Solving Nanotechnology Application Challenges with the Versatile and Scalable Microfluidizer® Technology

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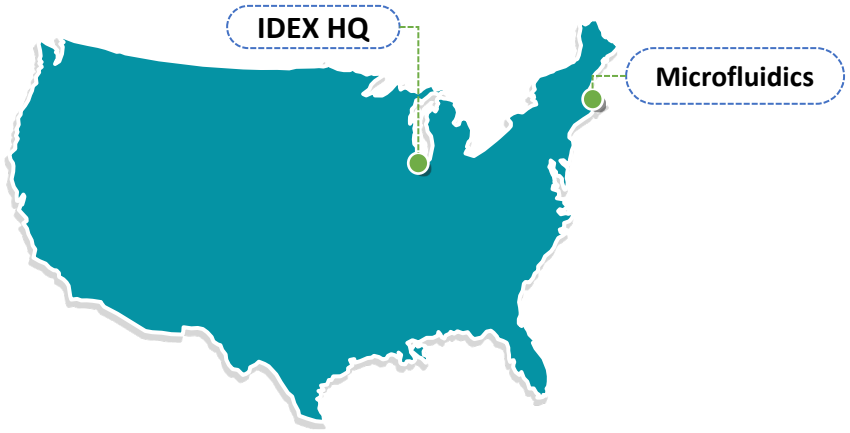
Agenda

- **Who we are**
- **Microfluidizer® Technology**
- **Manufacturing Considerations & Benefits of uniform processing**
- **Particle characterization techniques**
- **How can Microfluidizer technology solve nanotechnology application challenges:**
  - Biopharmaceutical applications
  - Cosmetic applications
  - High performance energy storage applications
  - Nutraceutical applications
- **The Microfluidizer product line**
- **Q&A**

Who Is Microfluidics

- Microfluidics was founded in 1983 to produce high shear fluid processors using Interaction Chamber™ technology.
- Headquartered outside of Boston, MA with localized support in 47 countries. Over 4000 processors sold to 2000 companies.
- Acquired by IDEX Corporation and grouped with Quadro, Fitzpatrick, Matcon and Steridose to form the MPT Platform.
- Microfluidizer Processors are used for R+D and manufacturing of active pharmaceutical ingredients, vaccines, inkjet inks, coatings, nutraceuticals and cosmetics.
- Microfluidics has vast applications and machine design experience.



