Microfluidics

Webinar Series

Principles of Particle Size Reduction and Characterization

July 29, 2010

Ian Gunniss
Microfluidics
Research Engineer
+1 617.969.5452 x314
igunniss@mfics.com

About Microfluidics

Who We Are

- Founded in 1983 outside Boston, MA
- 3,000 processors in 50 countries
- Technology Center (virtual tour online)

Our Technology

- Uniform particle size reduction
- Cell disruption with high protein recovery
- Bottom-up nanoparticle creation
- Continuous crystallization

LV1 Low Volume
(1 ml capable) processor

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

M-110EH-30
pilot/production scale

M-700 series commercial
production

More than Machines

Microfluidics Technology Center

- State-of-the-art nanotechnology research lab
- Processes over 100 applications every year
- Uniquely diverse range of application experience

Lab Services

- Proof of Concept testing
- Process development
- Scaleup consulting
- MRT evaluations

Customer Success Story

"The engineers in the Microfluidics Technology Center were extremely friendly and knowledgeable, and helped us to understand the effects of varying pressure and interaction chamber types on our product. By using **HORIBA particle size analyzers** in the lab, they were able to show us **results after each pass**.

This work was very valuable as it will help us **reduce production time** and **save cost** when we prepare to scale up. In fact, we were so pleased with the performance of the Microfluidizer processor that we **purchased an additional M-110P benchtop unit** for our internal research and development projects."

Piyush Patel, Ph.D., Director of Formulation and Analytical Development, Cephalon, Inc.

What We Do Best

- Nanoemulsions
- Encapsulation (liposomes, polymers, emulsions)
- Cell disruption
- Dispersions
- Deagglomeration

Example: Oil-in-water emulsion (**oil** and **water**)

Method One: Roto/stator mixer

5 minutes later…

Method Two: Microfluidizer

15+ YEAR later…

Select Applications

Pharmaceutical

- Vaccines and adjuvants
- Cancer therapeutics
- Inhalables
- Parenterals
- Antibiotics
- Anesthetics

Biotechnology

- *E. coli*
- Yeast
- Algae
- Mammalian
- Plant
- Insect
- Bacteria
- Fungi

Chemical	Energy	Nutraceutical / Food	Cosmetics
• Carbon nanotubes	• Fuel cells	• Functional foods	• Emulsions/creams
• Coatings and inks	• Photovoltaics	• Vitamins	• Skin treatment
• Sealants/waxes	• Batteries	• Fish oil (*omega-3*)	• Sunscreen
• LCD pigments	• Biodiesel	• Weight loss powders	• Makeup/mascara
• Resins/polymers		• Flavors	• Waxes/lipstick
• Adhesives/lubricants		• Controlled release	• Fragrances

Benefits of Uniform High Shear Processing

Smaller Nanoparticles

- Greater bioavailability
- Targeted drug/actives delivery
- Naturally optimized product quality (touch/feel/color/odor)

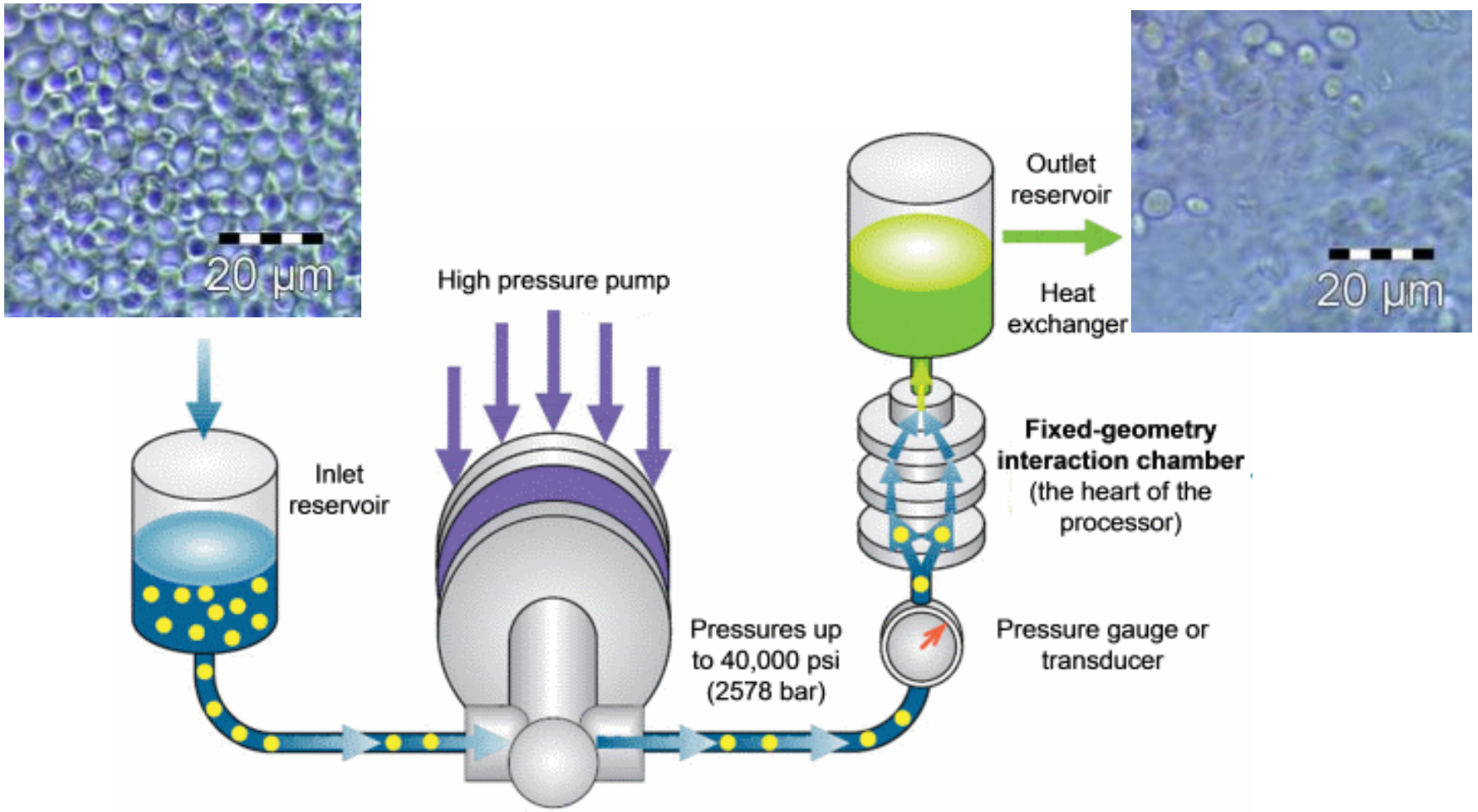
Narrow Particle Size Distribution

- Prolonged shelf life
- Uniform product characteristics
- Simplified downstream processing (e.g. sterile filtration < 200 nm)

Return on Investment

- Scaleup guaranteed
- Higher yield after cell rupture
- Less energy (passes, operation, cleaning)
- No contamination
- Continuous production & less raw materials

Microfluidizer® Processor



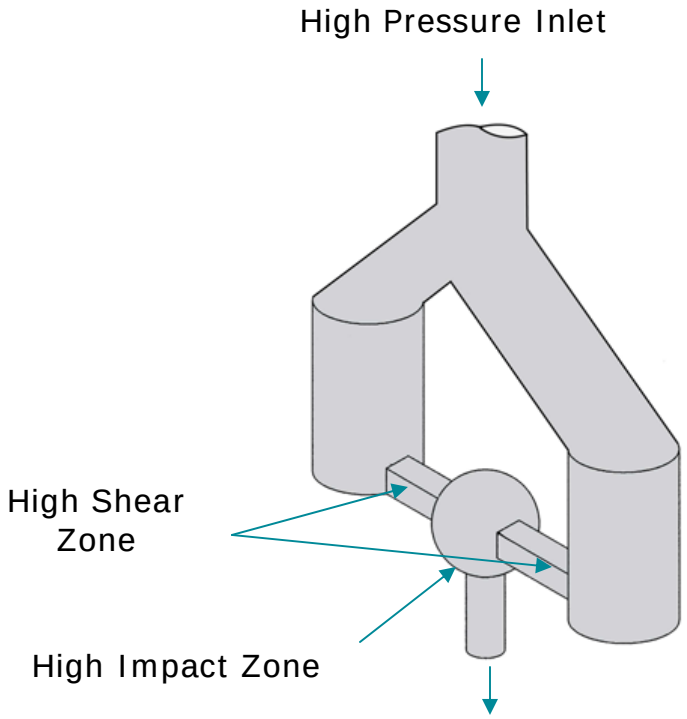
Heart of the Technology

Fixed-Geometry Interaction Chamber

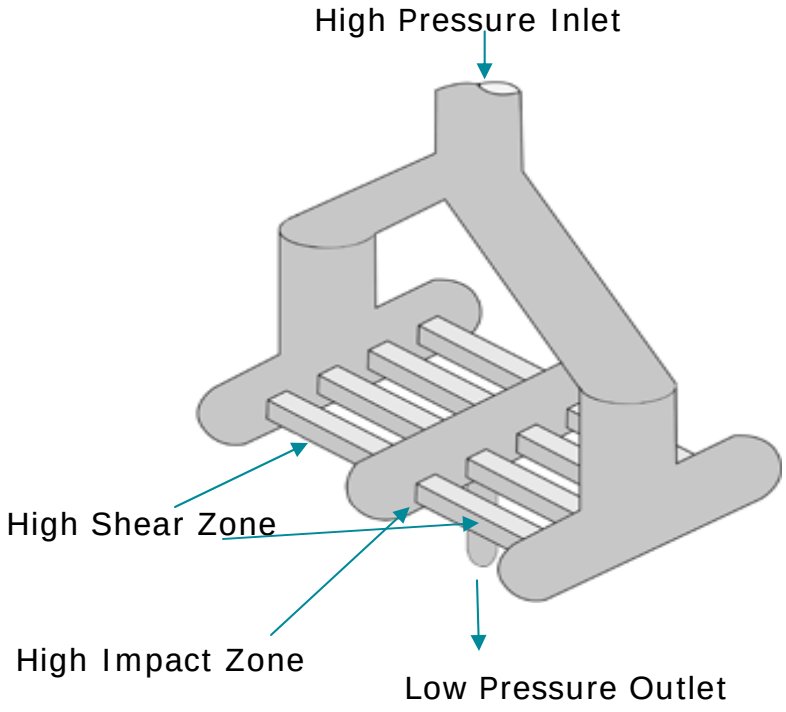
- Microfluidics exclusive
- Generates incredibly high shear and impact forces
- Precisely engineered microchannels
- Repeatable and scalable results
- Diamond or ceramic construction

