

Nanoparticles for Drug Delivery



Mark Bumiller

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Why Care about Particle Size?

Tablets

- Size of active ingredient effects dissolution & content uniformity
- Size influences tablet hardness
- Size and shape effects packing
- Size and shape effect powder flow

- Suspensions

- Same dissolution & content uniformity issues
- Ability to stay in suspensions
- Mouth feel



Particle Size and Dissolution

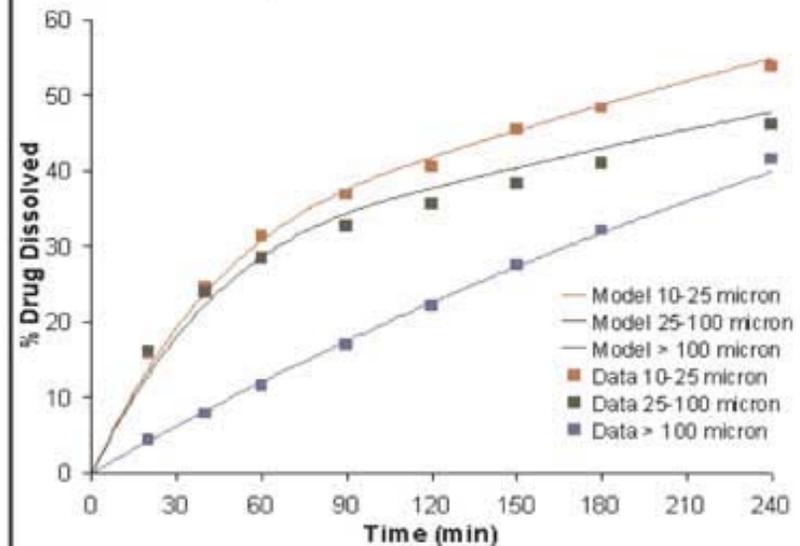
Equation 1.

$$\frac{dX_s}{dt} = -\frac{3DX_0^{1/3}X_s^{2/3}}{\rho hr_0} \left(C_s - \frac{X_d}{V} \right)$$

X_s is the mass of solid drug (mg),
 t is time (minutes),
 D is the drug diffusivity (cm²/min),
 X_0 is the initial drug mass (mg),
 ρ is the drug density (mg/mL),
 h is the diffusion layer thickness (cm),
 r_0 is the initial particle radius (cm),
 C_s is the drug solubility (mg/mL),
 X_d is the mass of dissolved drug (mg),
 V is the volume of dissolution media (mL).

FIGURE 4

Ondansetron Dissolution as a Function of Particle Size Fractions at pH 6.8. Data are From Model Predictions (Solid Lines) and Data Collected in Dissolution Experiments (Data Points).



David R. Friend, PhD; Gregory E. Parry, PhD; T. Francis, PhD; Gary Kupperblatt, PhD; Suggy S. Chrai, PhD; and Gerald Slack, Mathematical Modeling of a Novel Controlled-Release Dosage Form

Drug Delivery Technology,

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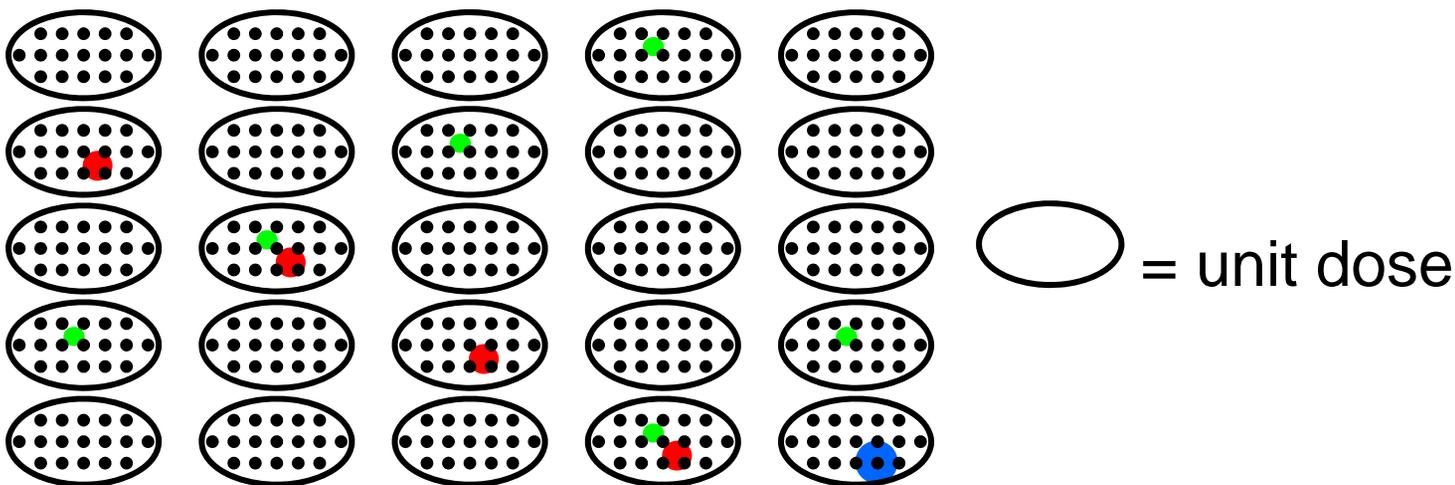
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Effect of API Particle Size on Content Uniformity



RECALLS AND FIELD CORRECTIONS: DRUGS -- CLASS II =====

PRODUCT Xactdose Phenytoin Oral Suspension, USP, 100 mg/4 ml unit dose cups, anticonvulsant. Recall #D-217-6.

CODE Lot numbers: 508608 and 508613 EXP 2/97.

MANUFACTURER [REDACTED]

RECALLED BY [REDACTED] (repacker), by letter dated July 16, 1996. Firm-initiated recall ongoing.

DISTRIBUTION QUANTITY Nationwide. 1,947 cases were distributed; firm estimated that 10-15% of the product remained on the market at time of recall initiation.

REASON Due to large particle size, some of the unit doses may not meet potency specifications.

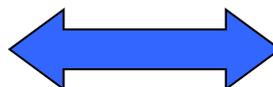
PRODUCT Leucovorin Calcium Tablets, Rx oral derivative of folic acid: (a) 5 mg; (b) 25 mg. Recall #D-088/089-7. Lot numbers: 6B107, 6H428, 6S162.

CODE

MANUFACTURER [REDACTED]

RECALLED BY [REDACTED] by letter dated January 2, 1997. Firm-initiated recall ongoing.

DISTRIBUTION QUANTITY Nationwide. (a) 2,614 unit cartons; (b) 180 unit cartons were distributed; firm estimated that 40% of the 5 mg and 75% of the 25 mg product remained on market at time of recall initiation. The particle size range of the bulk active ingredient is outside the normal range and could cause the product to fail the content uniformity test.



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Size Scale

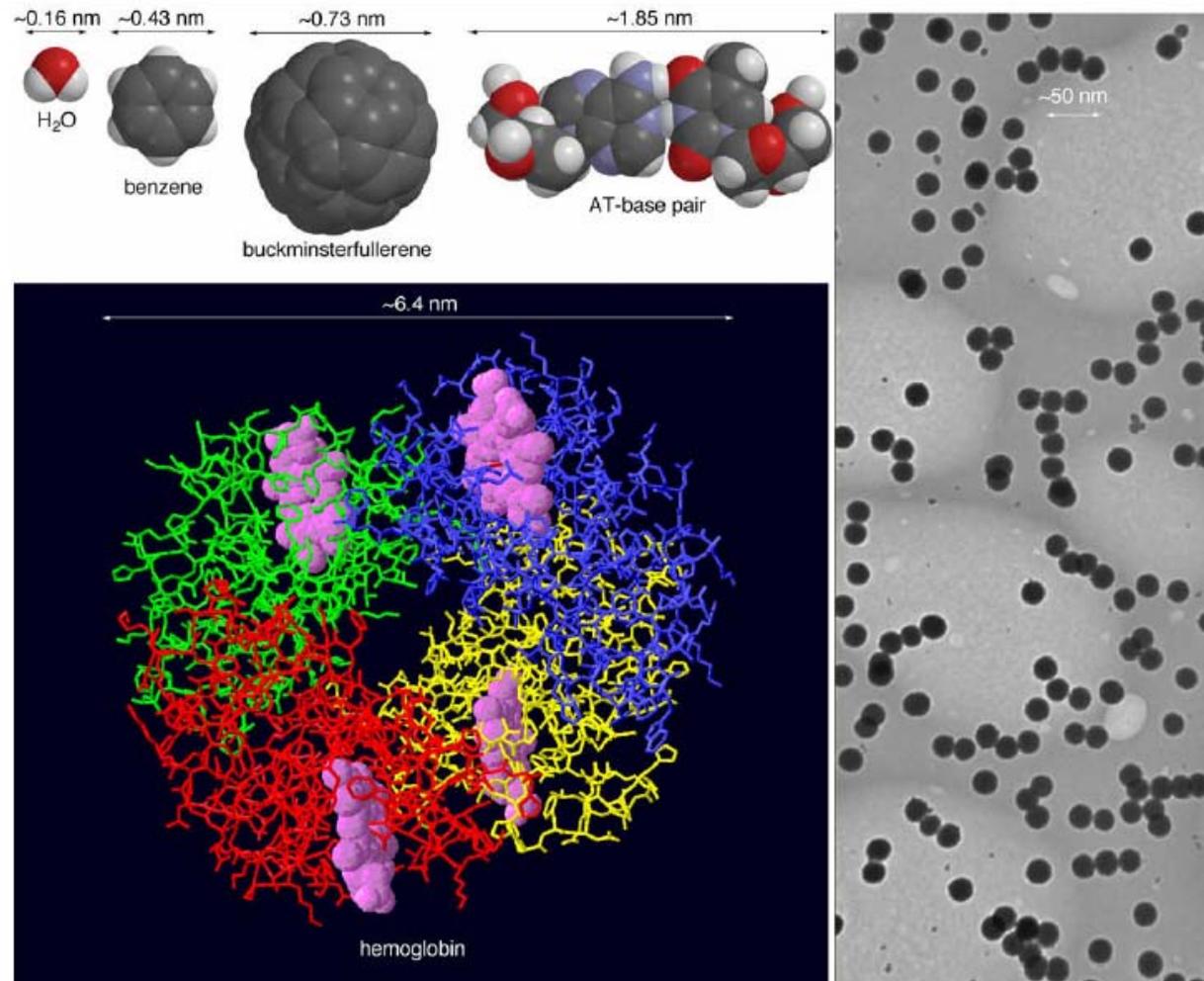
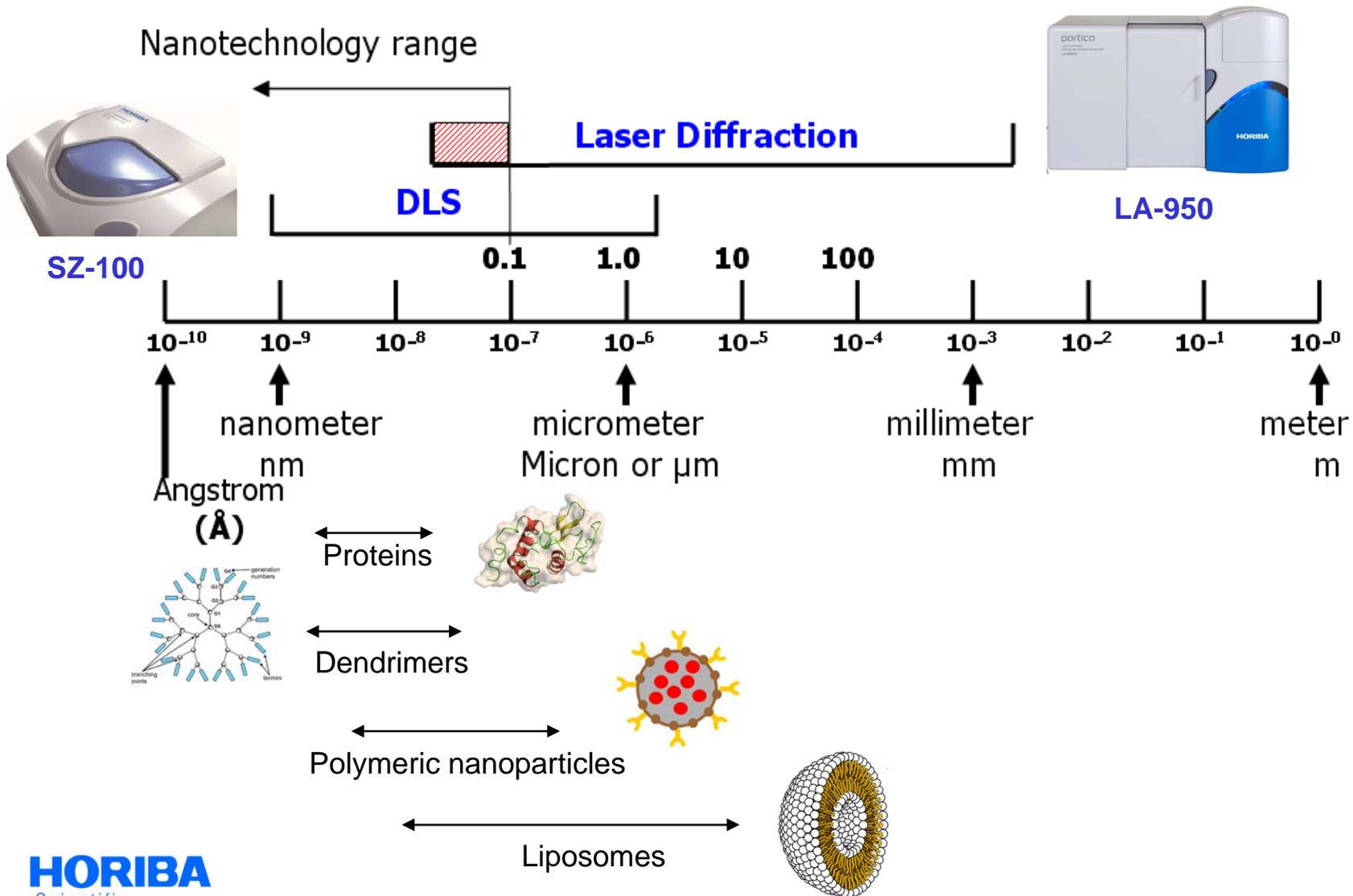


