Scaleable Manufacturing Methodology

Nanoemulsions and nanosuspensions Prepared by ultrahigh-shear fluid processing

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What is needed to facilitate formulation science?

Current approaches need systems which can:

- Physically create particles and droplets with submicron sizes
- Solubilize potent API's (active pharmaceutical ingredients) which resist formulation
- Encapsulate actives in biologically acceptable structures, such as polymers and liposomes
- Create nanoparticles by chemical reactions
- Disrupt biological cultured cells to recover proteins, with

  High yield Bioactivity retention Minimal contamination

BEST PRACTICES - PAST

- Conventional Homogenizers, media mills, rotor/stator and blade mixers
- Limits of operating pressure – usually 5000 to 20,000 psi
- Variable geometry in work zone
- Desired formulation may not be possible using older equipment

  OR cannot be produced economically (too many passes)
- Pressure cycling – high maintenance due to metal fatigue

BEST PRACTICES - CURRENT

- Today's formulation science relies on ultrahigh pressure fluid processing. High shear, properly applied, produces predictable, uniform nanostructures
- Truly constant pressure operation using position sensors and feedback control. Fewer passes, less metal fatigue from pressure cycling, less maintenance
- Control and automation options
- Microfluidizer® processors were developed and improved for more than 20 years. They now deliver consistent, reliable, and repeatable ultrahigh pressure fluid processing and allow continuous multistream chemical reaction

BEST PRACTICES – FUTURE

- Higher pressures. 50,000 psi + operating pressure systems. Some applications may be enabled or improved
- Routine application of Continuous Reaction Technology. Production of pure materials by continuous jet interaction
- Continue reducing cost of ownership. Less maintenance, fewer passes, energy efficiency, longer life wear components

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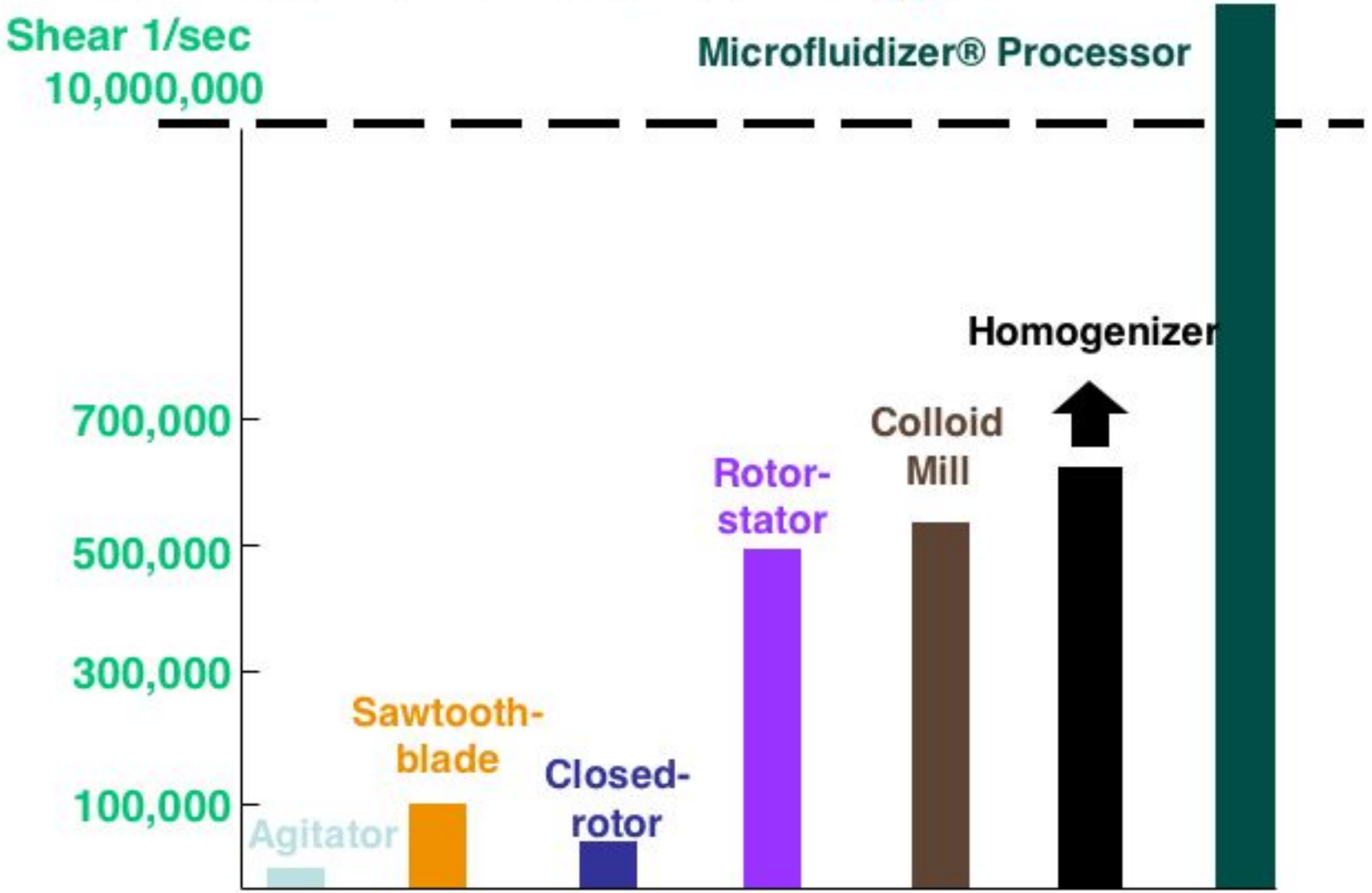
Shear Rates For Various Technologies



From Chemical Engineering, August 1998

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Microfluidizer Processor
ADVANTAGES

- Smaller structure sizes – typically 20 – 200 nm. Filter sterilization. Targeting.
- Tight dispersions – very uniform nanosuspensions and nanoemulsions
- Faster process times – up to 100 times faster
- Constant geometry and pressure – precise energy input control
- Higher energy input – typically 18,000 to 40,000 psi operating pressure
- Scaleability – precise shear control allows linear scaleup and constant product characteristics at any throughput. Designed repeatable shear field in processing zone
- Fixed geometry and no moving parts in processing zone ensures run-to-run repeatability and uniformity
- Easy to clean. Can perform dozens of experiments daily with a lab system
- Minimal contamination – contact surfaces are diamond, ceramic or selected alloys

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FORMULATION VERSATILITY

- **All routes of administration can be optimized**
  Injectable Oral Inhalation Topical Transdermal Buccal

- **Create designed nanoemulsions, nanosuspensions, encapsulated systems to :**
  - **Control formulation stability (storage, in vivo)**
  - **Control delivery rates**
  - **Determine pharmacokinetics**

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FORMULATION DEVELOPMENT

- System must scale up with confidence
- Determine manufacturing system, formulation composition and protocol to achieve desired product specifications
- May require parametric study of:
  - Formulation composition – API, adjuvants, surfactants, stabilizers
  - Process conditions – energy input, operating pressure, temperature control, throughput, passes, post-processing

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DEVELOPMENT TESTING

- Optimum product will result from a combination of process design and formulation science. BOTH must be studied interactively
- TESTING:
  - Design and perform parametric study of critical composition and process variables.
  - Refer to formulation databases to limit variable ranges. Composition information is usually available from R&D records of drug development.
  - Process variables include equipment selection and specification. Microfluidics' database and expertise can usually provide process variable ranges, including proposed operating pressure, interaction chamber recommendation, temperature control, passes and throughput.
- OBJECTIVES:

  Best composition to achieve desired pharmaceutical performance

  Best process conditions to support composition and product performance

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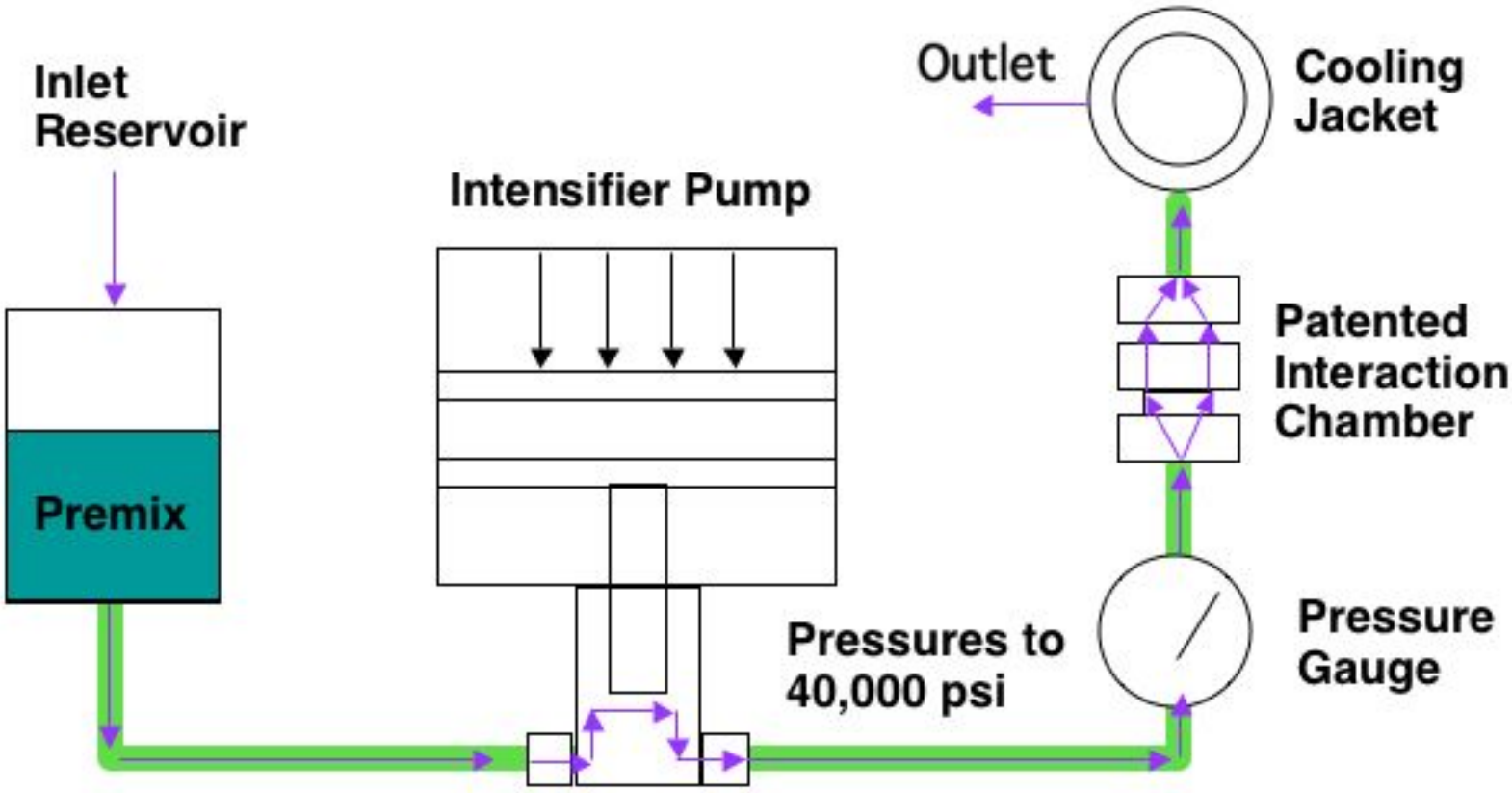
PROCESSOR CONSIDERATIONS

- Scaleable from lab amounts to full manufacturing needs
- Consistent, reproducible process result
- Constant operating conditions
- Clean-in place, sterilize-in-place, GMP compatibility demonstrated, validation assured
- Automated, recordable manufacturing operation
- Safe. Toxic containment available, pressure controls and safeguards

Microfluidizer - Principle of Operation



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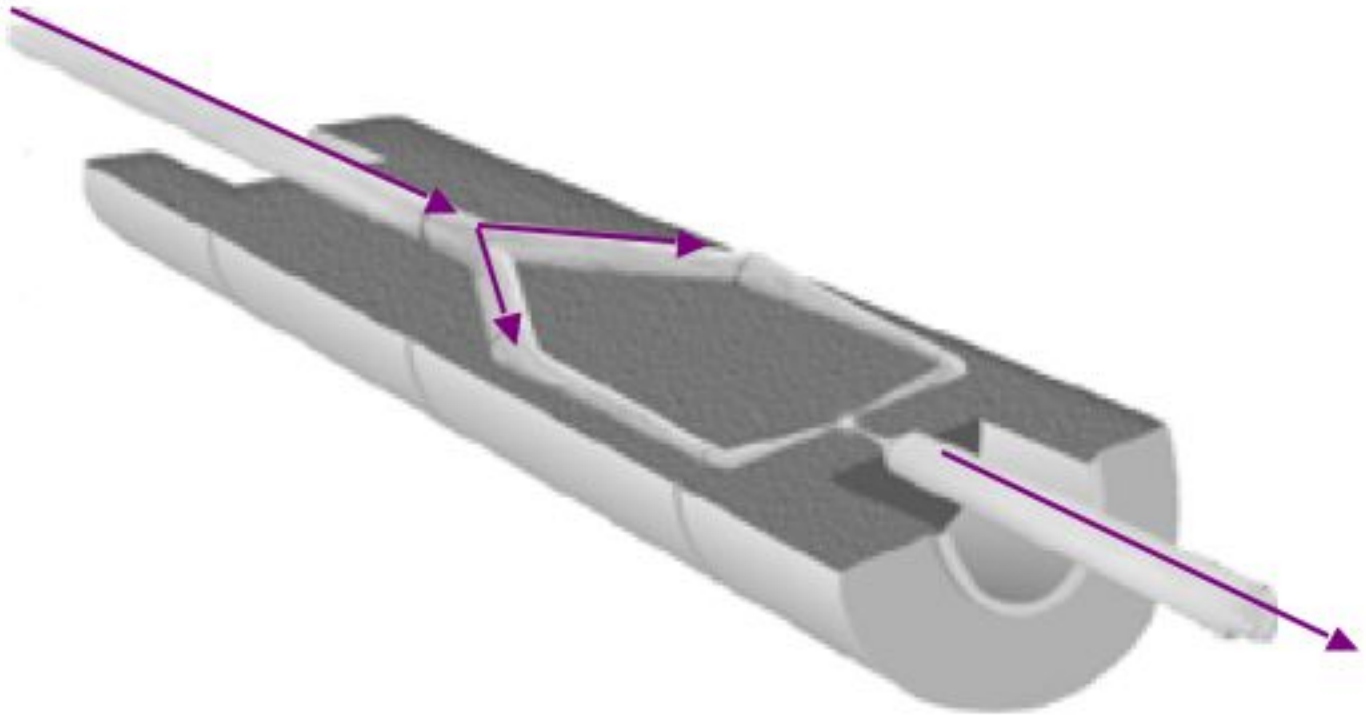
Y-Type Interaction Chamber Schematic