Interaction Chamber

"Y" Single-slotted

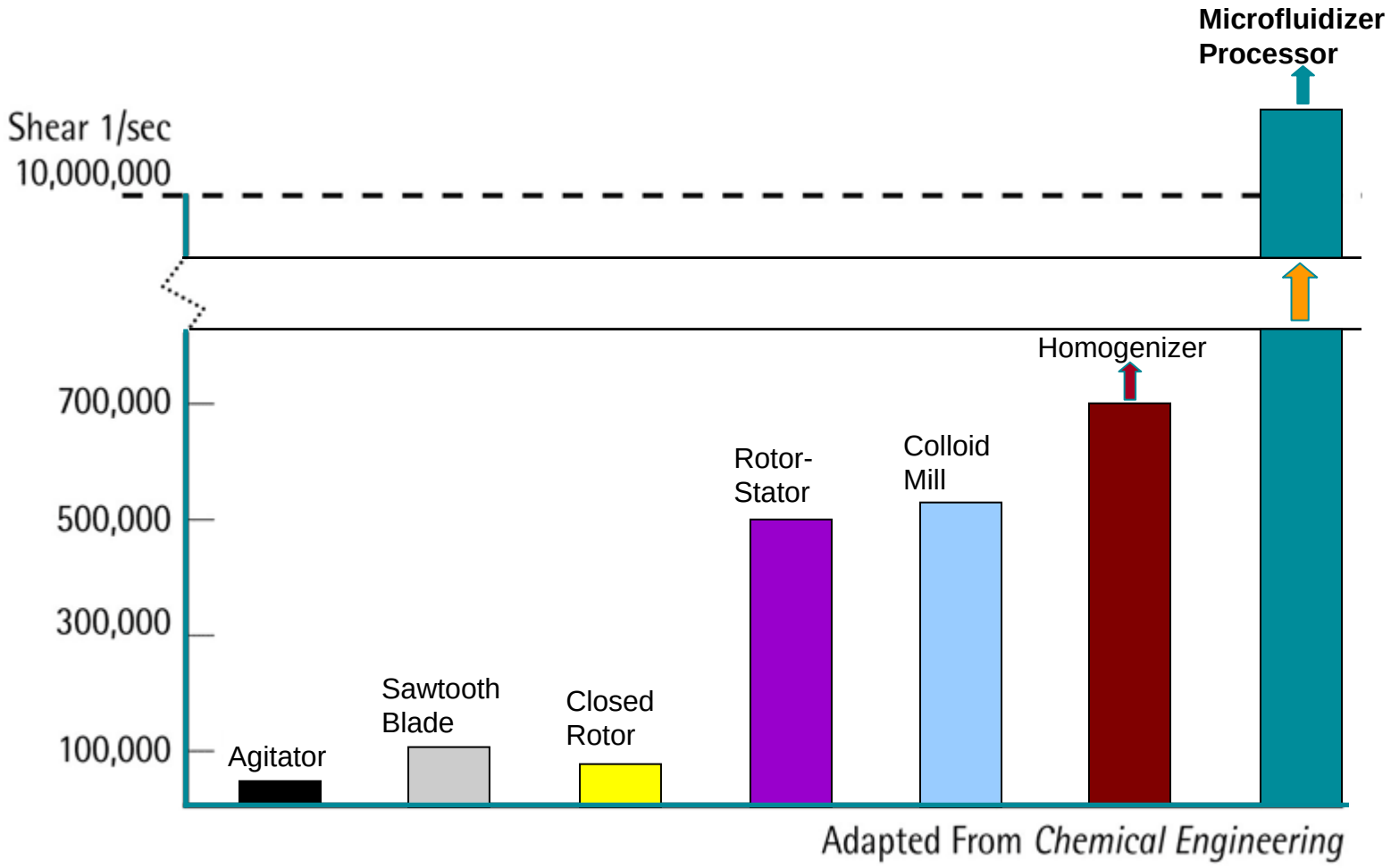


"Y" Multi-slotted



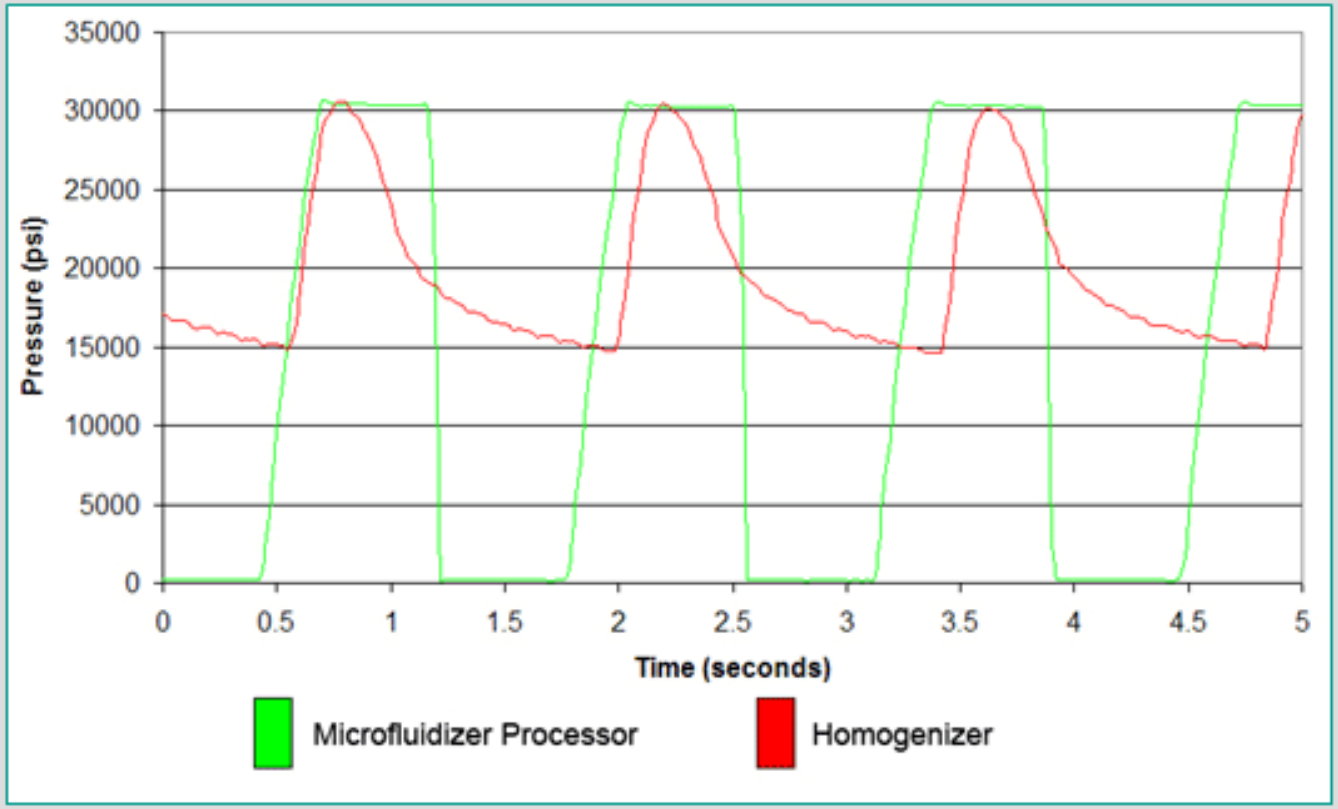
- Channel velocities over 400 m/s
- Channel minimum dimensions typically 50-300 microns
- Shear rates up to 10^7 s^{-1}; controllable mixing in the 25-50 nm scale
- Constant mixing conditions for entire batch
- Demonstrated scalability to tens of liters per minute

Shear Rates for Various Technologies



Constant Pressure Ensures Minimal Energy Input

Case in Point: *Pressure profiles while processing*



The homogenizer operates at maximum pressure for mere moments – approximately 7% of each cycle. Conversely, the Microfluidizer processor applies constant processing pressure for most of the power stroke, leading to a more uniform shear field.

Case Study: Microfluidizer vs. Homogenizer

- Oil-in-water emulsion to be used as a vaccine adjuvant
- Processed three identical batches on each technology

Critical Quality Criteria	Leading Homogenizer	Microfluidizer Processor
Average Particle Size	**185 nm** after **15 passes** (best achieved)	**141 nm** after **3 passes**
Goal: < 150 nm	✘	✓
Polydispersity	**43.1%** above 200 nm	**0.51%** Above 200 nm
Goal: < 10% above 200 nm	✘	✓
Active Concentration	**15%** loss of actives	**1%** loss of actives
Goal: < 2% loss of actives	✘	✓
Filter Area Required Per Liter of Product	**640** cm^2	**17** cm^2
	The leading homogenizer required ***38 times*** more filter area	

Based on these results, Corixa switched from their leading homogenization equipment to a Microfluidics production environment

Data courtesy of **Jedd Taylor**, *Corixa (now GlaxoSmithKline)*

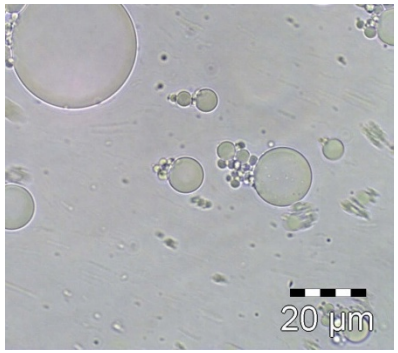
Common Mechanical Methods of Cell Rupture

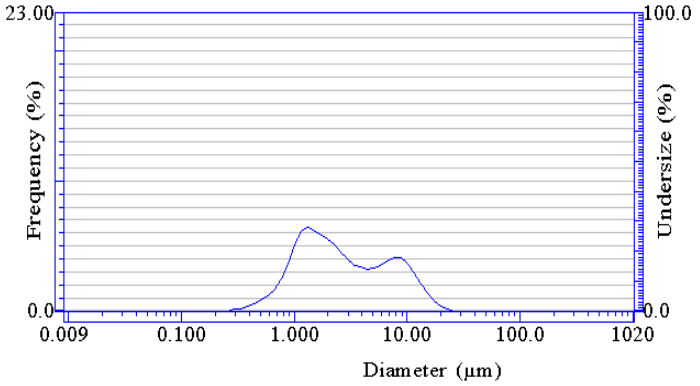
	Microfluidizer	Homogenizer	Sonicator	Bead Mill
Continuous	Yes	Yes	No	No
Scalable	Yes	Limited	No	Yes
Optimal Temp Control	Yes	Yes	No	No
Contamination Free	Yes	Yes	Yes	No
Minimum Volume	1ml*	10 ml	1ml	1 ml
Shear Rate Potential	Highest	High	High	Medium

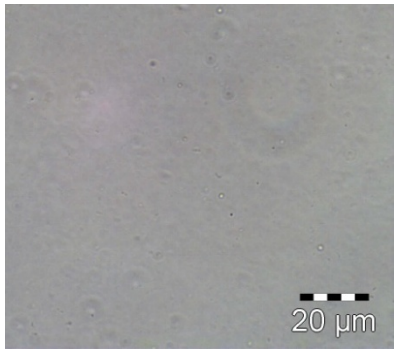
** Now available with the* **LV1 Low Volume** *Microfluidizer processor*

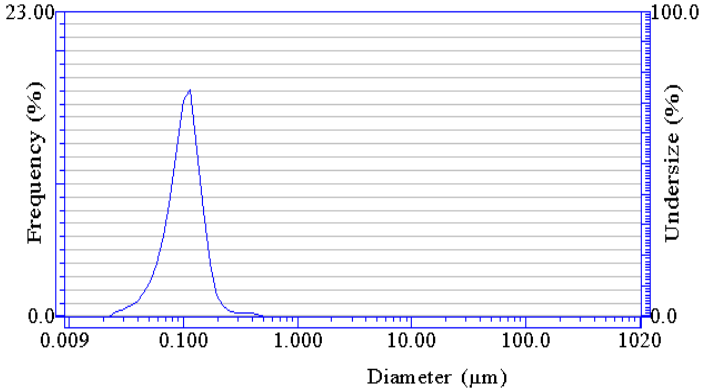
Opthalmic Drug Delivery

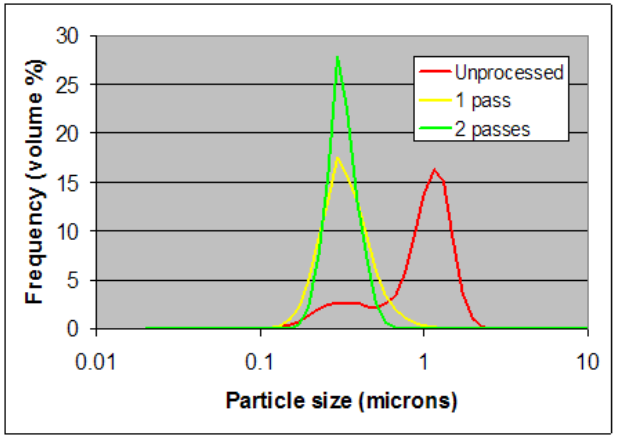
Particle size reduction – Ophthalmic drug delivery







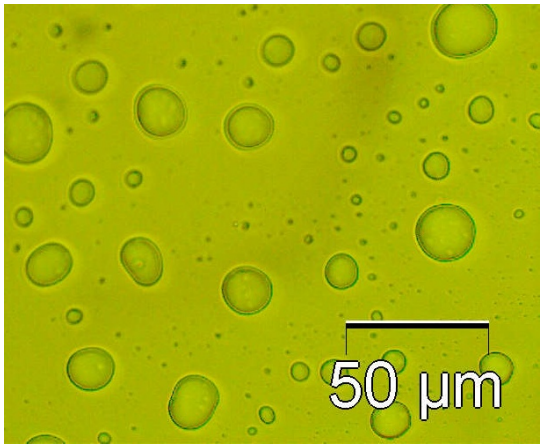




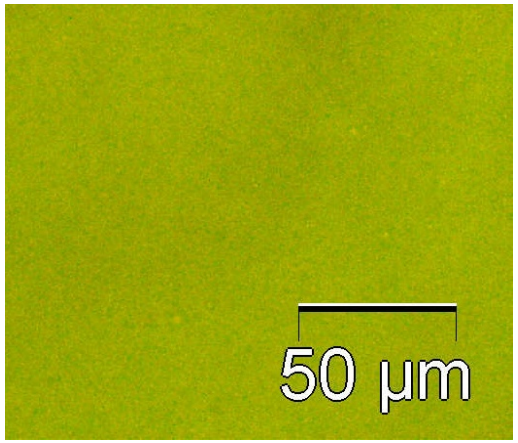
Median particle size (D50) after 1 pass @ 24,000 psi: ***96 nm***

O/W Emulsion - Fish Oil Encapsulation

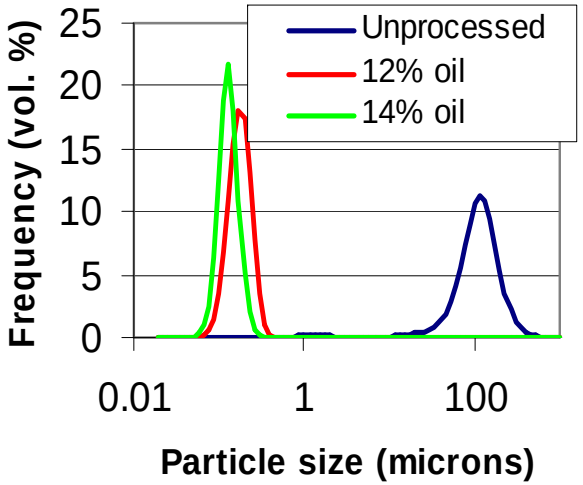
- Fish oil contains Omega 3 fatty acid, which is an essential nutrient.
- By encapsulating the fish oil, the undesirable taste can be reduced substantially and the oil is protected from oxidation