Figure 1. Sizes of organic molecules and biological macromolecules (left) in relation to silica nanoparticles (right).

Size, Technique, Samples



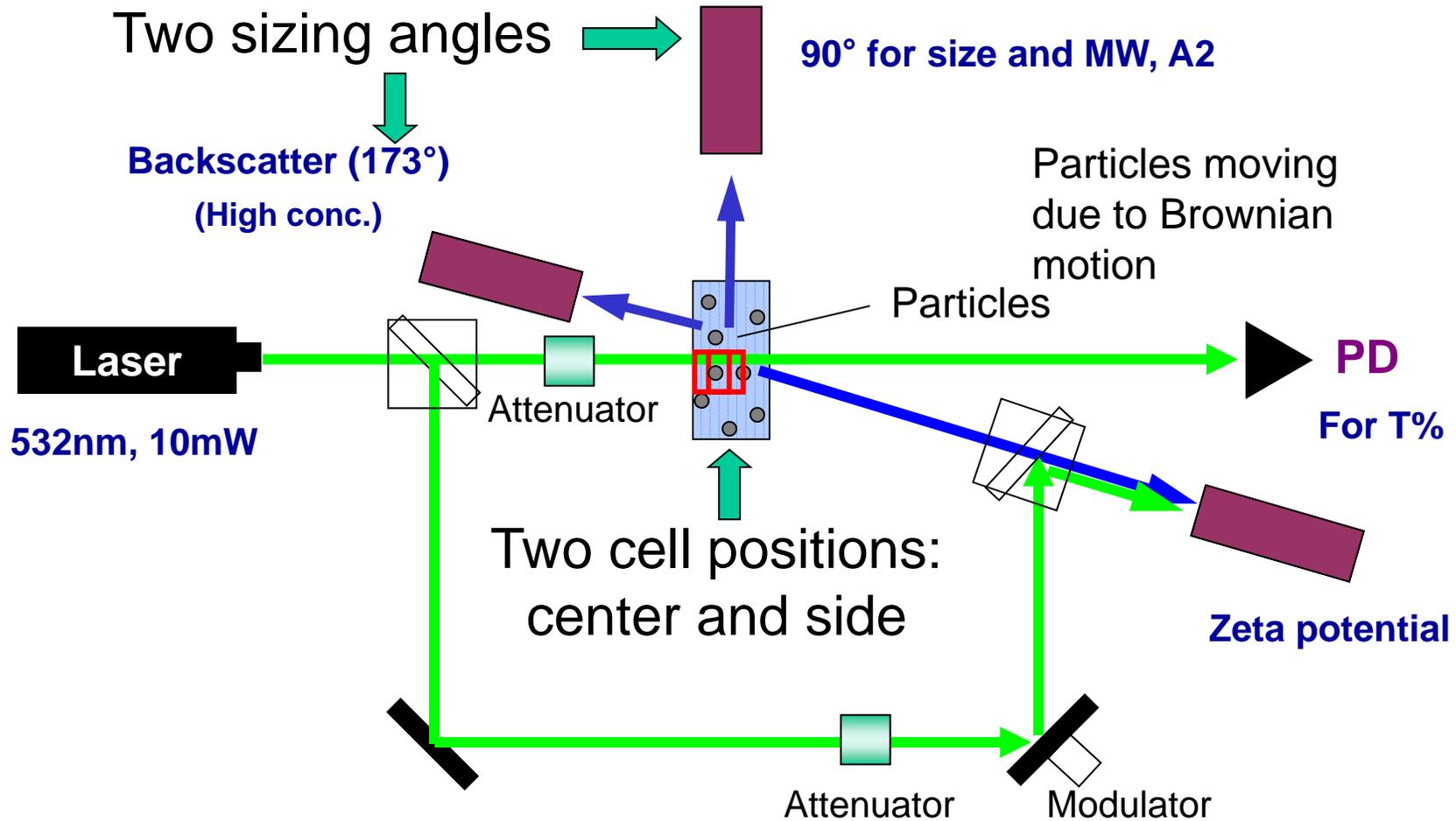
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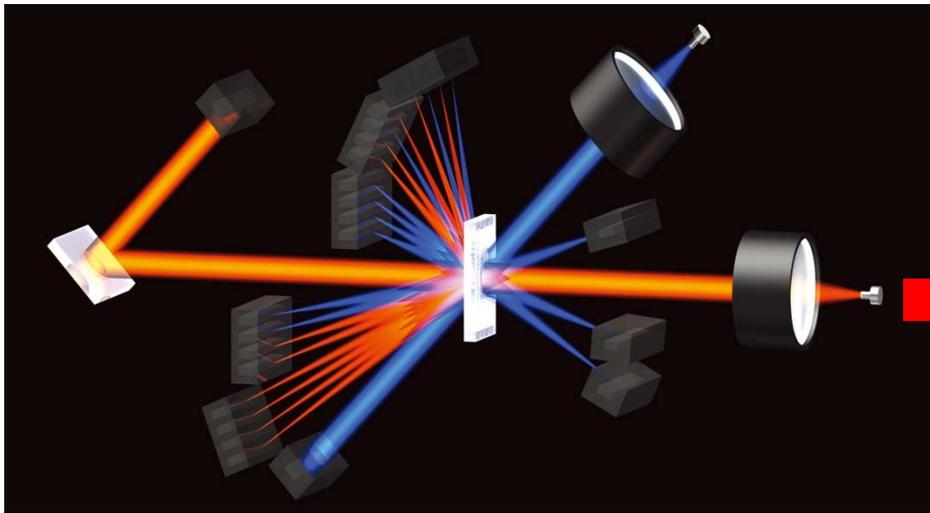
Particle Size by DLS: SZ-100



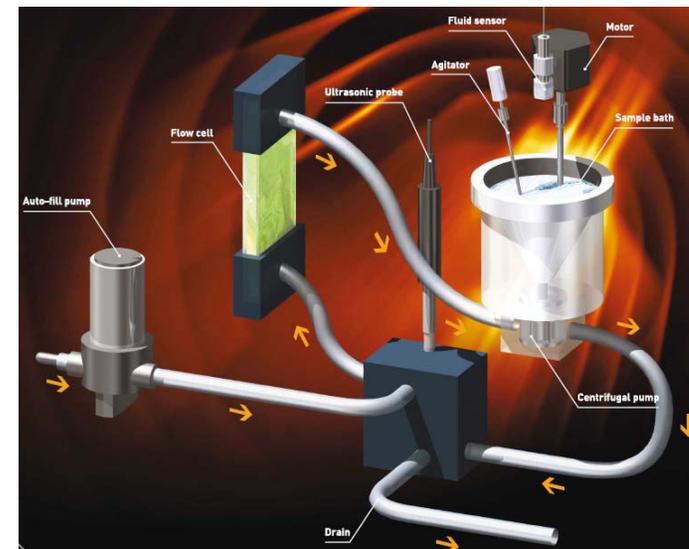
SZ-100 Optical Diagram

Laser Diffraction

Particle size 0.01 – 3000 μm



- Converts scattered light to particle size distribution
- Quick, repeatable
- Powders and suspensions
- Most common technique



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Why Nanoparticles?

