# How to Find the Right Particle Technology for Your Application

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# What we'll talk about

- A Structured Approach
- Technique Overviews
- Quick Selection Charts
- Q&A

# First Questions

- Why is the measurement being made?
- How will the data be used?
  - Accuracy vs. precision
- Which metric(s) correlates to product/process quality?
  - Size, shape, zeta potential, surface area, mW
- Need to match historic data?
- Who will use the instrument?
  - R&D, QC, students, multiple shifts
- How many samples per day/week/month?

# Particle Characterization Problem*?

*From Pohl, M., Choosing the right Particle size analyzer, Powder and Bulk Engineering, Feb 2008

Approximately 90% of the time the material characterization is the unique

Is it a material characterization issue?

Is it a particle characterization issue?

Yes

# Particle Characterization Problem*?

- Customers complain this batch doesn't perform like previous product
  - Investigate specific behavior & look for possible causes
  - Chemical or physical difference?
- I have a powder flow problem
  - Both particle size & shape influence flow
  - But so do other parameters (water content)
- This product isn't stable
  - Could be size and/or zeta potential
  - Cause could come from surface chemistry

# Choosing the Technique

Is it a particle characterization issue?

From Pohl, M., Choosing the right Particle size analyzer, Powder and Bulk Engineering, Feb 2008

Other Techniques

Particle Counting?

Which technique is most appropriate?

Contamination?
Filtered?
Need conc.?

Particle size distribution is most common problem/interest

# Second Questions

- Total cost of ownership
  - Initial cost, reagents, consumable parts, service rates, reliability (cost of down time)

- Service history
  - Knowledge of service engineers
  - Peace of mind

# What we'll talk about

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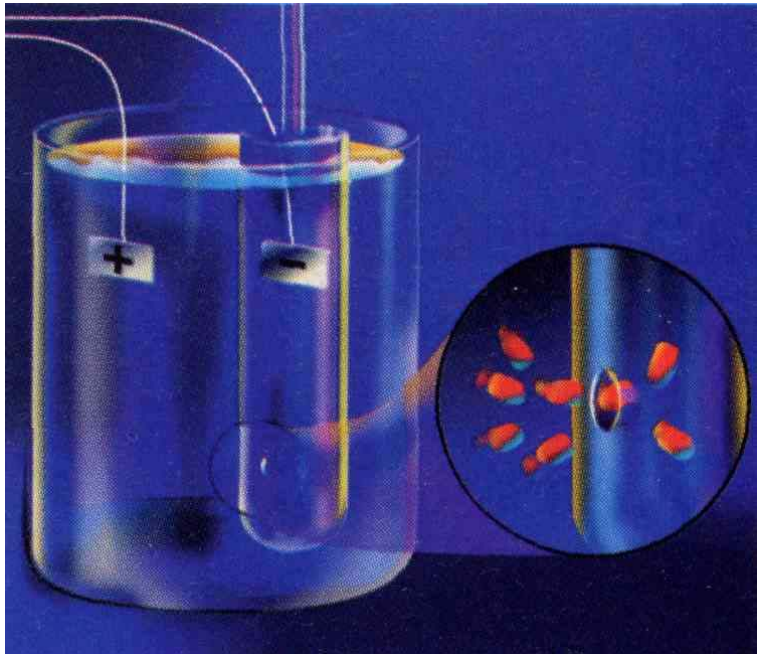
# Particle Counting

- Need to know particles/volume
  - Implies measuring contamination, typically in a filtered fluid
  - Particle size analyzers measure your product, not contamination
  - Air: use airborne particle counter
  - Liquid: use liquid particle counter or trap particles on filter and inspect filter
    - Coulter counter, light obscuration, some dynamic image analyzers

# Electrical Sensing Zone

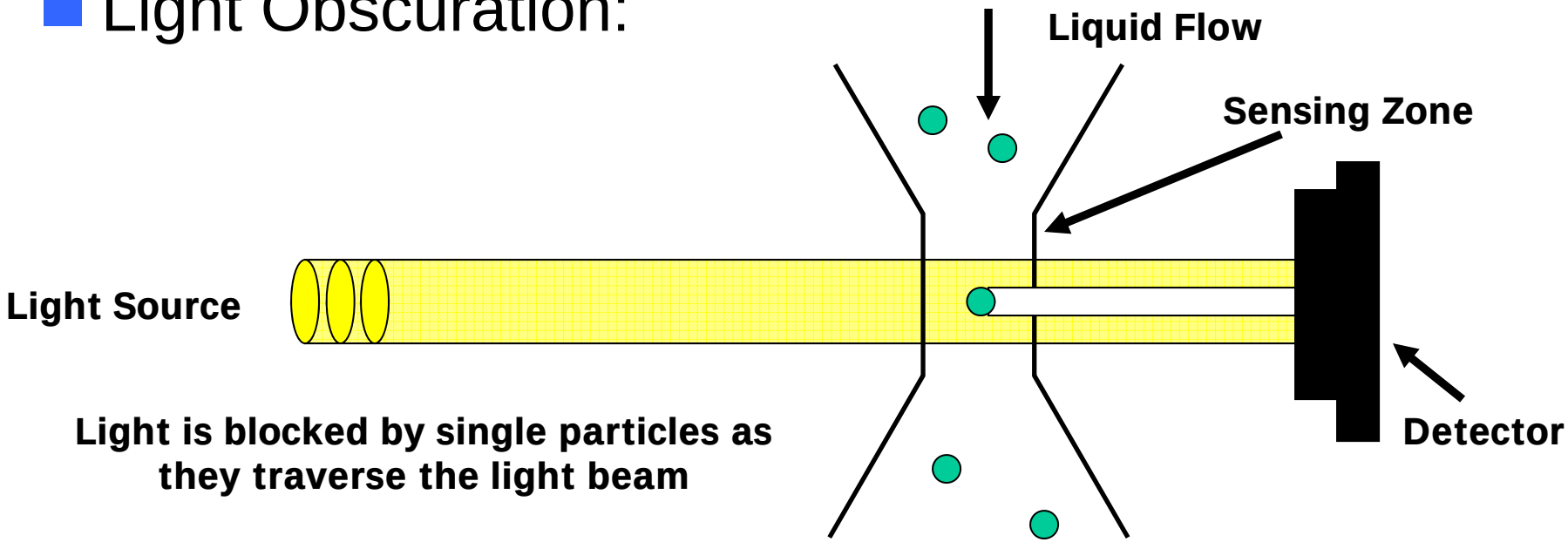
HORIBA

- Coulter Principle
  - Based on change in conductivity of aperture as particle traverses.
  - Requires conducting liquid.
  - Directly measures particle volume and counts.
  - High resolution
  - Used for blood cell counting now more than industrial applications




# Light Obscuration

- Light Obscuration:

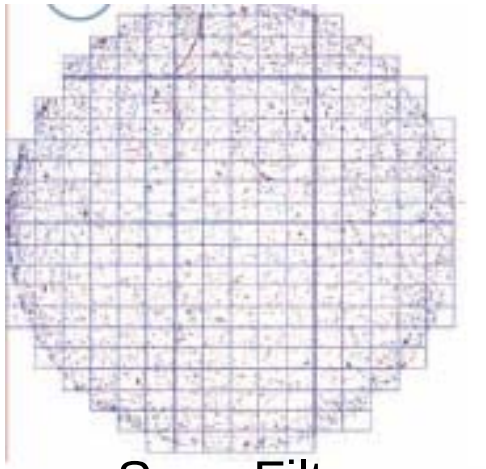



- Need to know concentration
- Filtered liquids
- Particles/mL @ size
- Particles in water, oil
- USP<788> testing
- High resolution histogram