Before



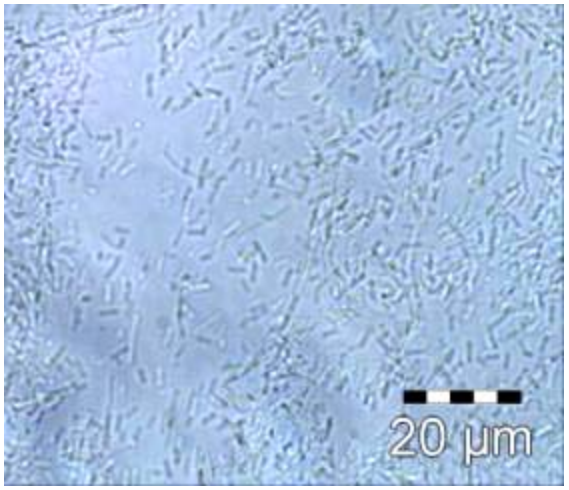
After



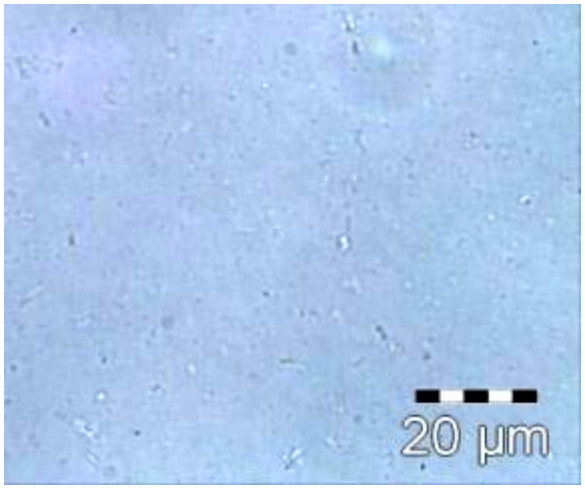
Median particle size of 12% fish oil emulsion after processing: 0.163 µm

Median particle size of 14% fish oil emulsion after processing: 0.119 µm

Cell Disruption - *E. Coli*



BEFORE



AFTER

***Process pressure*: 18,000 psi (1241 bar)**
***Chamber:* H10Z (100 microns)**
***Shear rate:* 5.58 X 10^{6} s^{-1}**

Reaching A New Low (...Volume)

New! LV1 Low Volume Processor

- Only high shear processor to operate on samples as small as **1 ml**
- Superior replacement for obsolete French press, limited ultrasonicator
- Fully scalable to lab, pilot and production volumes

New! LA-950 with MiniFlow Attachment

- 35 to 55 ml volume requirements
- Resistant to organic solvent
- Auto fill pump and auto-drain facilities

Low volume products are ideal for companies and universities working with precious or limited materials

Monitoring Particle Size Reduction

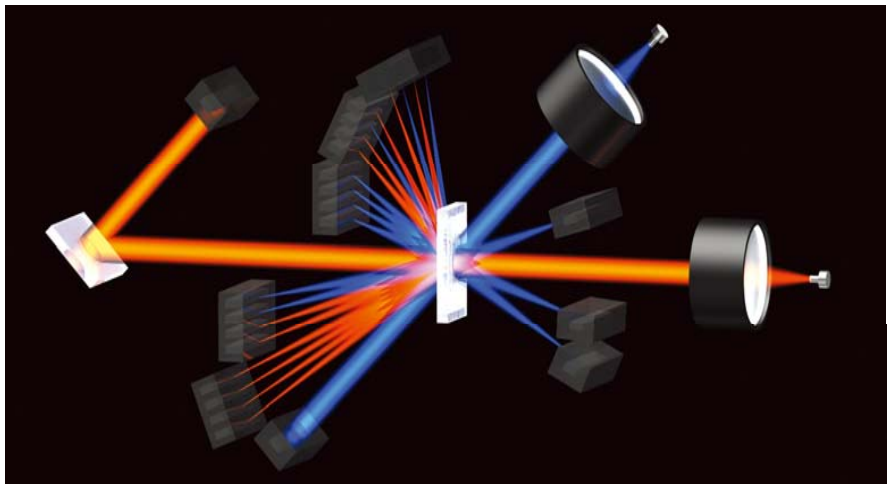
- Want wide dynamic range, before + after
- Ability to measure down to nanoparticle range
  - Less than 100 nm
- Fast, easy to use
- Small sample volume required
- HORIBA LA-950 ideal for this application

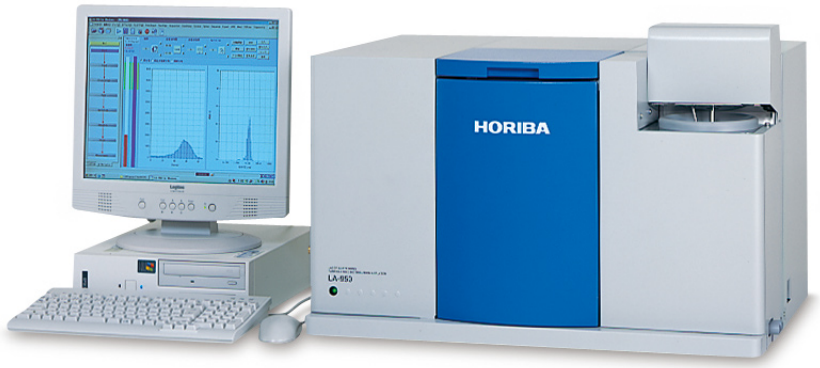
© 2010 HORIBA, Ltd. All rights reserved.

HORIBA

Laser Diffraction

Particle size 0.01 – 3000 µm



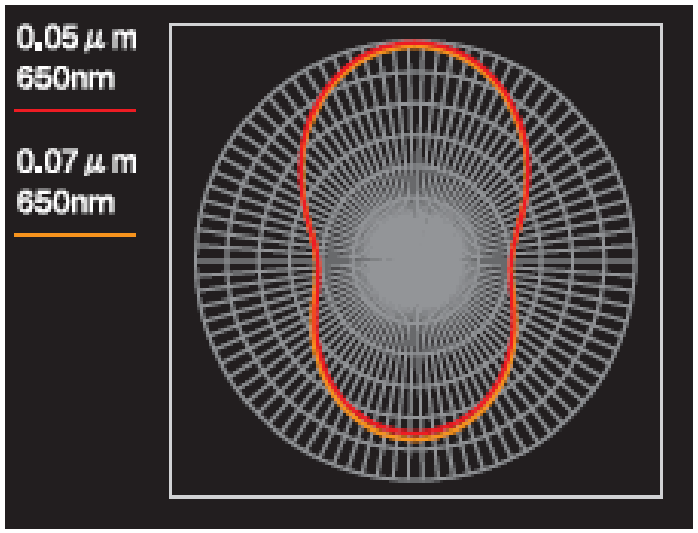


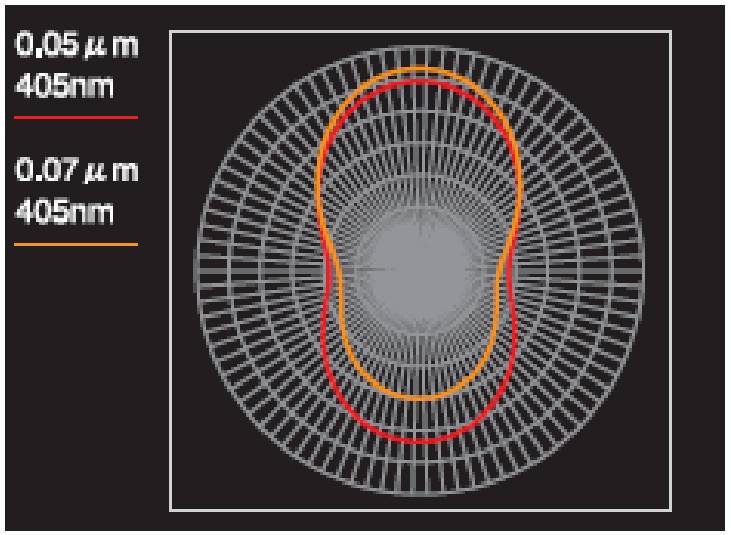
Laser Diffraction

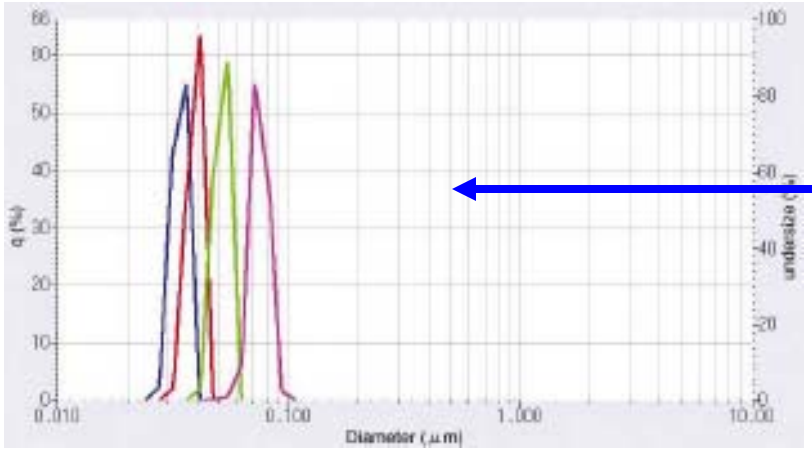
- Particle size 0.01 – 3000 µm
- Converts scattered light to particle size distribution
- Quick, repeatable
- Most common technique
- Suspensions & powders

© 2010 HORIBA, Ltd. All rights reserved.

Low End Sensitivity



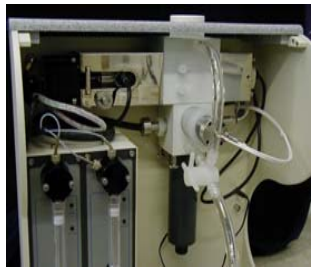


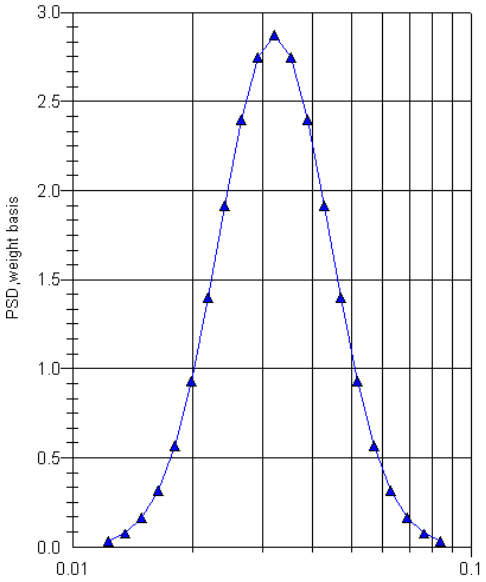


30, 40, 50, 70 nm
latex standards

© 2010 HORIBA, Ltd. All rights reserved.

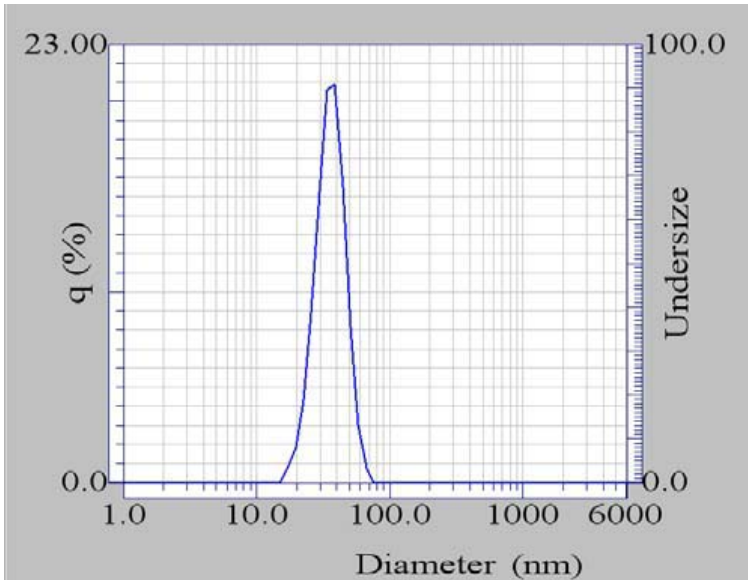
30 nm Colloidal Silica*





Mean Size : 0.0321(μm)

Figure 1: Typical particle size analysis for LUDOX TM on the DT-1201



Mean Size : 34.1(nm)

Figure 3: Typical particle size analysis for LUDOX TM on the LB-550

*see TN156 “Colloidal Silica as a Particle Size and Charge Reference Material on www.horiba.com/us/particle

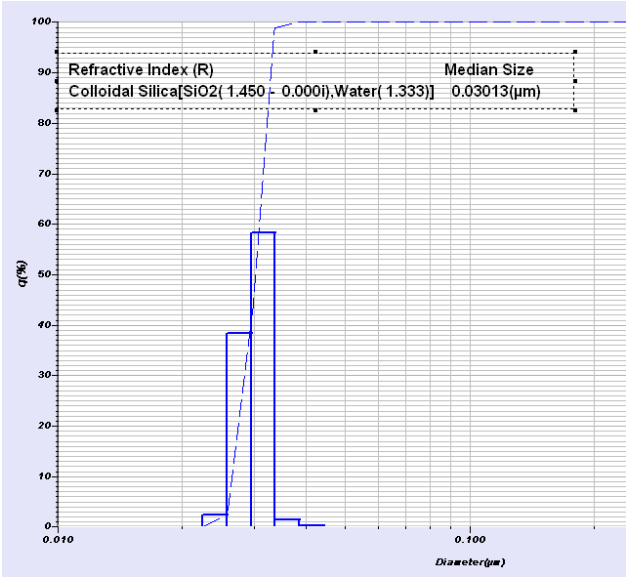
© 2010 HORIBA, Ltd. All rights reserved.