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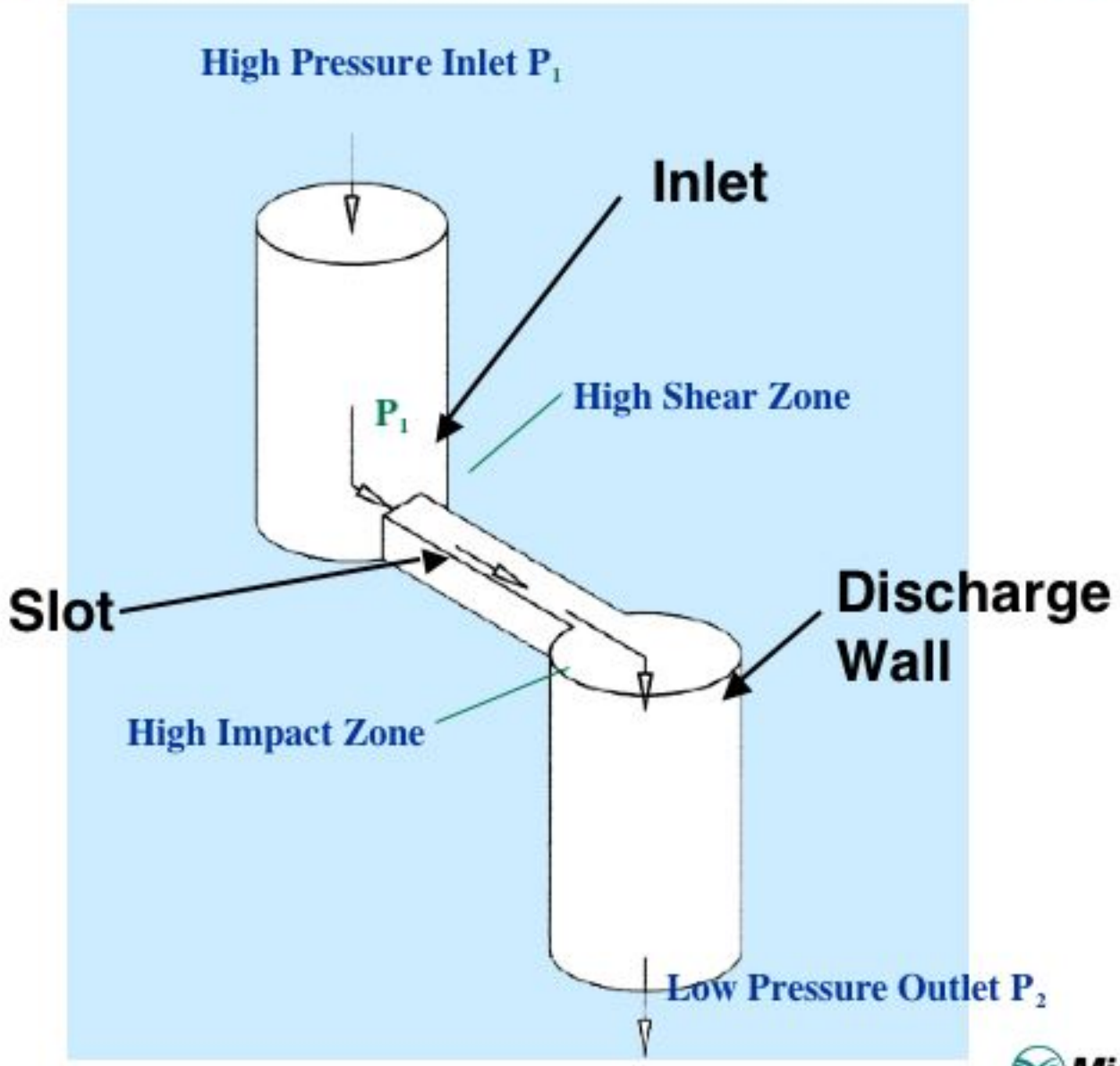
Interaction Chamber "Z" Type Single Slot



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Laboratory Equipment - Pneumatic

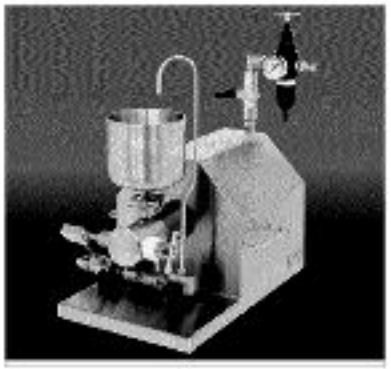
M-110S

M-110Y

M-110L

HC-2000

HC-5000



HC-8000

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Laboratory Equipment – Electro-hydraulic

M-110EH Microfluidizer® Processor

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Production Processor M700

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Production Processor M710

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M-710 Installation

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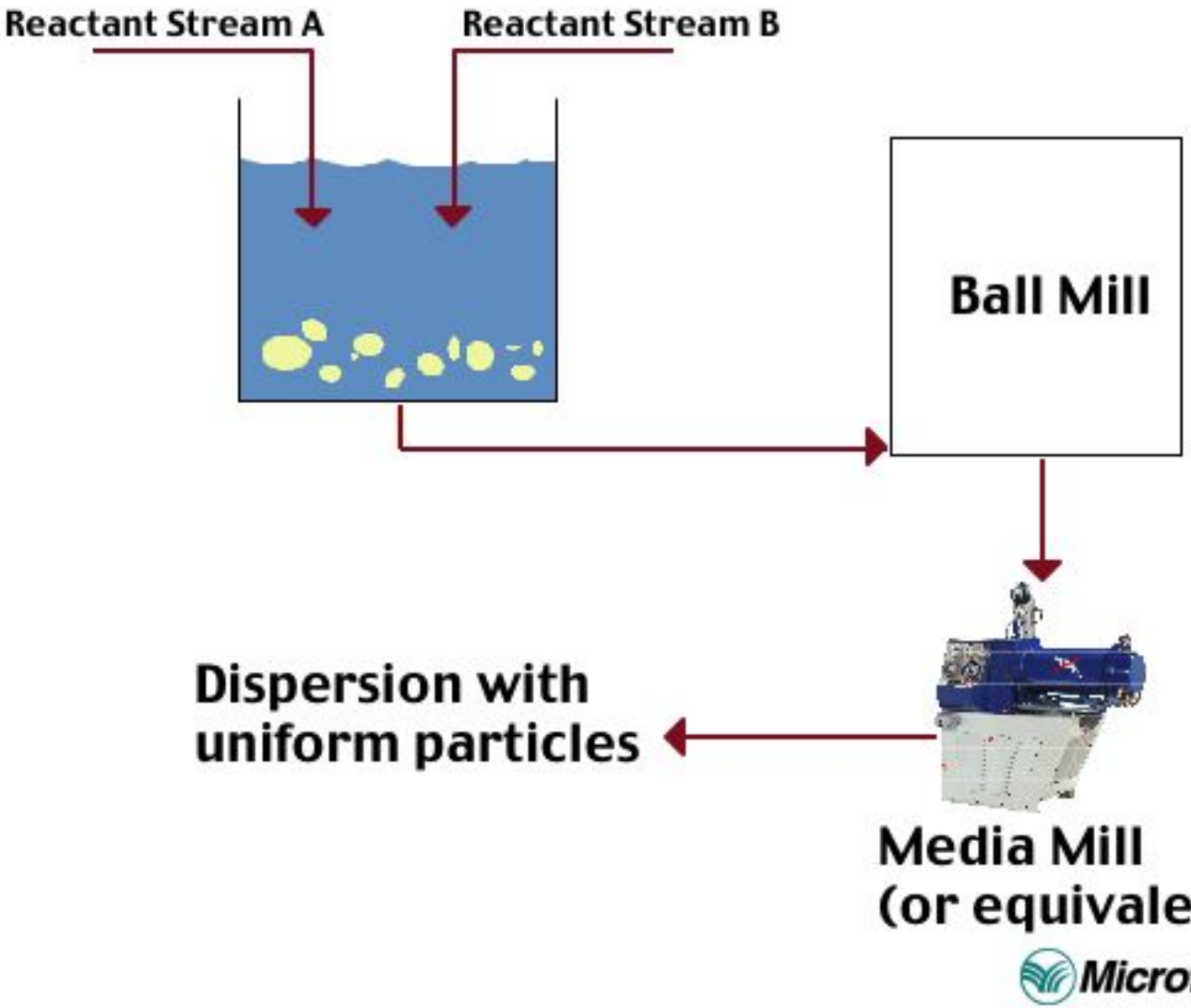
CONTINUOUS CHEMICAL REACTION TECHNOLOGY

