
# Microfluidics Reaction Technology (MRT) for Continuous, Bottom-Up Production of Drugs

**Thomai "Mimi" Panagiotou, Ph.D.**

*Chief Technology Officer, Microfluidics International*

*And*

**Robert J. Fisher**

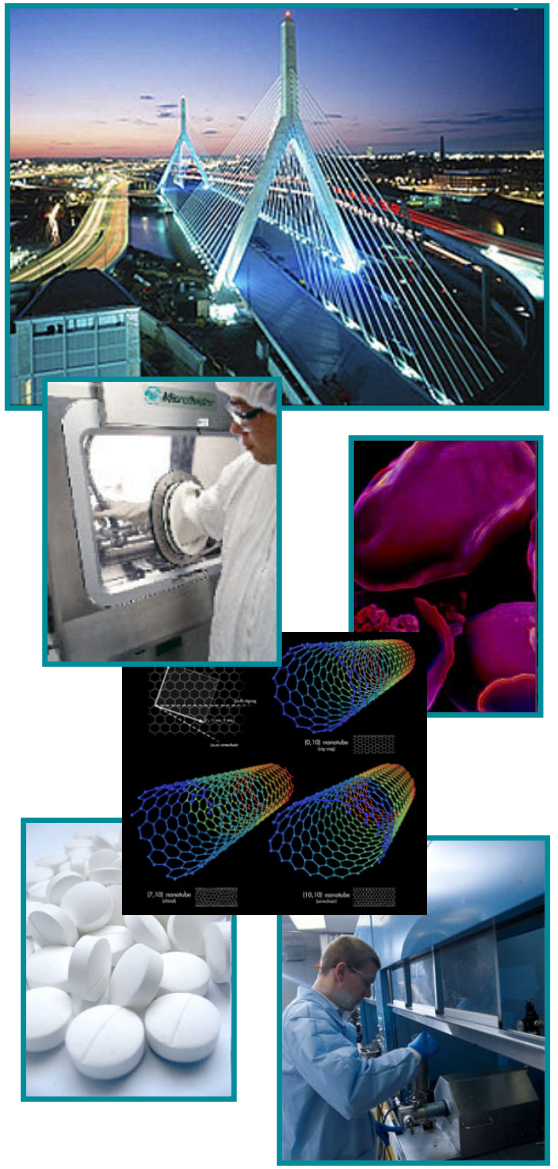
*Chemical Engineering, MIT*

# Microfluidics at a Glance

- **Microfluidizer®** high shear fluid processors for processing of multiphase fluids to produce nanomaterials
- "Top Down" and "Bottom Up"
- Lab to large scale processors are used for production of market drugs, vaccines, inkjet inks, coatings, nutraceuticals and cosmetics
- Holistic approach to development

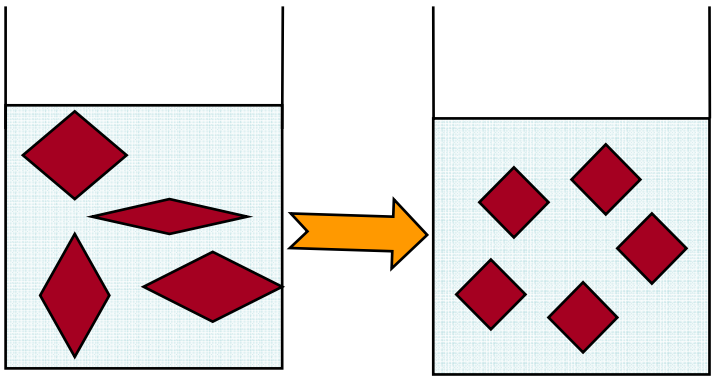
  Application

  Process Processor
- Headquartered in Boston, MA and Germany with localized sales and support in **47 countries**
- **27 years** serving customers worldwide



# Two *Continuous* Processing Technologies

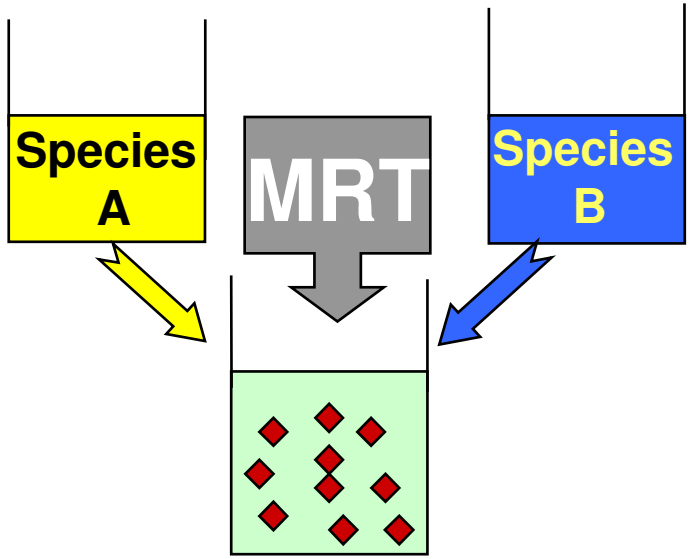
## Top down



**Microfluidizer Processors**

- Effective particle size reduction
- Narrow distribution
- Suitable for many applications
- Scaleup to tens of lpm

## Bottom up




**PureNano™ (MRT)**

- Crystallization, chemical reactions, emulsification
- Smaller, satble particles
- Precise structure control (polymorph)
- Low energy requirements
- High solid loadings

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# Pharmaceutical / Biotech Applications

## By indication

- Cancer drugs
- Anesthetics
- Inhalable drugs
- Anti-inflamatory
- Ocular drug
- Vaccine adjuvants