Low End Sensitivity

- Sensitivity: small particle detection

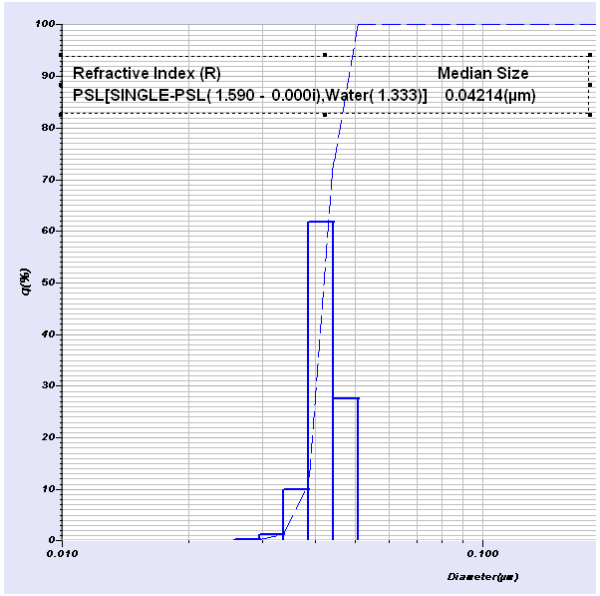
30 nm silica

S.P.Area	:	2.0183E+6(cm²/cm³)
Mean Size	:	0.02990(µm)
Variance	:	5.0313E-6(µm²)
Median Size	:	0.03013(µm)
Mode Size	:	0.0302(µm)
Skewness	:	-0.2901



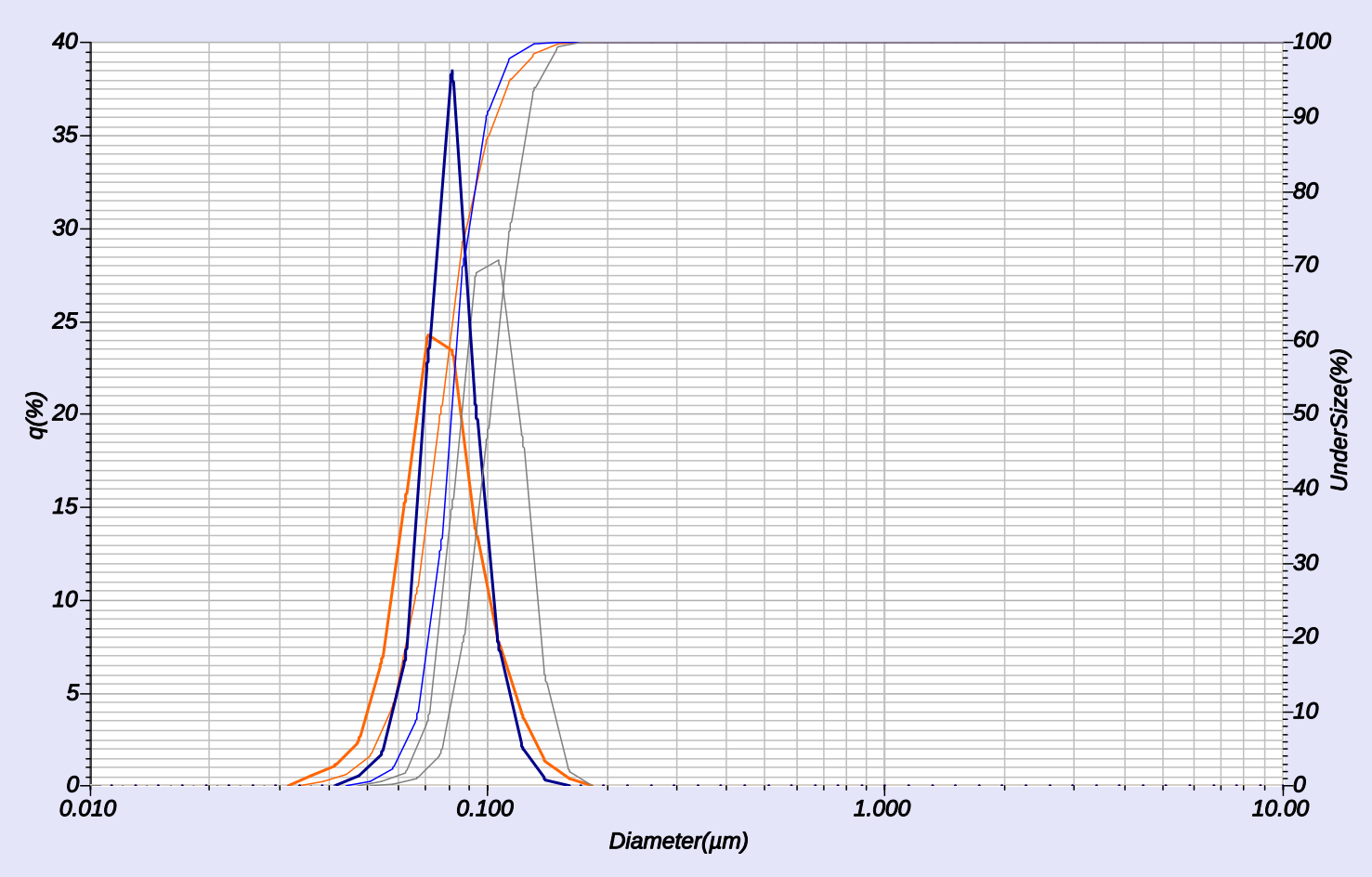
40 nm latex

S.P.Area	:	1.4253E+6(cm²/cm³)
Mean Size	:	0.04241(µm)
Variance	:	1.2759E-5(µm²)
Median Size	:	0.04214(µm)
Mode Size	:	0.0422(µm)
Skewness	:	-0.1514



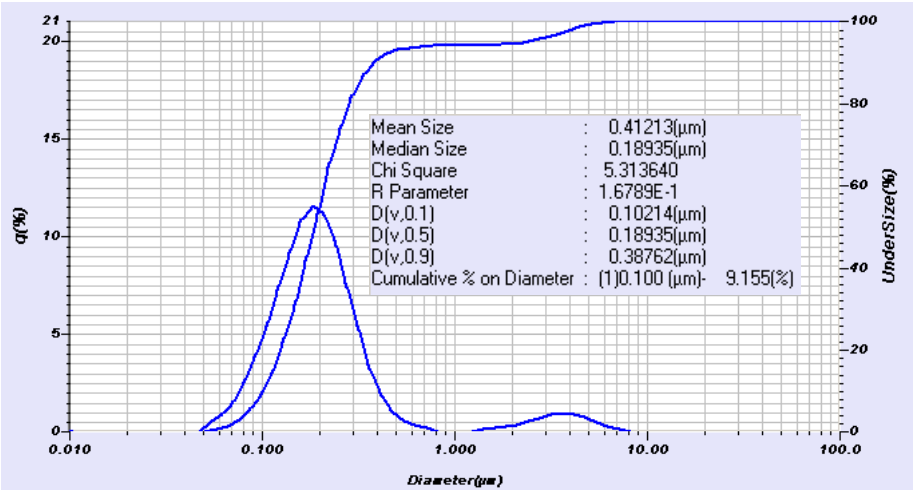
© 2010 HORIBA, Ltd. All rights reserved.

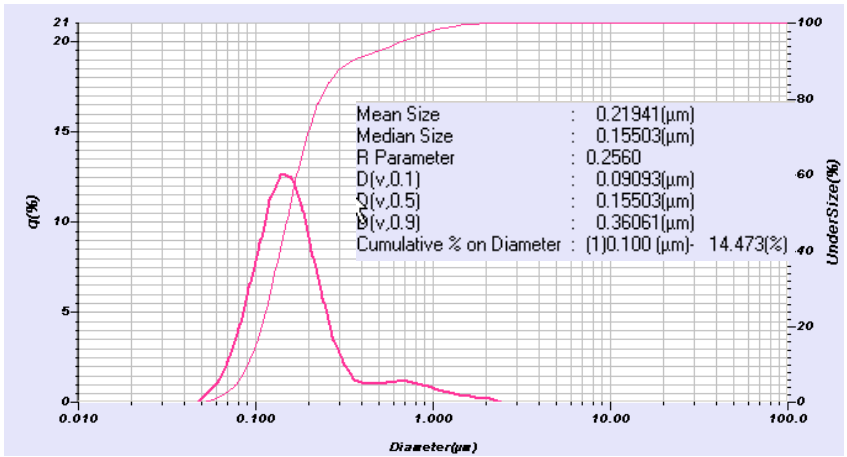
Low End Sensitivity: Pigments



© 2010 HORIBA, Ltd. All rights reserved.

Low End Sensitivity: Cosmetics

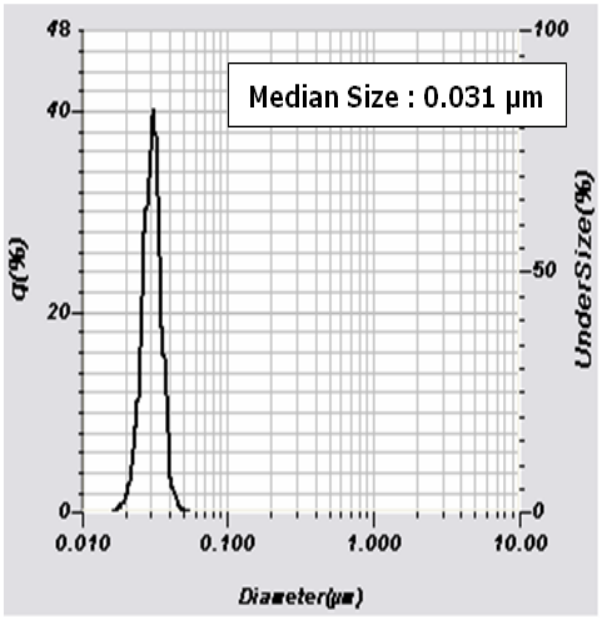




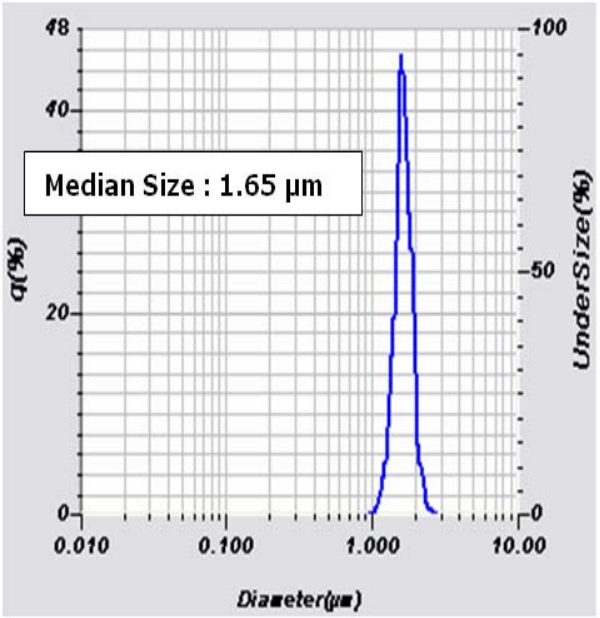
- Some (unfounded?) concerns with particles <100nm
- LA-950 good at determining sub 100nm particles
- Software set to display % under any given size
- Data shown left is for skin cream and TiO2 suspension

© 2010 HORIBA, Ltd. All rights reserved.

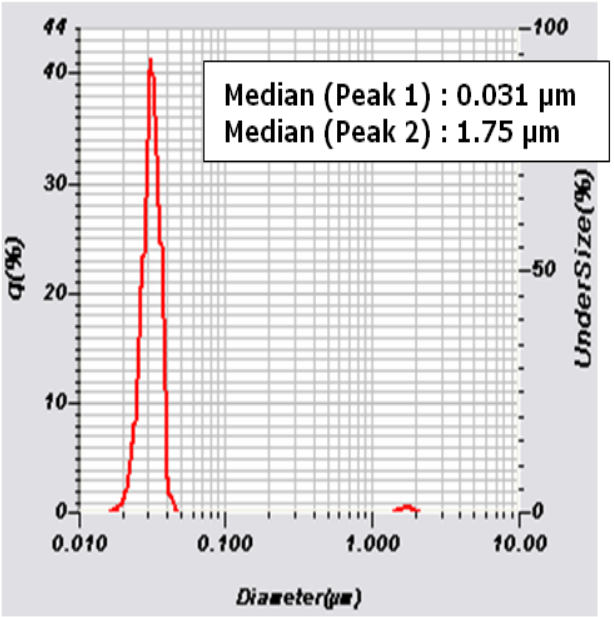
Detecting Second Population



Small silica



Geltech dopant

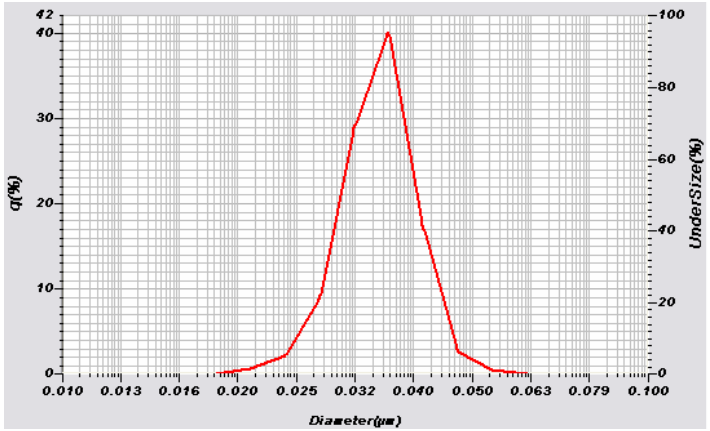


Finding 0.05% dopant

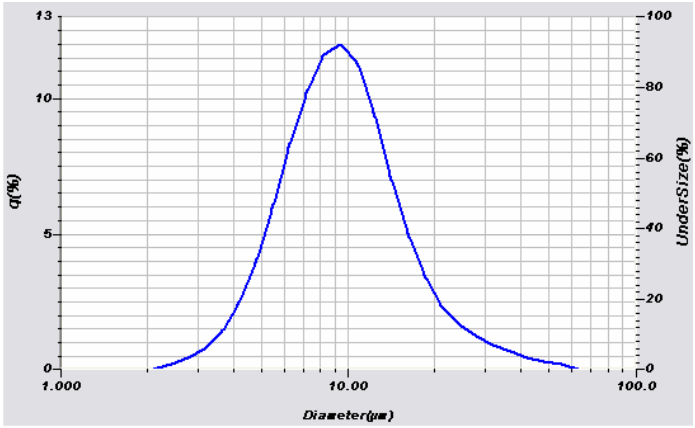
- Highest sensitivity system for detecting second population
  - Large particles or smaller particles

© 2010 HORIBA, Ltd. All rights reserved.