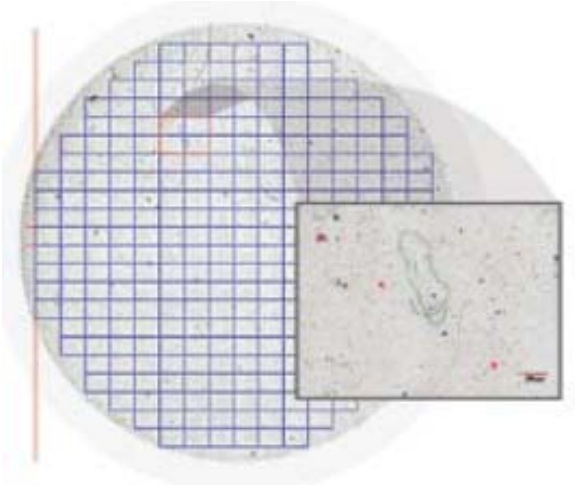
# USP<788> Filter Testing

Load Sample(s)


PSA300 Image Analyzer

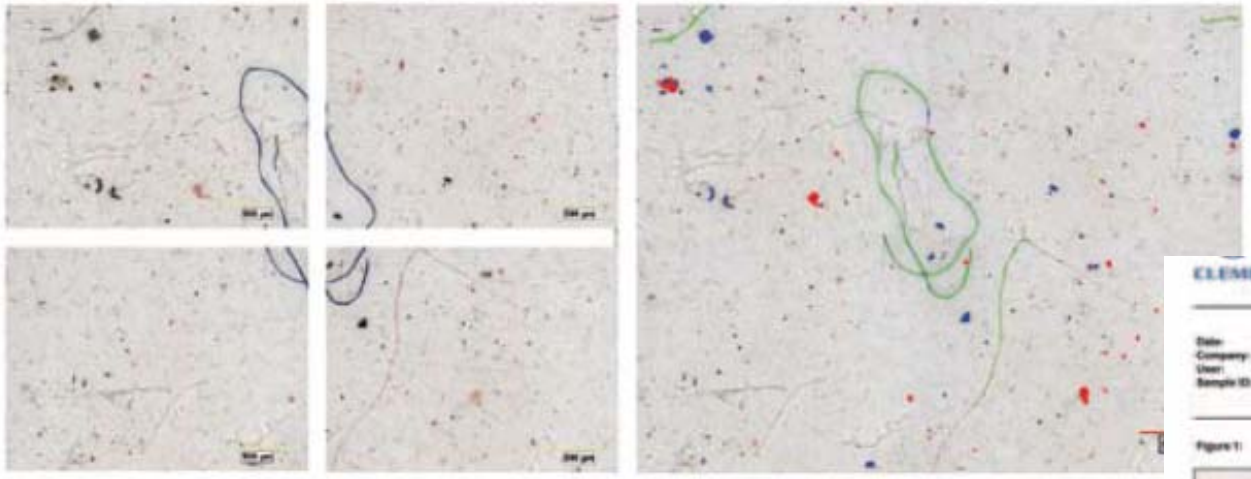


Scan Filter



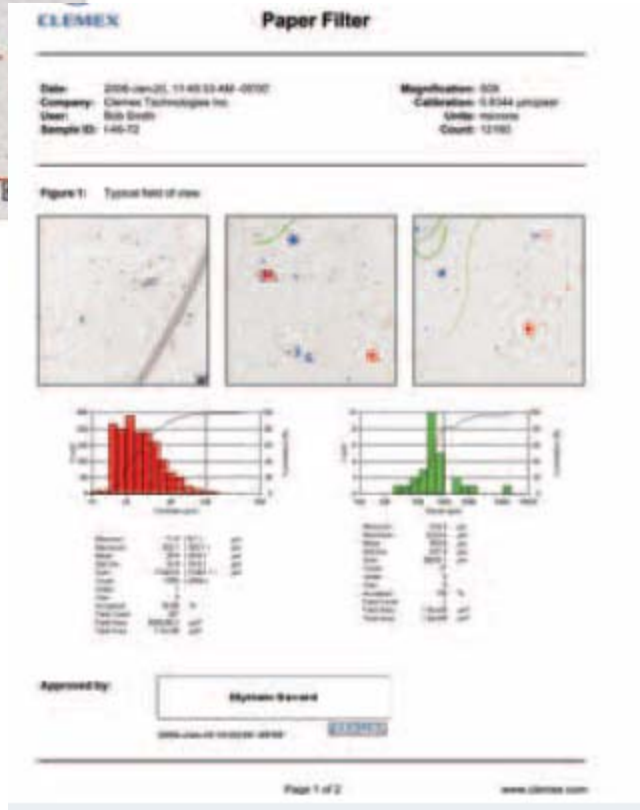
Count/Size all Particles

# USP<788> Filter Testing



Mosaic function stitches all scans
Complete fiber is analyzed

Generate Report



# SA-9600: BET Surface Area

HORIBA

- Surface area affects:
  - Dissolution, reaction, combustion, hydration
- Fastest measurement time
  - Dynamic (flowing gas) vs. static (volumetric)
- QC: easy to use, high throughput
- Lowest total cost of ownership
- Full software control
- TSA: 0.1 – 50 meter squared

# Method Comparison

HORIBA

## Dynamic (Flowing-Gas)

- Faster
- Easy to use
- Increased sensitivity to low SSA materials
- Higher throughput
- Lower operating costs
- Lower service costs

## Static (Volumetric)

- Slower
- Easy to use
- Low SSA ➡ longer measurement times
- Lower throughput
- Higher operating costs
- Higher service costs

# SA-9600 Surface Area Analyzer

- 0.1 - >2000 $m^2/g$
- Single or multi-point analysis
- One or three station systems
- Single point: up to 30 analyses per hour
- High value route to quick and easy surface area analysis

# The Wide World of Particle Sizing

What are possible techniques?

# Possible Criteria Affecting Selection

- Type of data desired
- Sample particle size range
- Sample concentration
- Sample behavior
- Sample type
- Industry acceptability

# Type of Data Desired

- Particle size (average)
- Particle Size distribution ($D_{10}$, $D_{50}$, $D_{90}$)
- Particle zeta potential
- Particle shape
- Surface area

# Sample Type

- Dry powder, suspension, emulsion, aerosol
- Size range, upper & lower limit
- Sample chemistry
- Particle shape
- Previous analysis technique
  - Data matching?
  - Is it a good fit?