Application to solubilization of API's by nanosuspension formulation

- **Many potent insoluble API's are difficult or impossible to formulate**
- **Grinding and high energy dispersion can be applied, but grinding introduces impurities, is often not capable of achieving desired size and size distribution. Dispersion cannot break covalent bonds and will often fail to produce desired structure sizes**
- **Recent summary (Rabinow) – shows value of stabilized nanosuspensions in treating a wide range of disease indications**
- **Newly developed MMR (Microfluidizer Mixer/Reactor) systems can consistently produce precipitated nanoparticles of controlled size**

MMR creates nanostructures by controlling growth of precipitating solids from two or more continuous reactant liquid streams.

Precipitation Batch Process



Drawbacks to Precipitation Batch Processes

- Allows competitive slow reactions to occur - i.e. allows impurities to form
- Reaction rates governed by diffusion of reactants from inefficiently mixed components
- Inefficient mixing = long batch times. Through-put is low.
- High capital costs due to multiple reactor needs
- Particle size and distribution, and purity, may be variable between reactors

Benefits of continuous controlled precipitation process

- Liquid structures in reaction zone are in nanometer size range. Diffusion resistance is minimal. Reaction rates near theoretical, not diffusion controlled
- Enables synthesis of materials having improved nanoscale homogeneity
- Improves phase purity of product in systems where multiple phases (contaminants) tend to form
- Enables the process of recrystallization

Recrystallization - a powerful tool for formulating water-insoluble materials (actives)

- Dissolve primary crystals that cannot be further reduced in size by grinding or dispersion - Reactant A
- Select water or other appropriate antisolvent - Reactant B
- Impinge reactants A & B in MMR system and recrystallize primary particles at a controlled rate and quench at desired size
- Agglomeration occurs after formation of nanoparticles
- Remove residual dissolving agent by multiple washing
- Redisperse into final formulation as nanosuspension

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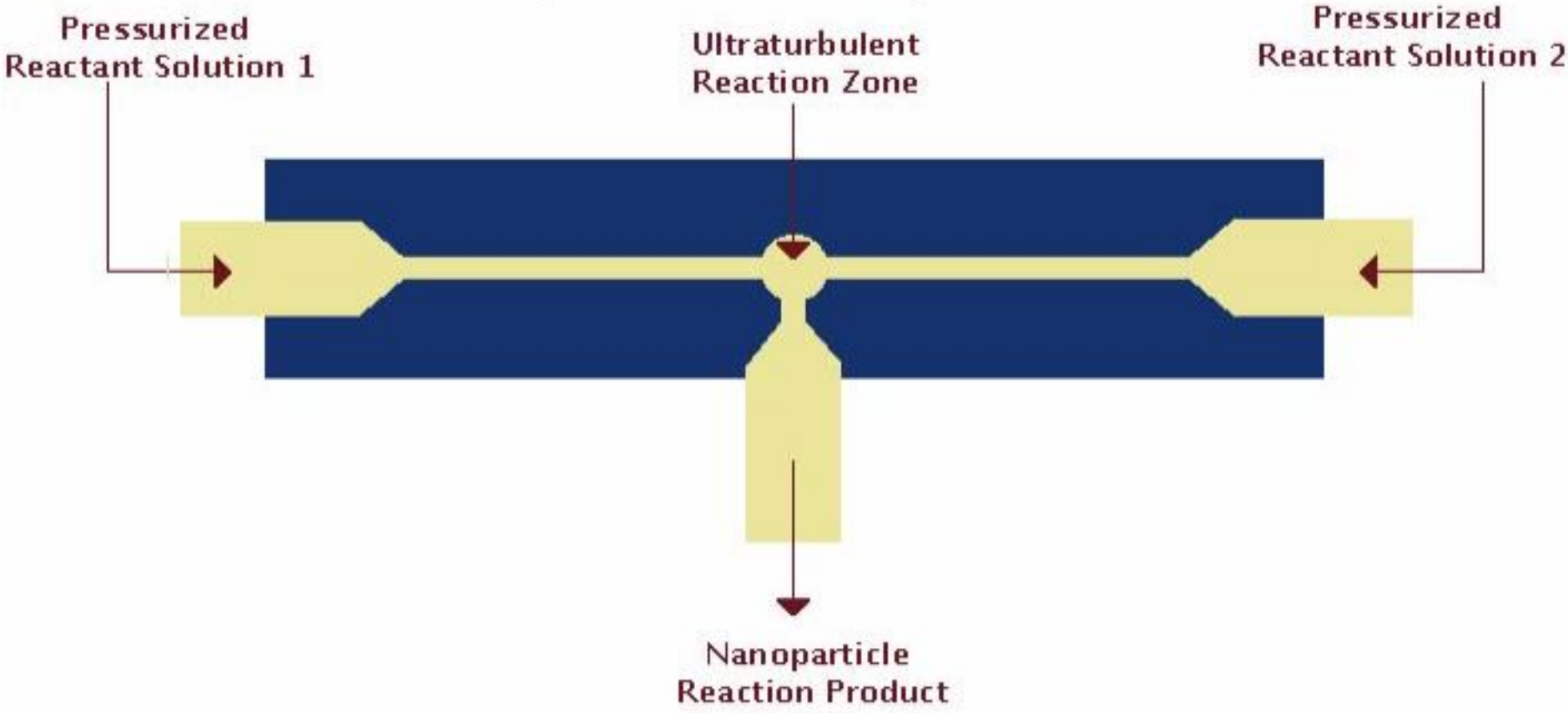
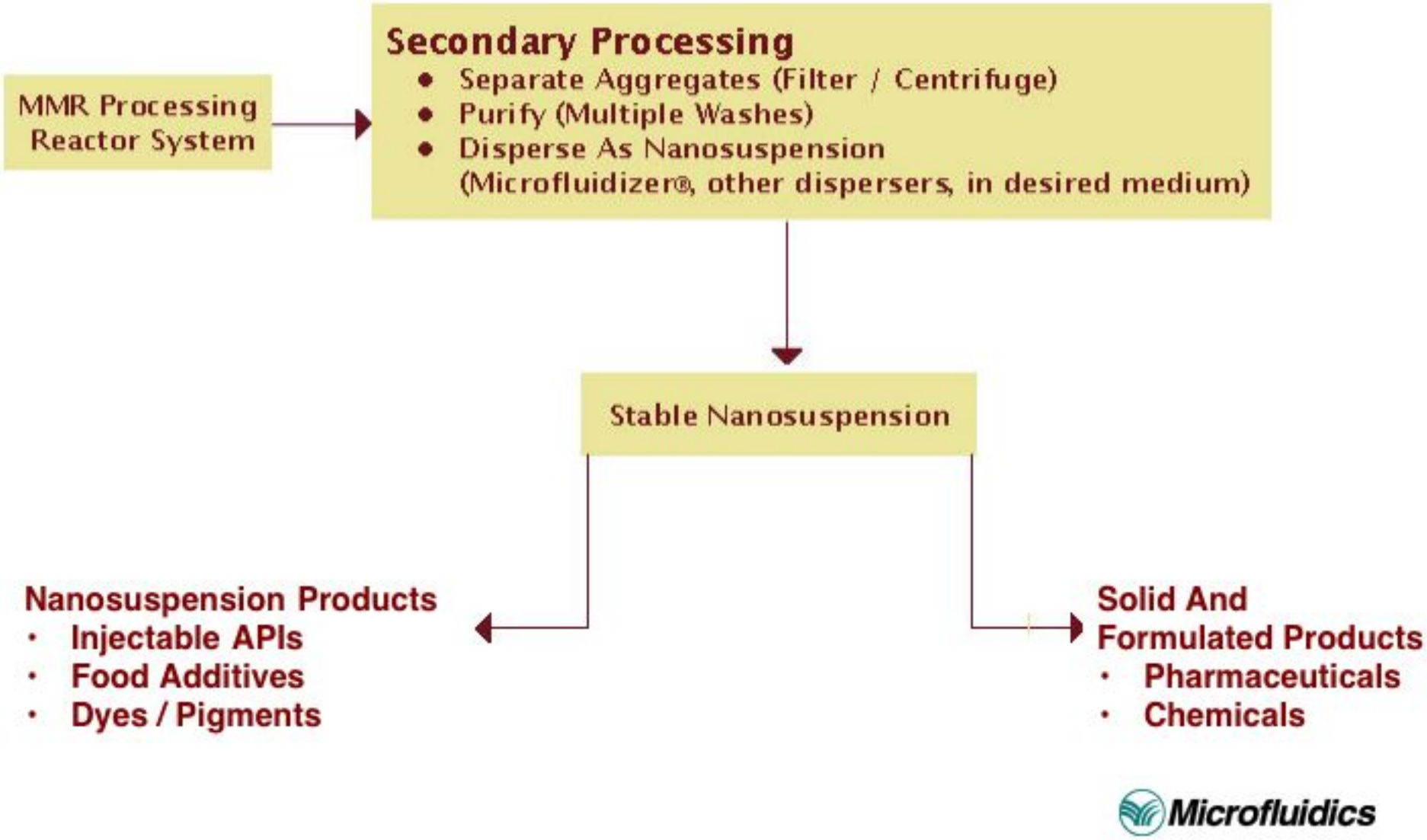
Nanomaterial Production System (Schematic)