What We Do Best

Material Processing Technologies

Nanoemulsions

Polymer nanoparticles

Polysaccharide Molecular Weight Reduction

Liposomes/LNPs

Cell disruption

Deagglomeration/Particle Size Reduction

M-110P "plug n' play" benchtop lab model

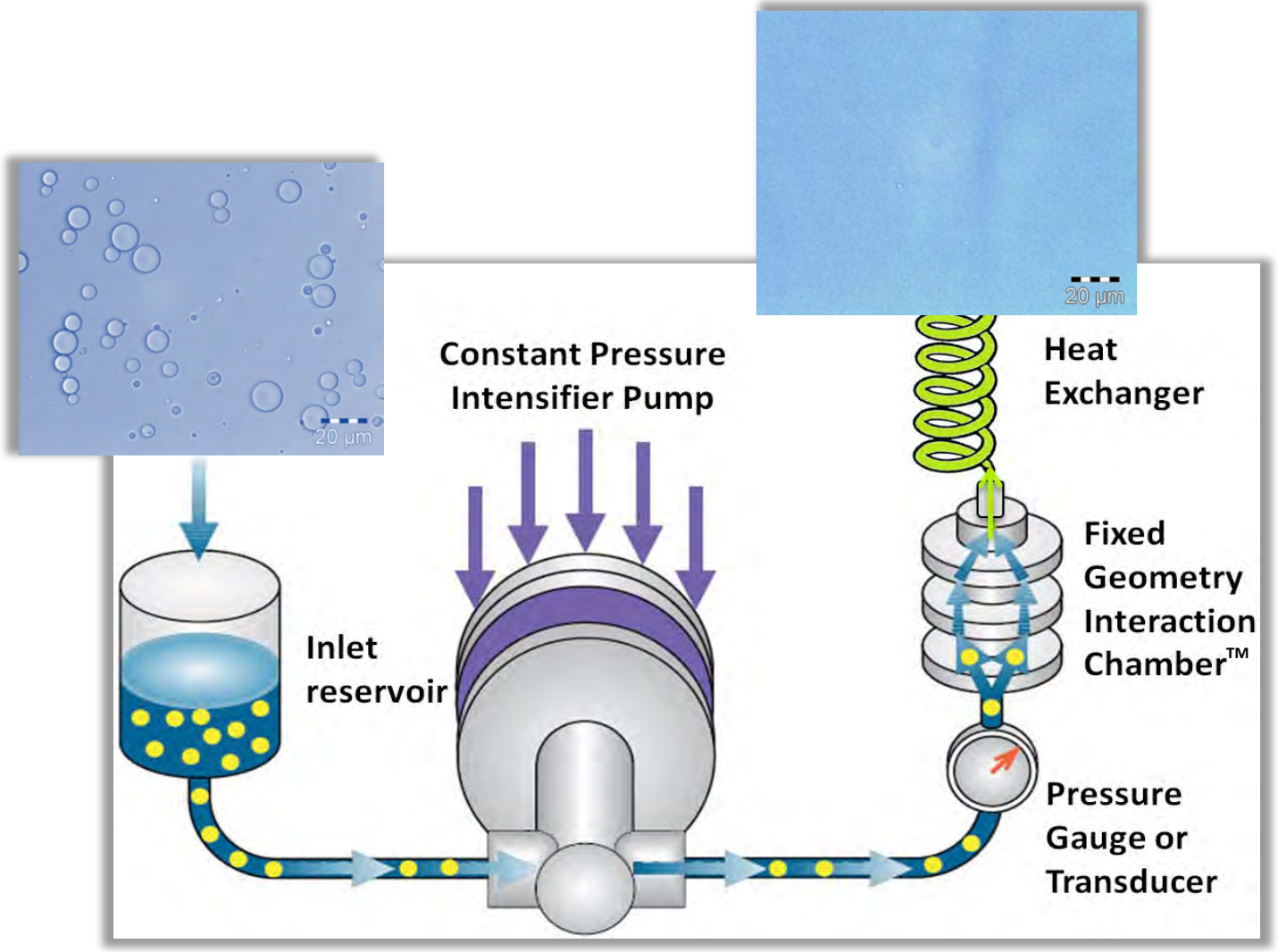
M-110EH-30 pilot scale processor

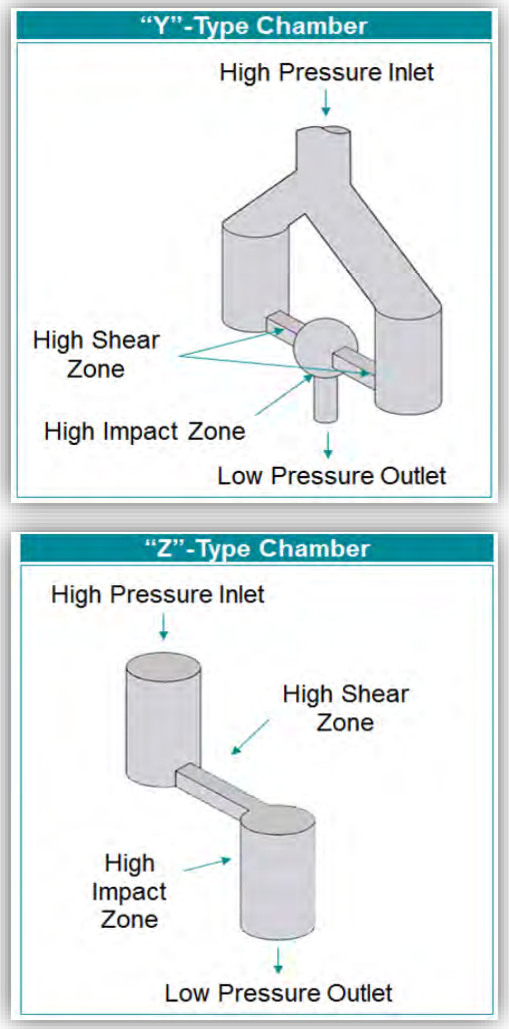
M-700 series production machine

Fixed-geometry Interaction Chambers

FITZPATRICK® MATCON® Microfluidics™ QUADRO STERIDOSE®

Microfluidizer® Technology



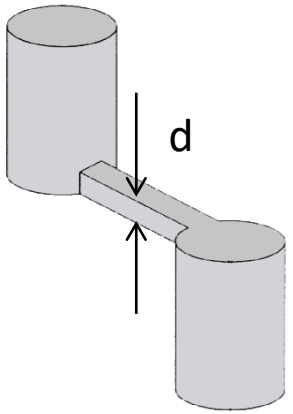


Schematic of Microfluidizer processor

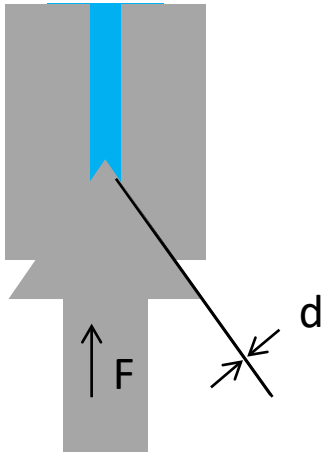
Constant Pressure Vs. Constant Volume

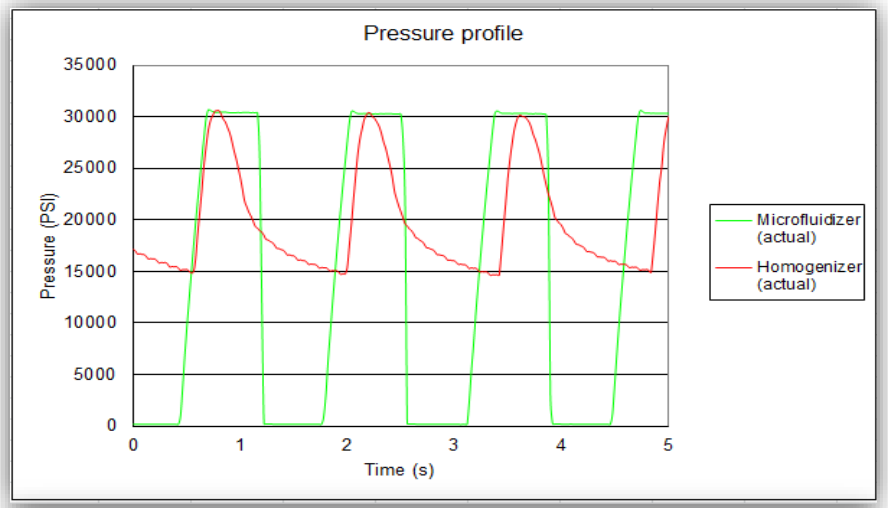
Material Processing Technologies

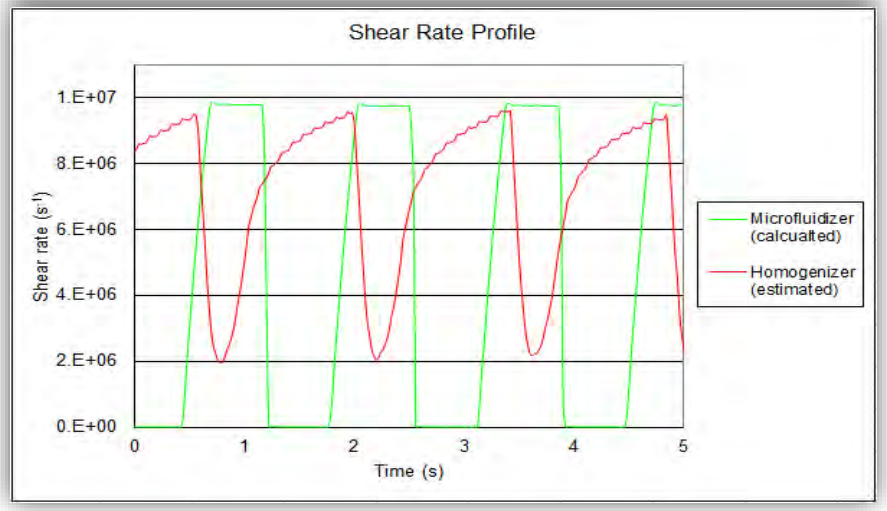
Interaction Chamber



Homogenizer Valve







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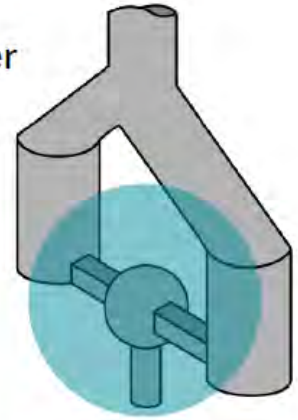
Microfluidizer® Technology – Scale-Up

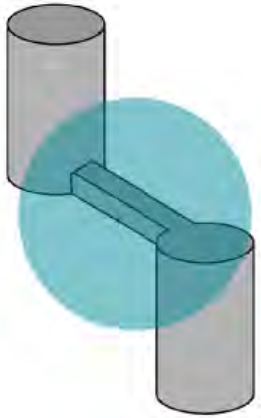
LABORATORY

PRODUCTION

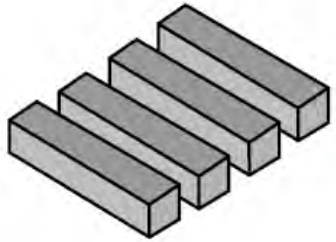
Y Chamber



Z Chamber

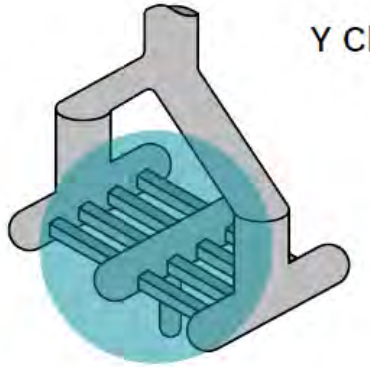


In production equipment, identical microchannels are aligned in parallel

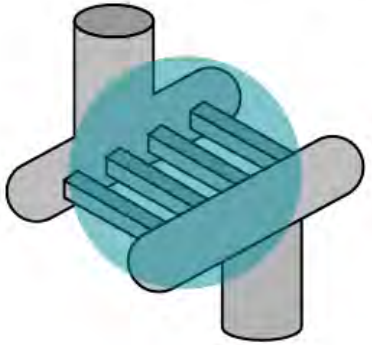


Production machines are certain to produce equivalent results as the benchtop models used in the lab.

Y Chamber



Z Chamber

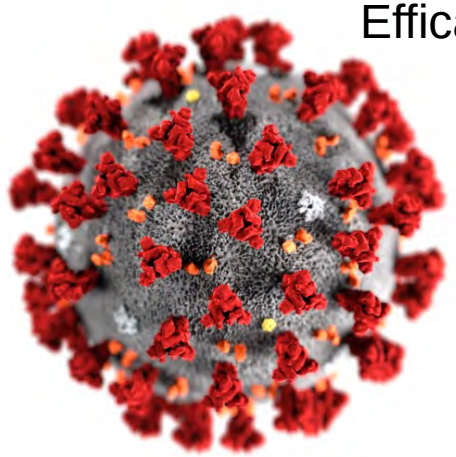


Manufacturing Considerations & Benefits of Uniform Processing

- **Manufacturing**
  - Target properties – Physicochemical properties (particle size and distribution, viscosity, texture, etc.)
  - From lab to production
    - Repeatability – Batch to batch consistency
    - Scalability – Large scale manufacturing
  - Allow easier downstream processes
    - Sterile filtration – Removal of bacteria by filtering through 0.22 micron (220 nm) rated filters
  - Meet regulatory requirements
- **Benefits of Uniform Processing**
  - Stability
  - Prolonged shelf life
  - Achieve desired/better appearance and feel
  - Less energy (passes, operation, cleaning)

Importance of knowing your particles

Efficacy



Stability

Power

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What We Do Best: Particle Characterization Techniques

Instrument	Technology	Measurement Output	Measurement Range	Typical Sample Amount*	Light Source/ Resolution
LA-960V2	Laser Diffraction	Particle Size	Wet: 10 nm to 5000 µm Dry: 100 nm to 5 mm	~10 mg to 5 g	650 nm Laser Diode 405 nm LED
LY-9610	Dynamic Image Analysis (Requires an LA-960V2)	Particle Size and Shape	Wet: 5 µm to 1000 µm	~10 mg to 5 g	LED Light
LA-350	Laser Diffraction	Particle Size	Wet: 0.1 µm to 1000 µm	~10 mg to 5 g	650 nm Laser Diode
ViewSizer 3000	Nanoparticle Tracking Analysis**	Particle Size Particle concentration	10 nm to 15 µm	350 µL to 3 mL	445 nm blue laser 520 nm green laser, 635 nm red laser with variable power output
SZ-100V2	Dynamic Light Scattering (DLS), Electrophoretic Static Light Scattering, Debye Plot Method	Particle Size, Zeta Potential, Molecular Weight	Particle Size: 0.3 nm to 10 µm Zeta Potential: -500 mV to +500 mV Molecular Weight: $1x10^3$ to $2x10^7$ g/mol	50 µL to 3 mL	532 nm Laser Diode (green) 17°, 90°, 173° detectors
CENTRIFUGE CN-300	Centrifugal Sedimentation	Particle Size	10 nm to 40 µm	10 µm (Line Start) 40 µm (Homogenous)	LED 470 nm (500 mW) Max acceleration: 30,000 G
SA-9600 Series	BET Flowing Gas Adsorption & Desorption	Surface Area	0.1 m^2 to 50 m^2	< 1 g	NA
PSA300	Static Image Analysis	Particle Size and Shape	0.5 µm to 1000 µm	1 mg to 10 mg	2.1 MP mono camera
Eyecon$_2$	Direct Imaging Particle Analysis	Particle Size and Shape	50 µm to 5500 µm	Continuous monitoring	12 x 3 High intensity, low energy RGB LEDs
ANALYSETTE 28	Dynamic Image Analysis	Particle Size and Shape	Dry: 20 µm to 20 mm Wet: 5 µm to 3 mm	Dry: 10 to 100 g Wet: 0.1 to 1 g	LED 2.59 microns per pixel