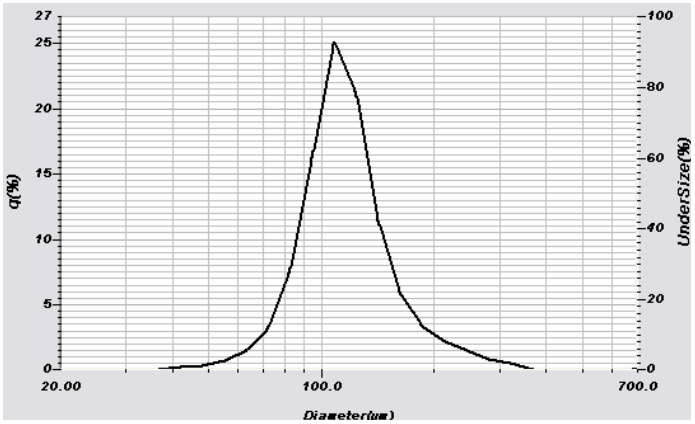
Small Sample Volume (MiniFlow)



Colloidal Silica (weak scatterer)
Median (D50): **35 nm**
Sample Amount: **132 mg**



Magnesium Stearate
Median (D50): **9.33 μm**
Sample Amount: **0.165 mg**

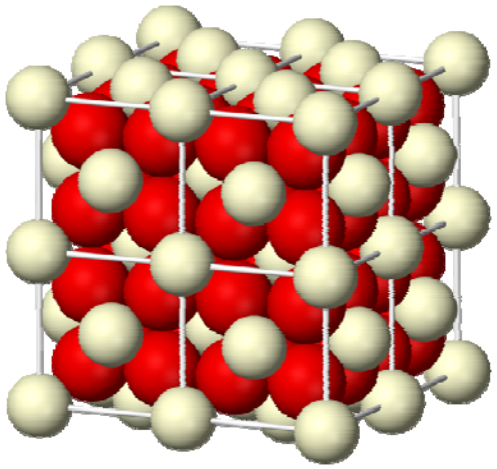


Bio-degradable Polymer
Median (D50): **114 μm**
Sample Amount: **1.29 mg**

© 2010 HORIBA, Ltd. All rights reserved.

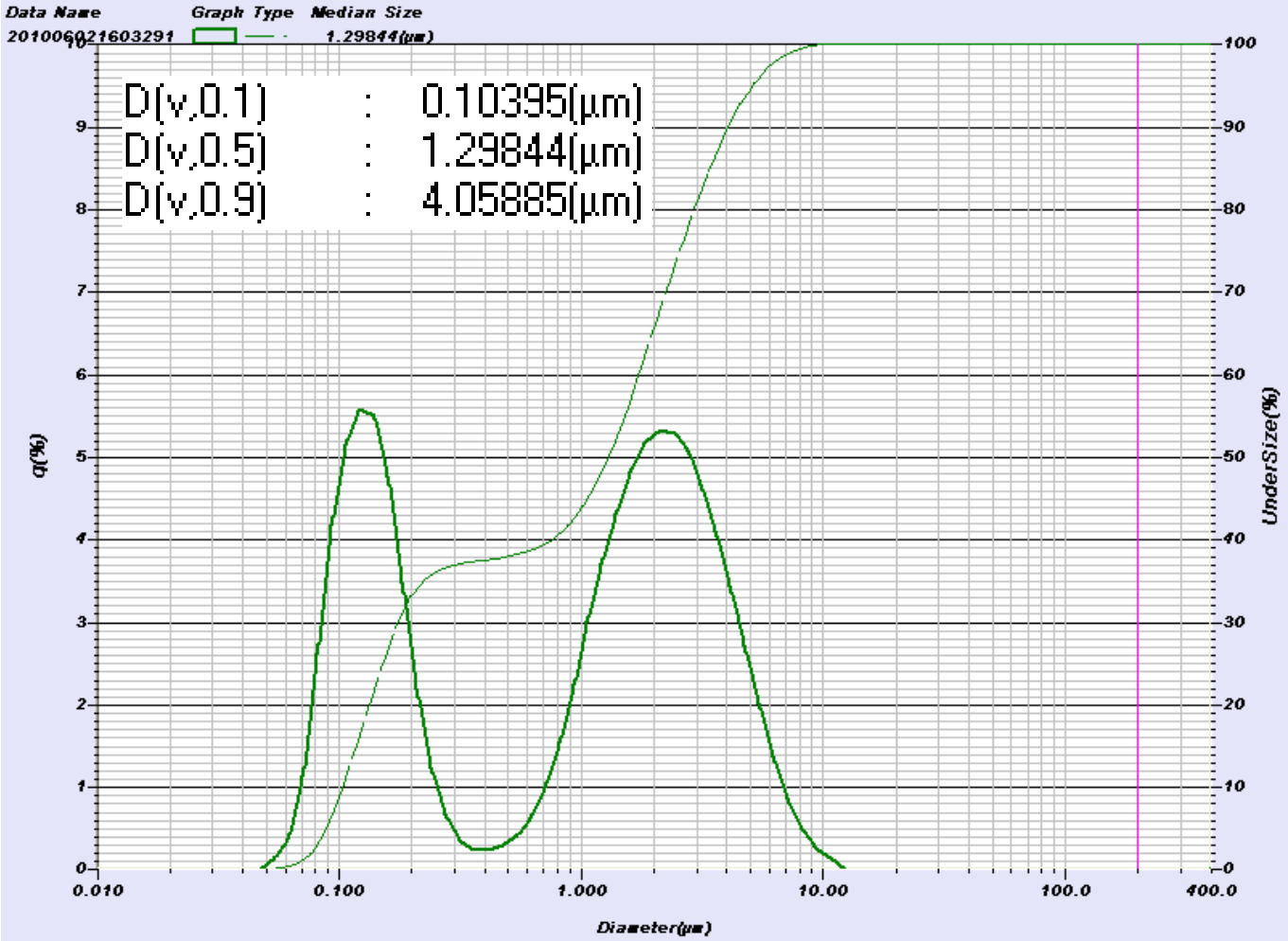
Ceria

- Cerium (IV) oxide: CeO2
- Used in ceramics, catalysts, CMP slurries
- In doped form used for solid oxide fuel cells
- Particle size is important for all of these applications
- Size reduction by M-110P Microfluidizer, particle size analysis by LA-950



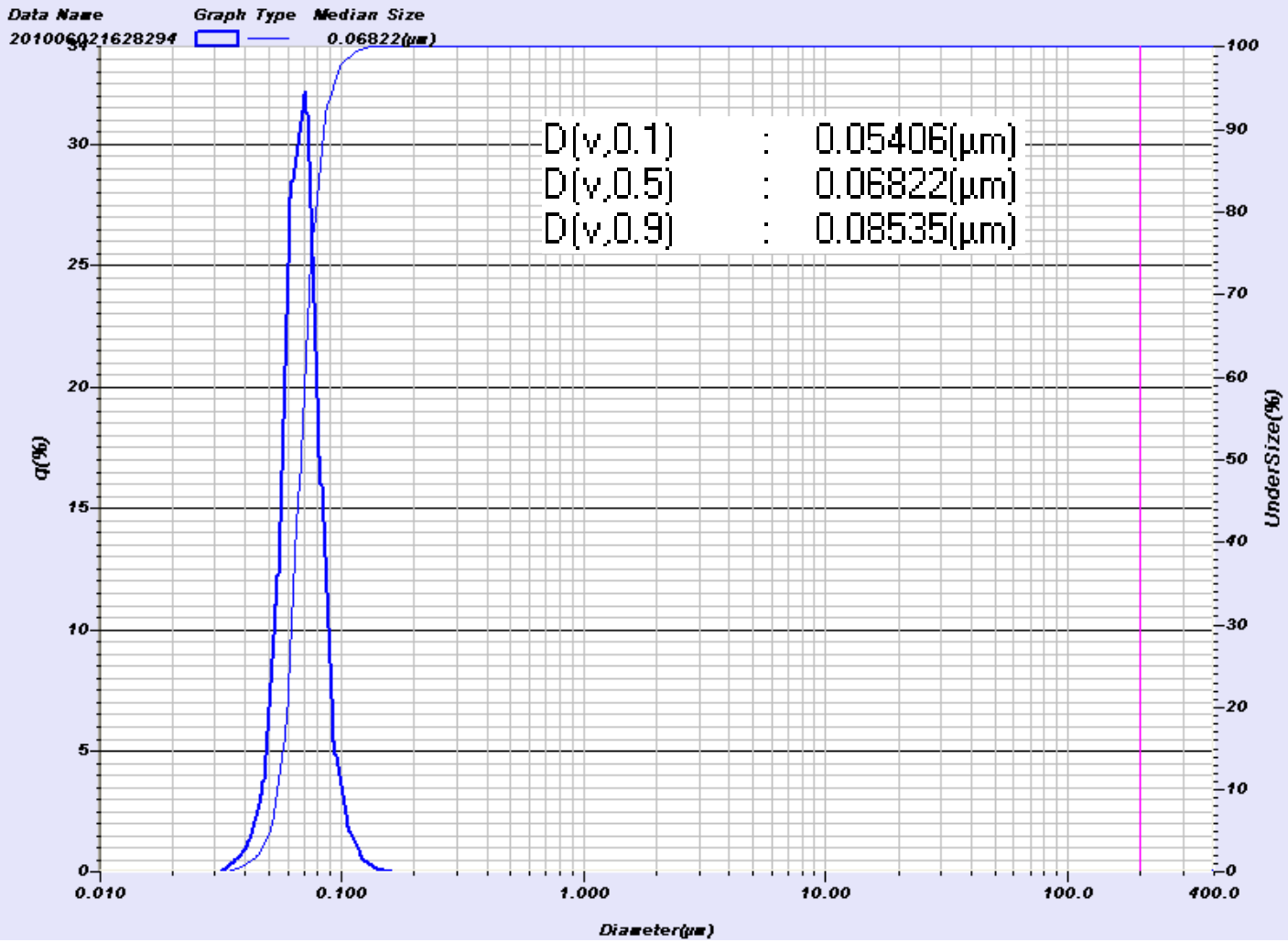
© 2010 HORIBA, Ltd. All rights reserved.

Ceria: Unprocessed



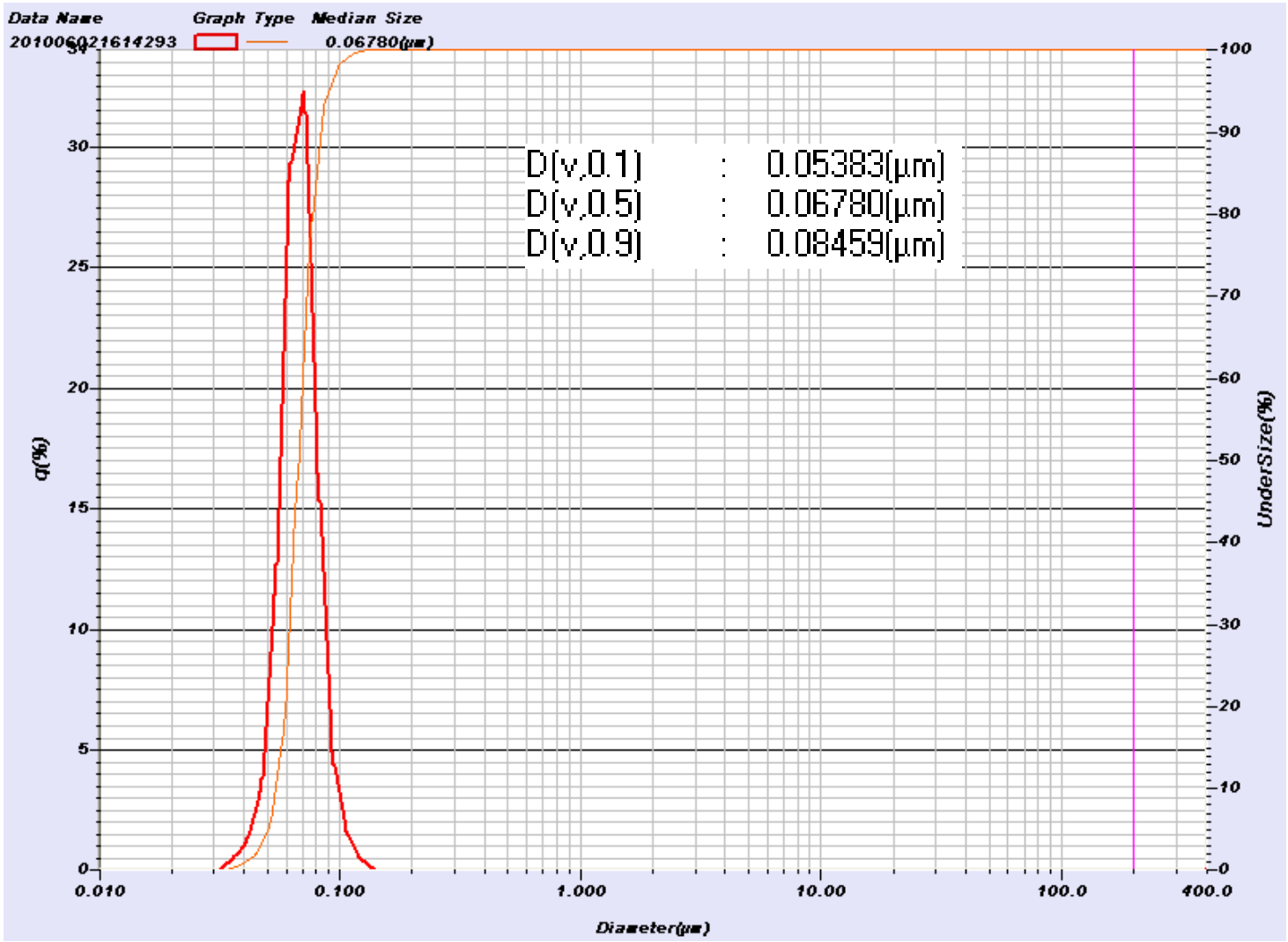
© 2010 HORIBA, Ltd. All rights reserved.