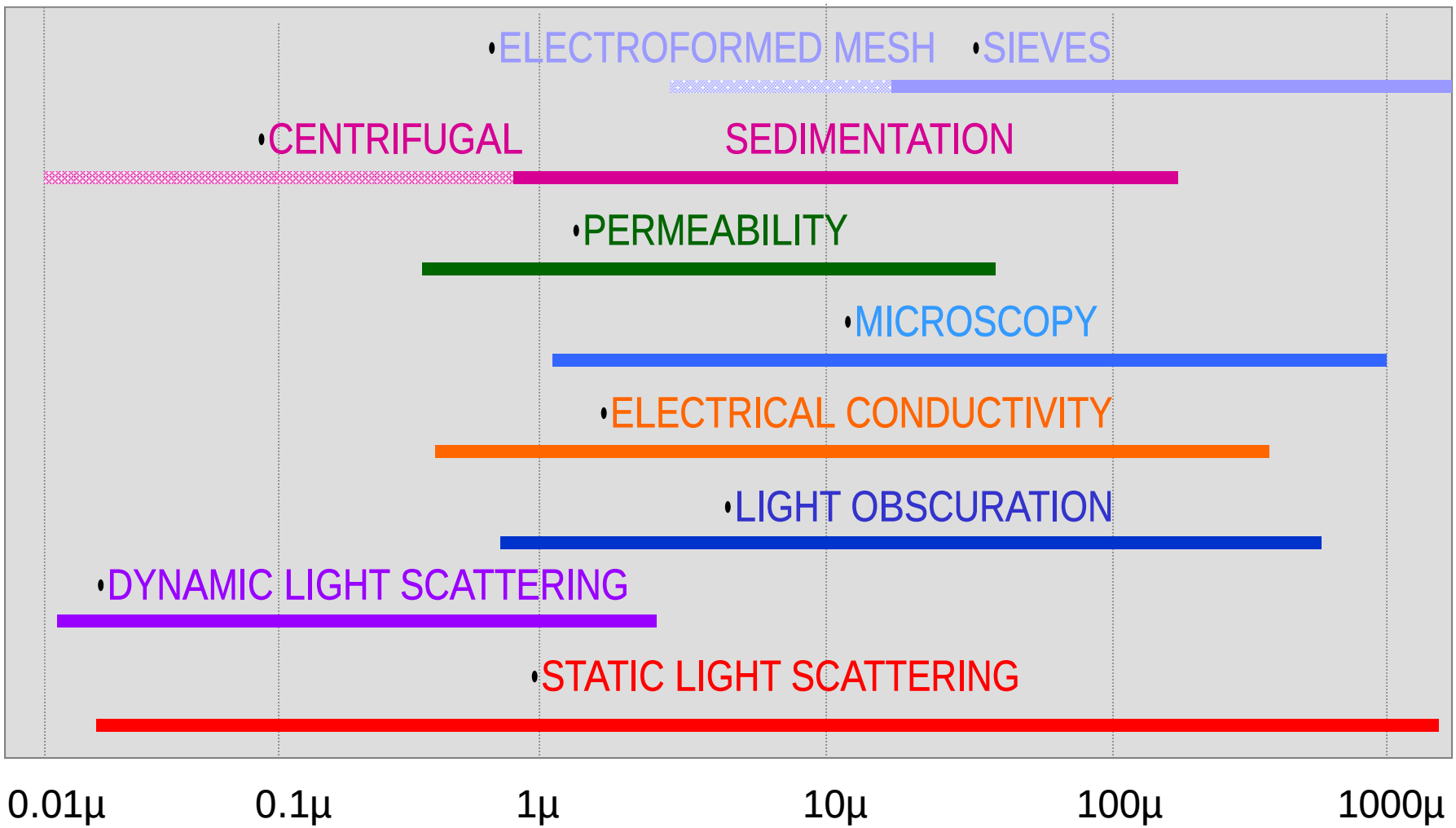
# Sample Behavior

- Is the typical sample stable?
- Is the sample stable at elevated or reduced temperatures?
- Can the sample be diluted without changing the particle size?
- Is the sample stable following dilution?
- Does the sample adhere to glass, plastic, metal, etc.?

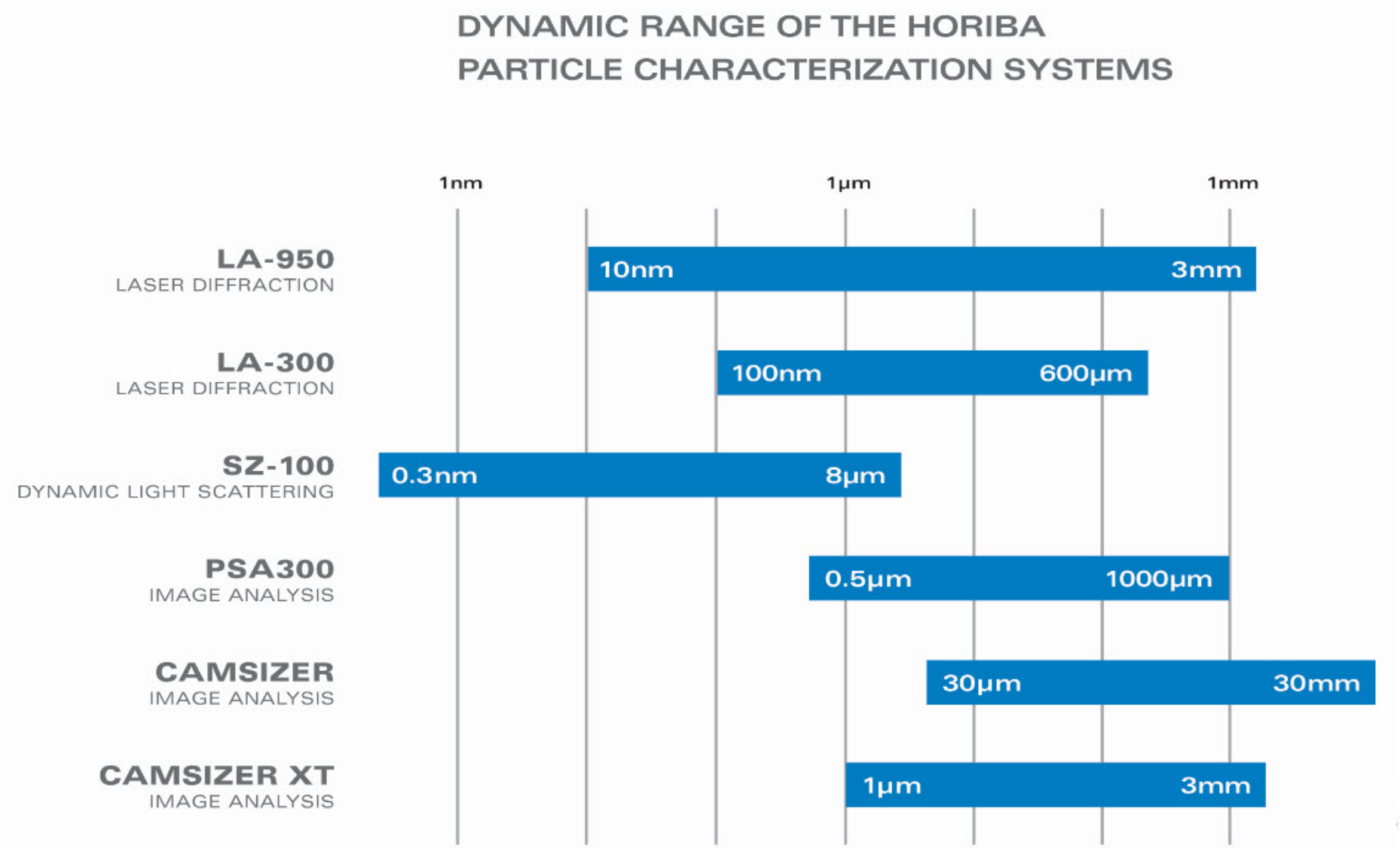
# Industry Acceptability

- Is there an ASTM or ISO Standard already in place?
- Is there a trade association standard?
  - USP/EP/JP, API, AASHTO, etc.
- Is there a supplier or end-user specification?
- Does it meet company standards?
- Is the technique consistent with a QA procedure development