** Amount is sample dependent.* *** Fluorescence nanoparticle tracking also available.*

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Material Processing Technologies

Biopharmaceutical Applications

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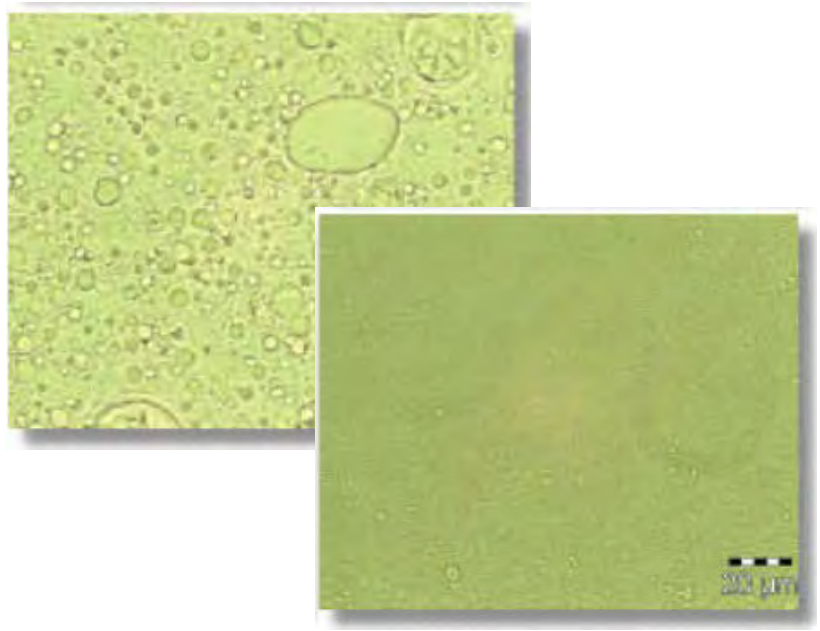
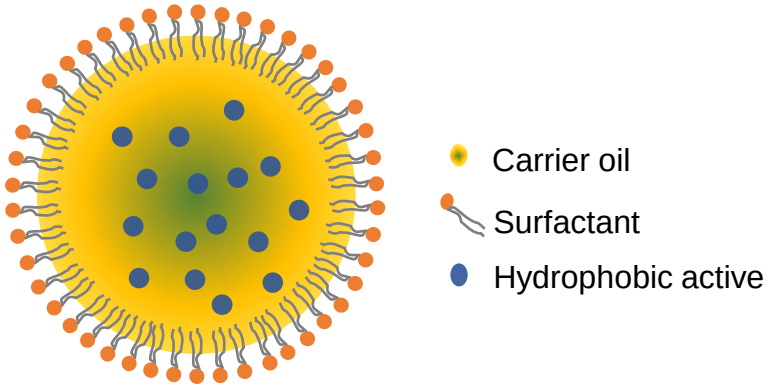
Nano-emulsions

- Two immiscible liquids with one finely dispersed in the other
- Any particles larger than ~1 um will result in “instability”
- Used in all industries
- Can be “oil in water (O/W)” or “water in oil (W/O)”
- Require some sort of “surfactant” or “emulsifier” to maintain stability

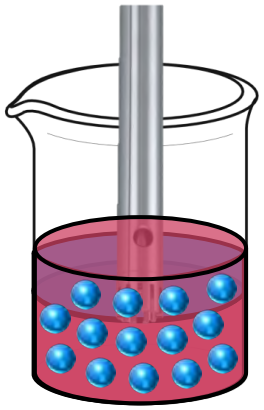


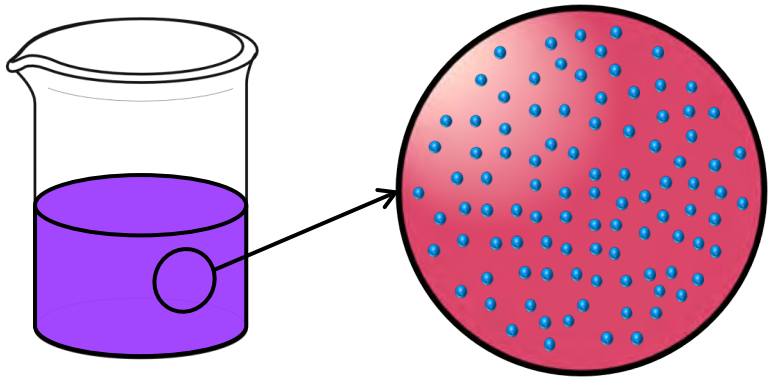
- Two main biopharma applications:
  1. Active Ingredient Delivery
  2. Vaccine Adjuvant



Nanoparticle Preparation (O/W)

- Water + Surfactant + (Hydrophilic API)
- Oil + Surfactant + (Hydrophobic API)
- Oil in Water Emulsion/Liposomes/Polymer NPs





Key process parameters:

- Pressure
- Type and size of interaction chamber
- Temperature
- Number of passes

Case Study - Vaccine Adjuvant Nano-emulsion

- Squalene-based oil-in-water emulsions as vaccine adjuvant
- Process scale-up for pandemic response
  - Scale-up objective: Manufacture 50 million total doses of adjuvant within 3 months
  - 1M dose daily batch size
  - Performance criteria
    - Particle size (average) ≤ 100 nm
    - Oil and excipient concentrations, homogeneous visual appearance, etc.
    - Filter sterilizable
  - cGMP facility

AAHI

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INFECTIOUS DISEASE RESEARCH INSTITUTE

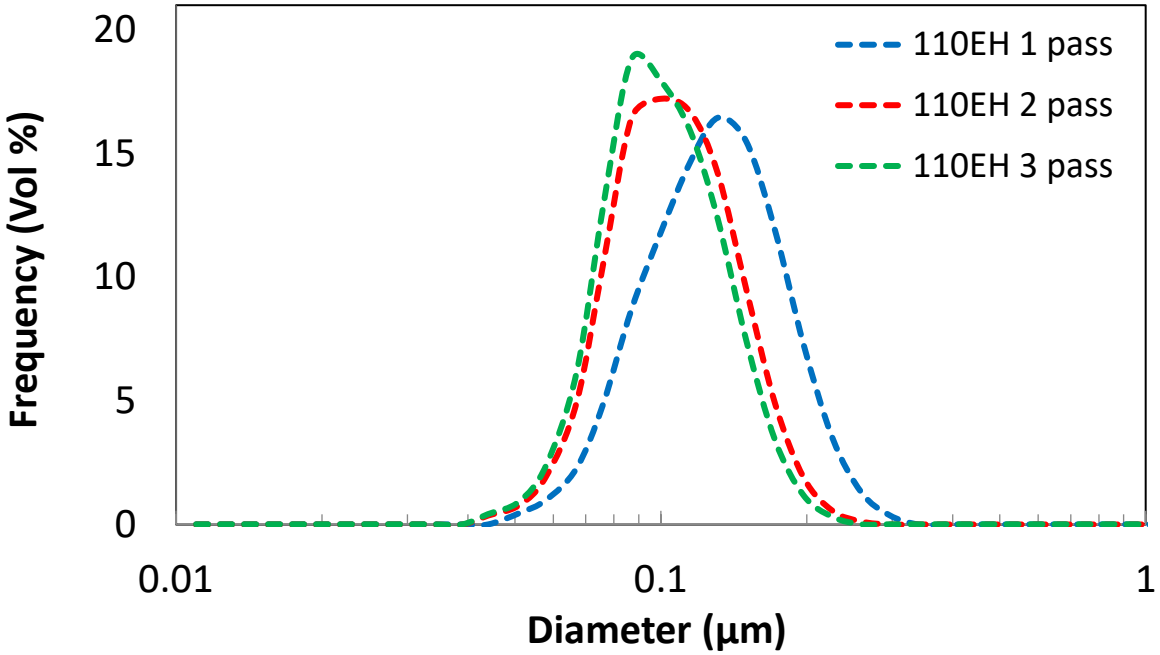
T. Phan, et.al. Pharmaceuticals, 2020 (13) 8.

Case Study - Vaccine Adjuvant Nano-emulsion

- Initial process: **4% oil, up to 10 passes**
- Optimized process: **30% oil 2 passes**
- Optimized process can be performed in 3% of the time of the initial process.