Ceria: 1 Pass



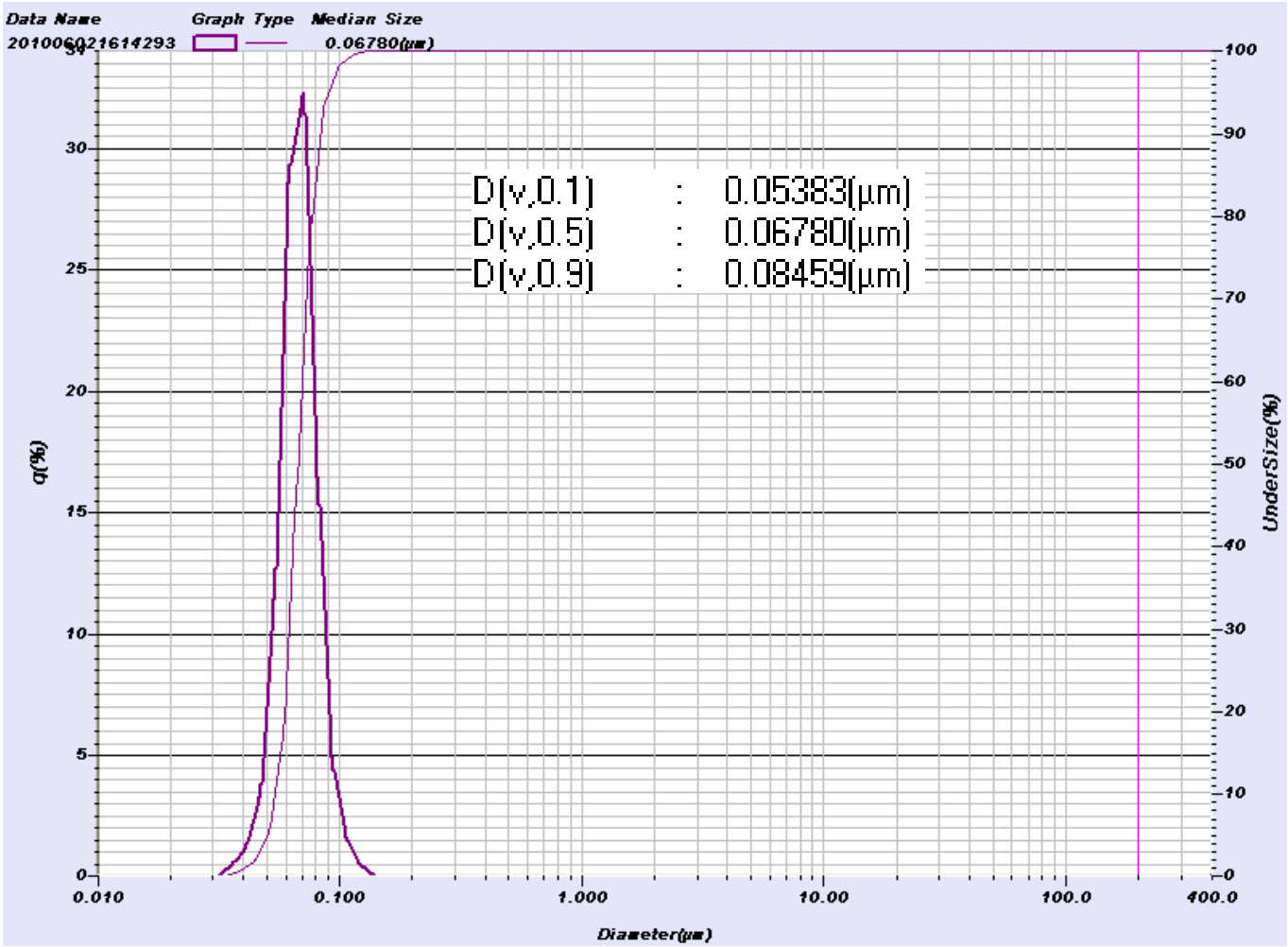
© 2010 HORIBA, Ltd. All rights reserved.

Ceria: 2 Passes



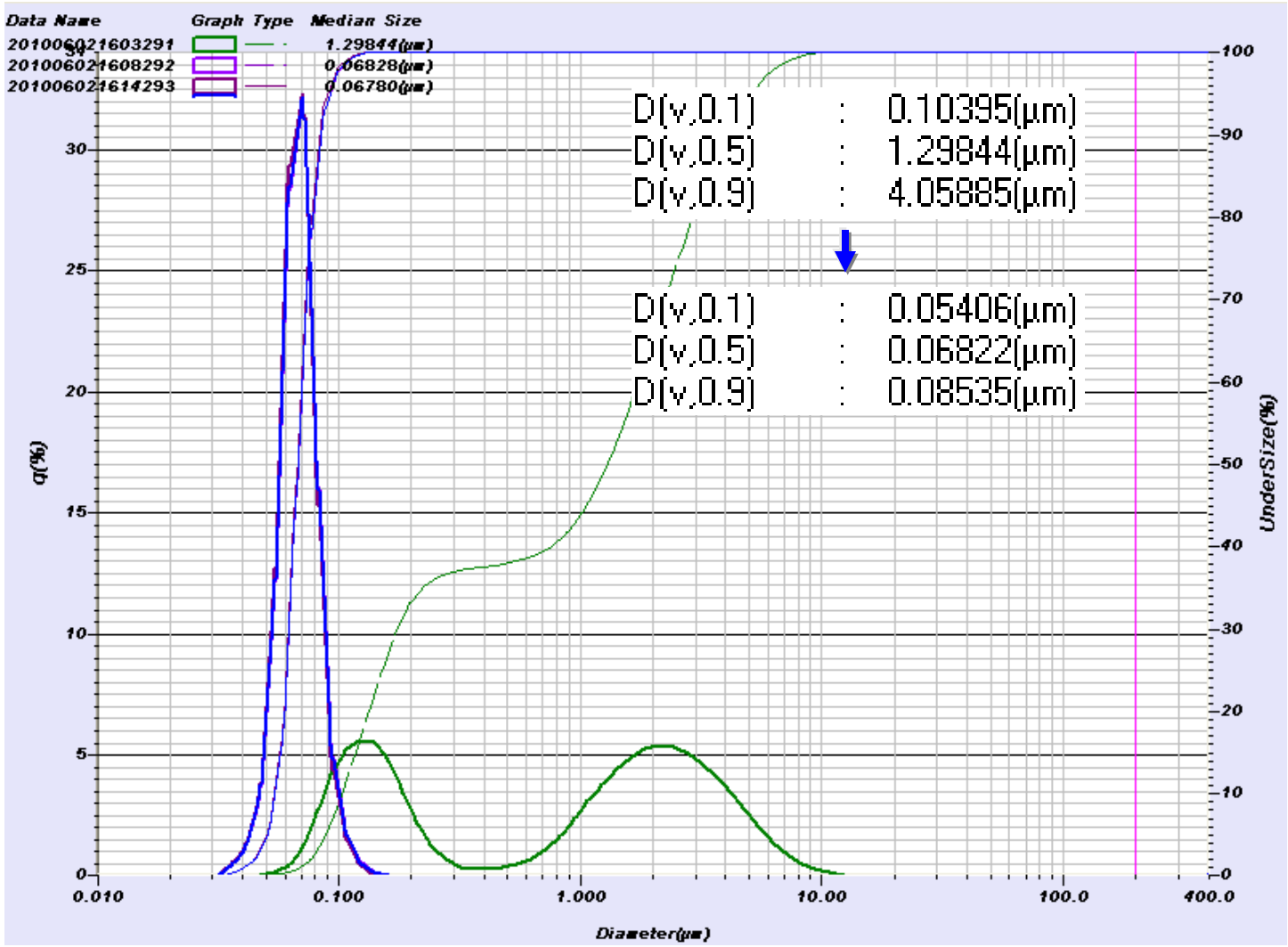
© 2010 HORIBA, Ltd. All rights reserved.

Ceria: 3 Passes



© 2010 HORIBA, Ltd. All rights reserved.

Ceria: Before, After Processing

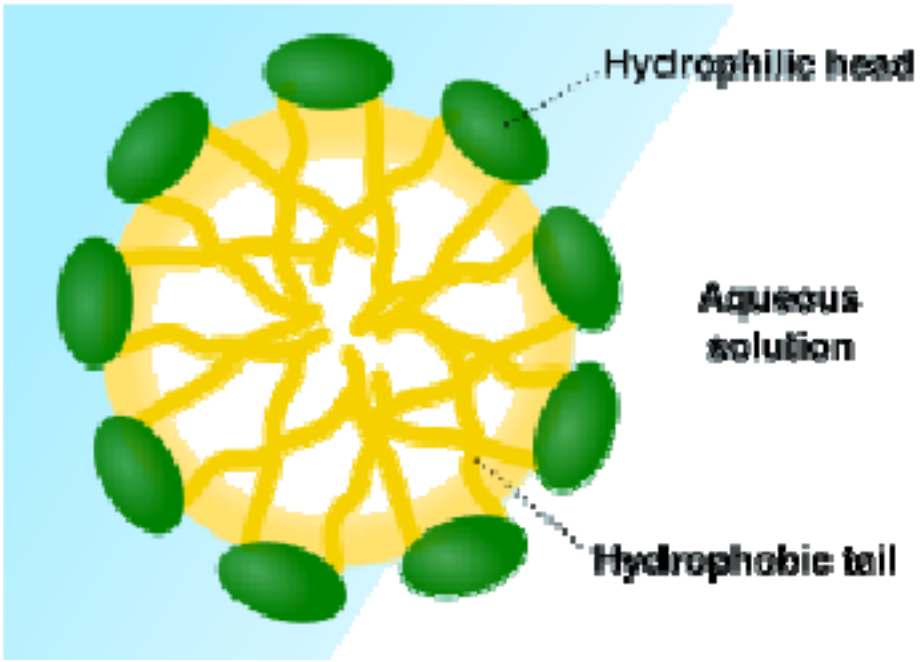


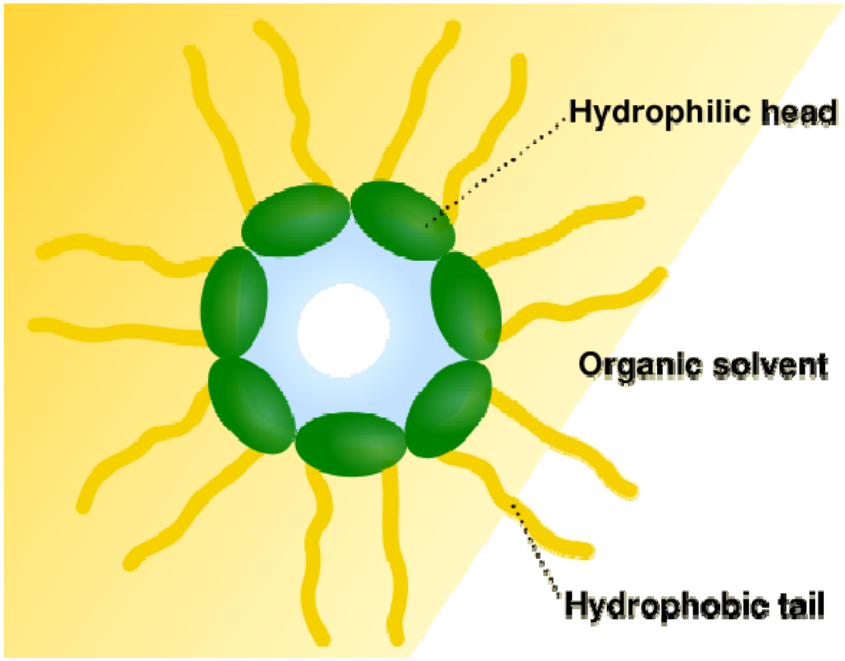
© 2010 HORIBA, Ltd. All rights reserved.