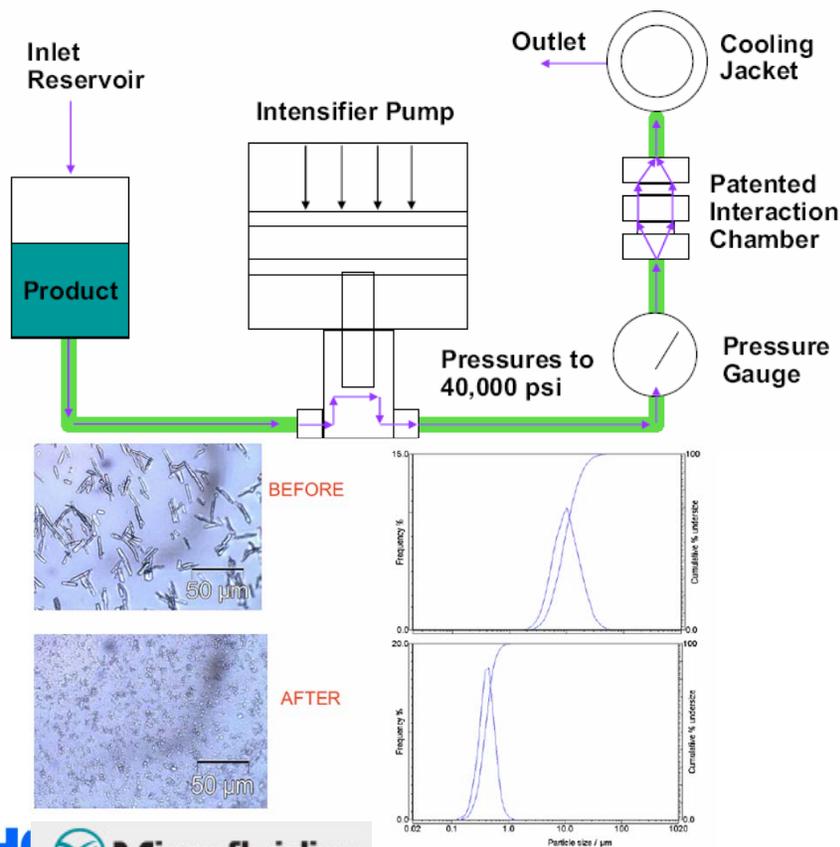
- Greater surface area/volume ratio = more exposed surface = faster dissolution
- Greater bio-availability, small drug doses and less toxicity
- Small enough to avoid removal by MPS
- Large enough to avoid rapid renal filtration
- Can cross cell membranes
- Interact on cell surface (receptors)

- Targeting

Making Nanoparticles

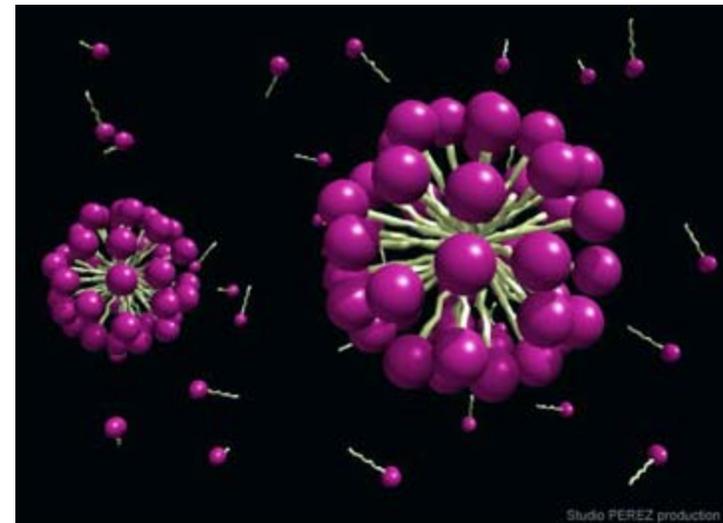
■ Top Down

- Make particles smaller



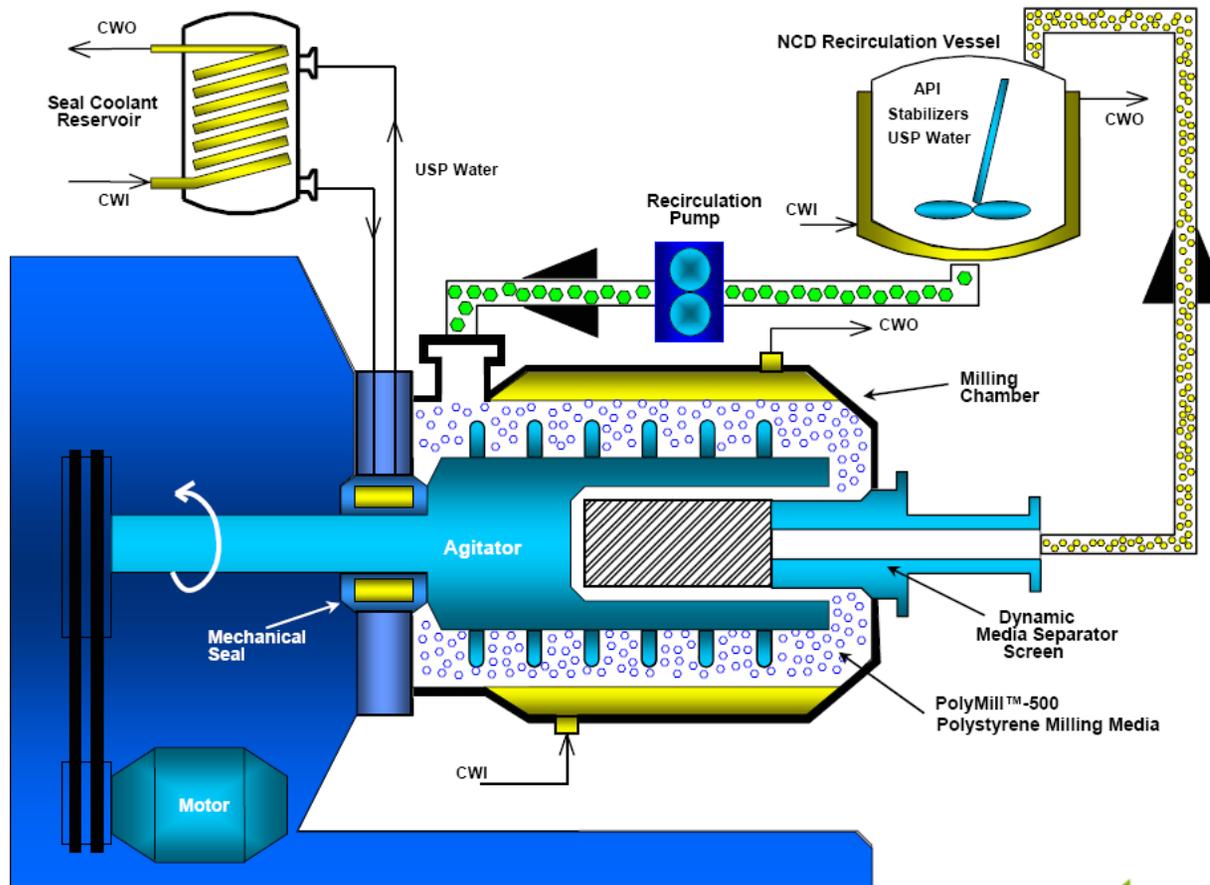
■ Bottom Up

- Build from atomic or molecular level up



Self assembly of micelles

API Processing Elan NanoCrystal® Technology



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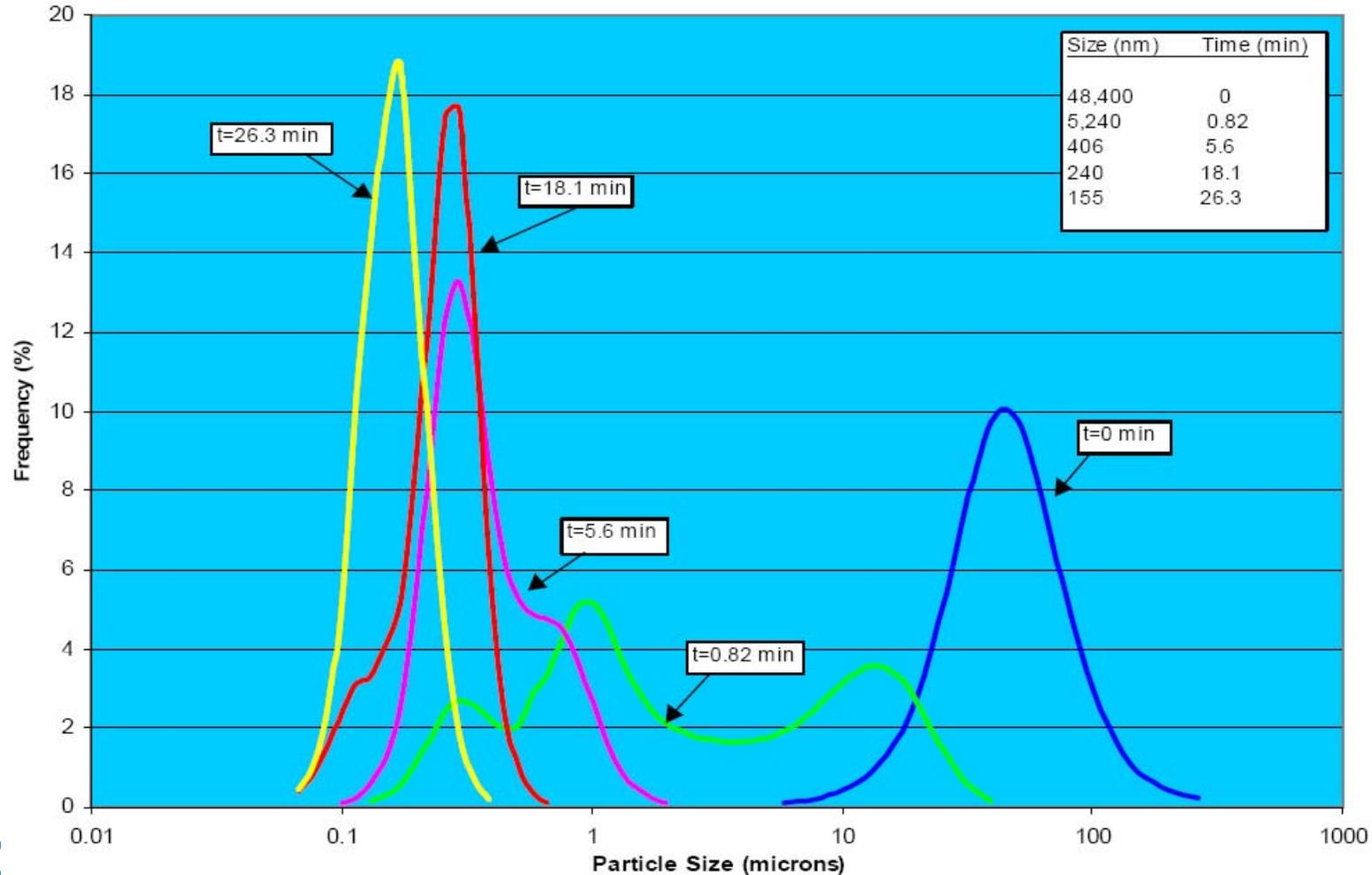
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Top Down: Elan NanoMill