Pilot scale results

M110EH (300 mL/min)

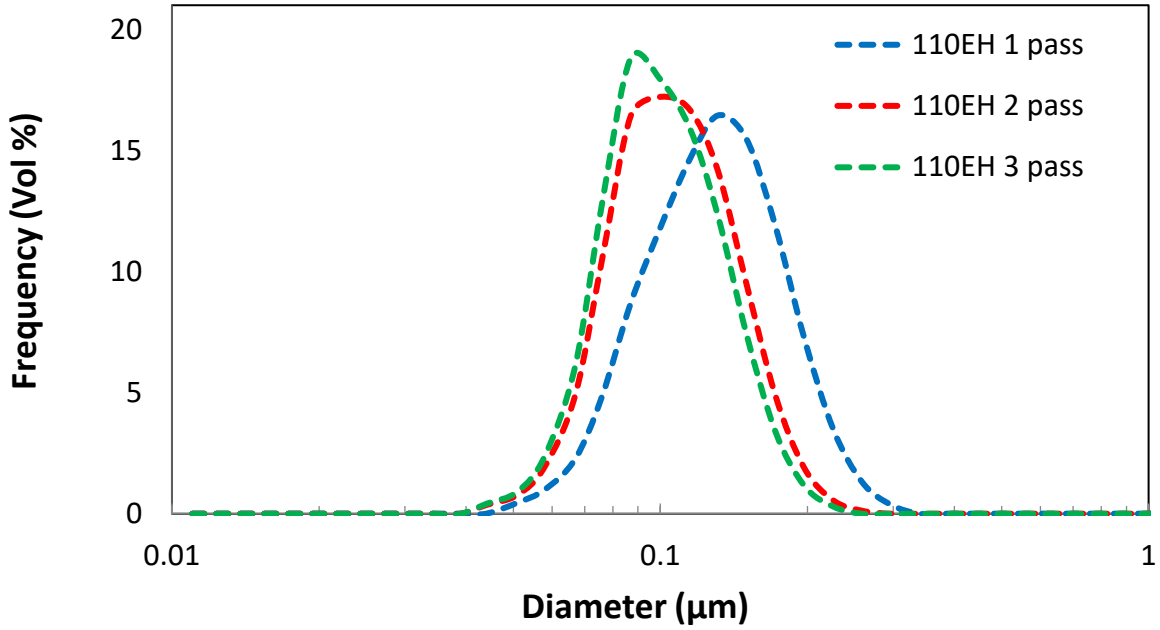


T. Phan, et.al. Pharmaceuticals, 2020 (13) 8.

Production scale results

- Particle size and distributions were almost identical
- Final optimized process improved the process efficiency and increased the production capacity to 5M doses/day (200 L batch size & less then 8 hrs. total processing time)

110EH (300 mL/min)



T. Phan, et.al. Pharmaceuticals, 2020 (13) 8.

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Cosmetic Applications

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Cosmetic Formulations

- **Emulsions are widely used in cosmetic products including:**
  - Perfume
  - Shampoo
  - Lotion
  - Cream
- **Other formulations include:**
  - Liposomes
    - Serum – Coenzyme Q10, Vitamin C, peptides, etc.
  - Dispersions
    - Facial/body exfoliating scrubs
    - Lipstick
    - Temporary tattoo ink
    - Collagen
- **Cell Disruption**

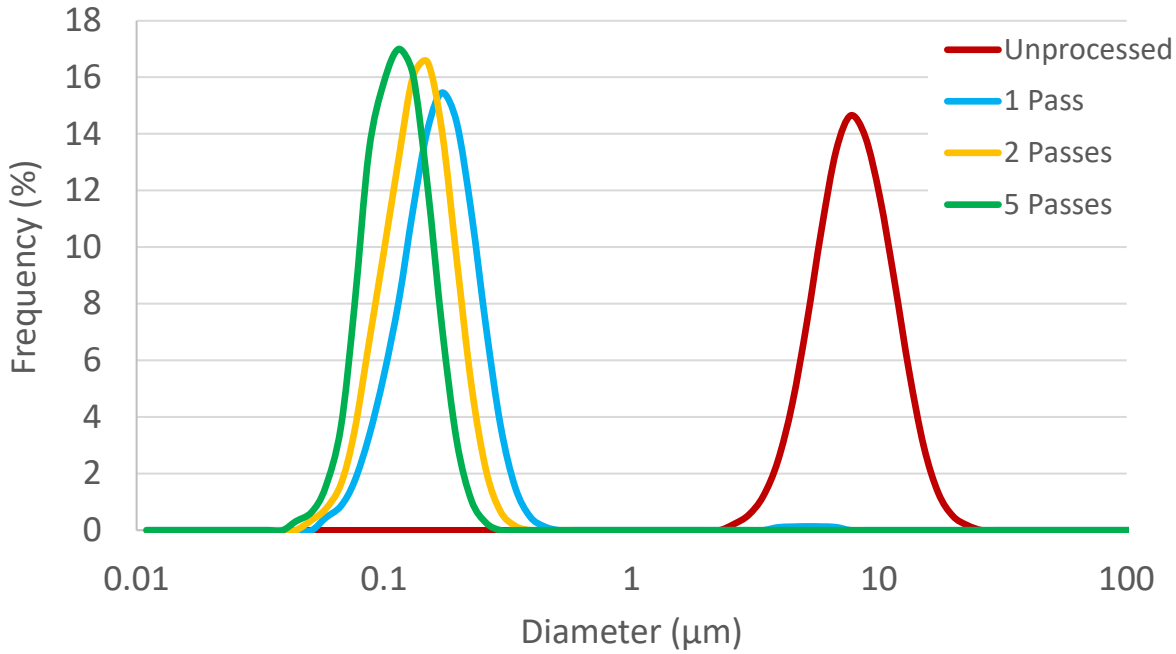
Emulsion for Alcohol-free Perfume

- **Alcohol is often the main ingredient in the composition of perfumes as a solvent for the aromatic compounds.**
- **Alcohol based perfume can cause skin dehydration and skin barrier damage, especially for sensitive skin.**
- **New trend such as the clean beauty movement pushes to remove solvents from perfume**
  - Perfume companies are therefore shifting to water-based alcohol-free formulations
  - Emulsion is the best approach
  - The alcohol-free alternatives need to resemble the alcohol-based product such as the translucent appearance, etc.
  - Small droplets help in this aim

Case Study – Perfume Emulsion

- **Goal:** To create an emulsion encapsulating fragrance with mean particle size ~ 100 nm.

	d10 (nm)	d50 (nm)	d90 (nm)	Mean (nm)
Unprocessed	4,563.5	7,350.3	11,729.8	7,832.69
1 Pass	95.6	156.5	241.7	191.40
2 Passes	82.4	129.1	191.6	133.91
5 Passes	71.2	105.6	154.8	109.88

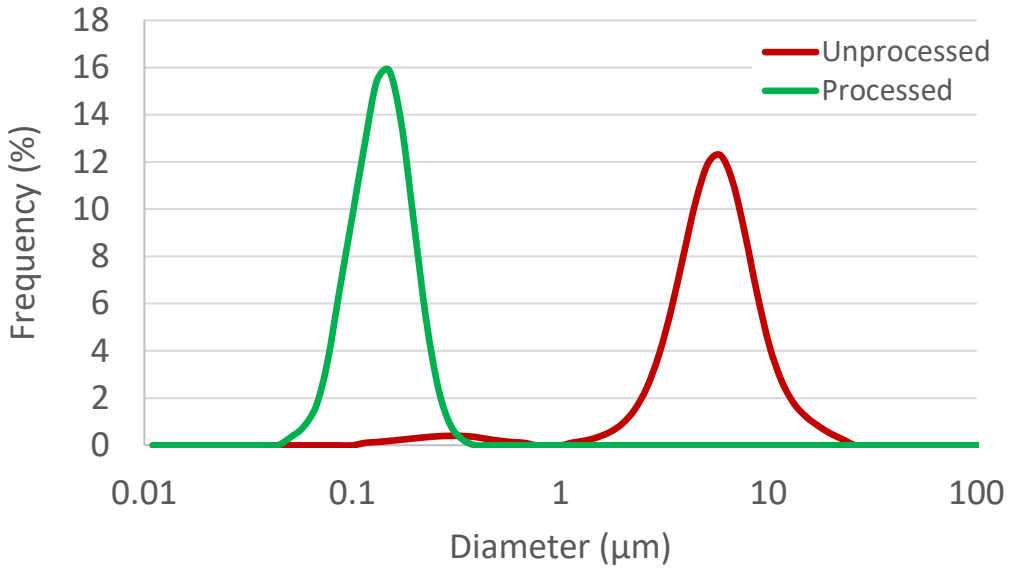


Case Study – Bond Treatment Shampoo Emulsion

- Hair bonds are responsible for the shape, strength, elasticity and shine of the hair.
- Broken bonds lead to brittle, damaged and eventually broken hair strands.