Self Assembly: Micelles

hates water Hydrophobic tail Hydrophilic head loves water

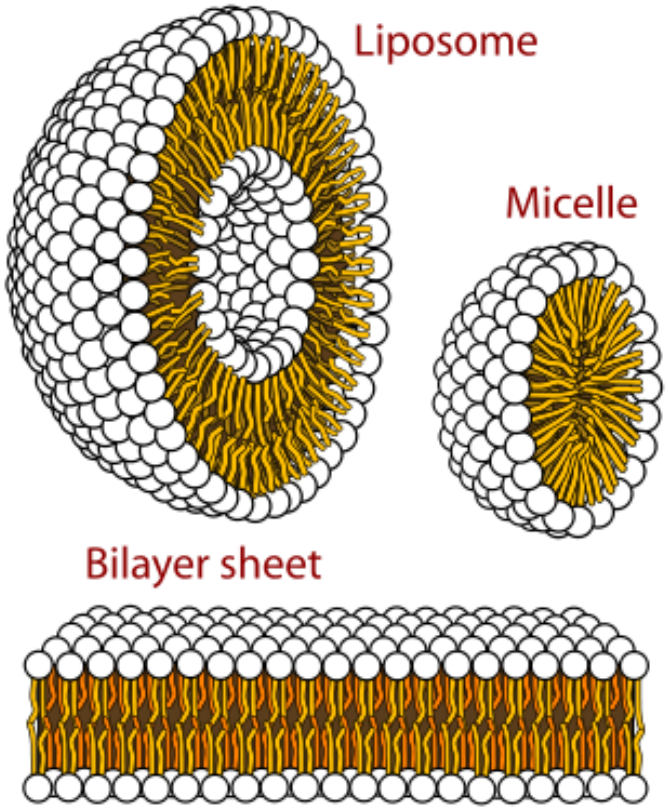
-c-h-c-h-c-h- R non polar +/- polar

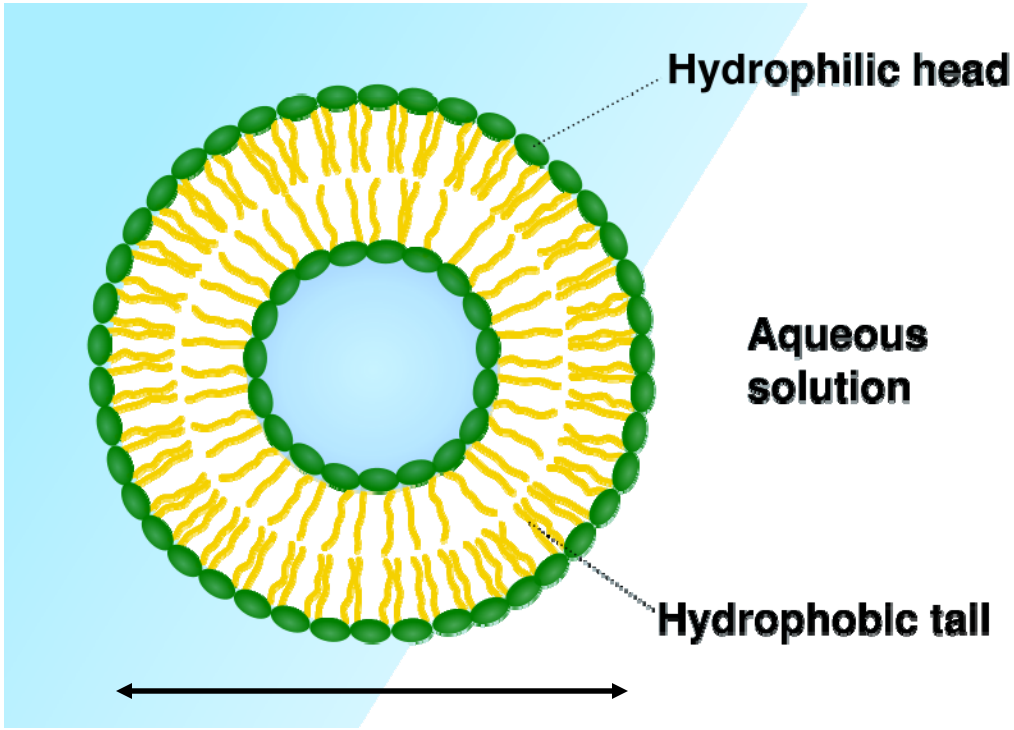




© 2010 HORIBA, Ltd. All rights reserved.

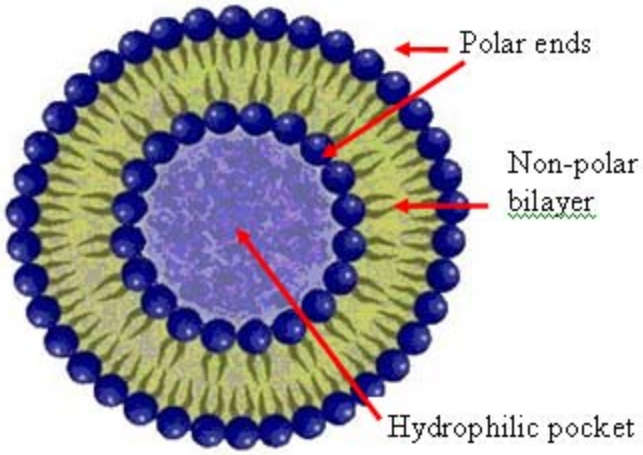
Liposomes



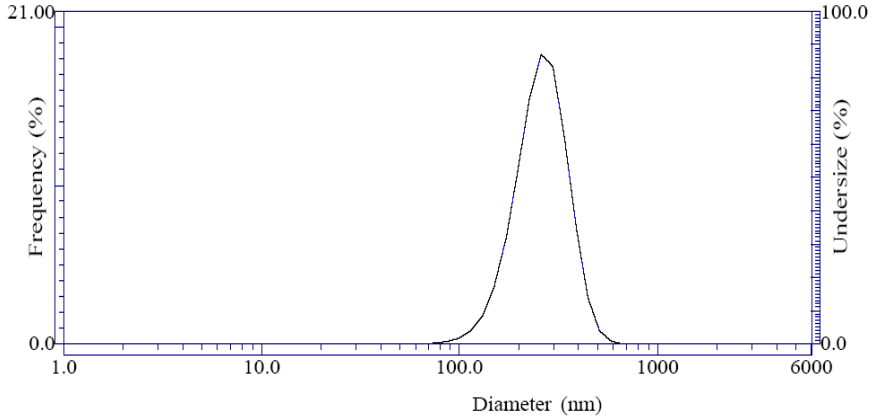


© 2010 HORIBA, Ltd. All rights reserved.

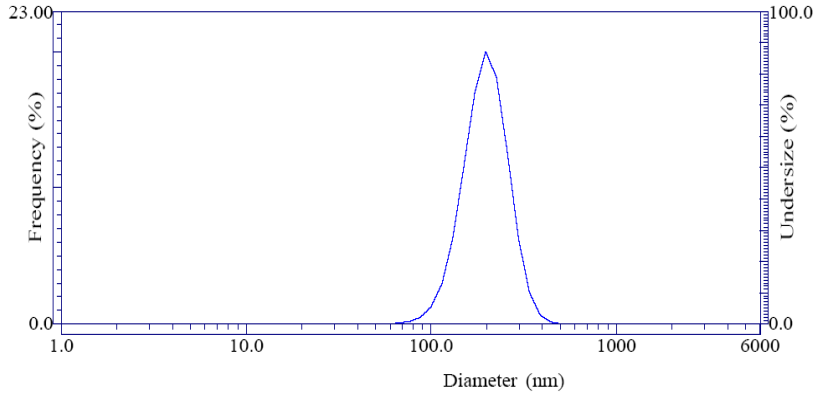
DLS Application : Liposomes



LB-550 DLS System



Liposome particle size after 5 passes through a 100 mm membrane ~ 250 nm

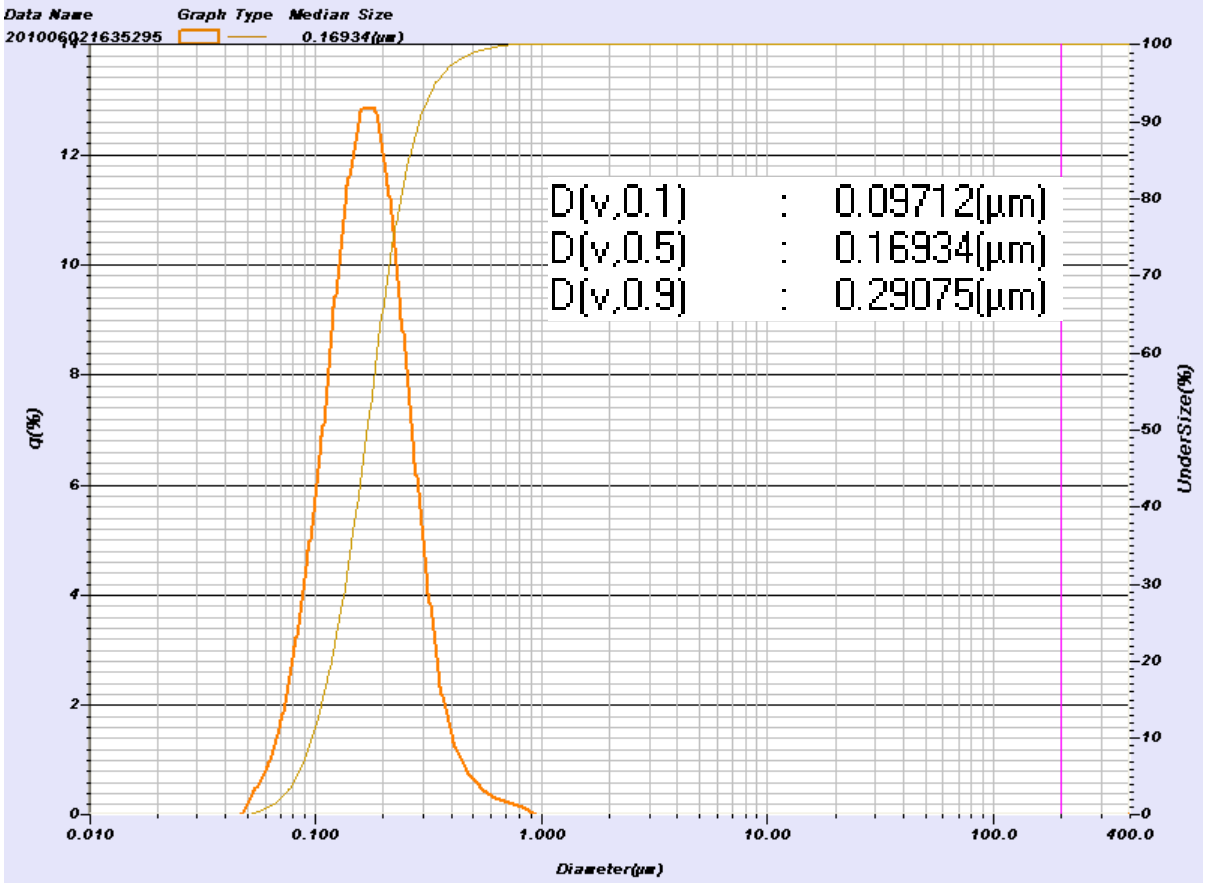


Liposome particle size after 20 passes through a 100 mm membrane ~ 150 nm

© 2010 HORIBA, Ltd. All rights reserved.

Liposome: Unprocessed

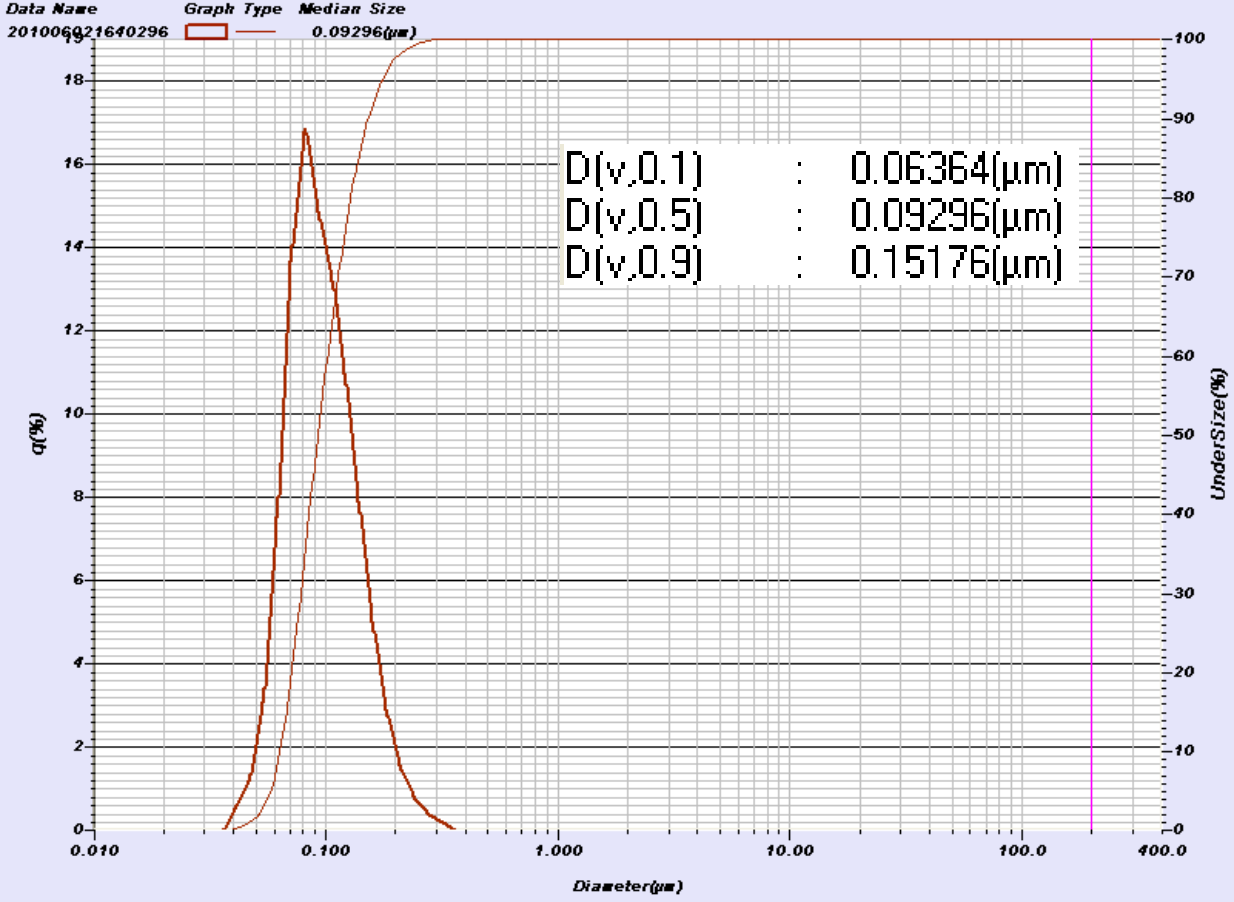
Measured on LA-950



© 2010 HORIBA, Ltd. All rights reserved.