## By delivery method

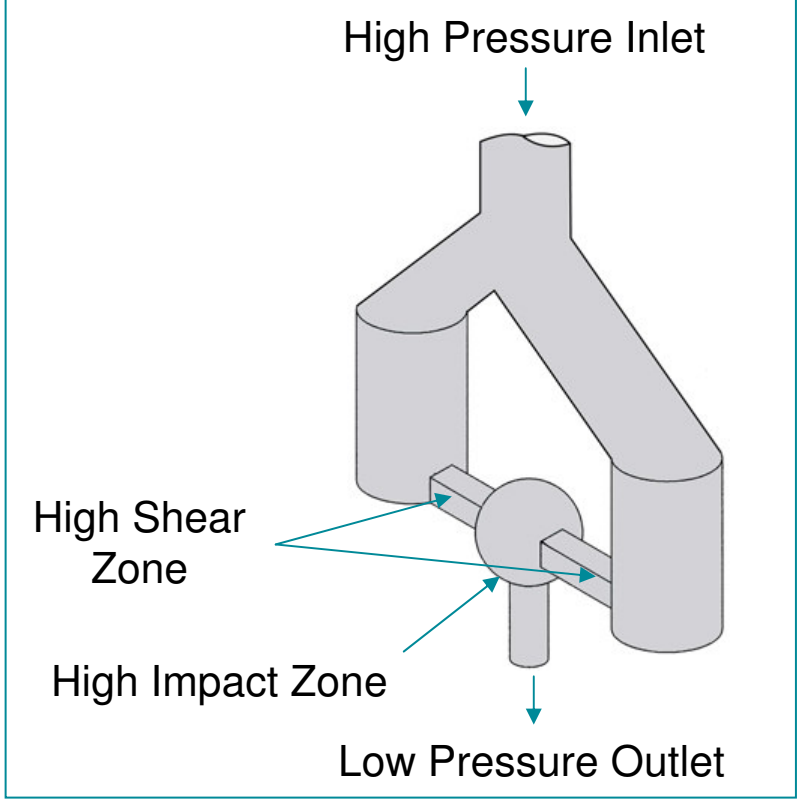
- Injectables
- Inhalables
- Orals
- Transdermals
- Targeted delivery
- Control delivery
- Medical devices

## By material type

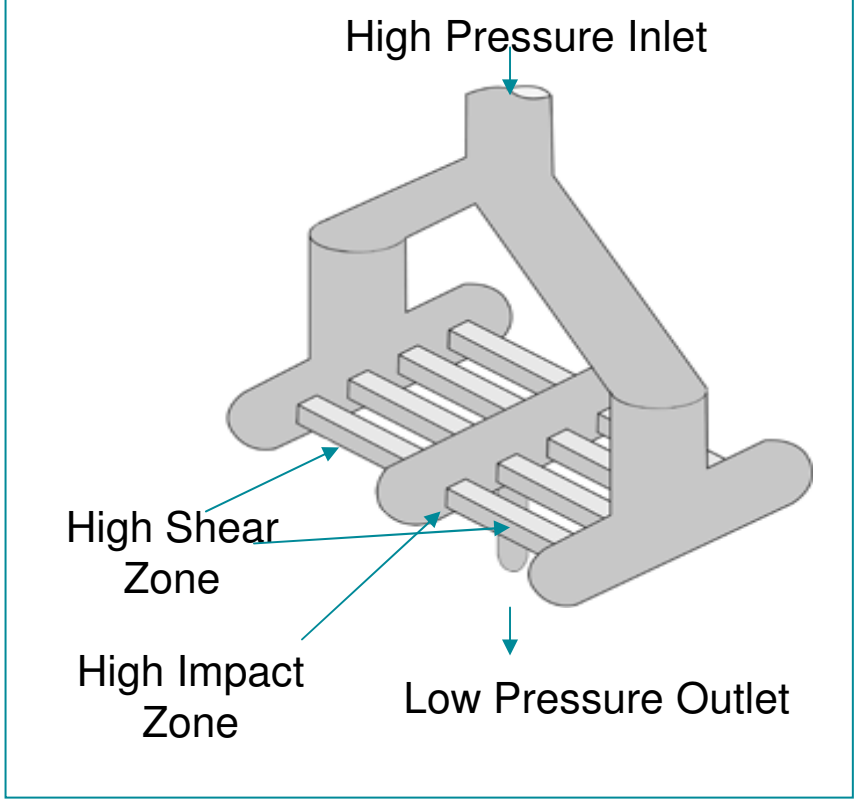
- Emulsions for delivery of hydrophobic drugs
- Liposomes for delivery of hydrophobic/hydrophilic drugs
- Drug particles with tailored structure (crystalline/amorphous)
- Polymer drug encapsulation