# Size Range by Technique



# Size Range by HORIBA Technique



# From PQRI Group*

**Table 1.** Nominal Particle-Size Ranges Measured by Laboratory Sizing Methods

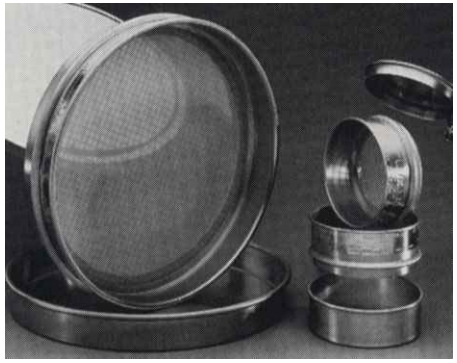
| Technology | Optimal Particle Shape | Size Range (μm) | | Distribution | | Sample | |
|---|---|---|---|---|---|---|---|
| | | Min | Max | Width | Modality | Dispersion | Concentration |
| Acoustic spectroscopy | ○ ▢ | 0.01 | 10 | | | Wet | High |
| Chord-length measurement | ○ ▢ | 1 | 10000 | | | Wet | Low high |
| Disc centrifuge | ○ ▢ ▭ ▱ | 0.005 | 100 | | | Wet | Low |
| Dynamic image analysis | ○ ▢ ▭ | 0.05 | 3500 | | | Wet & dry | Low |
| Elliptically polarized light scattering | ○ ▢ ▭ | 0.05 | 10 | | | Wet | Low |
| Electrical sensing zone | ○ ▢ ▭ ▱ | 0.4 | 1600 | | | Wet | Low |
| Hydrodynamic chromatography | ○ ▢ ▭ ▱ ∿ | 0.01 | 50 | | | Wet | Low |
| Laser diffraction | ○ ▢ | 0.01 | >5000 | | | Wet & dry | Low |
| Light obscuration | ○ ▢ | 0.5 | 5000 | | | Wet | Low |
| Photon correlation spectroscopy | ○ ▢ ▭ ▱ | 0.003 | 3 | | | Wet | Low |
| Polarization intensity differential scattering | ○ ▢ | 0.04 | 0.4 | | | Wet | Low |
| Sieve analysis | ○ ▢ | 5 | 10000 | | | Wet & dry | High |
| Scanning electron microscopy | ○ ▢ ▭ ▱ ∿ | 0.001 | 5 | | | Wet & dry | Low |
| Static image analysis (optical microscopy) | ○ ▢ ▭ ▱ ∿ | 1 | 10000 | | | Wet & dry | Low |
| Time of flight | ○ ▢ ▭ ▱ | 0.3 | 500 | | | Wet & dry | Low |

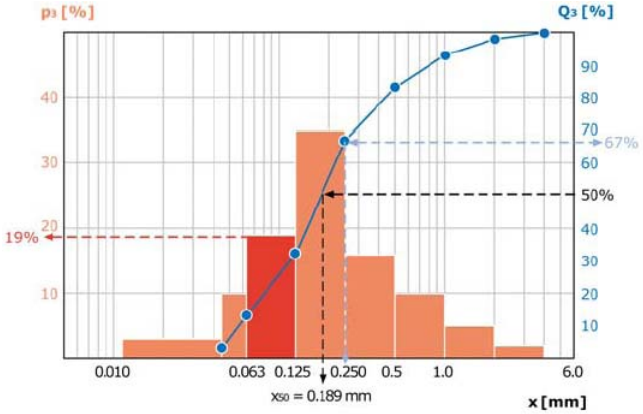
○, spherical; ▢, blocky; ▭, acicular; ▱, platy, tabular, bladed; ∿, fibrous.

*PQRI Recommendations on Particle-Size Analysis of Drug Substances Used in Oral Dosage Forms
JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 96, NO. 6, JUNE 2007

# Sieves

- Weight % sample caught on known screen sizes
- Solid particles 20 μm – 125 mm
- Low equipment cost
- Direct measurement method
- Some automation/calculation available






| Size class [mm] | | | $p_3$ [%] | $Q_3$ [%] |
|---|---|---|---|---|
| | < | 0.045 | 3.0 | 3.0 |
| 0.045 | - | 0.063 | 10.0 | 13.0 |
| **0.063** | **-** | **0.125** | **19.0** | **32.0** |
| 0.125 | - | 0.250 | 35.0 | 67.0 |
| 0.250 | - | 0.500 | 16.0 | 83.0 |
| 0.500 | - | 1.000 | 10.0 | 93.0 |
| 1.000 | - | 2.000 | 5.0 | 98.0 |
| 2.000 | - | 4.000 | 2.0 | 100.0 |
| > 4.000 | | | 0.0 | 100.0 |

$x_{50}$ = 0.189 mm

More information available through www.retsch.com

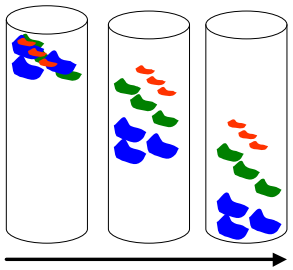
# Sedimentation

## Stokes Law

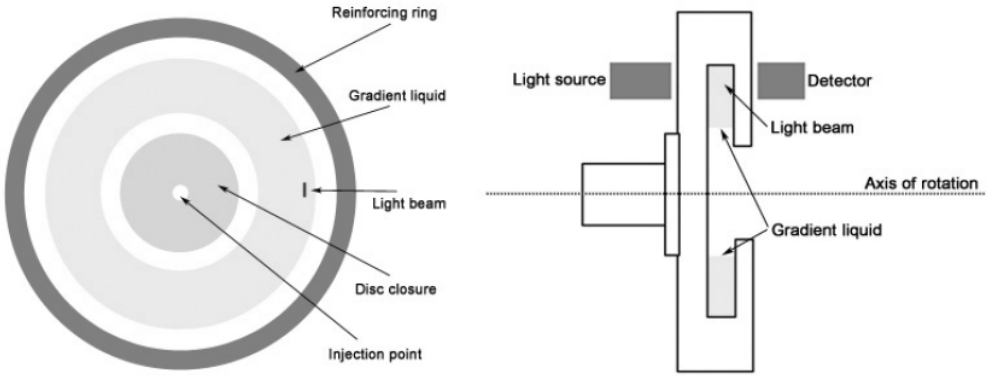
$$D = \sqrt{\frac{18\,\mu\,V_p}{(A - B)\,G}}$$

Vp = Settling velocity of discrete particle
G = Gravity constant
A = Density of Particle
B = Density of Carrier Fluid
D = Diameter of discrete particle
μ = Viscosity of Carrier Fluid

Sedimentation of same density material in a viscous medium



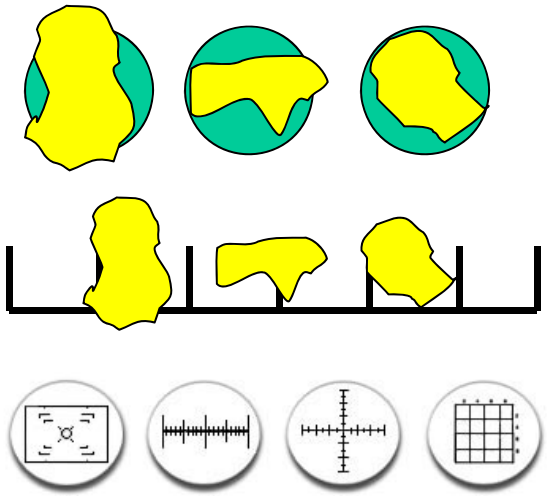
Time




Disc centrifuge

# Manual Microscopy

- Inspect particles in a given field of view
- Repeat process for a number of fields
- Use graticule to obtain size
- Get size, shape sometimes count information
- Referee technique: direct