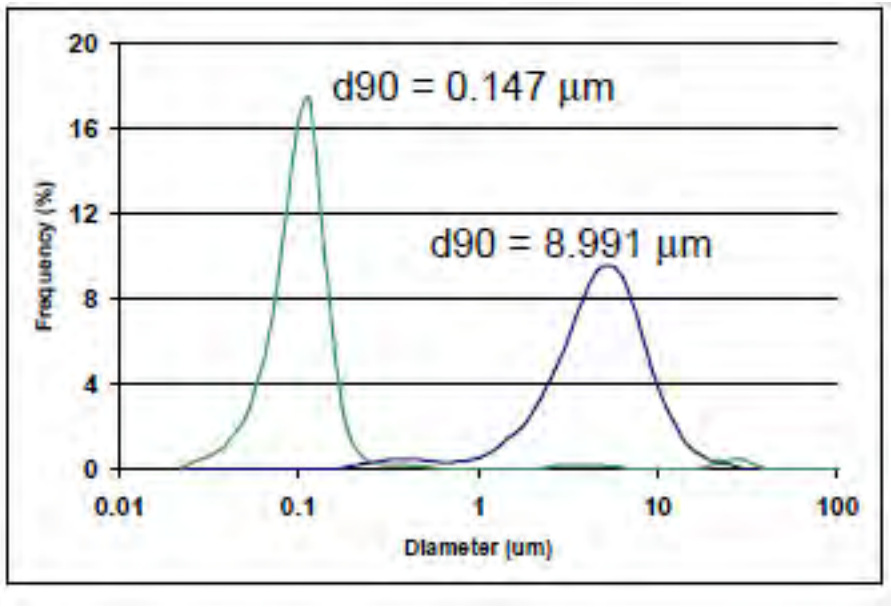
- **Goal:** To produce a stable homogeneous emulsion (D50 < 200 nm & D90 < 300 nm) used as specialty shampoo that help regenerate bonds and repair damaged hair.

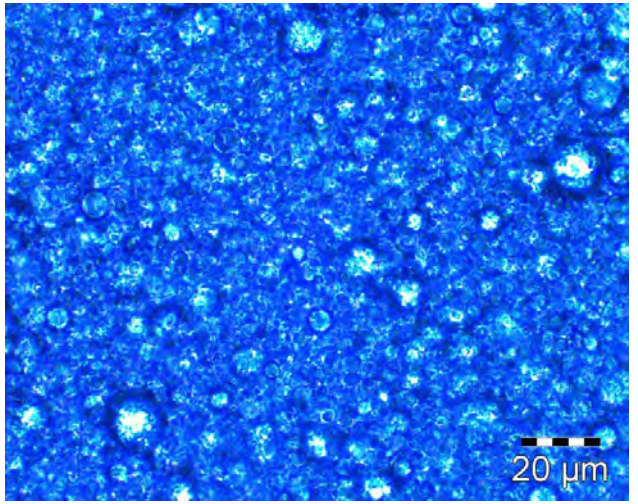
	d10 (nm)	d50 (nm)	d90 (nm)
Unprocessed	2,629.8	5,143.6	9,248.8
Processed	82.2	130.2	197.6



Case Study – Liposomal Botulinum Toxin

- Botulinum toxin is a highly potent neurotoxic protein
- In cosmetic applications, botulinum toxin is used for reduction of facial wrinkles by relaxing the facial muscles underneath after injection.
- **Goal:** To reduce the particle size of the liposomal formulation < 200 nm for transdermal delivery.





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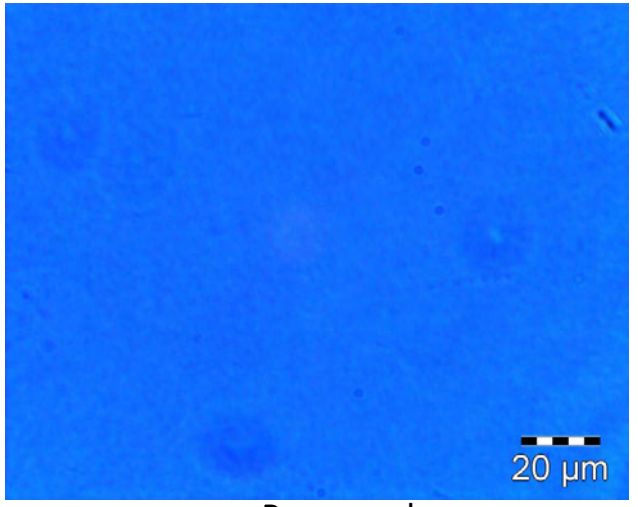

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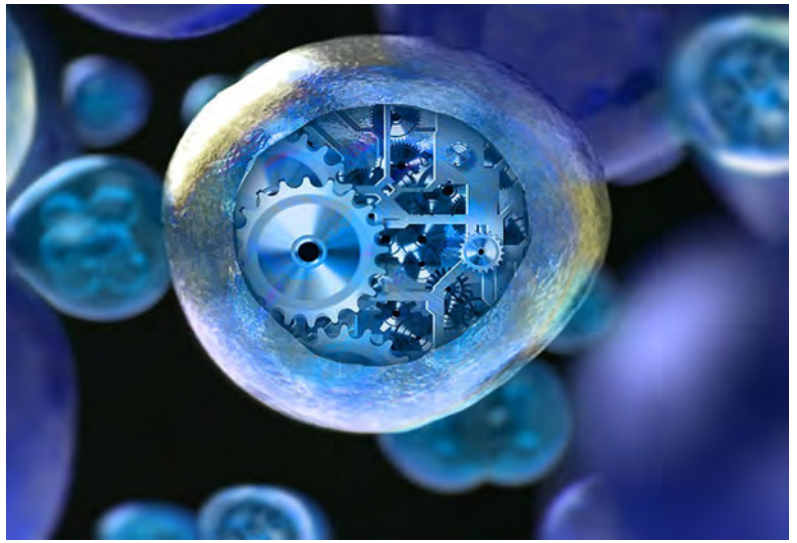
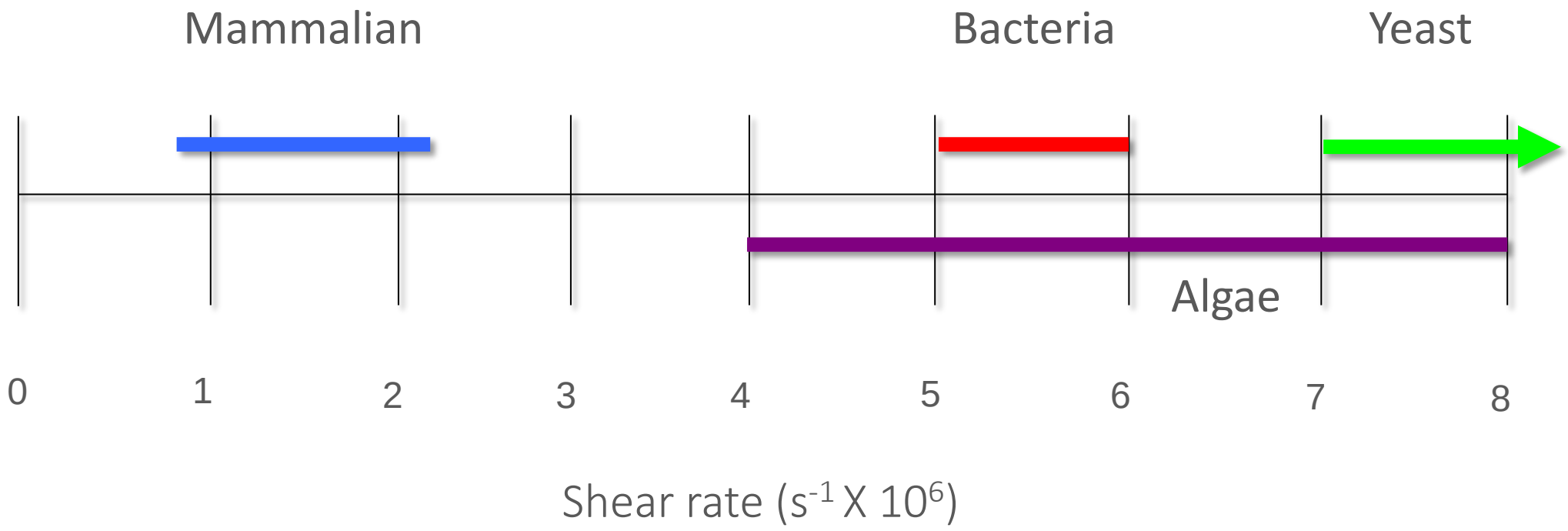
Cell Disruption

- **The generation of important enzymes, proteins and other products from microbes has been developed and used for the last 50 years**
- **Cell rupture is required any time that products are not expressed extracellularly and thus must be recovered via lysing**
  - Recombinant proteins and enzymes are often grown in *E. Coli* or *S. Cerevisiae* which do not excrete them.
  - A variety of cells are used in cell based cultured food/nutraceutical products.
  - Adeno Associated Viruses (AAVs) are the leading platform for gene therapies.
  - Algae cells currently being used for biofuel generation must be lysed to access bio diesel precursor.