# Interaction Chamber – High velocity impinging jet

## "Y" Single-slotted

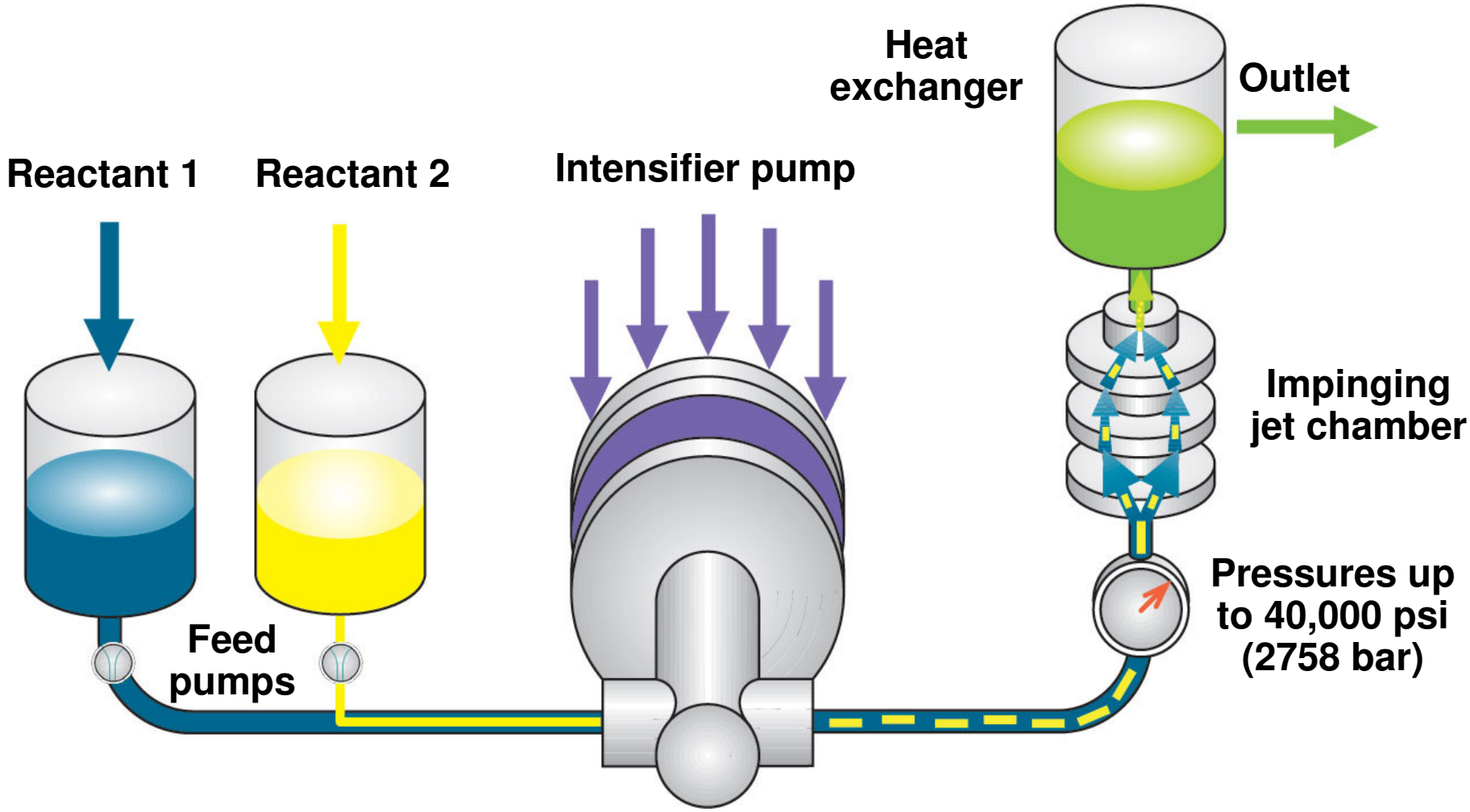



## "Y" Multi-slotted

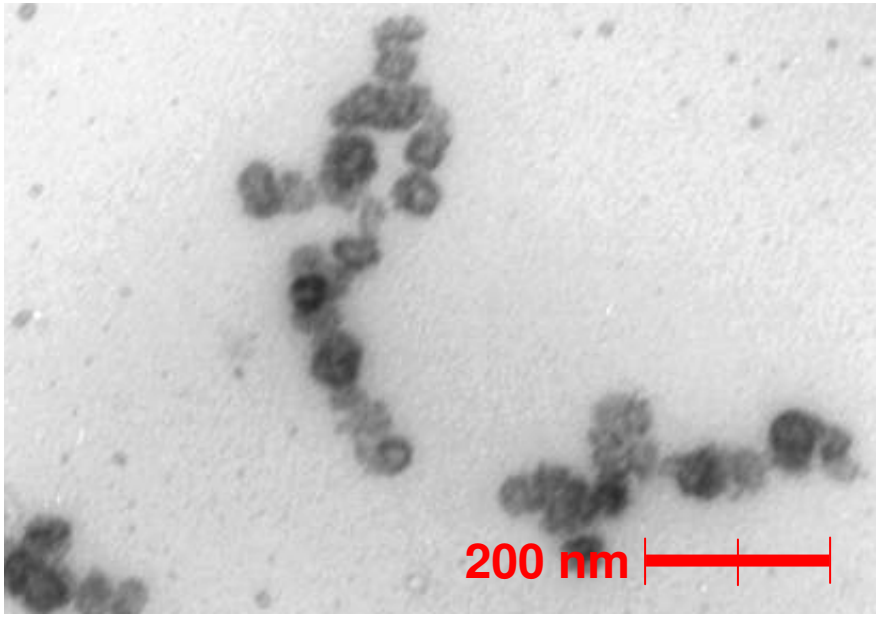


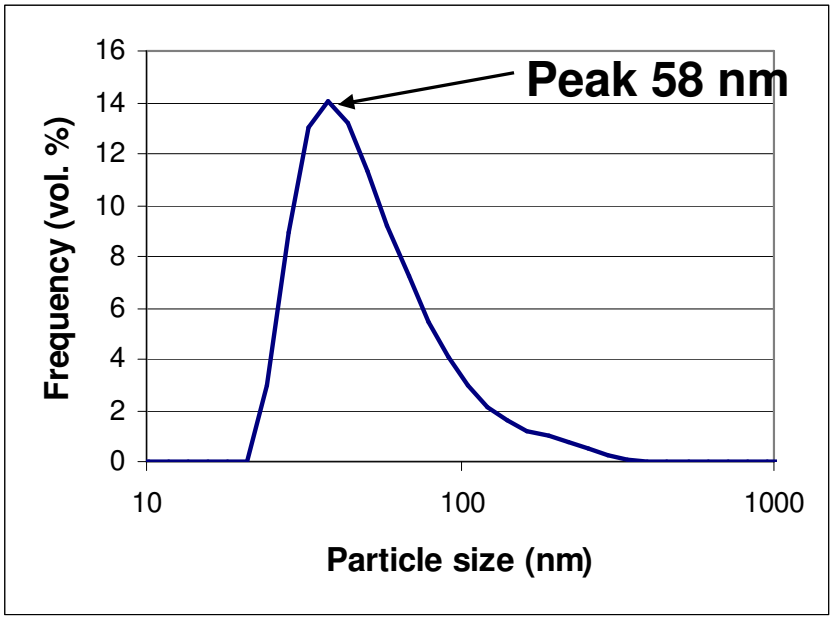

- Channel velocities over 400 m/s
- Channel minimum dimensions typically 50-300 microns
- Shear rates up to $10^7$ $s^{-1}$; controllable mixing in the 25-50 nm scale
- Constant mixing conditions for entire batch
- Demonstrated scalability to tens of liters per minute