**Advantages**

- Simple
- Inexpensive
- Can see shape

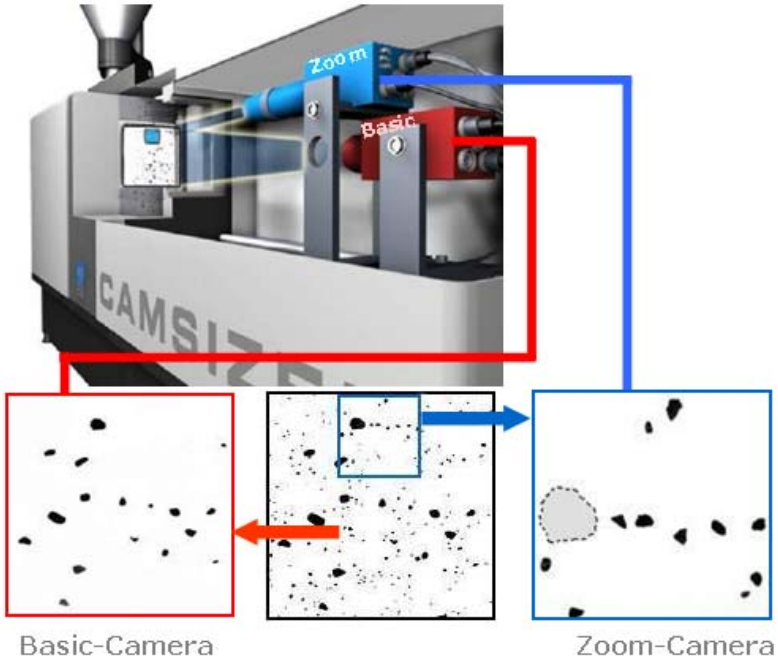
**Disadvantages**

- Slow
- Measures very few particles
- Very tedious

# Need Shape Information?

Dynamic:
particles flow past camera

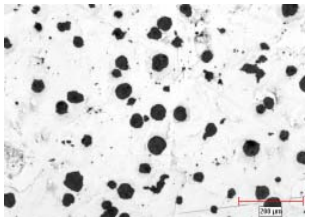
Static:
particles fixed on slide,
stage moves slide




# Basic Operations

Objective & camera

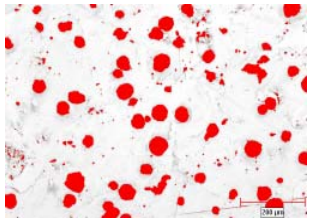
**Image Acquisition and enhancement**



**Focus, take picture**

Subjective or automatic

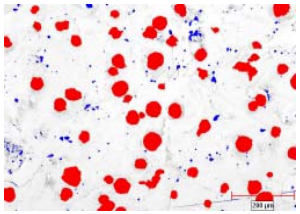
**Thresholding**



**Separate particles from background**

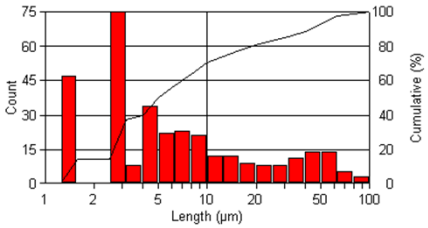
Decisions or black box

**Image Processing**



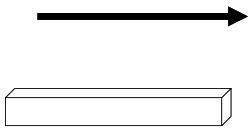
**Edge definition, fill particles, Separate touching particles**

**Measurements**




**Create size & shape distributions**

# Static Image Analysis: PSA300




Sample preparation device necessary* to disperse powders onto slide(s).
Load powder into nozzle, pull vacuum, release.

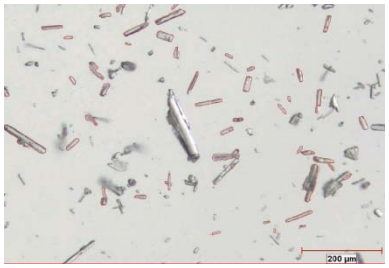
Load slide onto automated stage
Move slide, stop, take image, repeat
Higher magnification = smaller particles

*unless large free flowing powder

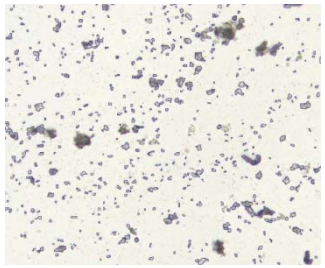
# Static Image Analysis Applications

- Powders, suspensions 0.5 – 1000 µm
- Size and shape information
- Also count when analyzing filters

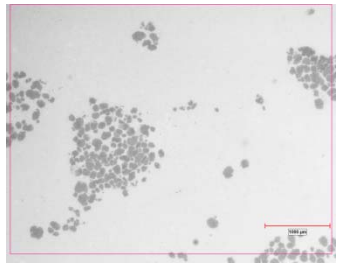
API's



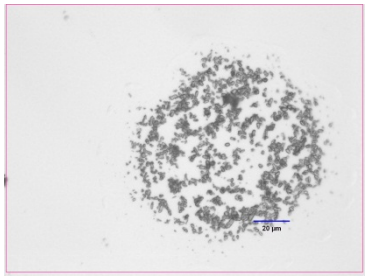
Excipients



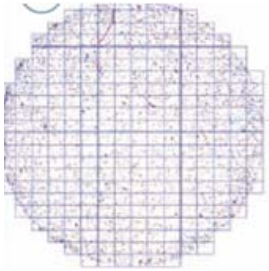
Lotions



Aerosols



Filters



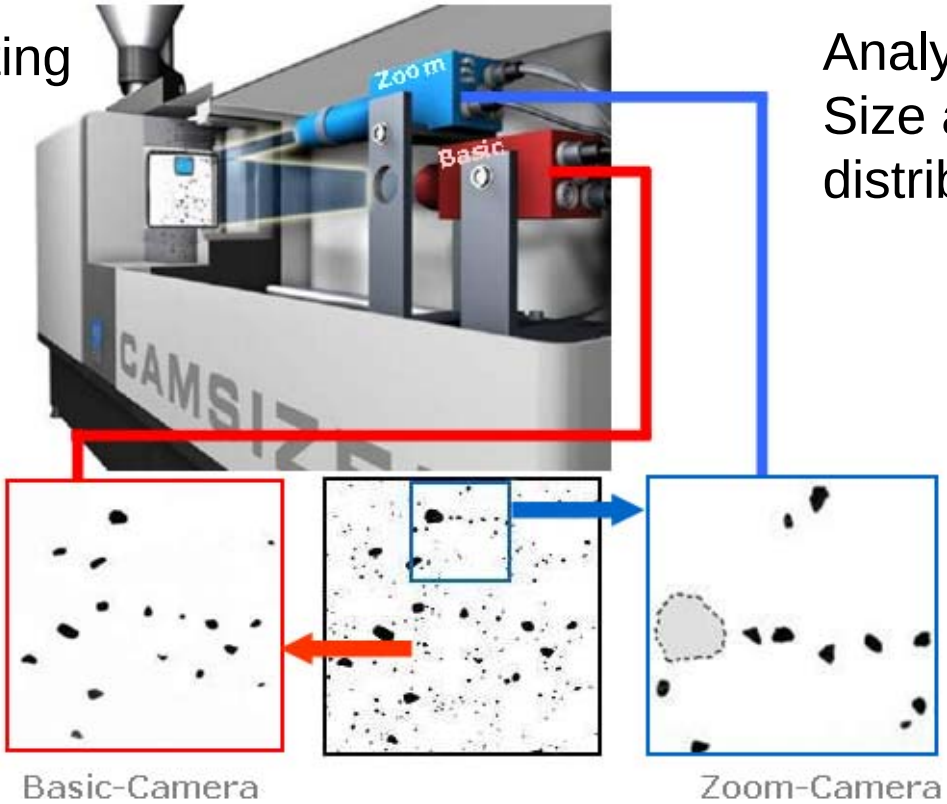
Widely used in pharmaceutical R&D
But also wherever shape info. required