Liposome: Processed by Microfluidizer

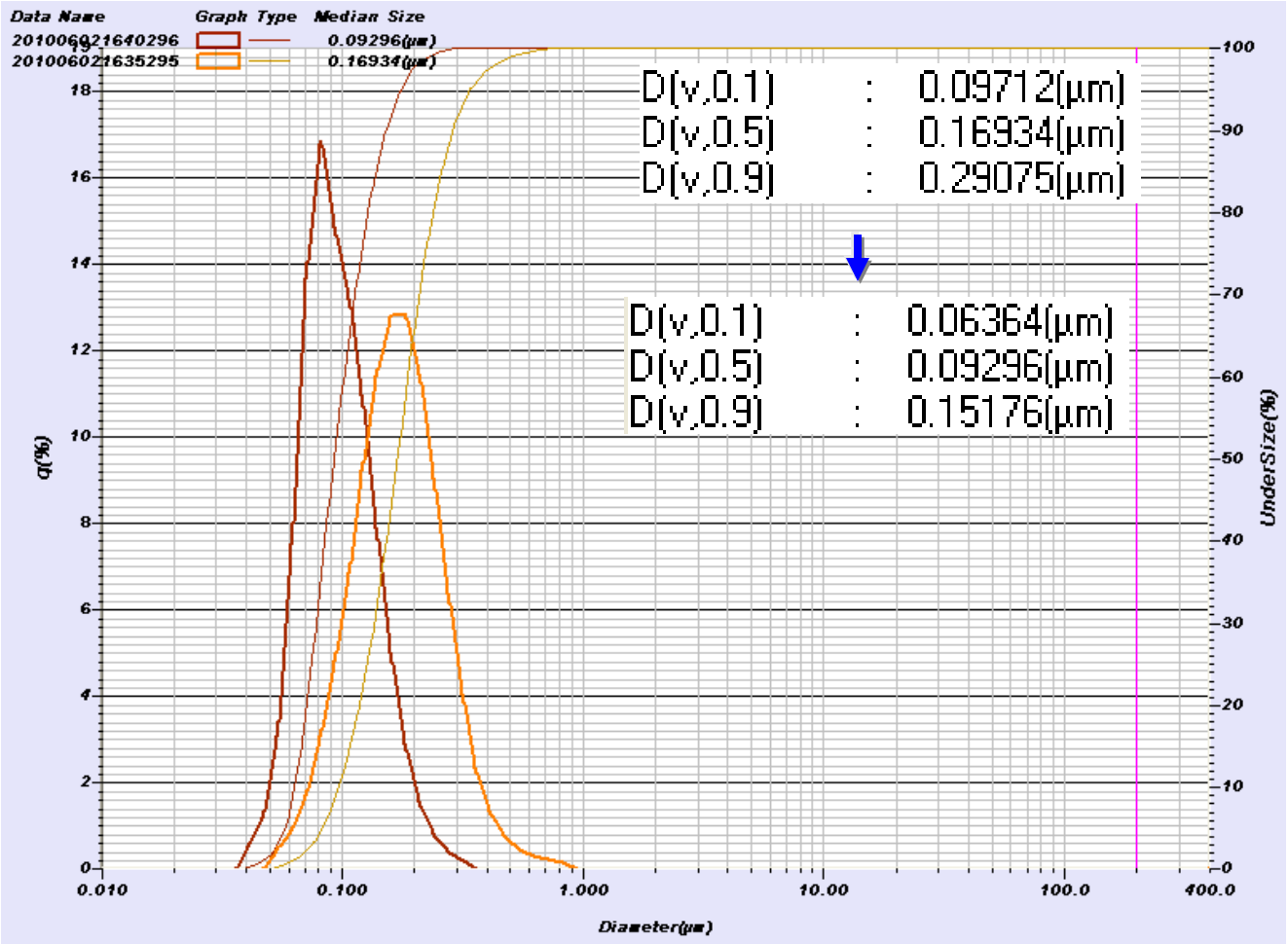
Measured on LA-950



© 2010 HORIBA, Ltd. All rights reserved.

Liposome: Before, After

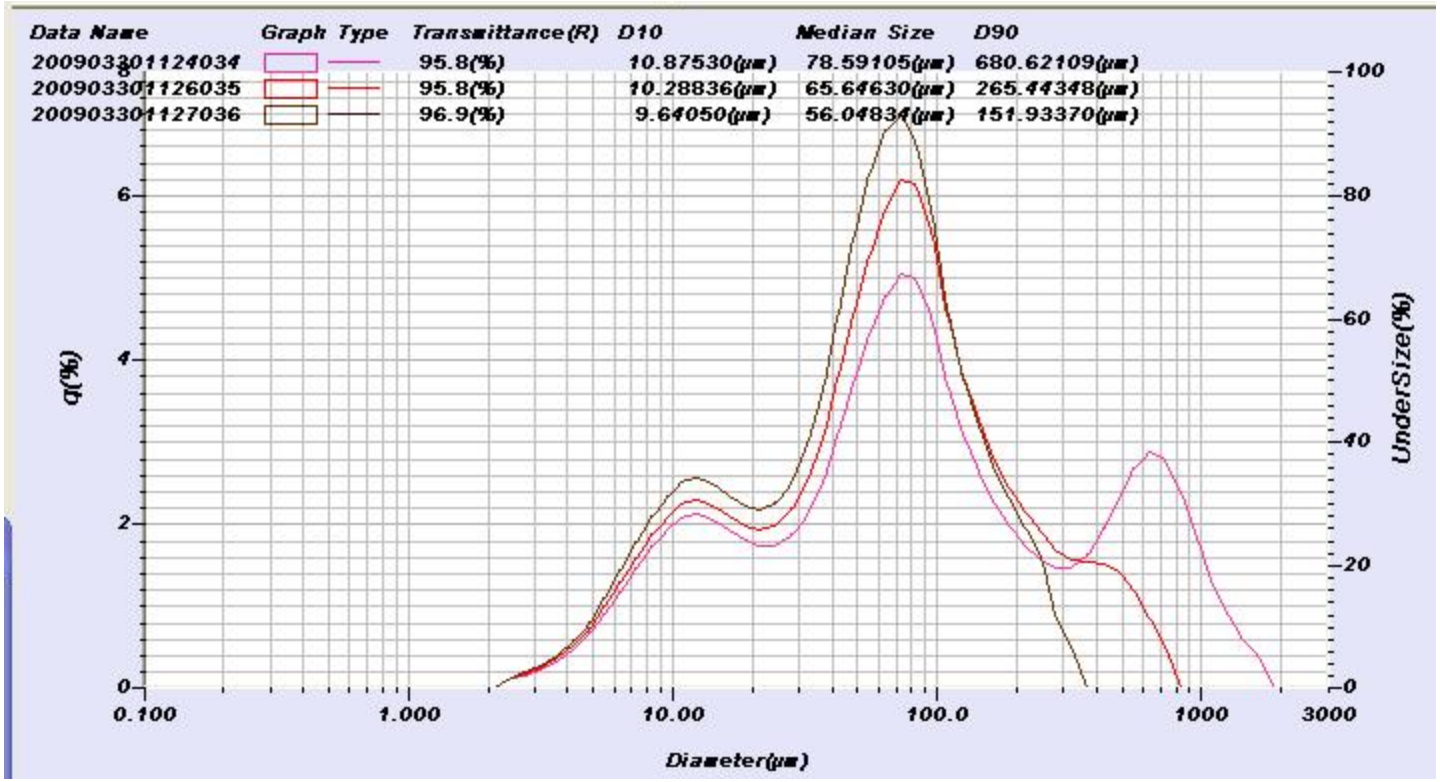
Measured on LA-950



© 2010 HORIBA, Ltd. All rights reserved.

Not Always Small Particles

Dry Powder Feeder: API



© 2010 HORIBA, Ltd. All rights reserved.

Laser Diffraction

- Most popular method
  - Wide dynamic range, wet and dry, automation
- LA-950 unique ability to measure 30 nm – 3000 µm
- Unique Method Expert software
- Unique USP & ISO calculations
- Best small particle detection, smallest sample volume requirements

© 2010 HORIBA, Ltd. All rights reserved.

HORIBA

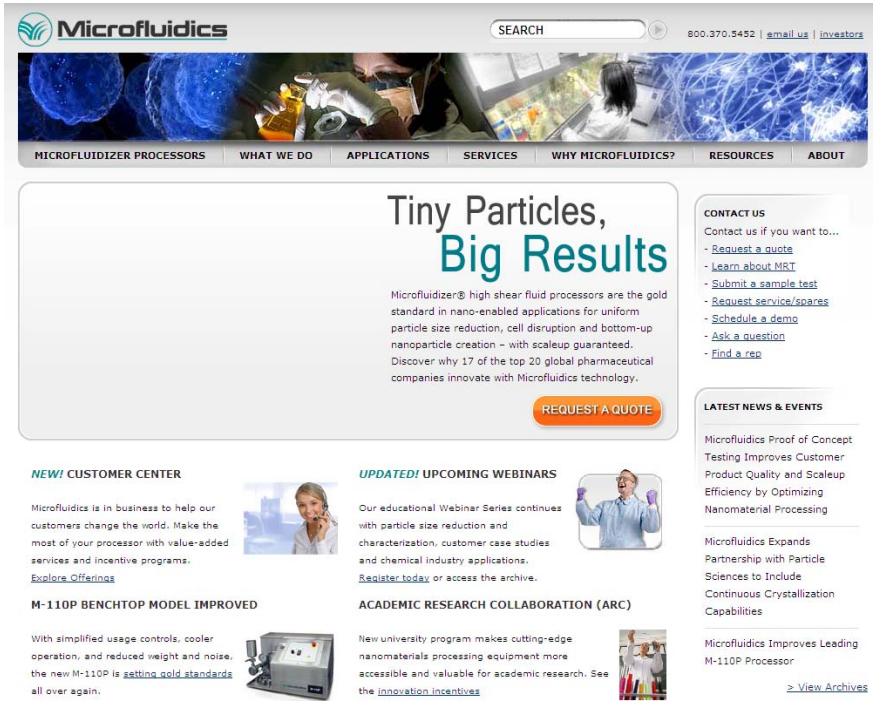
Summary

- Microfluidics excels at particle size reduction technology
  - No other technology generates such small, narrow distributions
- HORIBA LA-950 excels at analyzing particles in this size range
  - Highest sensitivity, smallest sample volume
- Microfluidics and HORIBA have been partners for > 15 years
- Thanks for your attention

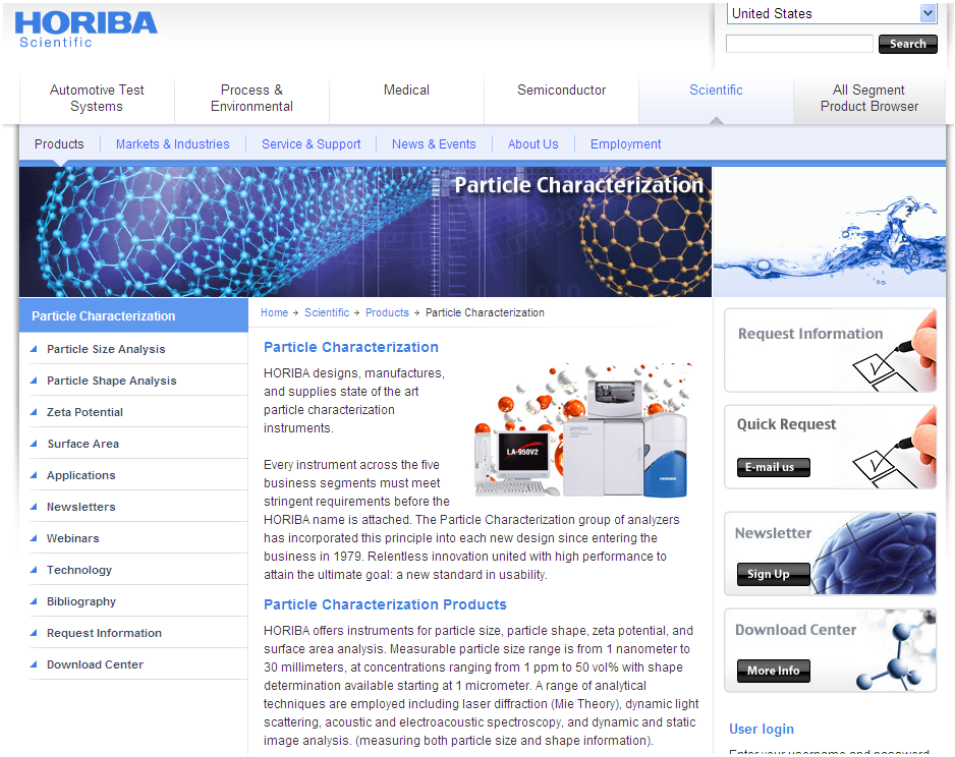
© 2010 HORIBA, Ltd. All rights reserved.

To Learn More

www.microfluidicscorp.com



www.horiba.com/us/particle



© 2010 HORIBA, Ltd. All rights reserved.