# PureNano™ - MRT Configuration



# Azithromycin Crystallization



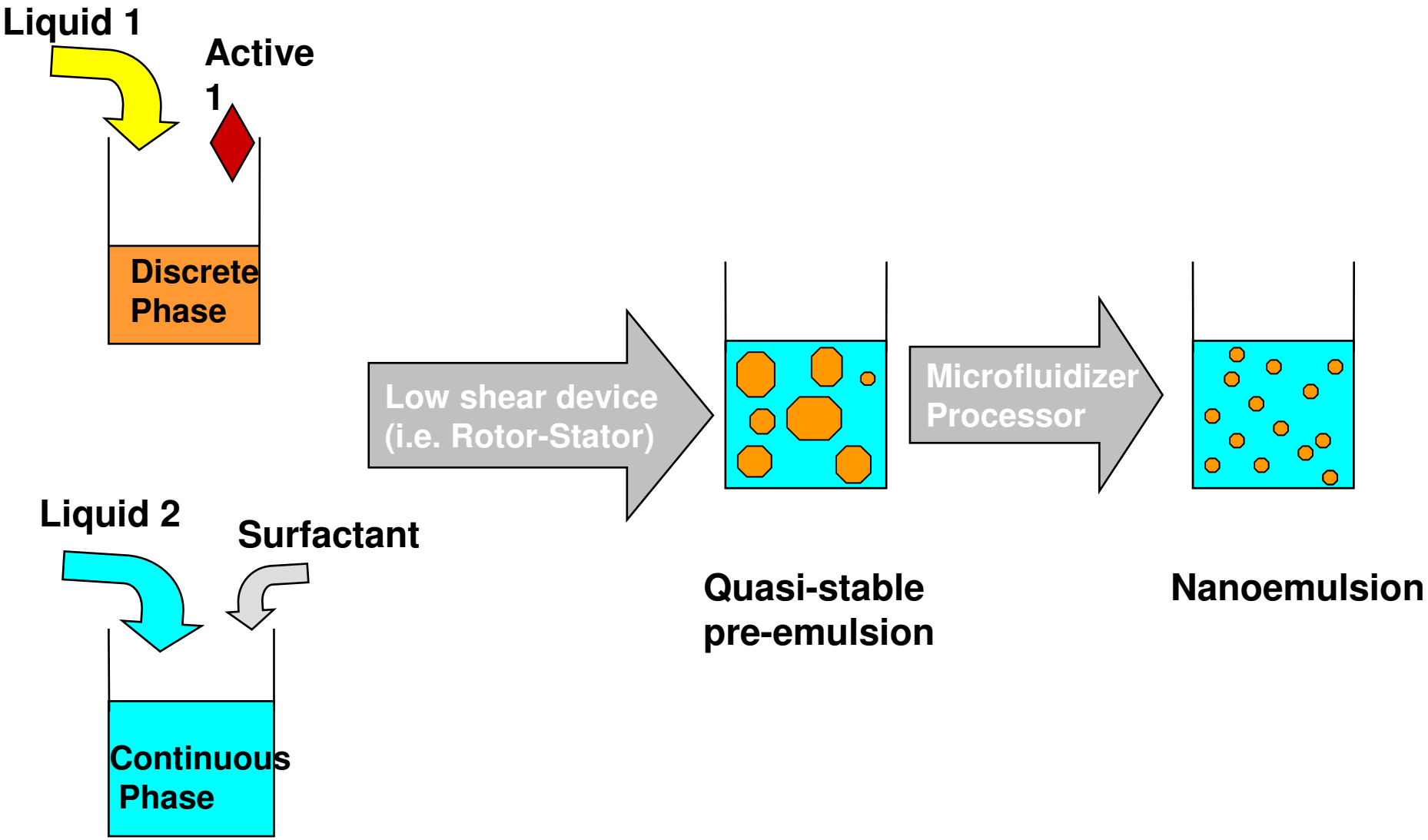




- **Concentration:** 75 mg Azithromycin/ml of DMSO
- **DMSO to water ratio:** 1:4
- **Z-average PS:** 82 nm
- **Critical process parameters:**
  - Solvent/anti-solvent type
  - Supersaturation
  - Temperature
  - Mixing intensity

**Particles were stable - NO SURFACTANTS WERE USED**

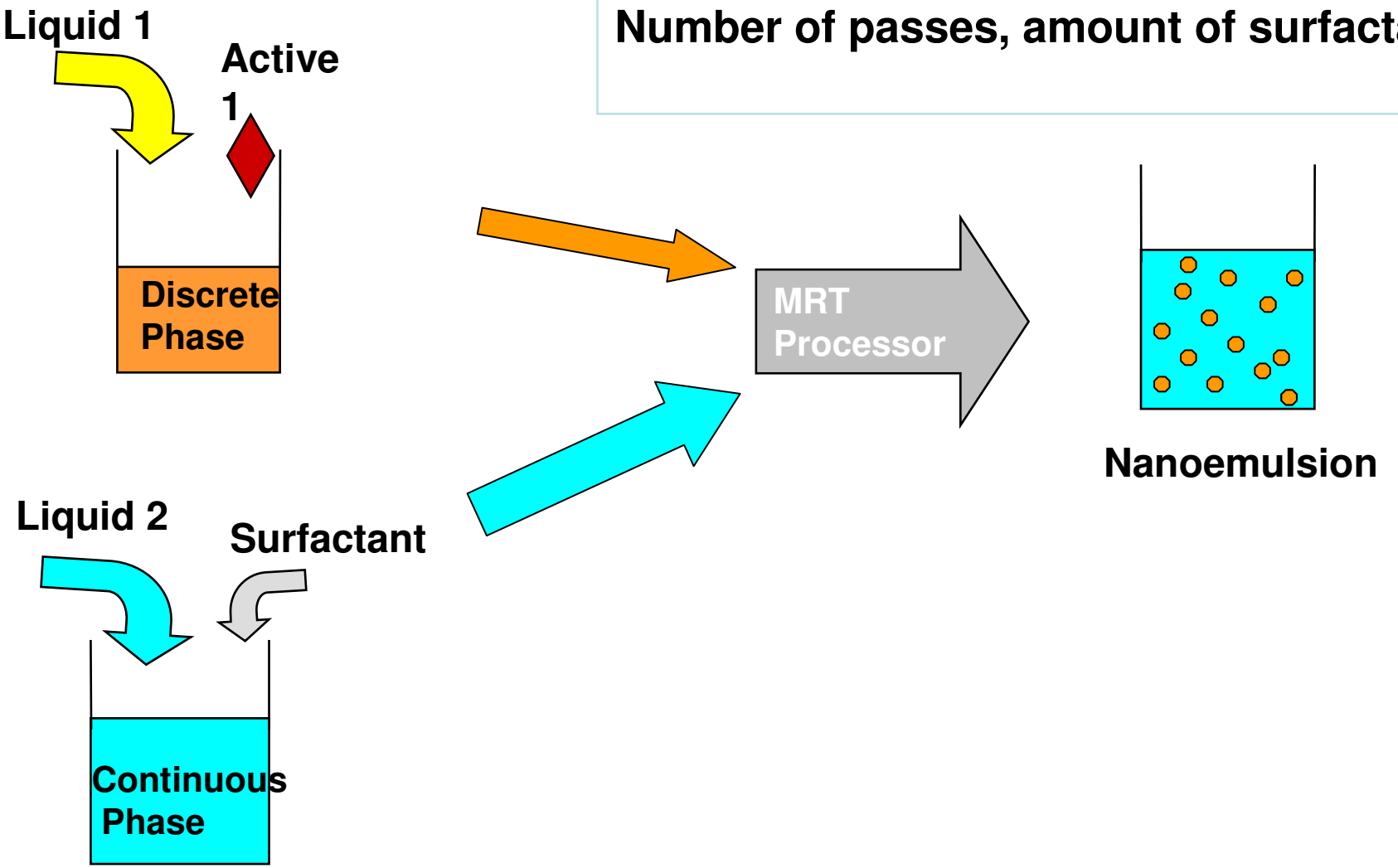
*T. Panagiotou, et al NSTI-Nanotech 2007, www.nsti.org, ISBN 1420063766 Vol. 4, pp. 246-249, 2007.*