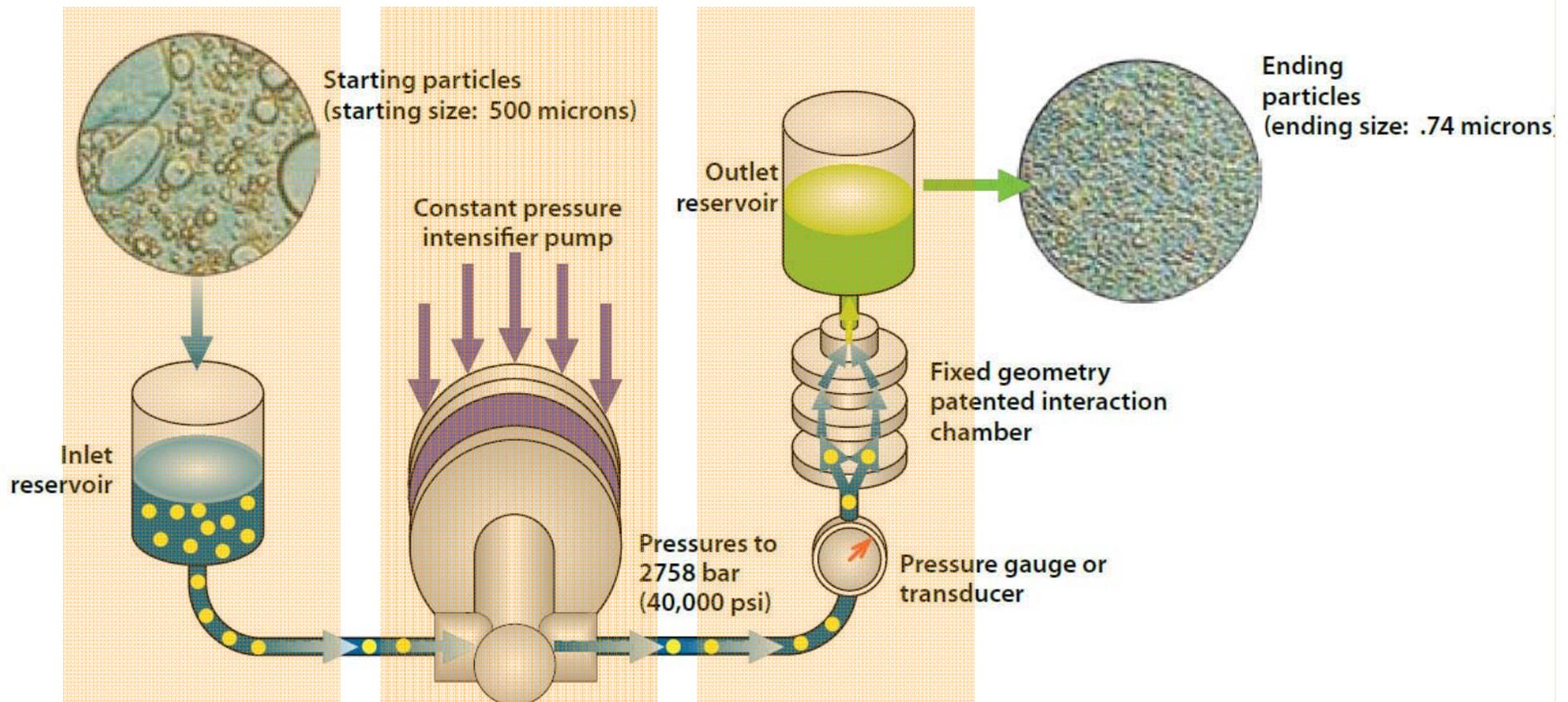


Size Reduction Measured on LA-950

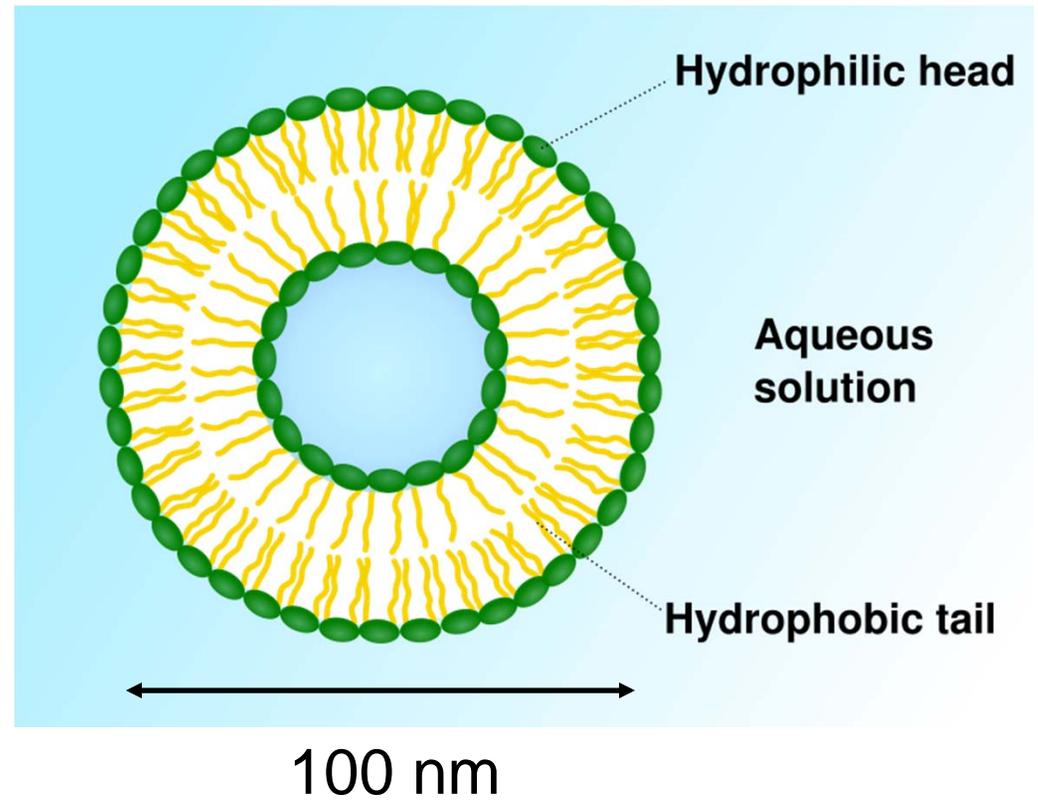
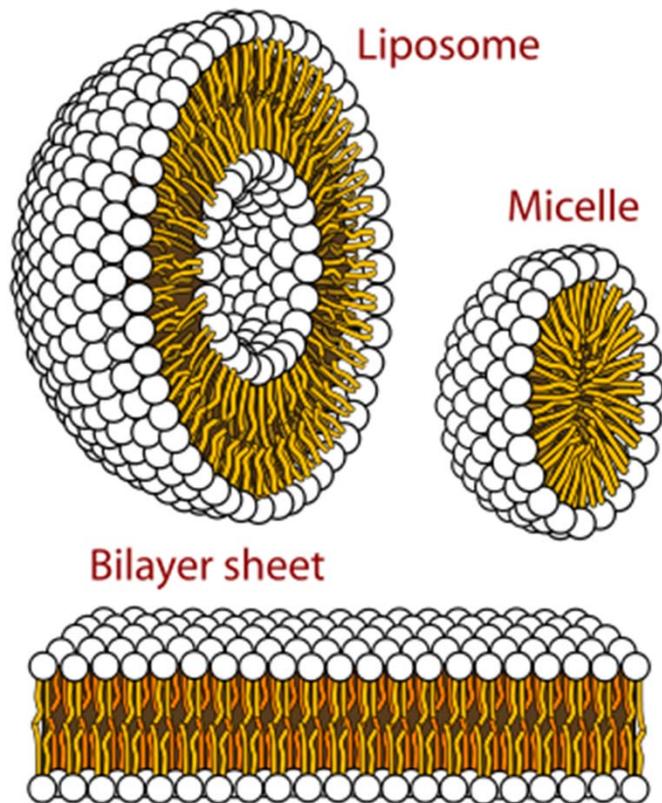
NanoMill-10 Particle Size vs. Mill Residence Time