Separate high-pressure pumps (up to 30,000 psi) feed the reactant solutions, through shear-inducing microchannel passages, into an ultraturbulent reaction zone, of microliter size. Collision of the streams results in creation of nanometer-size liquid structures in which reaction occurs, resulting in uniform nanoparticles of precipitated reaction product.

MMR Post-Reaction Flowchart (1)
For Nanomaterial Production



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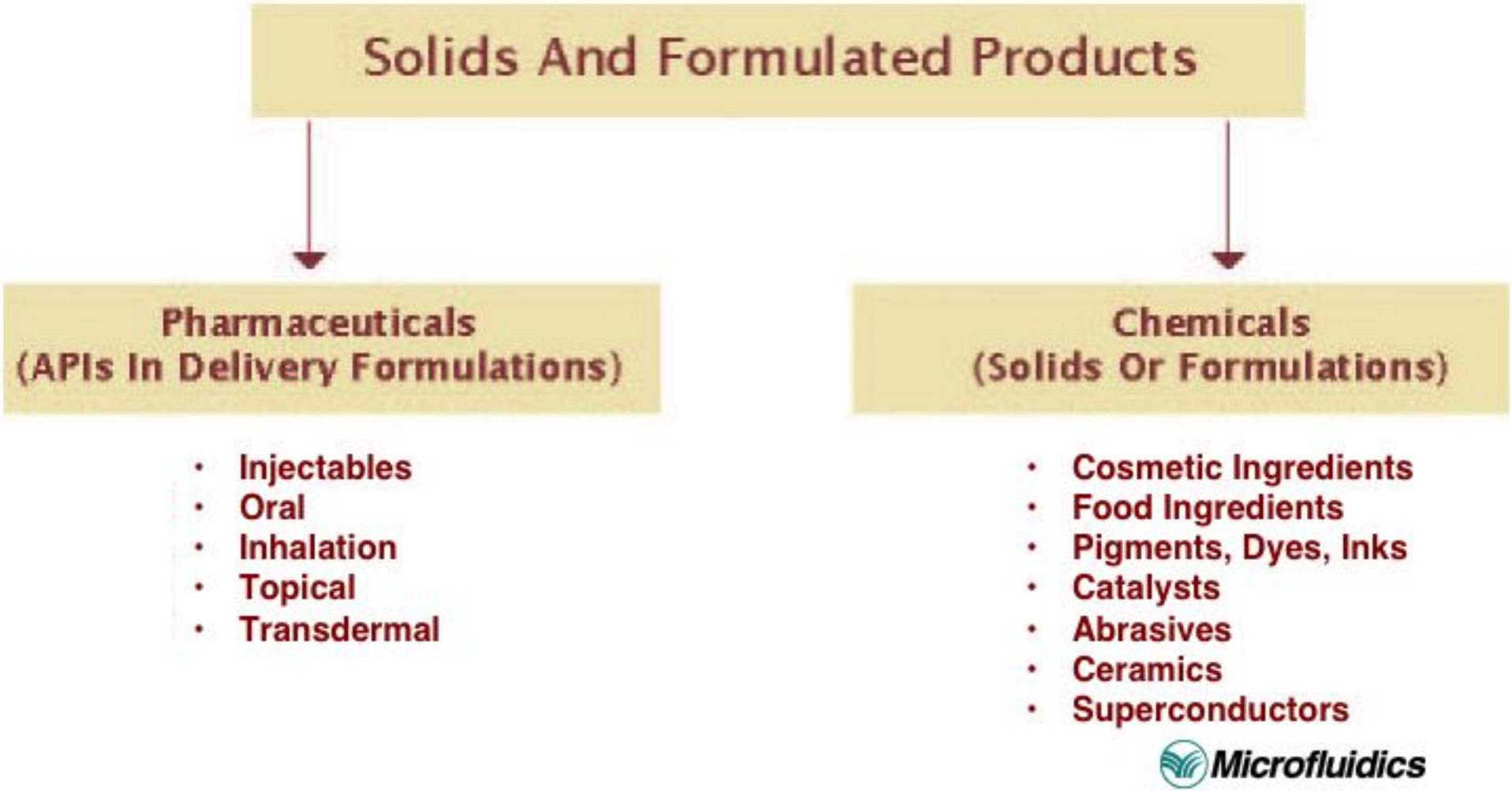
MMR Post-Reaction Flowchart (2)
For Nanomaterial Production