# Emulsion Production – "Top Down"

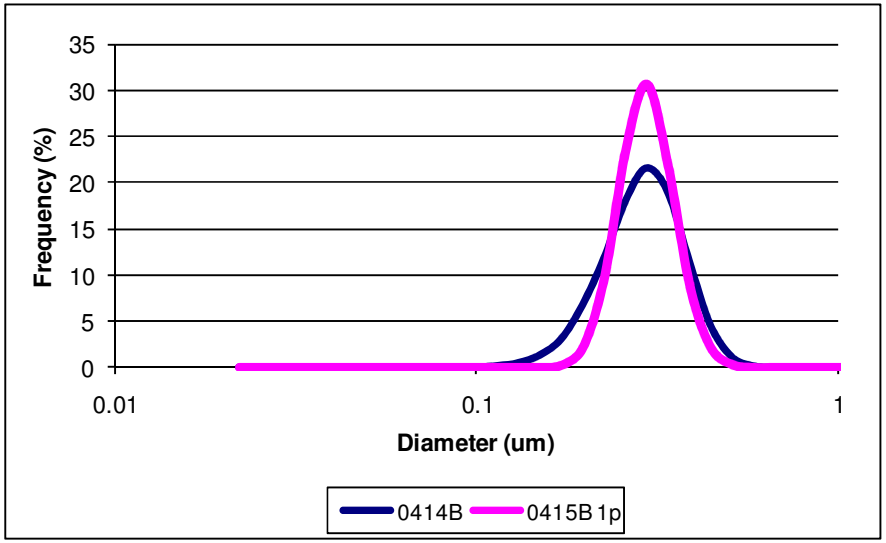


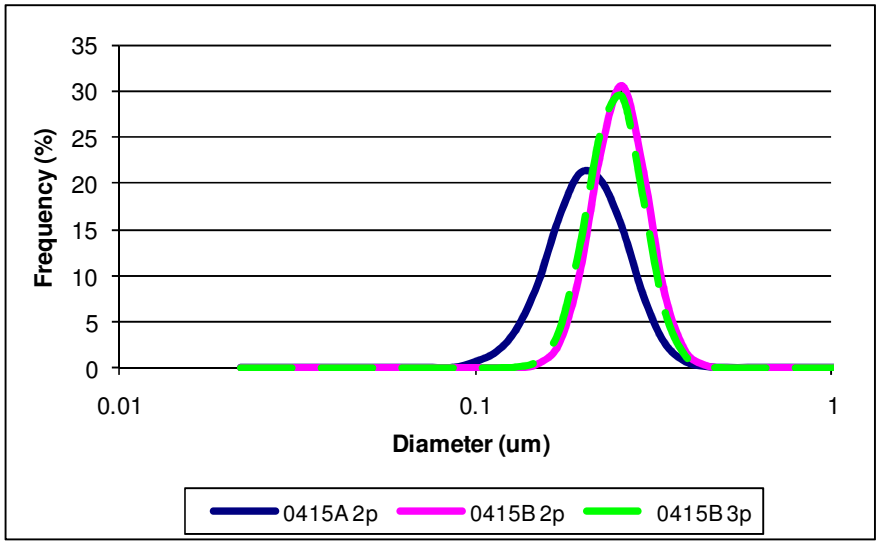
# Emulsion Production – "Bottom Up" (No Need for Pre-emulsion)

**Any more benefits?**
**Number of passes, amount of surfactant?**



# 40% o/w emulsion with 2.4% wt. surfactant




**= PN** **= Top Down**

**= Top Down**

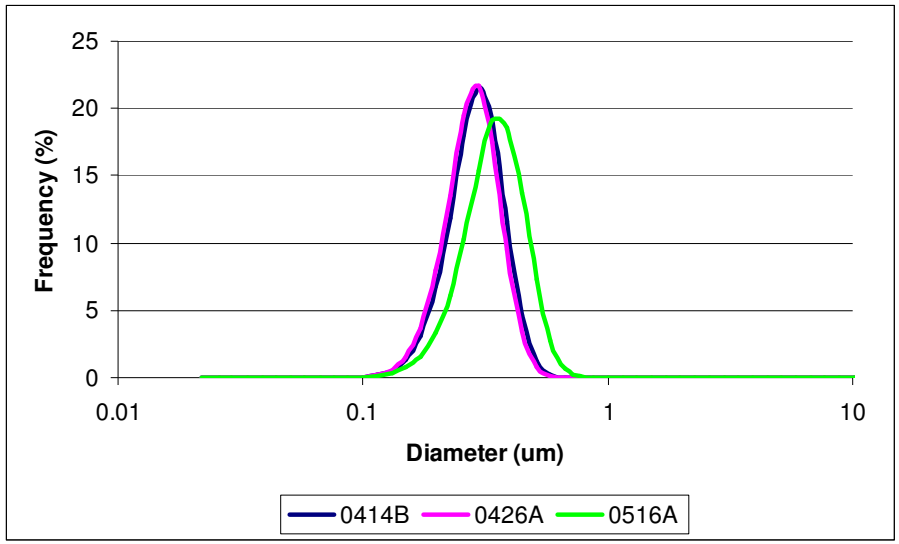
## Single pass

- **Top down and PN method gave similar results**

## Two passes

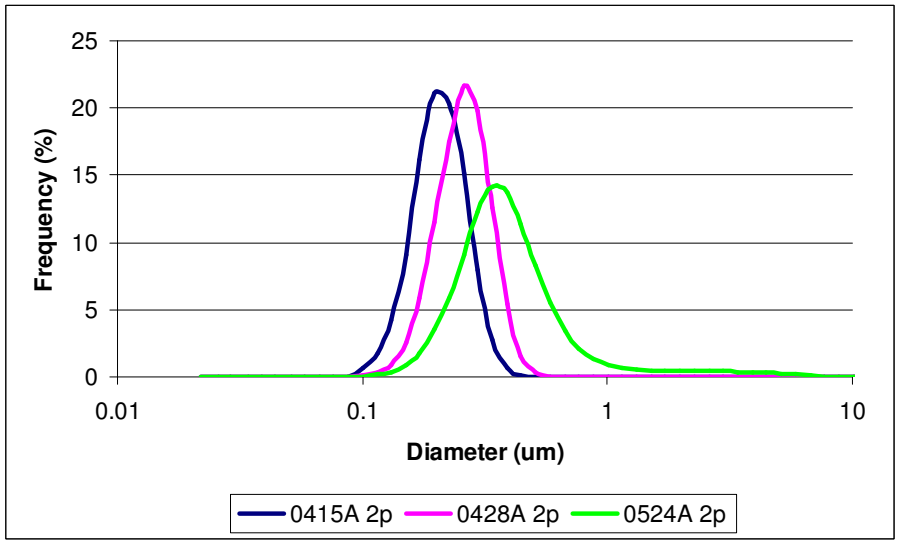
- **PN median 19% (46 nm) smaller than 2 top-down passes with pre-mix**
- **PN median 17% (39 nm) smaller than 3 top-down passes with pre-mix**
- **Top-down particle size plateaued, while PN achieved smaller sizes**