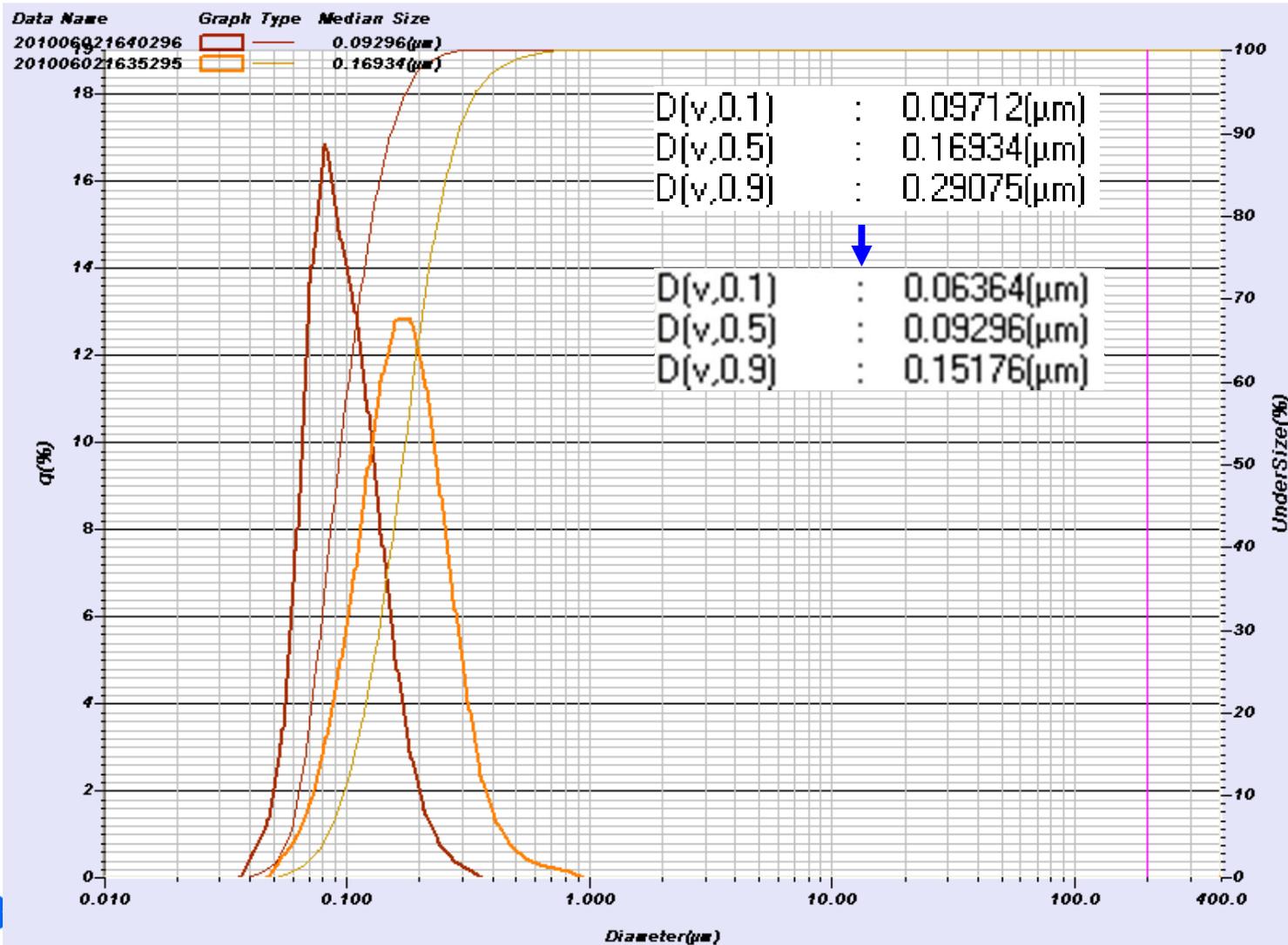
API Processing Microfluidizer*



Liposomes

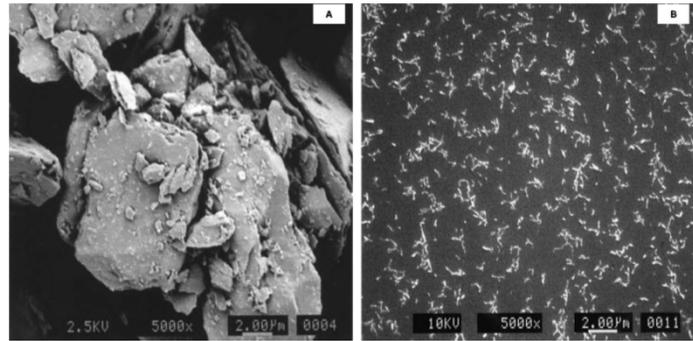


Liposome: Before, After Microfluididizer

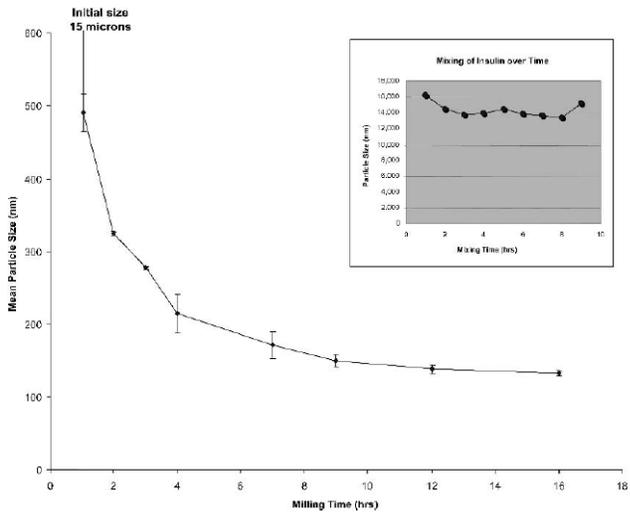
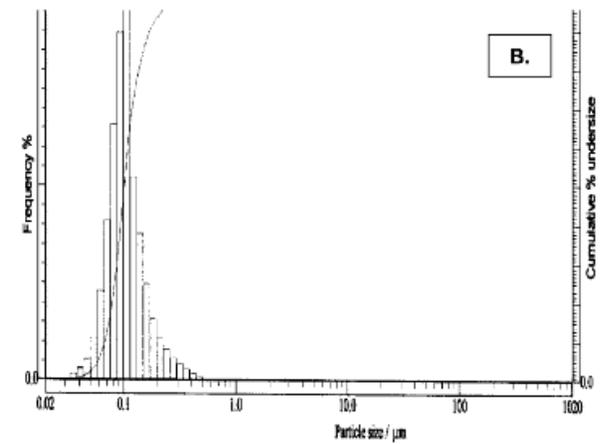
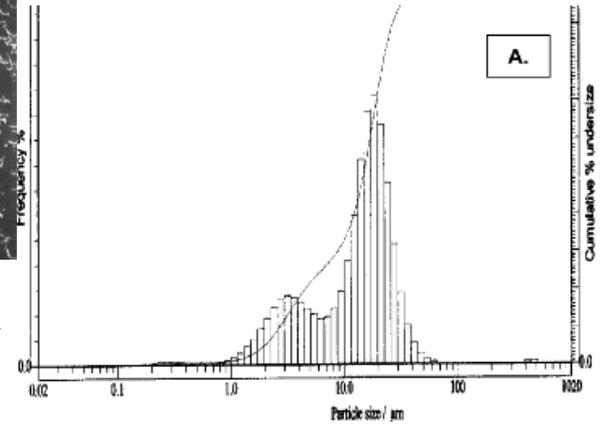


Size Reduction Measured on LA-950*

- Zn-insulin
- Starting mean size 16.162 μm
- Milled in sodium deoxycholate and water at neutral pH

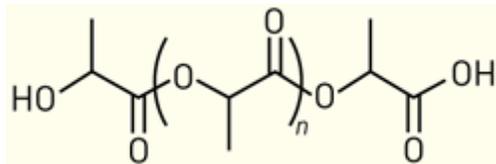
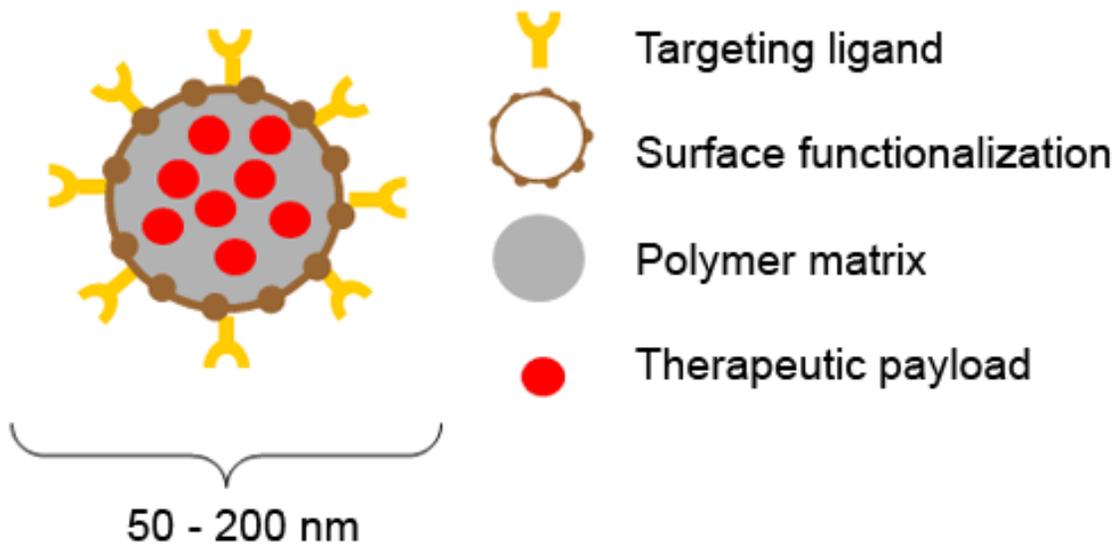


Un-milled Milled

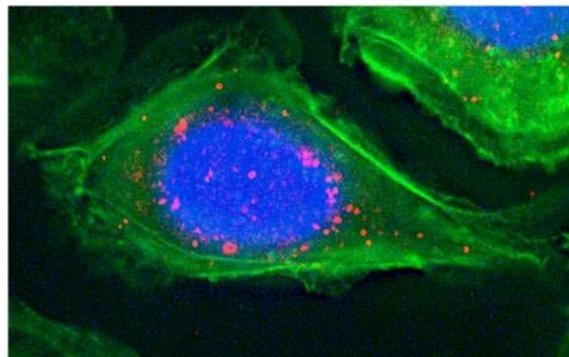


*Merisko-Liversidge et. Al., Insulin Nanoparticles: A Novel Formulation Approach for Poorly Water Soluble Zn-Insulin, *Pharmaceutical Research*, Vol. 21, No. 9, September 2004

PLA Nanoparticles for Drug Delivery



PLA



Targeting ligand provides recognition, enabling targeted nanoparticles to identify and bind to their intended target site.

Surface functionalization shields targeted nanoparticles from the immune system.

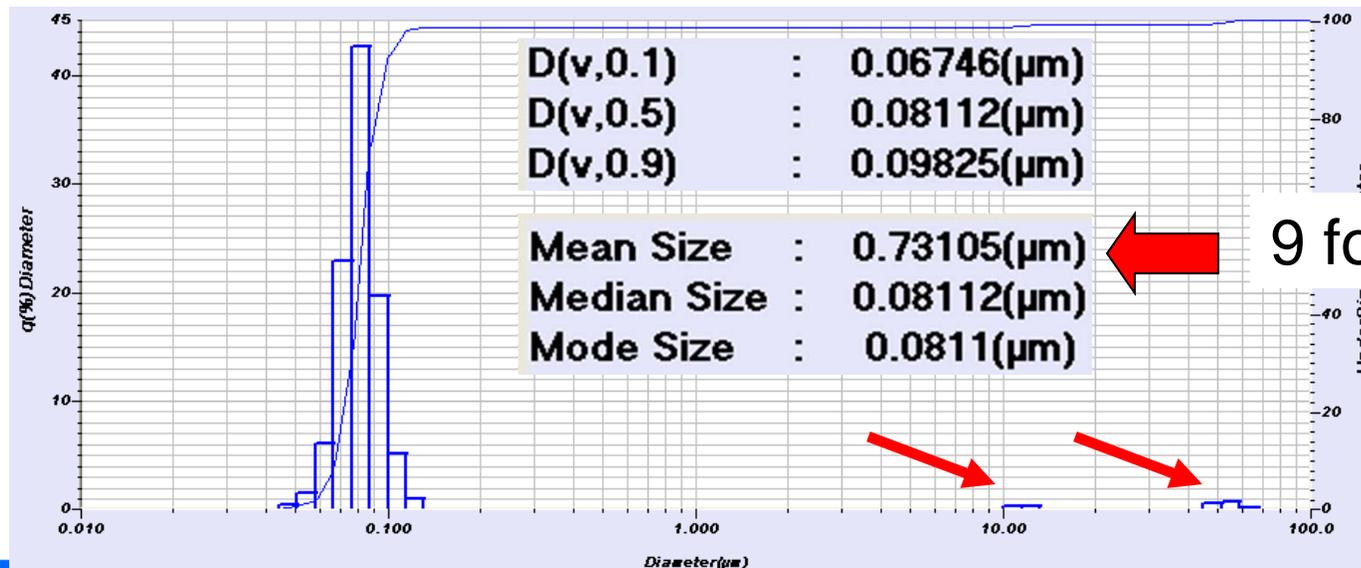
Polymer matrix encapsulates payload molecules in a matrix of biodegradable polymers .

Therapeutic payloads include small molecules, peptides, proteins, etc.