Laboratory MMR System (Microfluidizer Mixer/Reactor)

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Production MMR Processor

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Ongoing Experimental Programs

- Controlled Recrystallization of API's
- Synthesis of API's
- Nutraceutical and cosmetic ingredient preparation
- Encapsulation in polymer carriers
- Optimizing cell disruption
- Vaccine adjuvant nanosuspensions
- Nanoemulsions for chemotherapy

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Selected Applications Laboratory Results for Submitted Samples

- Cell Disruption Examples
- Drug Nanoemulsion Example
- Drug Nanosuspension Examples
- MMR Insoluble Drug Recrystallization to Nanosuspension Example

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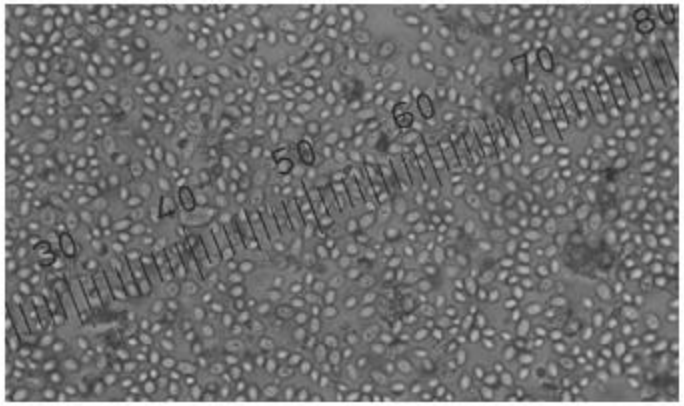
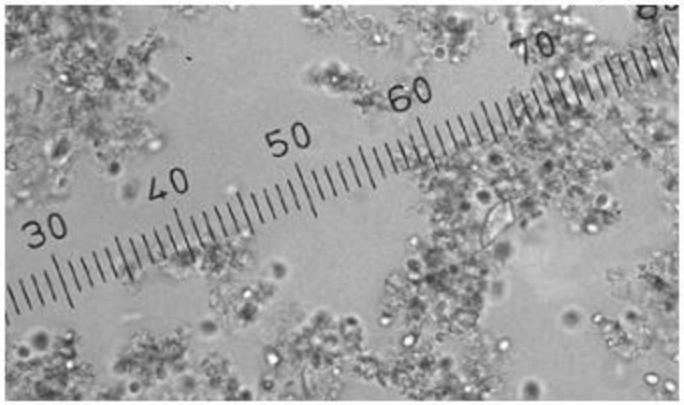
Industry:	**Biotechnology/Pharmaceutical**
Product:	**Yeast Cell**
Test Objective:	**Obtain 90% cell disruption of yeast cells**
Processor:	**M-110EH**
Chambers:	**• Interaction Chamber (downstream) H10Z** **• Auxiliary Processing Module (upstream) H30Z**
Number of passes:	**5**
Shear per pass:	**5,780,000 sec^{-1}**
Process Pressure:	**25,000 psi**

Before Processing
(Magnification 400 X,1 division = 2.5 μm)



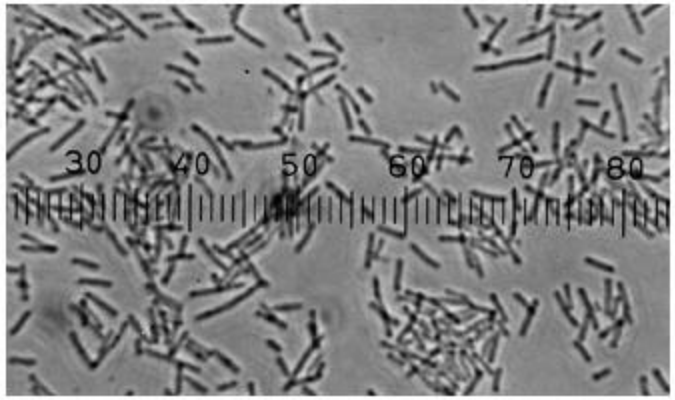
5 Passes
(Magnification 400 X,1 division = 2.5 μm)



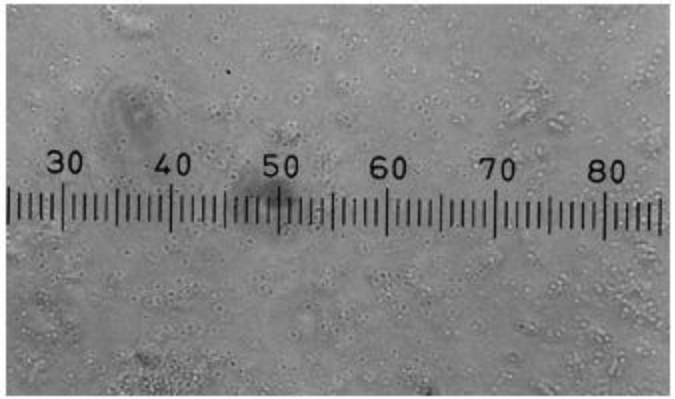
Summary of Results: Achieved greater than 90% cell disruption after 5 passes using the M-110EH Microfluidizer® materials processor.

Industry:	**Biotechnology/Pharmaceutical**
Product:	**E.Coli suspension**
Test Objective:	**Achieve a high degree of cell disruption**
Processor:	**M-110EH**
Chambers:	**• Interaction Chamber (downstream) H10Z** **• Auxiliary Processing Module (upstream) H30Z**
Number of passes:	**1**
Shear per pass:	**4,800,000 sec^{-1}**
Process Pressure:	**18,000 psi (1241 bar)**

Before Processing
(Magnification 1000 X, 1 division=1 micron)



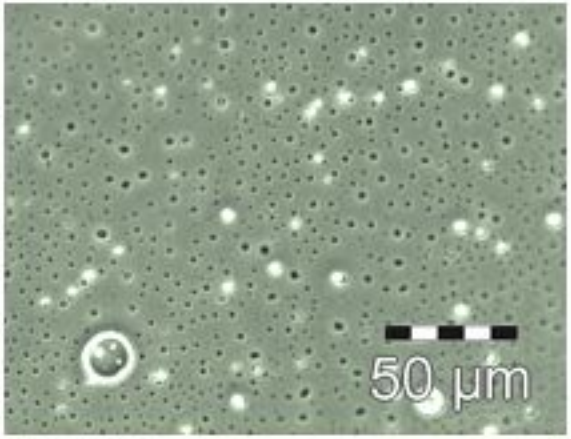
1 Pass
(Magnification 1000 X, 1 division=1 micron)



Summary of Results: Estimated that greater than 95% cell disruption was achieved after 1 pass at 18,000 psi using an M-110EH Microfluidizer® materials processor.