# 40% o/w emulsion with varying surfactant concentration




**Deliver the oil over 1 pass (PN)**

- **Shape of peaks identical**
- **Emulsion starts to break down with 1.8% T80**




**Deliver the oil over 2 passes (PN)**

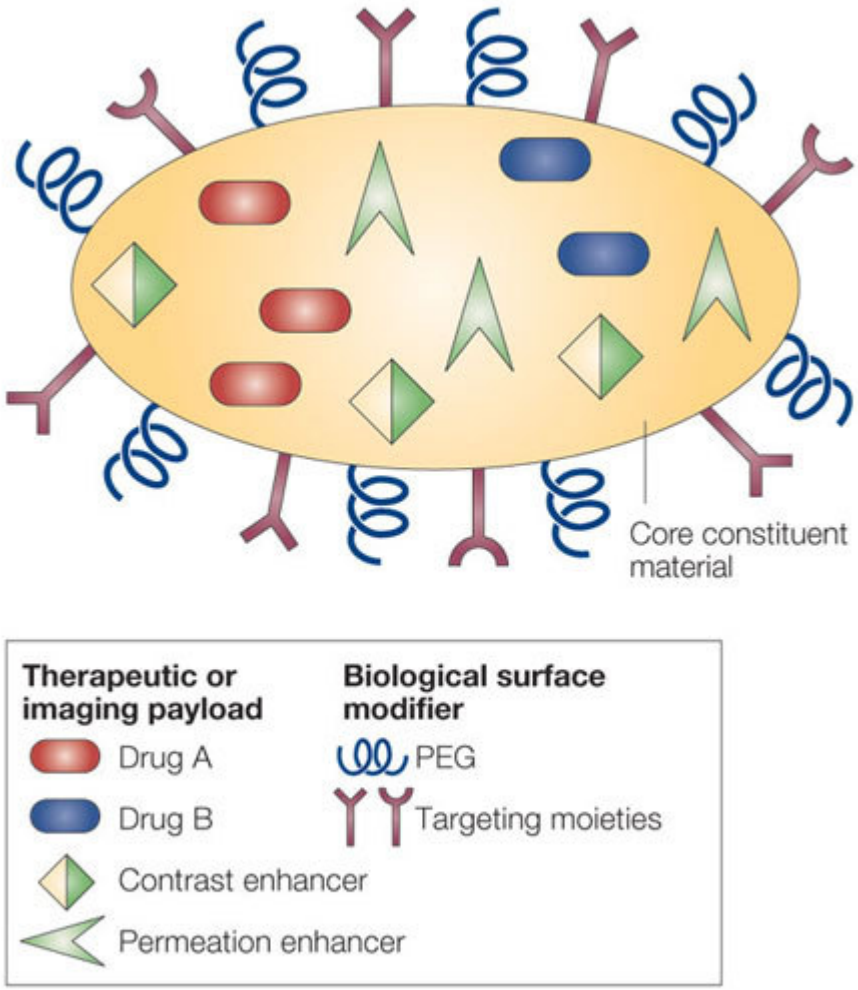
- **1.8% is not sufficient**
- **2.4% and 2.0% both decrease further with oil delivery delayed over an additional pass**

**Surfactant**

**= 2.4%  = 2.0%  = 1.8%**

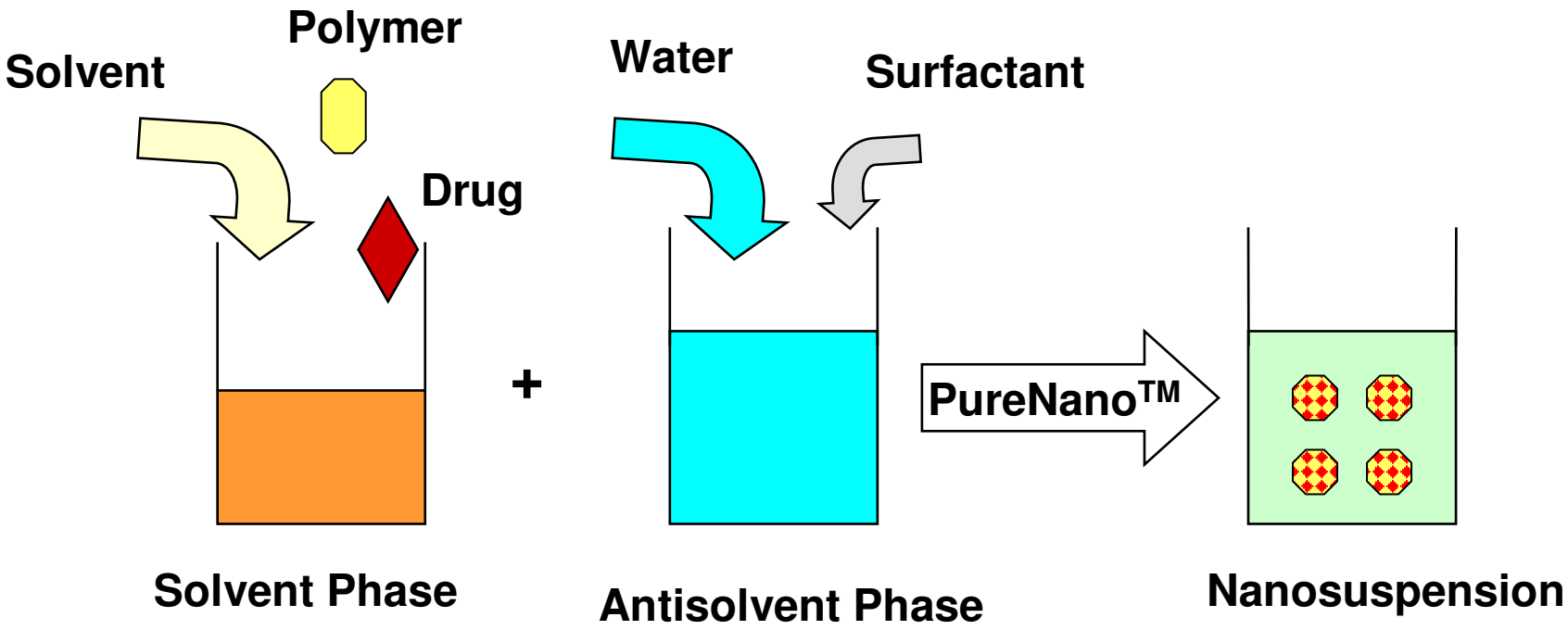
# Multi-functional Nanosystems

- Combination drug products
- Drug and resistance modulator
- Drug and energy delivery (heat, light, and sound)
- Drug and imaging agent