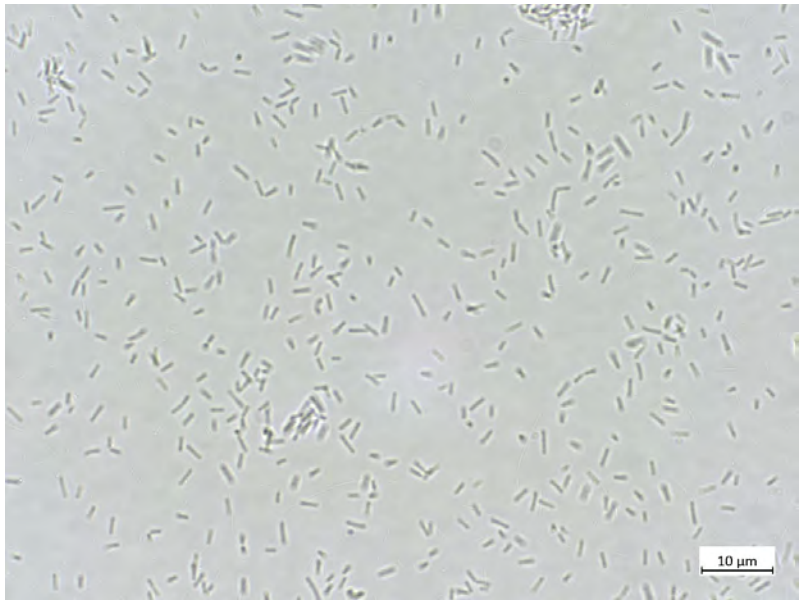
Synthetic Biology: Shaping & Accelerating Translation Research & Healthcare (biotechscope.com)

Shear Rates Required For Cell Rupture

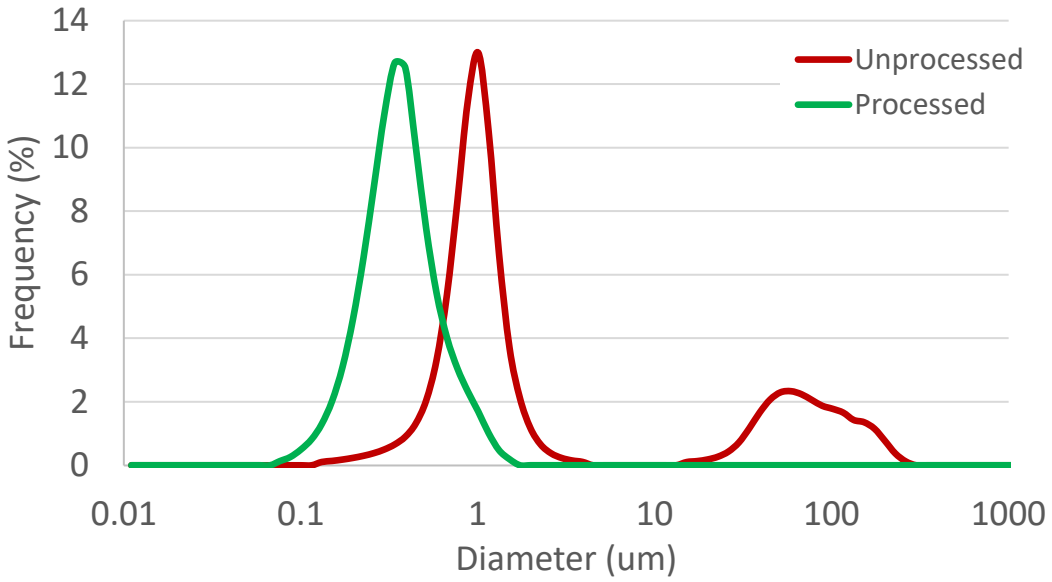


Bacterial Cell Disruption

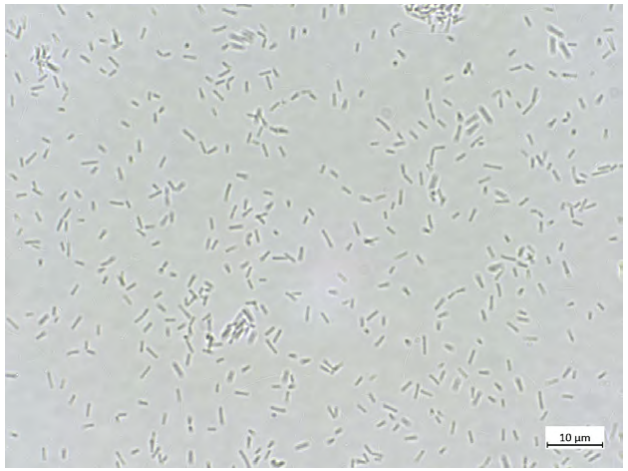
- **Bacteria have found key role in the production of compounds used in cosmetic industry such as oligosaccharides, exopolysaccharides, proteins, enzymes and peptides, etc.**
- **Bacillus**
  - A Gram-positive, rod-shaped and spore-forming bacteria.
  - Spores of certain species exhibit significant resistance to environmental stresses including UV light exposure, which can be potentially useful for cosmetic applications.
  - The cells need to be ruptured to release spores.



Case Study – Bacillus Cell Disruption



	d10 (um)	d50 (um)	d90 (um)	Mean (um)
Unprocessed	0.5828	1.0291	80.2685	21.43264
Processed	0.1819	0.3329	0.641	0.37904



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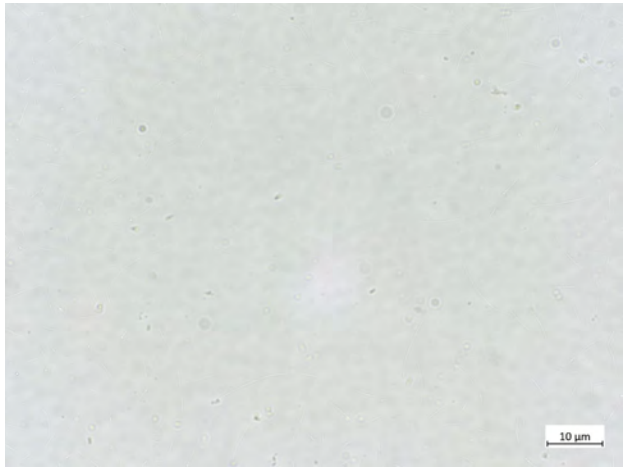

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High Performance Energy Storage Applications

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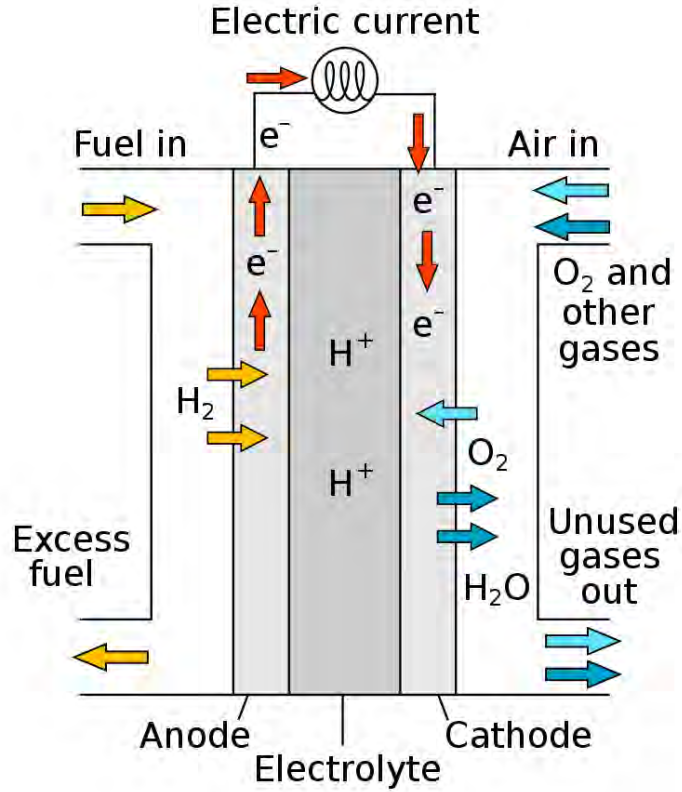
High Performance Energy Storage

- **The rapid increase of alternative, especially clean and renewable, energy led to continuously growth in the demand for energy storage**
  - Batteries, supercapacitors, fuel cells, etc.
- **Carbon based materials have gained extensive interests with their unique properties**
  - Electrical, thermal and mechanical
- **Carbon based materials**
  - Activated carbon
  - Carbon nanotube (CNT)
  - Graphite/Graphene
  - Quantum dots (carbon dots)