Nanoparticles for Drug Delivery



Good batch



Bad batch

9 fold increase

PLA Nanoparticle A: DLS & Diffraction

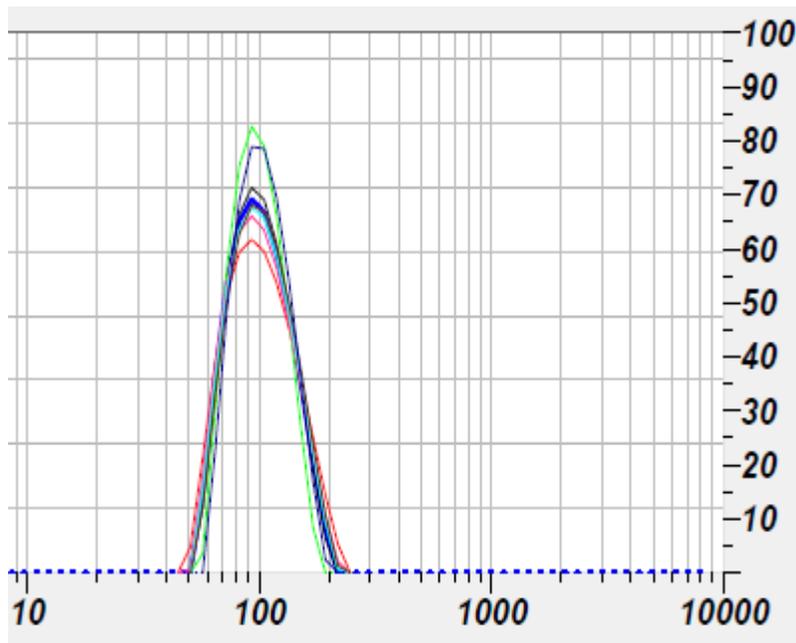
DLS on SZ-100

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	98.2 nm	29.6 nm	87.6 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	98.2 nm	29.6 nm	87.6 nm

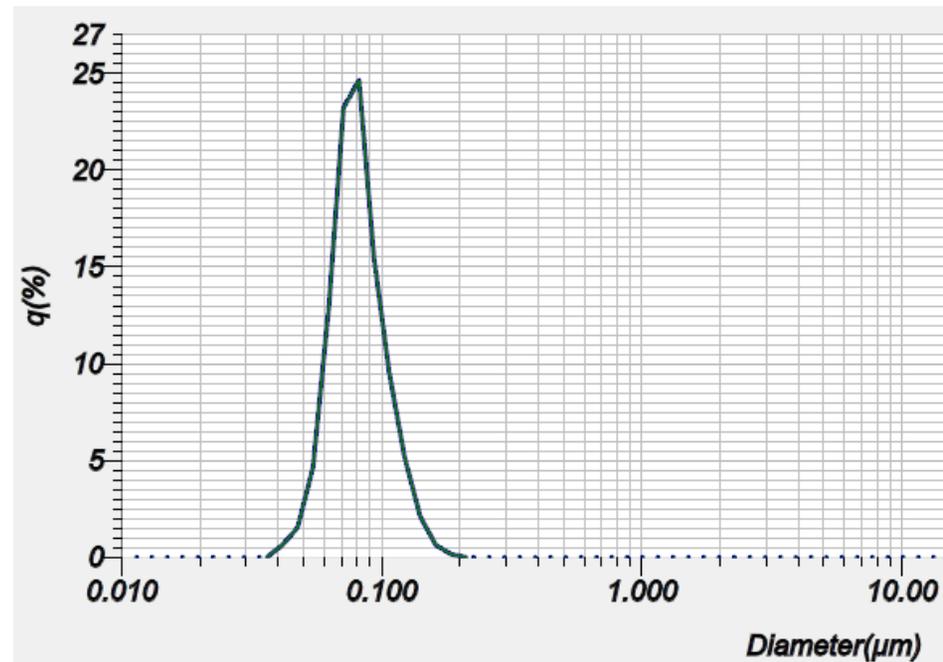
Cumulant Operations

Z-Average : 90.1 nm



Laser diffraction by LA-950

Median Size : 0.07944(μm)
Mean Size : 0.08295(μm)
Mode Size : 0.0798(μm)



PLA Nanoparticle B: DLS & Diffraction

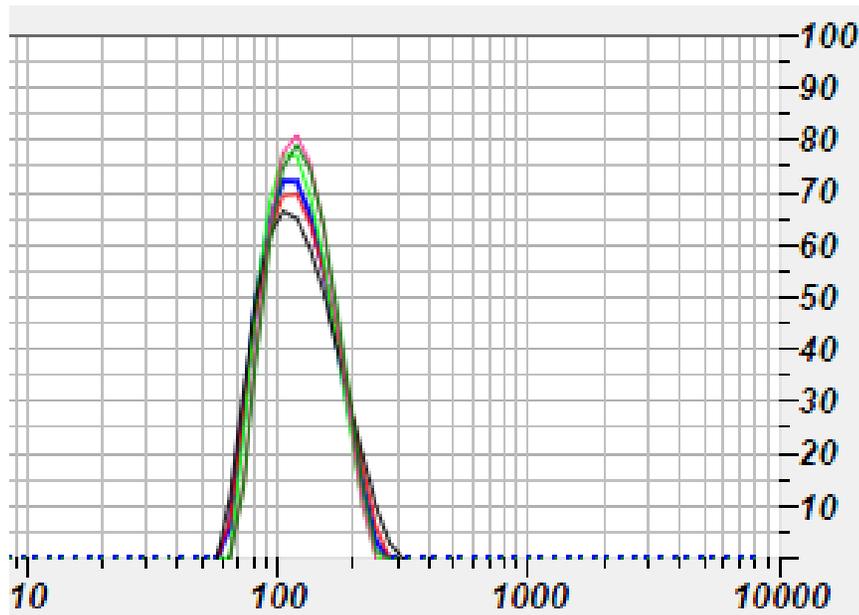
DLS on SZ-100

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	117.2 nm	35.6 nm	99.5 nm
2	--	-- nm	-- nm	-- nm
3	--	-- nm	-- nm	-- nm
Total	1.00	117.2 nm	35.6 nm	99.5 nm

Cumulant Operations

Z-Average

: 106.7 nm

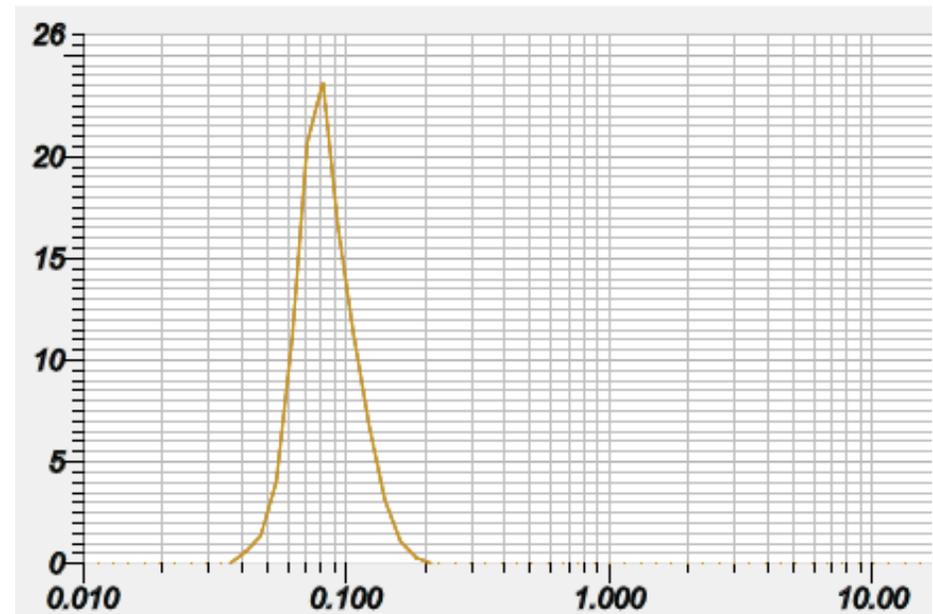


Laser diffraction by LA-950

Median Size : 0.08186(μm)

Mean Size : 0.08605(μm)

Mode Size : 0.0806(μm)



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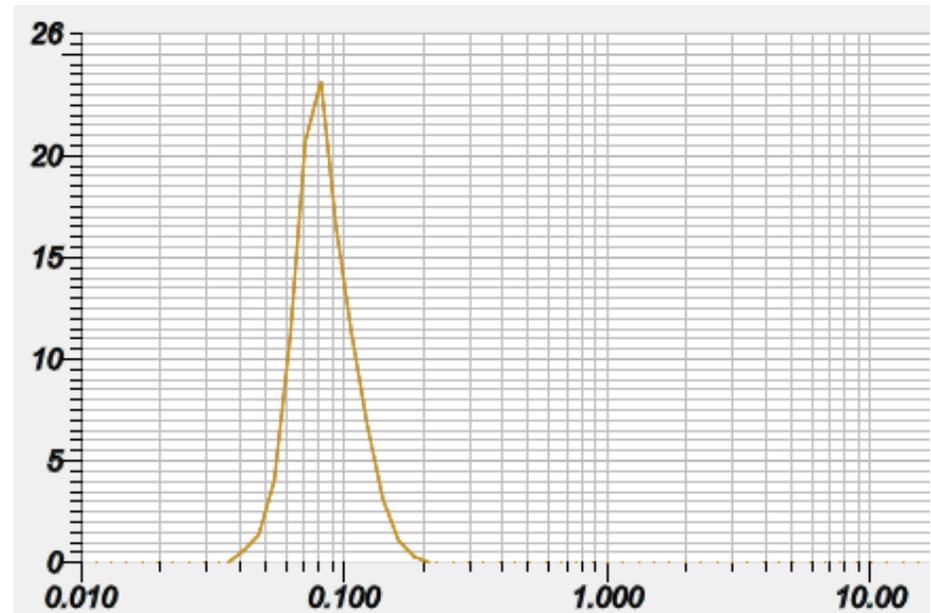
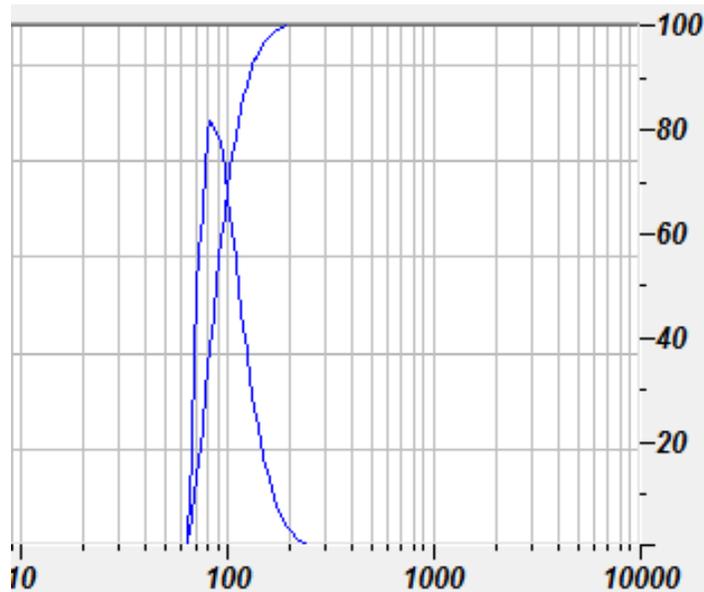
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Intensity vs. Volume Results

Mean by DLS 117 to 95 nm

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	94.7 nm	23.8 nm	78.7 nm
2	--	-- nm	-- nm	-- nm
3	--	-- nm	-- nm	-- nm
Total	1.00	94.7 nm	23.8 nm	78.7 nm