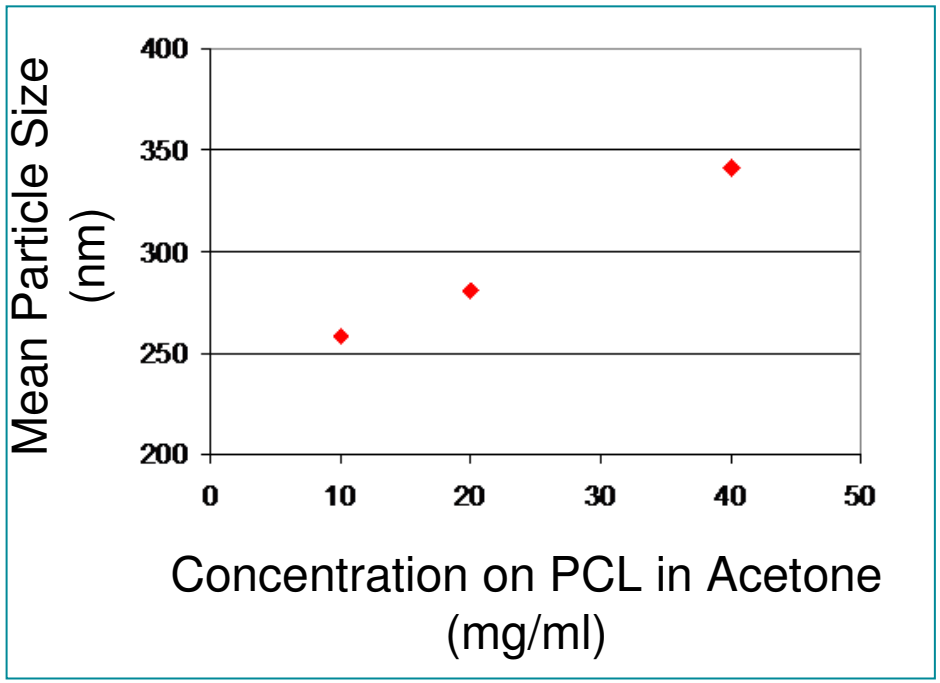

*Ref. M. Ferrari.* Nat Rev Cancer., *5(3):161-71 (2005).*

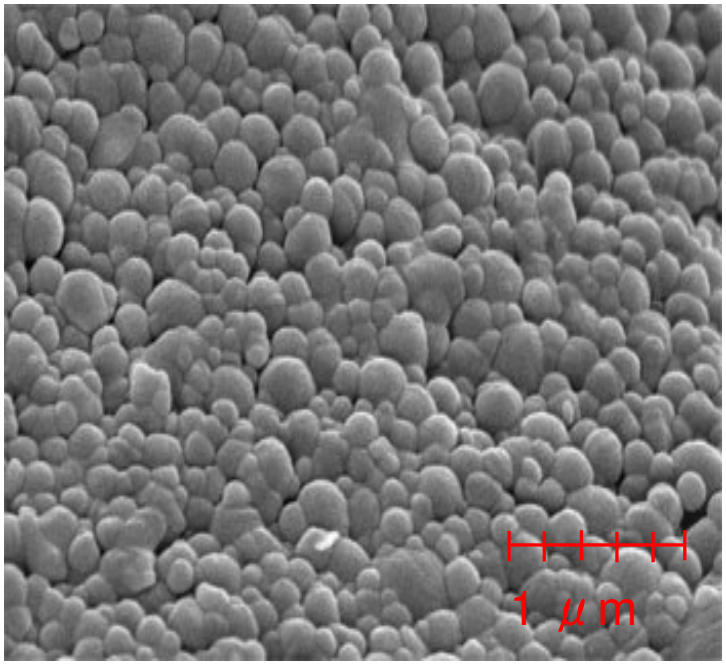
# Bottom-up Precipitation/Nanoencapsulation Using PureNano™




- Solvent is miscible with water
- Polymer and API precipitate as soon as the solvent and the water phase mix
- Post processing includes removal of solvent