Abrasives

# Dynamic Image Analysis: CAMSIZER

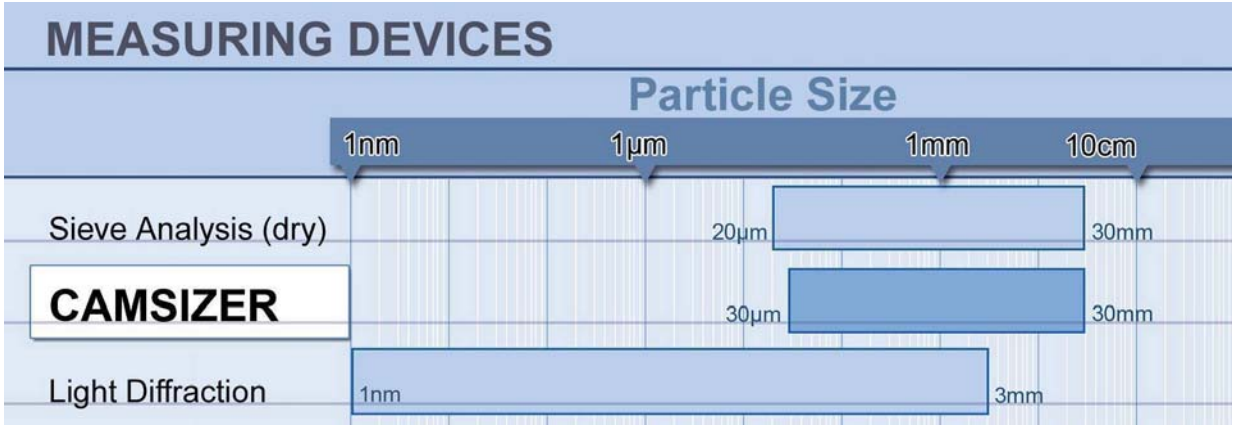
Size and shape from 30 µm – 30 mm

Particles fall from vibrating tray through inspection zone. Two cameras take images of particles