Particle Size Reduction

Drug Nano-emulsion (cancer drug)



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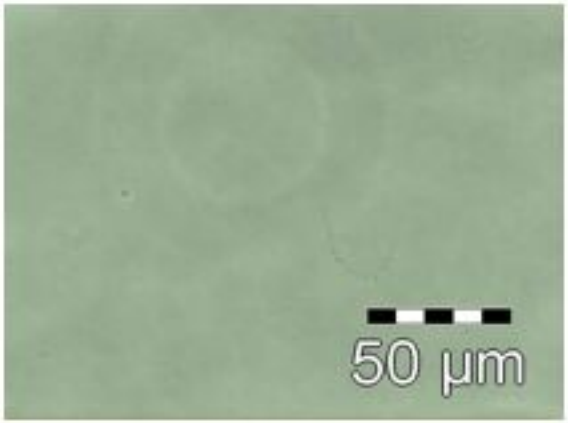

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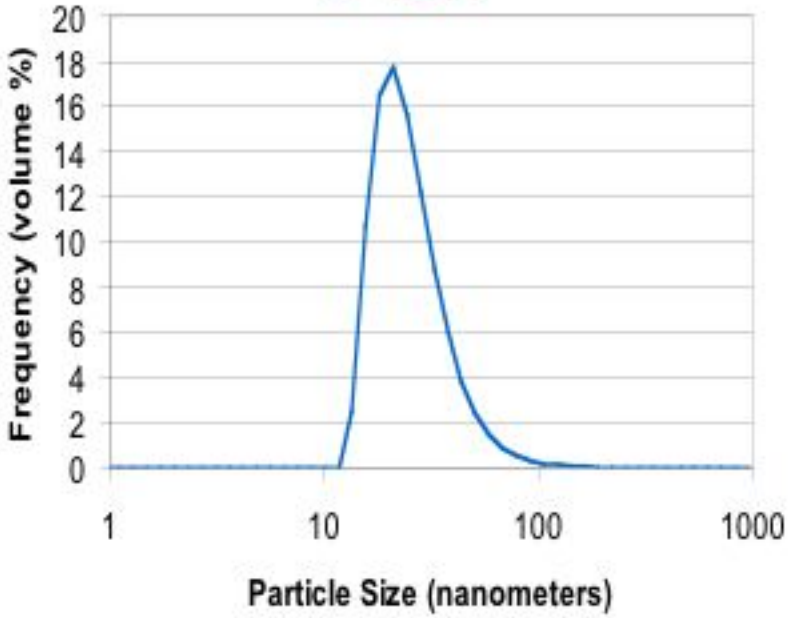

- Median particle size (D50) AFTER: **45 nm**

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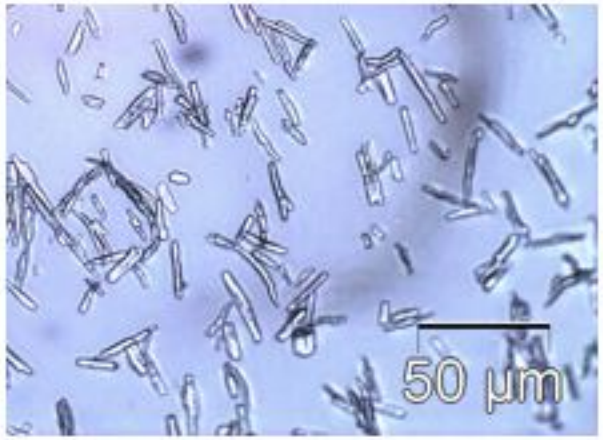
Particle Size Reduction

Drug Nano-suspension



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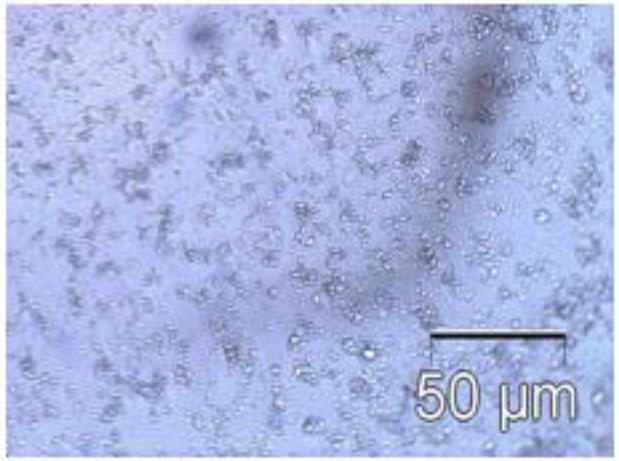

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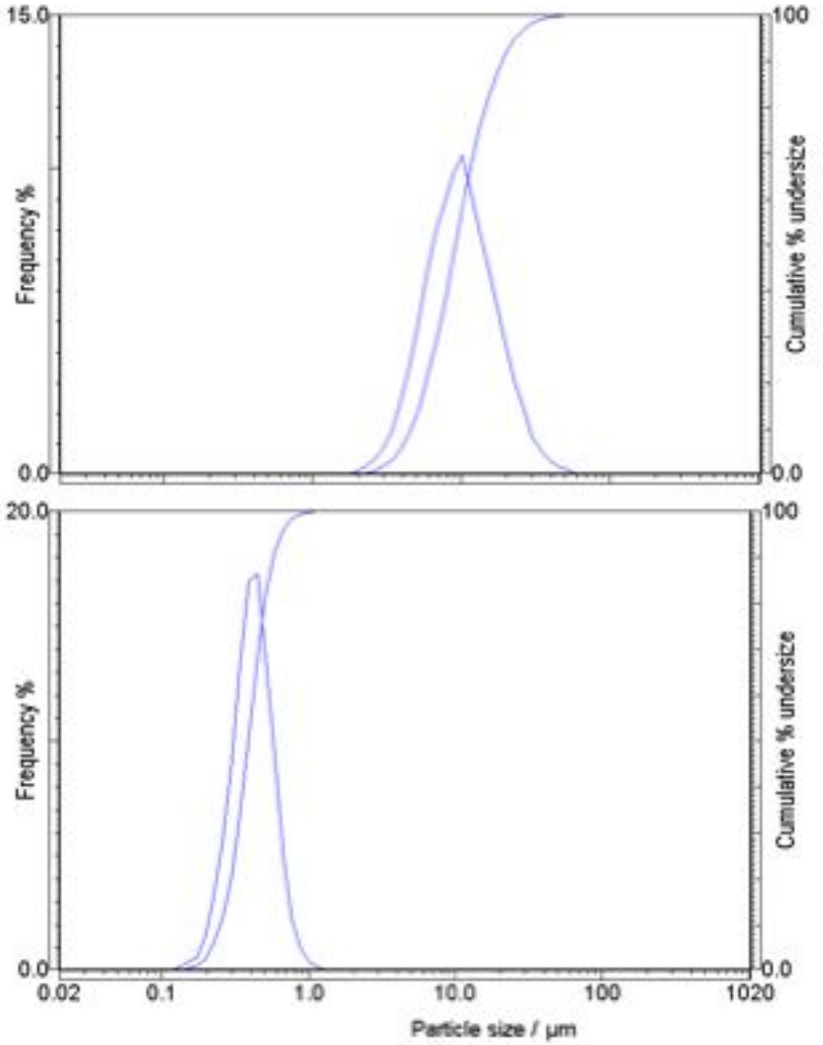