# PCL particles - Effects of Key Process Parameters



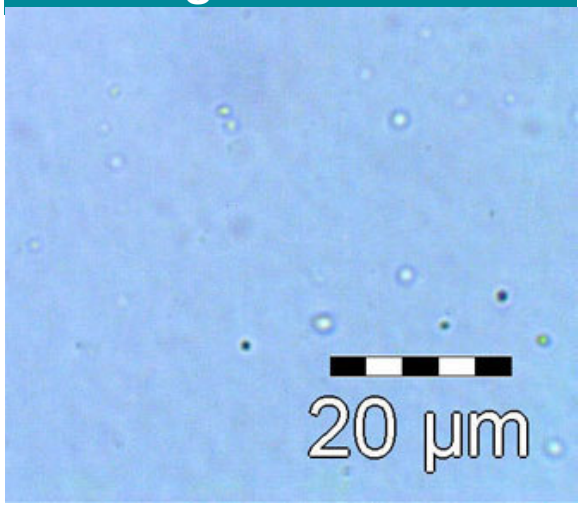




- **PCL particles**
- **Mixing ratio: 1:9**
- **Pressure: 100 MPa**

**PCL nanoparticles created by PureNano™**

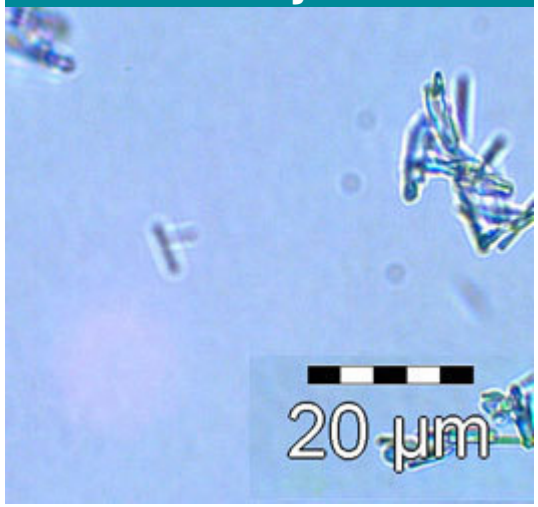
# Drug Encapsulation

## Polymer Encapsulation Using PureNano™



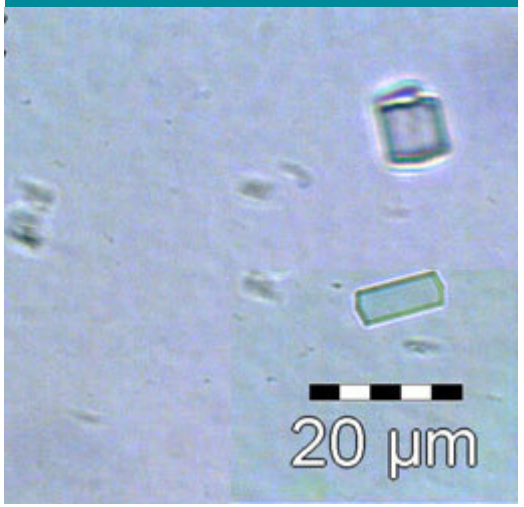

**20 mg/ml PLGA +10 mg/ml CBZ in acetone mixed with water using PureNano™ (1:3 ratio)**

## BASELINE
## No Polymer




**10 mg/ml CBZ in acetone mixed with water using PureNano™ (1:3 ratio)**

## Polymer Encapsulation in Beaker



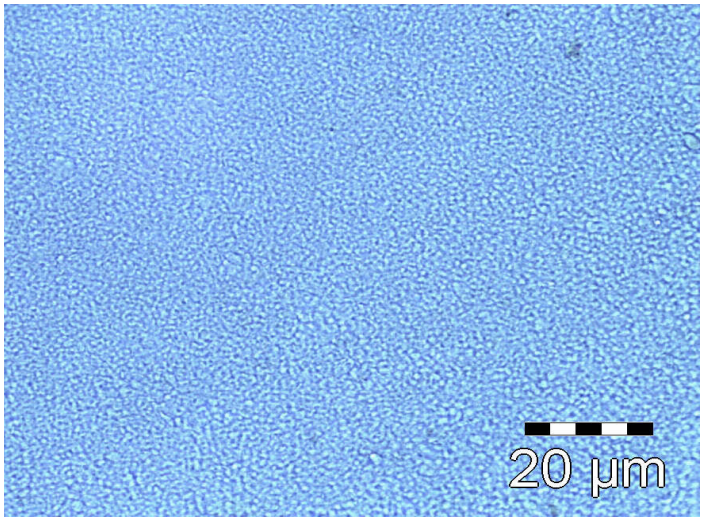

**20 mg/ml PLGA +10 mg/ml CBZ in acetone mixed with water using PureNano™ (1:3 ratio)**

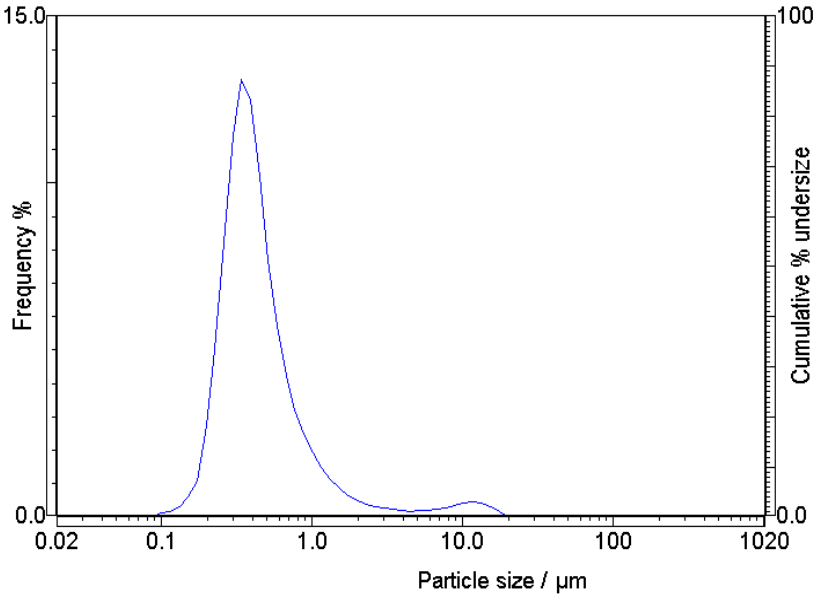
# Drug Encapsulation – MRT

| Polymer Matrix | Initial Polymer Concentration (mg/ml) | Initial Drug Concentration (mg/ml) | Encapsulation Efficiency (%) | Final Drug Concentration in Nanoparticles (wt. %) |
|---|---|---|---|---|
| PLGA | 5 | 2.5 | 66.7 | 25.6 |
| PLGA | 5 | 1.25 | 56.9 | 12.0 |
| PCL | 5 | 1.25 | 58.9 | 13.2 |

# Organic Calcium Salt in Sub-micron Particles (3-phase Reaction)

- **Process:** Acid-Base reaction
- **Reactants:** Calcium hydroxide ($Ca(OH)_2$) water slurry and a fatty acid melt at 65-85ºC; reactant streams are immiscible
- **Product:** Stable calcium salt nanosuspension with over 38% solids




- Median particle size (D50): 367 nm

# PureNano™ - Processes of and Advantages

- **Crystallization , precipitation**
  - Controlled size micro/nano particles
  - Smaller particles, lower energy than “top down”
  - Control of crystalline structure -high purity material

- **Chemical reactions (single-,multi- phase)**
  - Expedited chemical reactions
  - Enhanced selectivity/minimizes side reactions
  - Particle size control

- **Nanoencapsulation**
  - High encapsulation efficiency

- **Emulsification**
  - Avoid the need for pre-processing
  - Potentially minimizes the amount of surfactant

- **Adsorption/chemisorption**

# PureNano™ Machine Specifications


- **Flow rate:** ~500 ml/min
- **Reactant streams:** Two
- **Flow rate ratio:** 1:1, 1:2,… 1:50
- **Utility requirements (electrical):**
~ 3 phase 50/60 Hz service, 208/230/460V, 20A max