Median Size : 0.08186(μm)
Mean Size : 0.08605(μm)
Mode Size : 0.0806(μm)



Laser Diffraction vs. DLS

- Both laser diffraction and DLS can measure 30 – 1000 nm
- Which to use?
- Sample volume
- Published data for sample type
- Beware volume vs. intensity distributions
- Also need zeta potential? Then DLS

Fenofibrate nanosuspensions*

	SLS				DLS	
	Mean	D10	D50	D90	Z average	PDI
NS 120 nm	123±4	72±1	113±3	188±7	219±2	0.204±0.005
NS 140 nm	138±2	79±1	130±2	210±4	215±4	0.184±0.013
NS 160 nm	156±12	80±2	138±5	237±13	280±5	0.189±0.024
NS 180 nm	184±5	92±2	168±5	293±9	296±3	0.183±0.021
NS 270 nm	266±3	97±1	193±3	501±10	381±10	0.265±0.041
NS 650 nm	645±79	142±29	365±89	1491±100	618±25	0.207±0.036
NS 800 nm	797±109	155±64	647±214	1630±53	714±79	0.566±0.444
NS 1070 nm	1068±44	247±40	918±42	2099±73	–	–

Flavor emulsions **

	D₅₀ (vol. basis) LA-950	D₅₀ (vol. basis) SZ-100	Z-avg. Diam. SZ-100
E-1	129.8	146.6	118.3
E-2	149.8	170.5	138.7
E-3	110.0	100.2	112.7
E-4	49.4	45.5	32.4

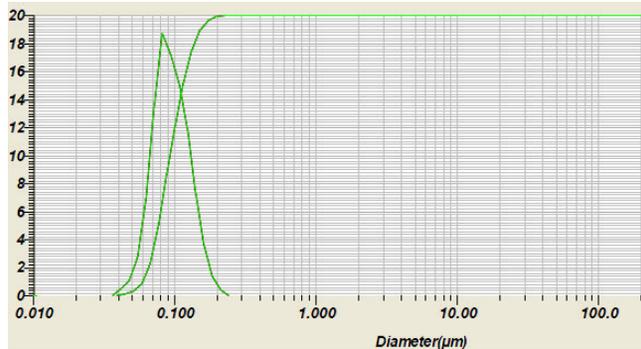
* Anhalt et. al., Development of a New Method to Assess Nanocrystal Dissolution Based on Light Scattering, Pharm Res (2012) 29:2887–2901

**AN203 DLS vs. Diffraction of Flavor Emulsions

PLA Nanoparticles

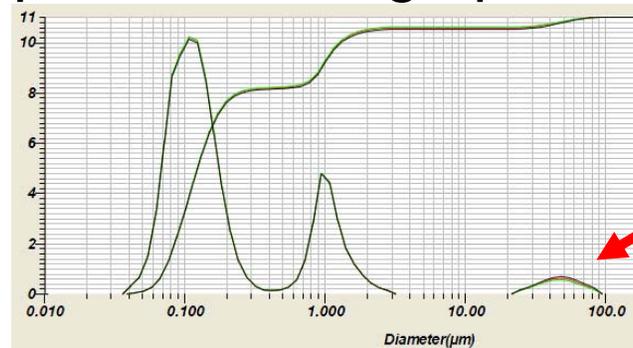
Laser diffraction or dynamic light scattering?

Good batch



Sample Name	D(v,0.1)	D(v,0.5)	D(v,0.9)
50928-6-1	0.06541(μm)	0.09222(μm)	0.13789(μm)
50928-6-1	0.06541(μm)	0.09222(μm)	0.13788(μm)
50928-6-1	0.06540(μm)	0.09221(μm)	0.13787(μm)

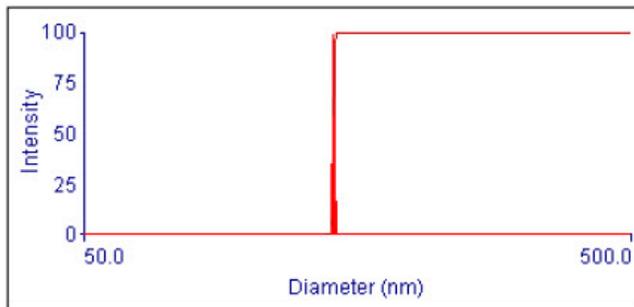
Spiked with large particles



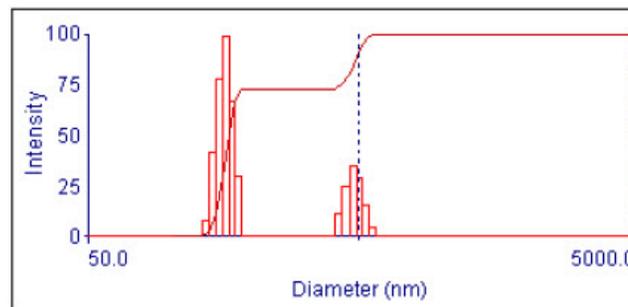
Sample Name	D(v,0.1)	D(v,0.5)	D(v,0.9)
50928-6-2	0.07348(μm)	0.13085(μm)	1.21951(μm)
50928-6-2	0.07345(μm)	0.13065(μm)	1.20702(μm)
50928-6-2	0.07360(μm)	0.13155(μm)	1.25225(μm)

(DLS) would never see this

DLS found second peak, but not >10 μm particles



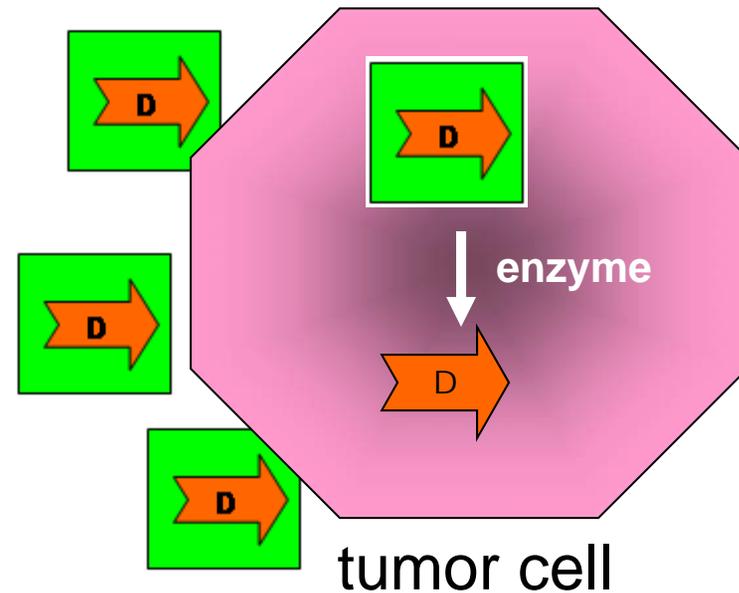
Multimodal Size Distribution



Multimodal Size Distribution

Colloidal Gold: Drug Delivery*

- Cancer therapy delivers drug to all rapidly dividing cells
- Prodrugs delivered in inactive form 
- Once delivered, metabolized in vivo into active metabolite 
- Study: Immobilize prodrug activating enzyme onto colloidal gold particles
- Enzymes: genetically modified nitroreductase from *E. coli*; NfnB and Cys-NfnB



Colloidal Gold Modified with a Genetically Engineered Nitroreductase: Toward a Novel Enzyme Delivery System for Cancer Prodrug Therapy, Vanessa V. Gwenin, Chris D. Gwenin, and Maher Kalaji *Langmuir*, 2011, 27 (23), pp 14300–14307

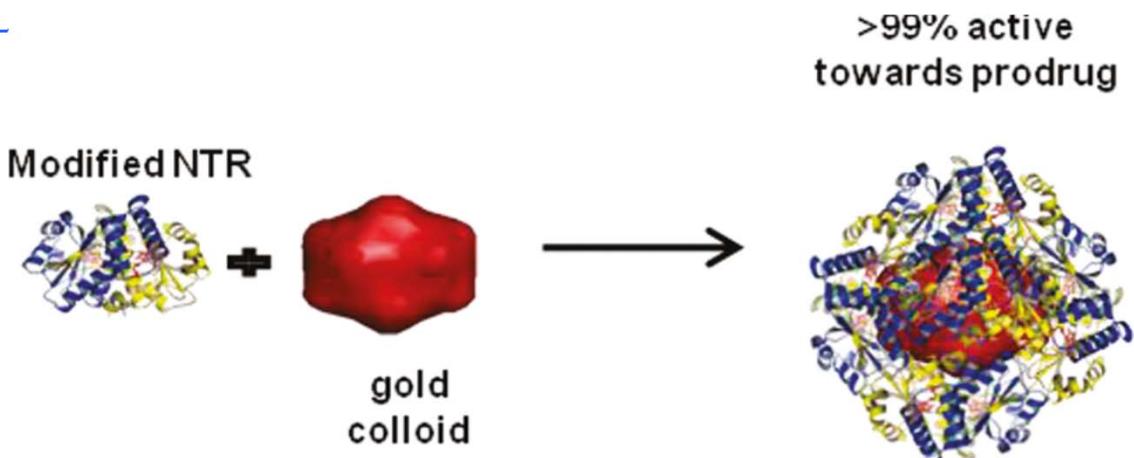
Colloidal Gold: Drug Delivery*

- Start with 50nm gold particles
- Incubate with varying molar equivalents (90:1, 180:1, 270:1, 360:1, and 450:1) of purified recombinant Cys-NfnB or His-NfnB overnight at 4C
- Analyzed on SZ-100 for particle size and zeta potential

Colloidal Gold Modified with a Genetically Engineered Nitroreductase: Toward a Novel Enzyme Delivery System for Cancer Prodrug Therapy, Vanessa V. Gwenin, Chris D. Gwenin, and Maher Kalaji *Langmuir*, **2011**, 27 (23), pp 14300–14307

Colloidal Gold: Drug Delivery*

- Base particle
Size 51 nm
Zeta potential - 52 mV
- NfnB ~ 5 nm
- Combined ~ 60 nm



		Molar ratio of enzyme to gold colloid				
		90:1	180:1	270:1	360:1	450:1
His-NfnB-gold colloid	Size (nm)	53.5	57.5	82.6	69.7	75.4
	Zeta-potential (mV)	-43	-31.7	-30.7	-33.3	-30.4
Cys-NfnB-gold colloid	Size (nm)	56.3	59.8	61.1	69.8	69.7
	Zeta-potential (mV)	-23.4	-25.3	-26.0	-27.7	-34.2