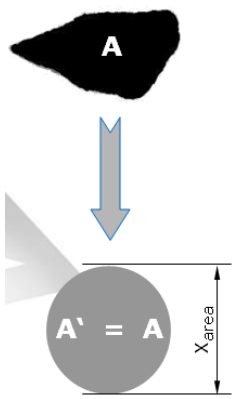


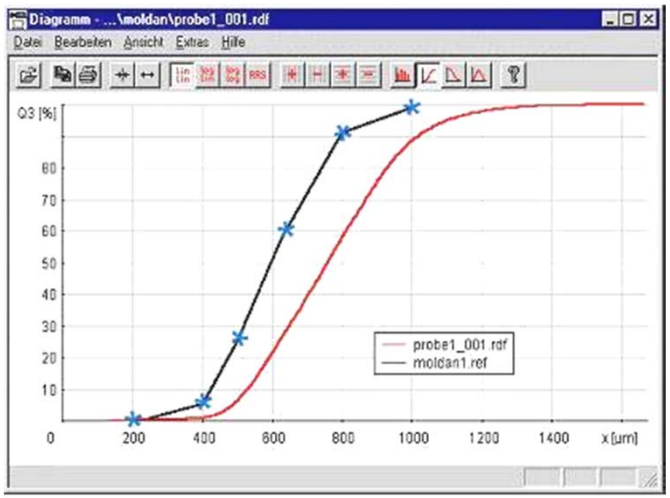

Analyze images
Size and shape distributions

# Replace Sieve Analysis

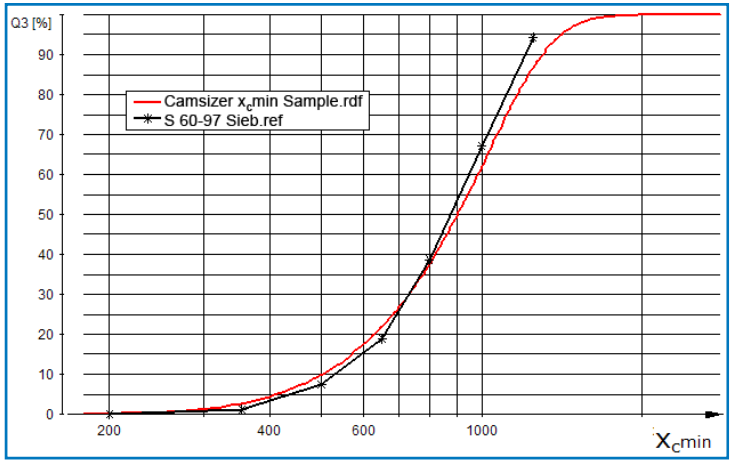



Similar size range, $X_{cmin}$ matches sieve results, quick + shape





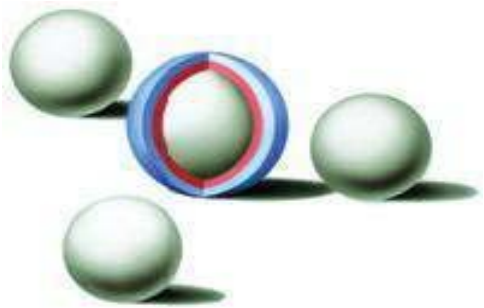


# Dynamic Image Analysis Applications

- Powders 1 µm – 30 mm

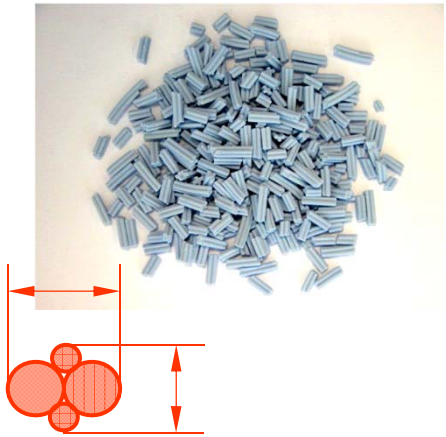
Glass beads

Sugar spheres

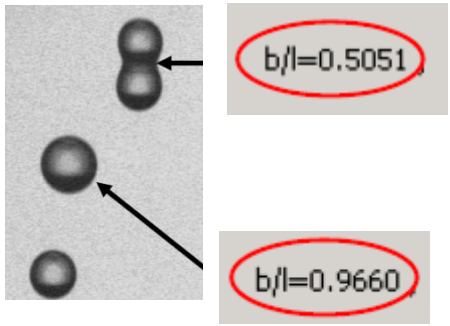


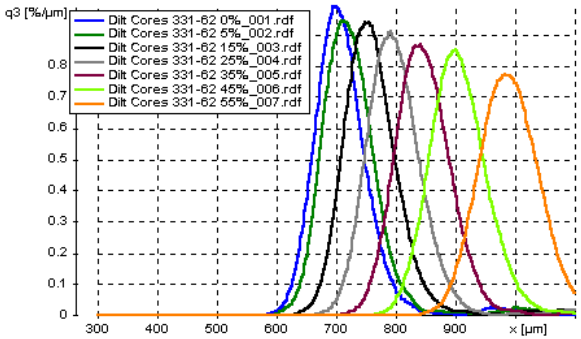
Fertilizers

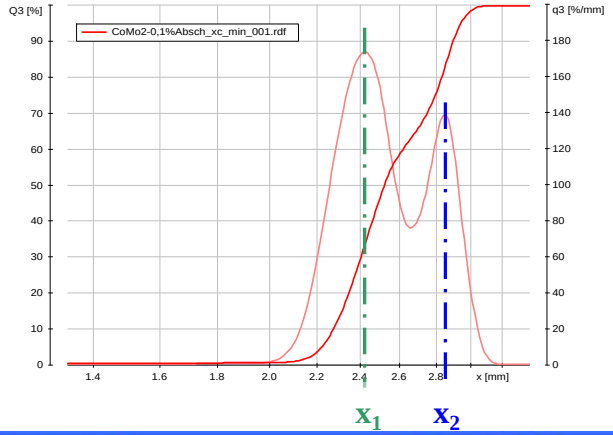
Catalysts



Coating thickness



# Need Wide Dynamic Size Range?

- **Laser Diffraction**
- 10 nanometer – 3 mm
- Suspension, emulsion, powder, paste, gel
- Ultra durable
- Converts light scatter to size distribution
- Low total cost of ownership

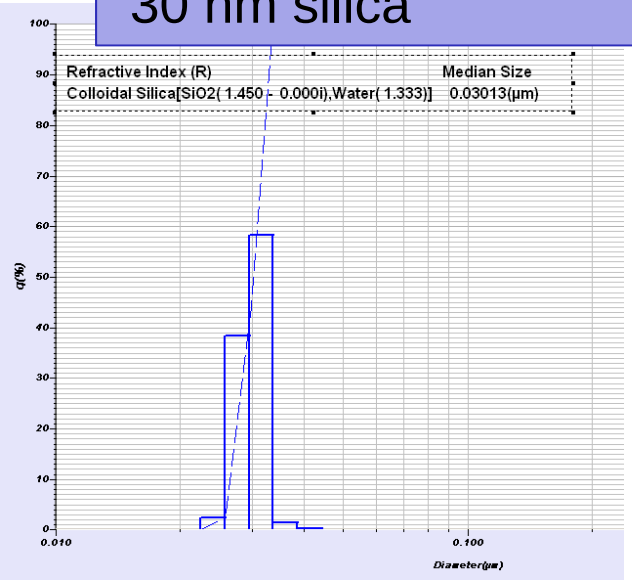
# Small Particle Detection

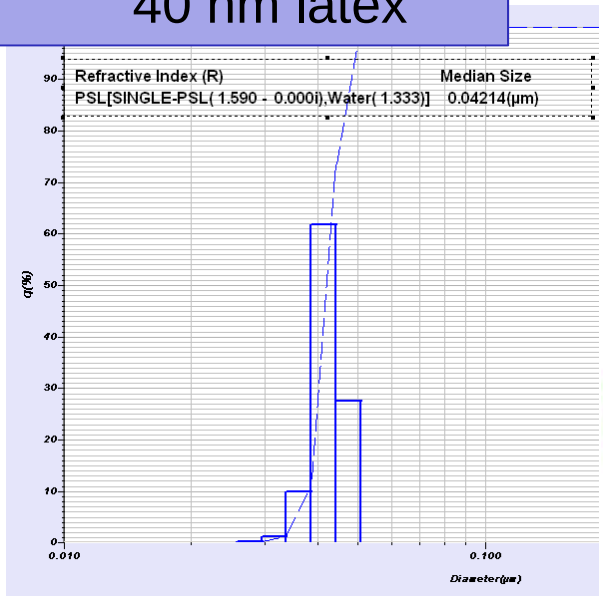
| | | |
|---|---|---|
| S.P.Area | : | 2.0183E+6(cm²/cm³) |
| Mean Size | : | 0.02990(µm) |
| Variance | : | 5.0313E-6(µm²) |
| Median Size | : | 0.03013(µm) |
| Mode Size | : | 0.0302(µm) |
| Skewness | : | -0.2901 |