- Median particle size (D50) AFTER: **385 nm**

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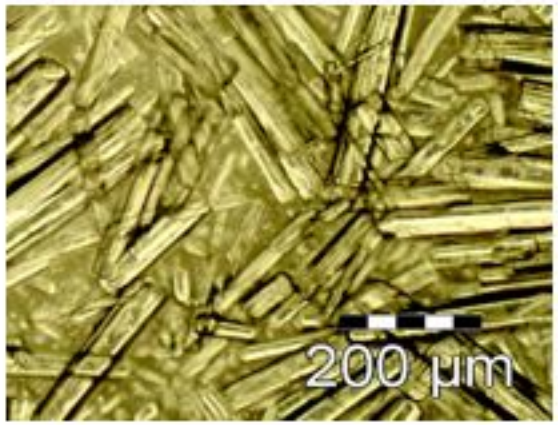
Scaling up Drug Nanosuspension



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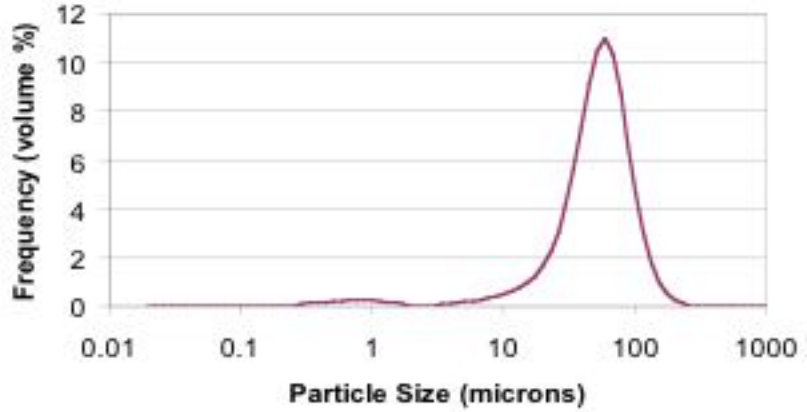

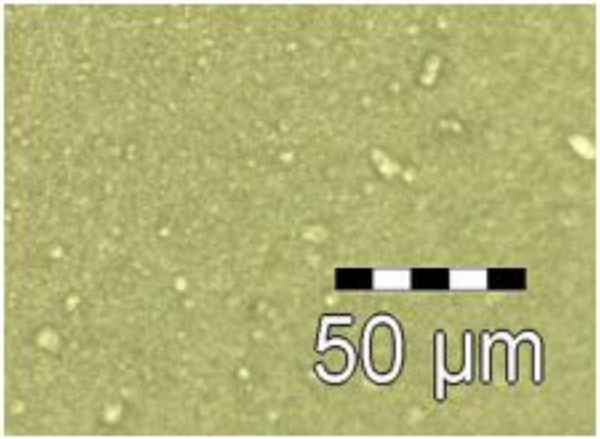

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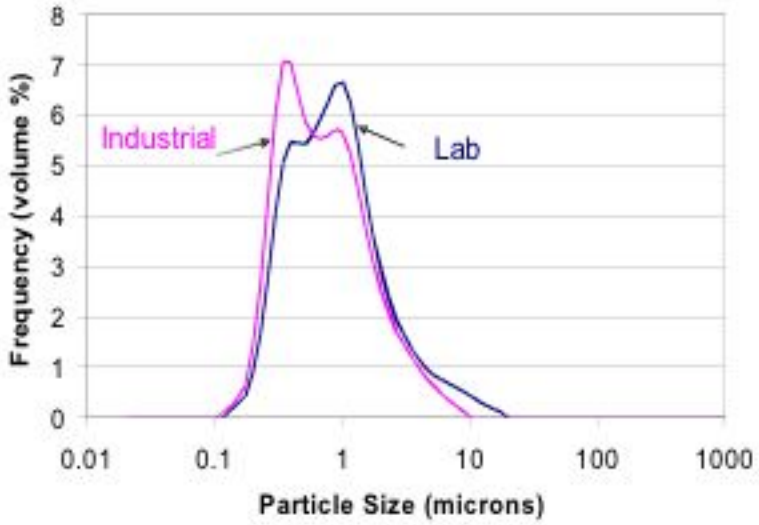

- Median particle size with **Lab machine** (D50): **773 nm**
- Median particle size with **Industrial scale machine** (D50): **614 nm**

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MMR Application

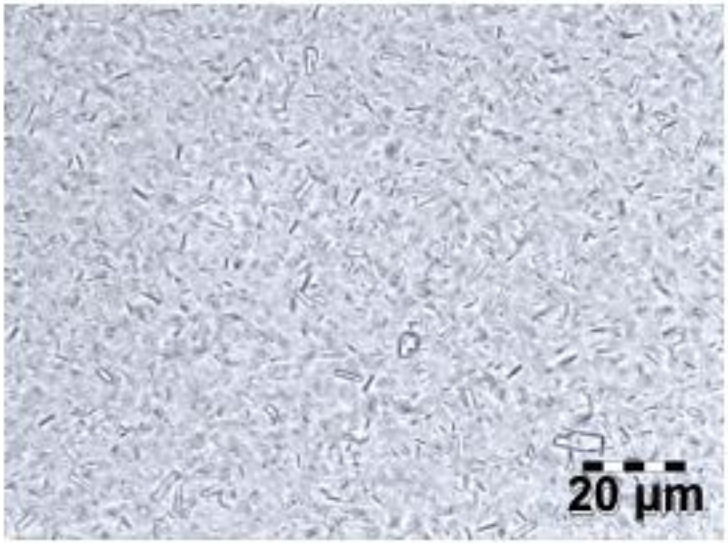
Drug Nanosuspension

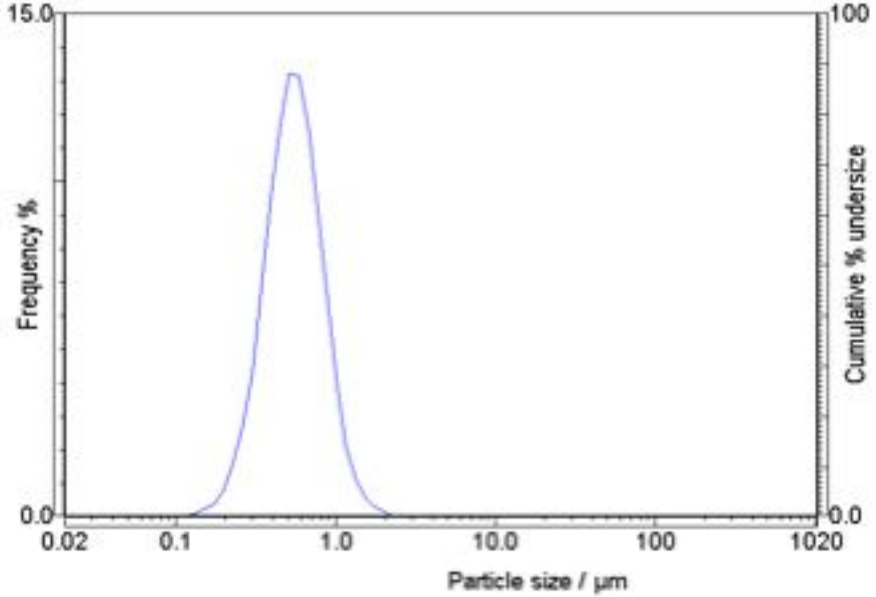
Process: **Solvent/Anti-Solvent recrystallization**

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

Reactants: **Drug solution and water – reactant streams are miscible**

Product: **Drug nanosuspension**





- Median particle size (D50) AFTER: 480 nm

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