High Performance Energy Storage – Fuel Cell

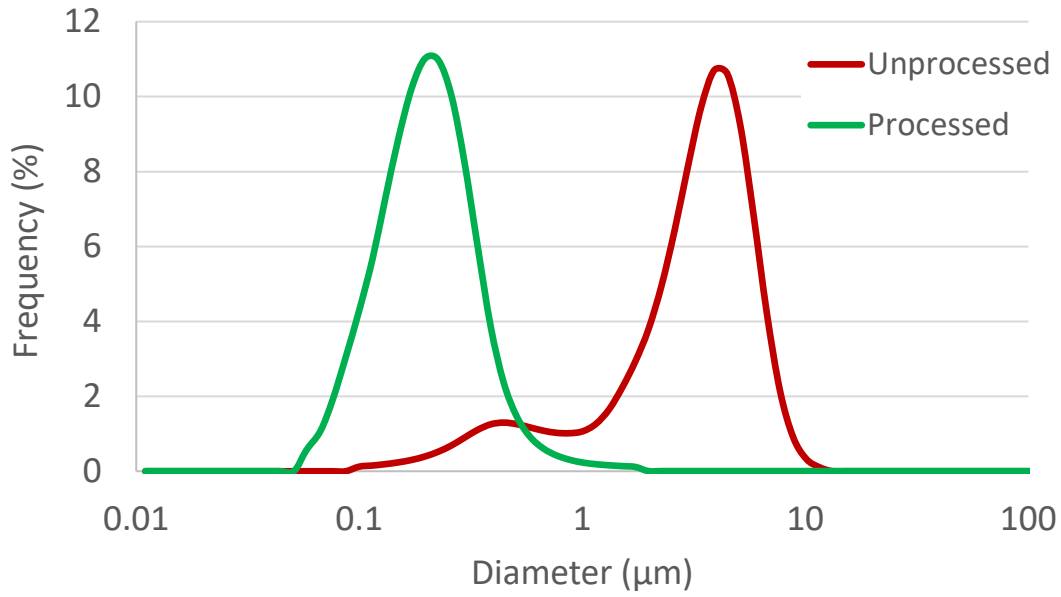
- **Fuel cells**
  - A device convert chemical energy of fuels, e.g., hydrogen or other fuels, to electricity.
  - Can be used in a wide range of applications across multiple sectors including transportation, industrial/commercial/residential buildings, and long-term energy storage for the grid.
  - Can achieve much higher efficiency than conventional combustion-based technology with zero or very low emissions.
  - Proton exchange membrane (PEM) fuel cell (A.K.A polymer electrolyte membrane fuel cell) is one of the leading technologies.
  - Catalyst layer – catalyst ink includes Pt/C and ion-conducting polymer (ionomer).
  - Catalyst ink needs to be finely dispersed to help achieve increased efficiency/power density and reduced cost.



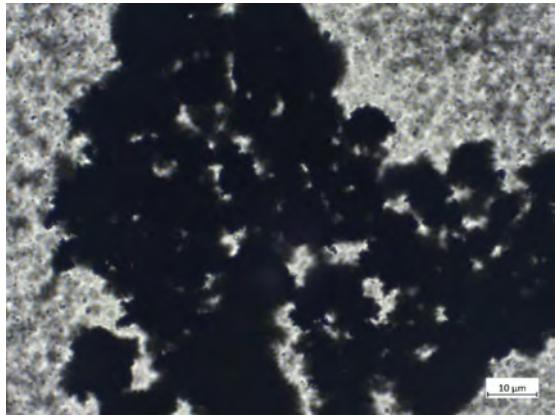
Fuel cell - Wikipedia

Case Study – Fuel Cell Catalyst Ink Dispersion

- **Goal: To produce a homogenous dispersion with particle size below 1 µm.**



	d10 (µm)	d50 (µm)	d90 (µm)	Mean (µm)
Unprocessed	0.6149	3.1831	5.6094	3.23388
Processed	0.0973	0.1877	0.3477	0.21711



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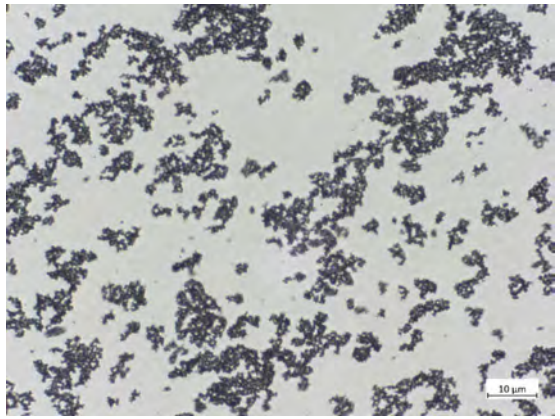

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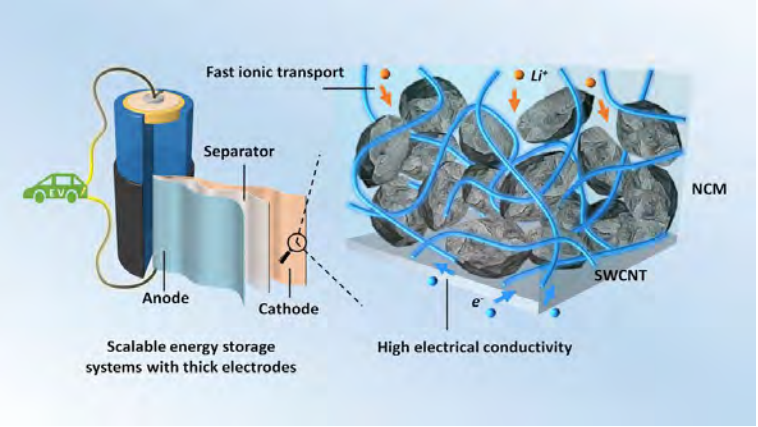
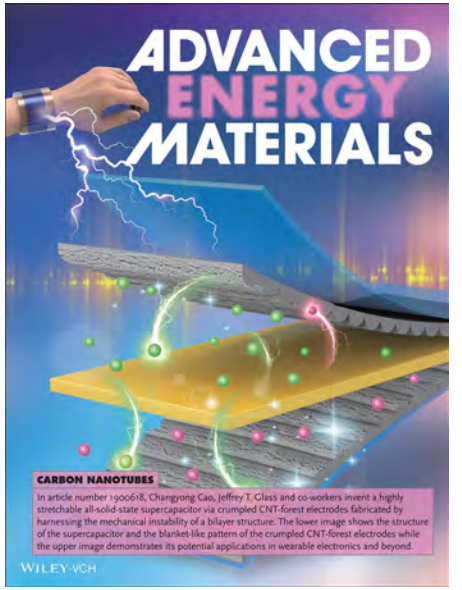
High Performance Energy Storage – Battery/Supercapacitors

- **Li-ion batteries**
  - Electrodes account for ~ 25% of total battery cost.
  - Their design and material is one of the biggest challenges and limitations
    - Low electrical, thermal and ionic conductivity.
    - Poor mechanical behavior during charging cycles.
    - Degradation issues.
  - CNT is a promising candidate for electrodes by providing much improved power, energy storage and lifecycle.
- **Supercapacitors**
  - High energy density and fast charging/discharging capability.
  - Electrochemical double-layer capacitors (EDLC) typically use carbon materials as electrodes.
    - Charge is stored by electrostatic interaction between electrolyte ions and the surface of electrodes.
    - High specific surface areas are important for capacitance values and the charge stored.
- **In both cases, creating uniformly dispersed/deagglomerated carbon-based formulations is required.**



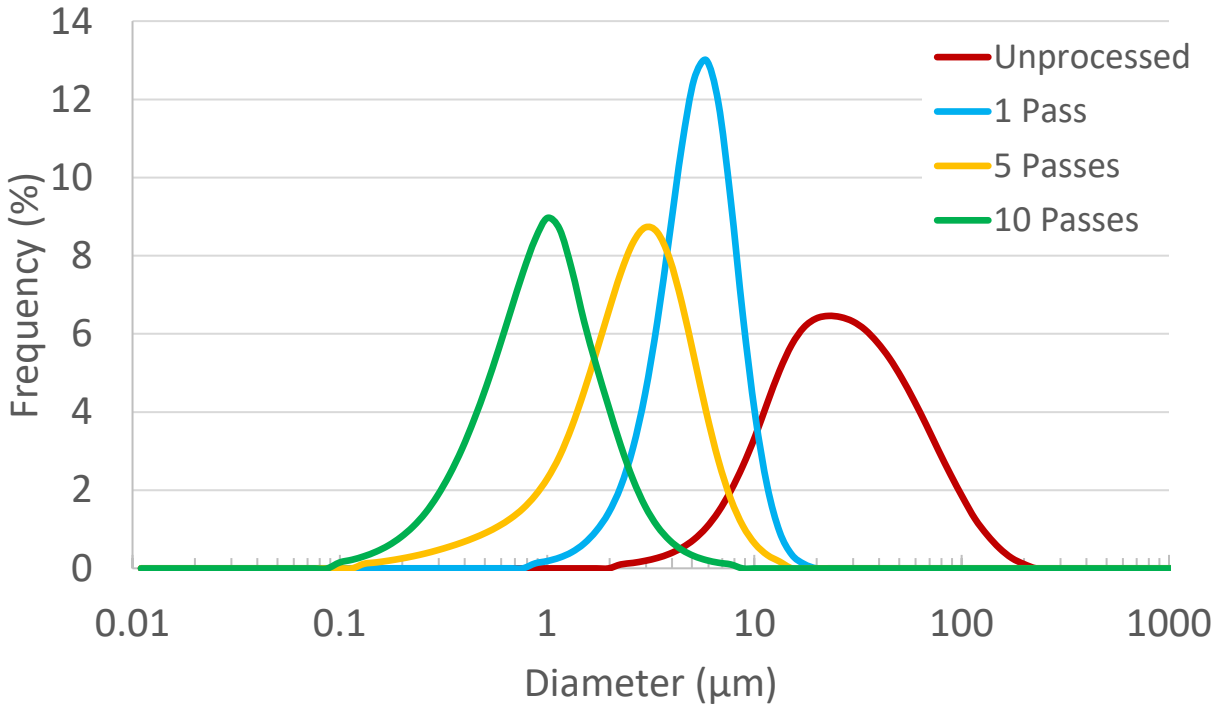
Applied Physics Reviews



Advanced Energy Materials

Case Study – CNT Dispersion for Battery/Supercapacitors

- **Goal: To process CNT dispersion and reduce particle size below 3 µm with a relatively low fluid viscosity.**



	d10 (µm)	d50 (µm)	d90 (µm)	Mean (µm)
Unprocessed	9.01194	24.34478	68.272	32.77909
1 Pass	2.66463	5.02324	8.34985	5.31699
5 Passes	0.84501	2.52312	5.25458	2.86426
10 Passes	0.35063	0.89103	1.9867	1.07812