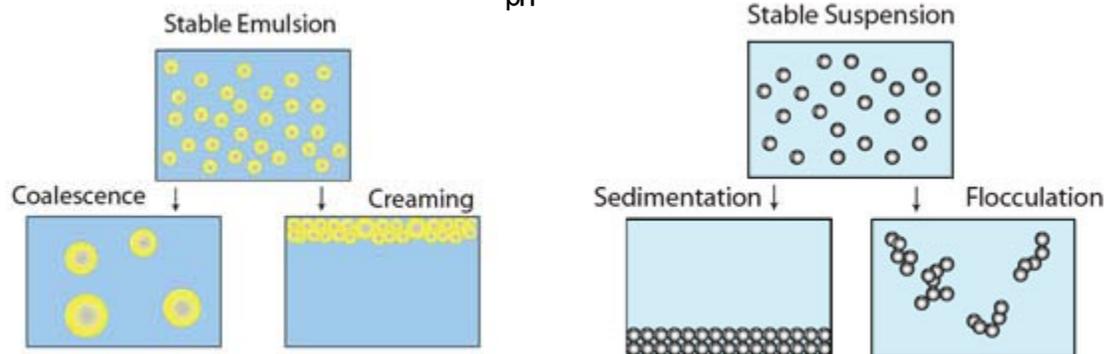
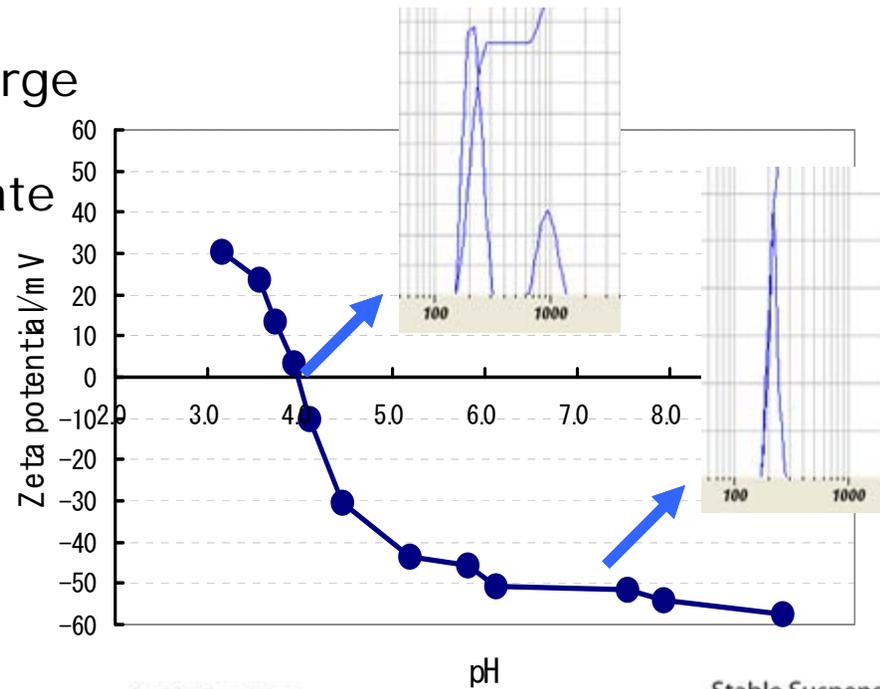
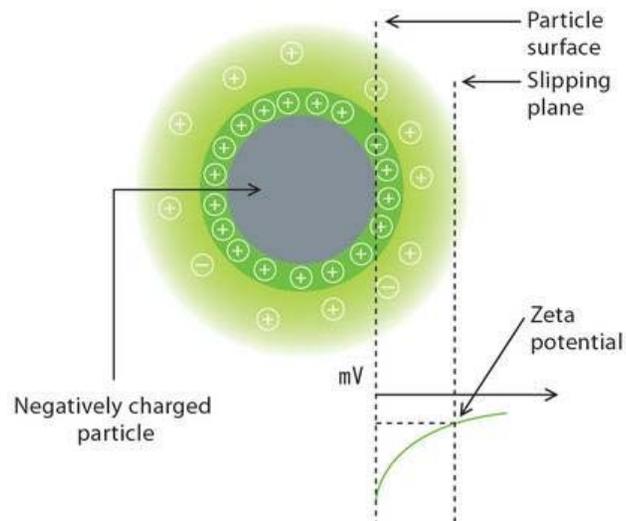
less ordered

more ordered

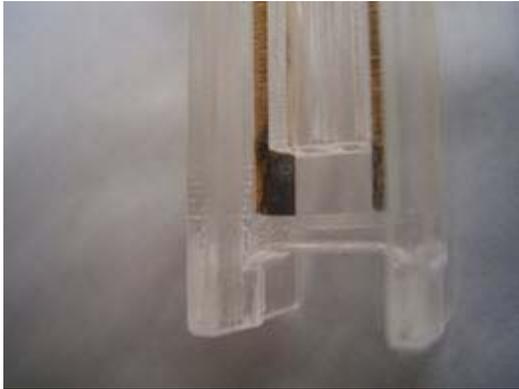
Colloidal Gold Modified with a Genetically Engineered Nitroreductase: Toward a Novel Enzyme Delivery System for Cancer Prodrug Therapy, Vanessa V. Gwenin, Chris D. Gwenin, and Maher Kalaji *Langmuir*, 2011, 27 (23), pp 14300–14307

Zeta Potential: Dispersion Stability, IEP

Measures particle surface charge
 High zeta potential = stable
 Low zeta = unstable, aggregate



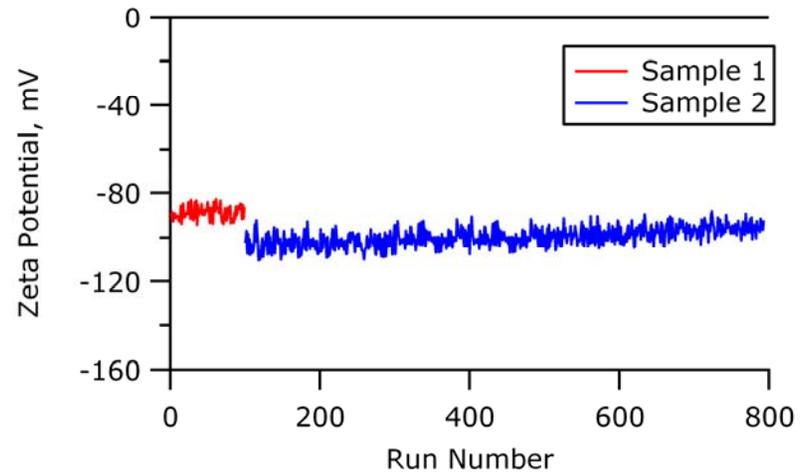
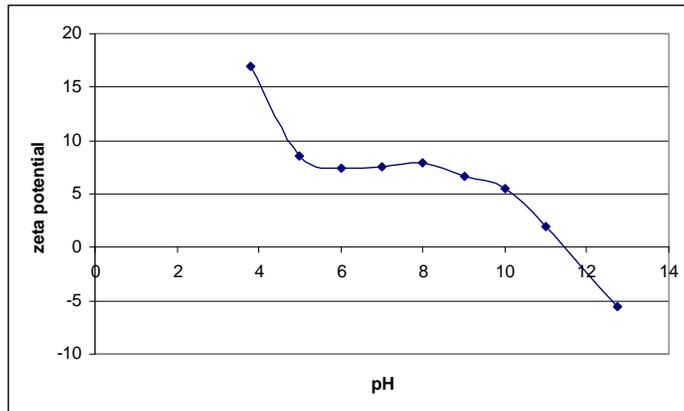
Zeta Potential Cells



Gold coated electrodes (ruined)



Carbon coated electrodes



800 measurements with one cell

HORIBA Scientific IEP 3.4 nm protein

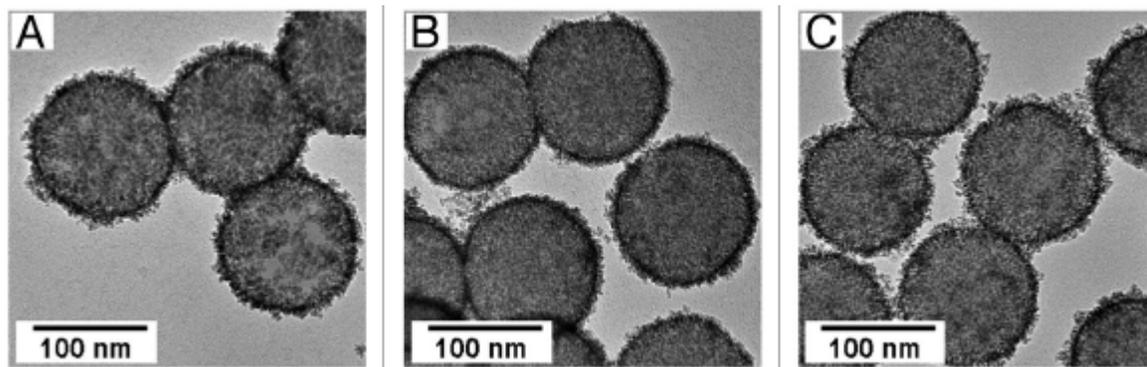
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Zeta Potential: Study Surfaces*

FePt-nanoparticle/PDDA/silica composite particles
concentrations of PDDA aqueous solutions,
(A) 1 wt%, (B) 5 wt% and (C) 7 wt%



“modification of negatively charged silica template particles with a cationic polymer resulted in the zeta potential of the silica template particles changing from negative to positive. The adsorption of PDDA molecules on the surface of silica particles was confirmed by measuring their zeta potentials.”

*Fuchigami et. al., Size-tunable drug-delivery capsules composed of a magnetic nanoshell, Biomatter 2:4, 313–320; October/November/December 2012

Summary

- Both DLS and laser diffraction successfully used for size of nanoparticles for drug delivery
- DLS for smallest sizes, sample volume, concentration
 - Also zeta potential
- Laser diffraction when also need to detect large particles

Resources: www.horiba.com/particle

HORIBA Scientific

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Particle Characterization

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Particle Characterization

HORIBA designs, manufactures, and supplies state of the art particle characterization instruments.

Every instrument across the five business segments must meet stringent requirements before the HORIBA name is attached. The Particle Characterization group of analyzers has incorporated this principle into each new design since entering the business in 1979. Relentless innovation united with high performance to attain the ultimate goal: a new standard in usability.

Particle Characterization Products

HORIBA offers instruments for particle size, particle shape, zeta potential, and surface area analysis. Measurable particle size range is from 1 nanometer to 30 millimeters, at concentrations ranging from 1 ppm to 50 vol% with shape determination available starting at 1 micrometer. A range of analytical techniques are employed including laser diffraction (Mie Theory), dynamic light scattering, acoustic and electroacoustic spectroscopy, and dynamic and static image analysis. (measuring both particle size and shape information).

HORIBA's advanced designs and powerful software, combined with flexible sample handling systems are available to meet every analysis need. These instruments can incorporate small volume pumping systems for precious materials, high throughput automation, dry powder dispersers and temperature controlled flow systems in order to provide the user with the best possible solution with none of the trade-offs that might otherwise be necessary.

Particle Size

- Laser diffraction
 - LA-950V2
 - LA-300
- Dynamic light scattering
 - SZ-100

Request Information

Quick Request

E-mail us

Particle Size Essentials

eBook

Newsletter

Sign Up

Download Center

More info

Member login

Please enter your e-mail address and password in order to login on to www.horiba.com. We may ask you later to answer additional questions if you are the first time to this area.

E-Mail Address:

Password:

Login

← Receive news of updates

← View application notes, webinars, etc.

Thank-you

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