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Nutraceutical Applications

FITZPATRICK® MATCON® Microfluidics™ QUADRO STERIDOSE®

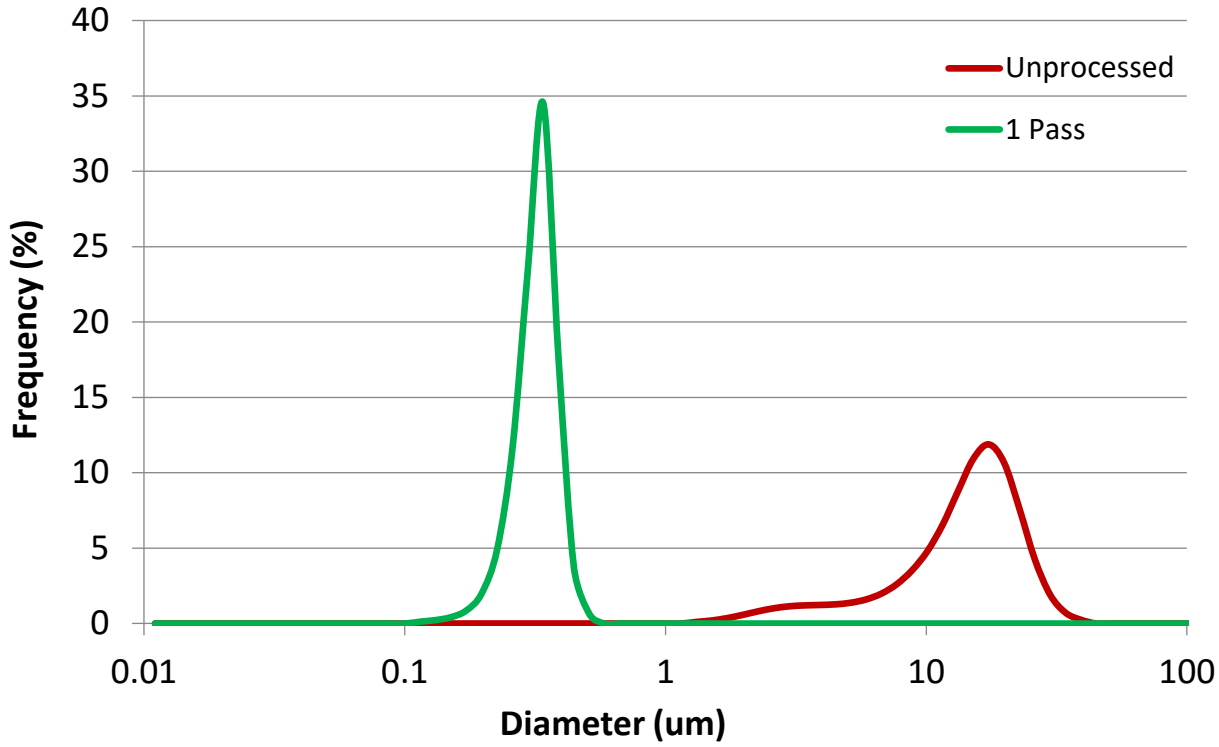
Flavor Emulsion

- Flavor emulsions are water based and usually highly concentrated flavors.
- Does not contain alcohol compared to flavor extracts, which means can retain flavor longer to achieve more potency.
- Able to create custom flavors with many flavors, colors and styles.
- Can be used in both beverages and a variety of edible products.
- Small and uniform particle size is needed to ensure stability as well as achieve desired appearance.

Case Study – Flavor Emulsion

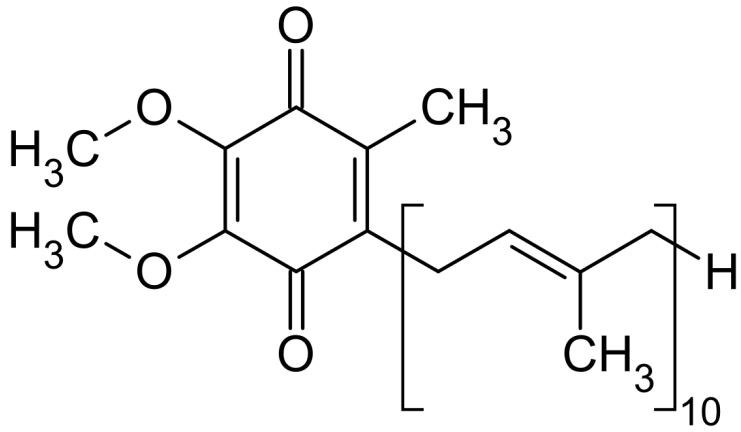
- **Goal: To produce stable flavoring emulsion**

	d10 (nm)	d50 (nm)	d90 (nm)	Mean (nm)
Unprocessed	5,445.19	15,169.69	369,676.57	69,104.05
1 Pass	229.6	303.7	371.95	300.86



Nutraceutical Emulsion

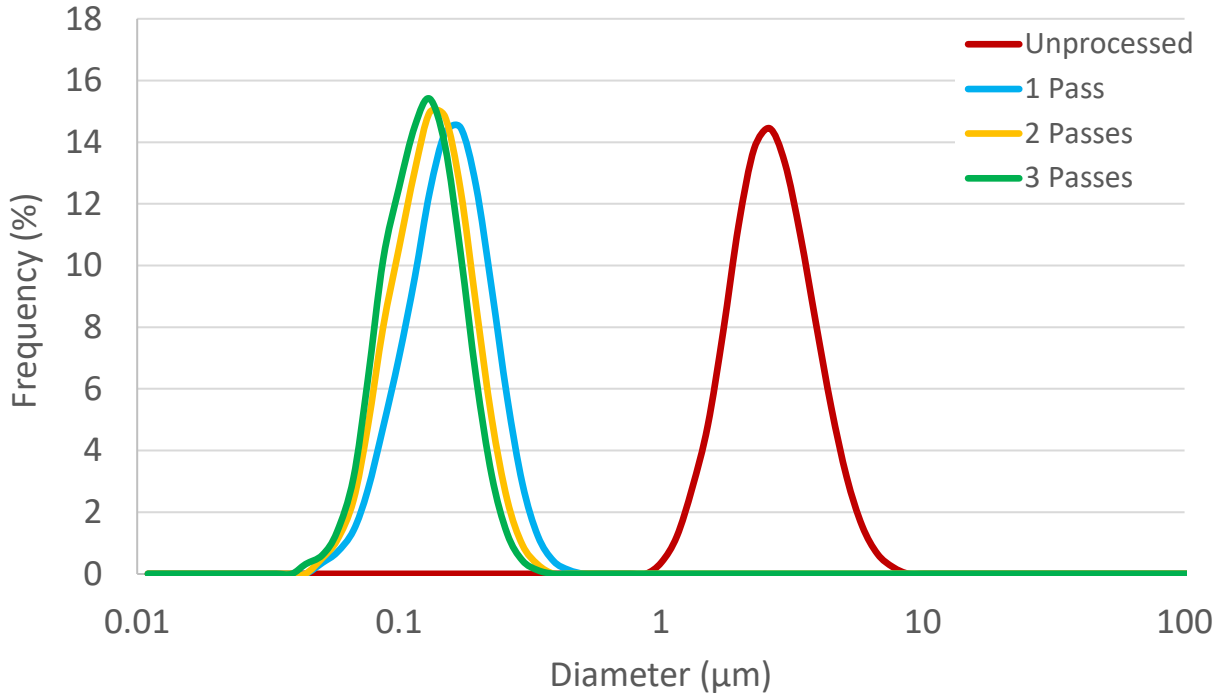
- **Coenzyme Q10 (CoQ10) is the most common form of coenzyme Q in humans.**
  - Helps convert food into energy.
  - Found in almost every cell in the body.
- **Is not approved by US FDA for treating any medical condition.**
- **Is a powerful antioxidant – used as dietary supplement and ingredient in some cosmetics.**
- **Insoluble in water (fat-soluble).**
  - Formulate into O/W nanoemulsions can help increase bioavailability.
  - Uniform particle size can also help increase stability and shelf life.



Case Study – Nutraceutical Emulsion

- **Goal: To produce a stable and uniform CoQ10 emulsion with average particles size < 200 nm**

	d10 (nm)	d50 (nm)	d90 (nm)	Mean (nm)
Unprocessed	1,531.00	2,442.20	3,998.50	2.632.57
1 Pass	87.4	145.6	228.0	153.17
2 Passes	77.9	124.9	193.1	131.25
3 Passes	73.5	115.7	177.4	121.39



Diverse Product Portfolio

Material Processing Technologies

Whatever your batch size, utility, and regulatory requirements, we have a model to suit your needs.

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Thank you! & Questions?

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