| | | |
|---|---|---|
| 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 |

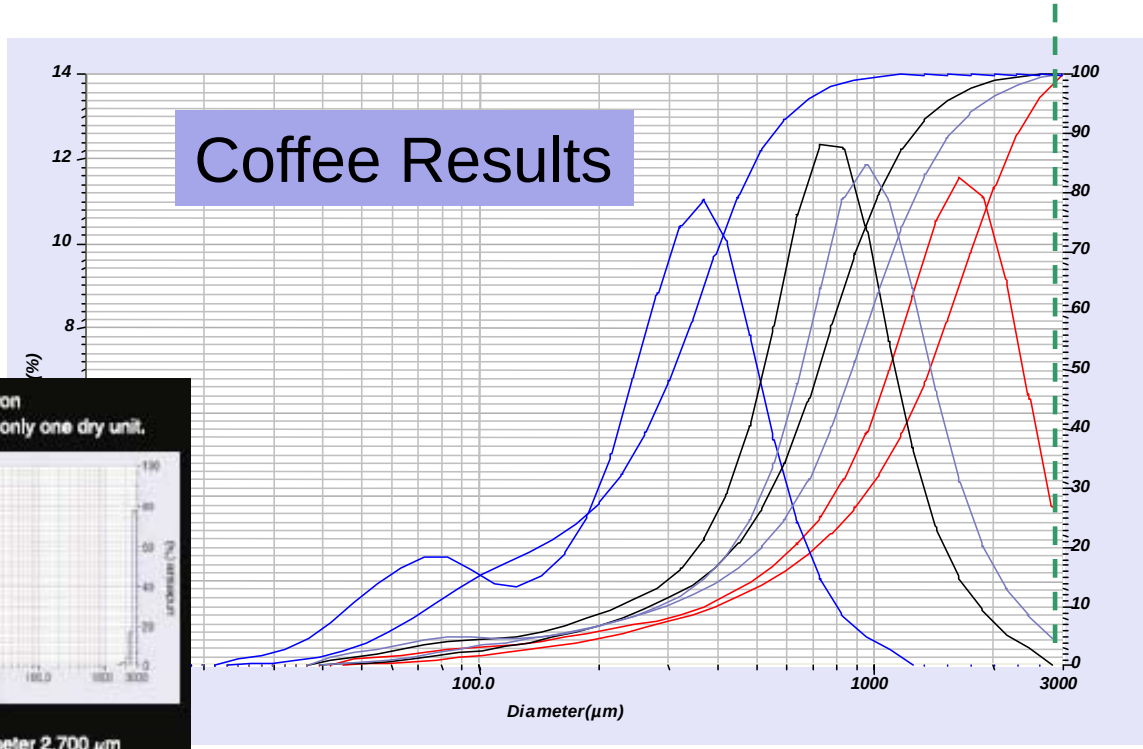
30 nm silica

40 nm latex



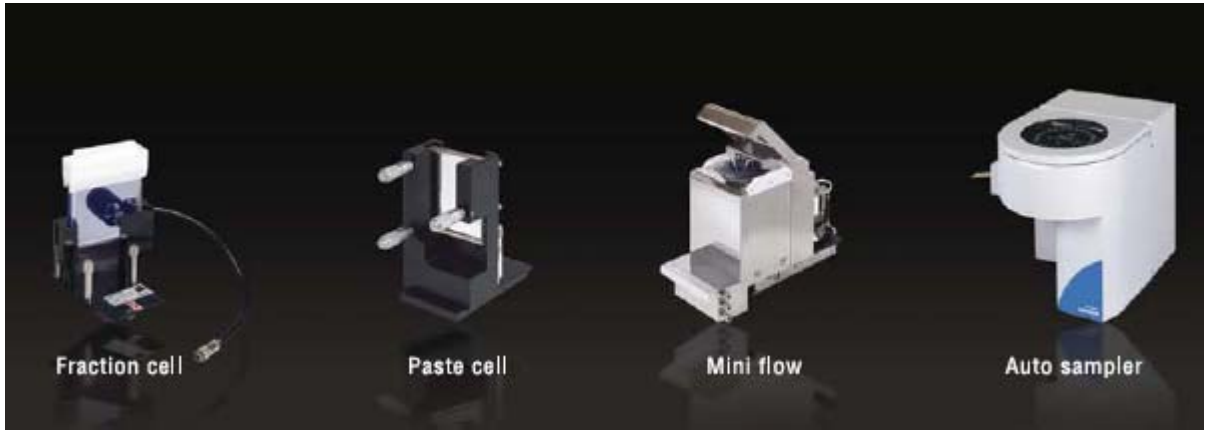




# Large Particle Detection





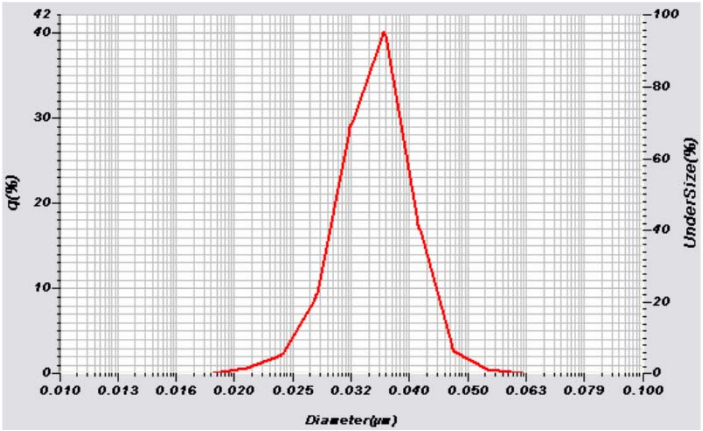
# Smaller Sample Volume



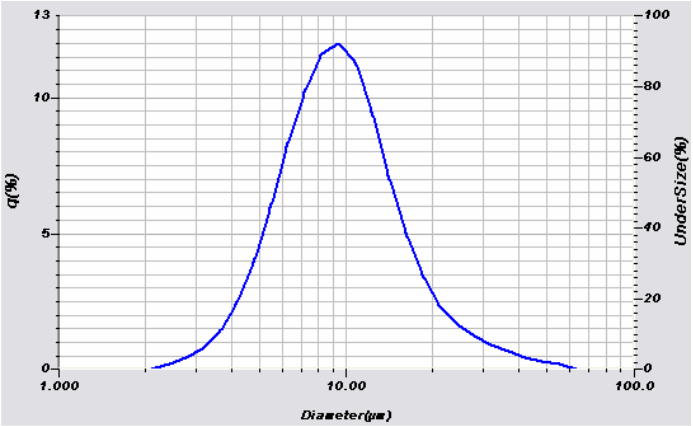

5 ml 35 ml 100 ml

- Wide range of sample cells depending on application
- High sensitivity keeps sample requirements at minimum
- Does the sample need dispersion?

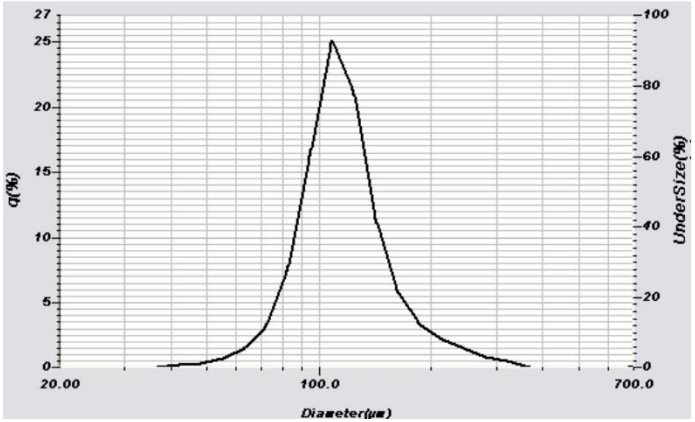
# Small Sample Volume (MiniFlow)




Colloidal Silica (weak scatterer)
Median (D50): **30 nm**
Sample Amount: **132 mg**



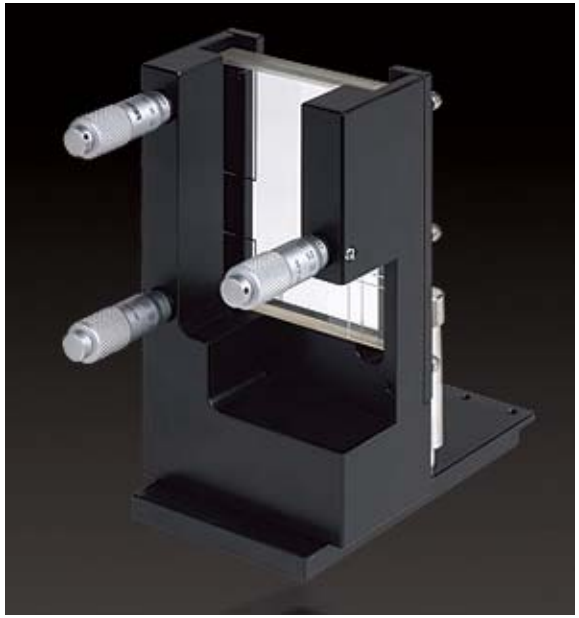

Magnesium Stearate
Median (D50): **9.33 µm**
Sample Amount: **0.165 mg**




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

# Paste Cell

1. Insert spacer between glass pieces and gently press pieces together using micrometers. Record micrometer values.
2. Using syringe, carefully inject Glycerin as the blank solvent between paste cell windows.
3. Depress BLANK to take a background reading of the dispersant.
4. Clean the paste cell.
5. Carefully place small amount of gel containing sample between paste cell windows.
6. Adjust micrometer values such that the gap between the paste cell windows amounts to 0.35 mm.
7. Take 3 consecutive measurements.
8. Repeat 1-7 for second sample.



| File name | D(v,0.1) | D(v,0.5) | D(v,0.9) |
|---|---|---|---|
| | 5.882 | 7.333 | 9.161 |
| | 5.879 | 7.33 | 9.163 |
| | 6.216 | 7.48 | 9.237 |
| | | | |
| Average | 5.992 | 7.381 | 9.187 |
| Std. Dev. | 0.194 | 0.086 | 0.043 |
| CV (%) | 3.233 | 1.162 | 0.471 |

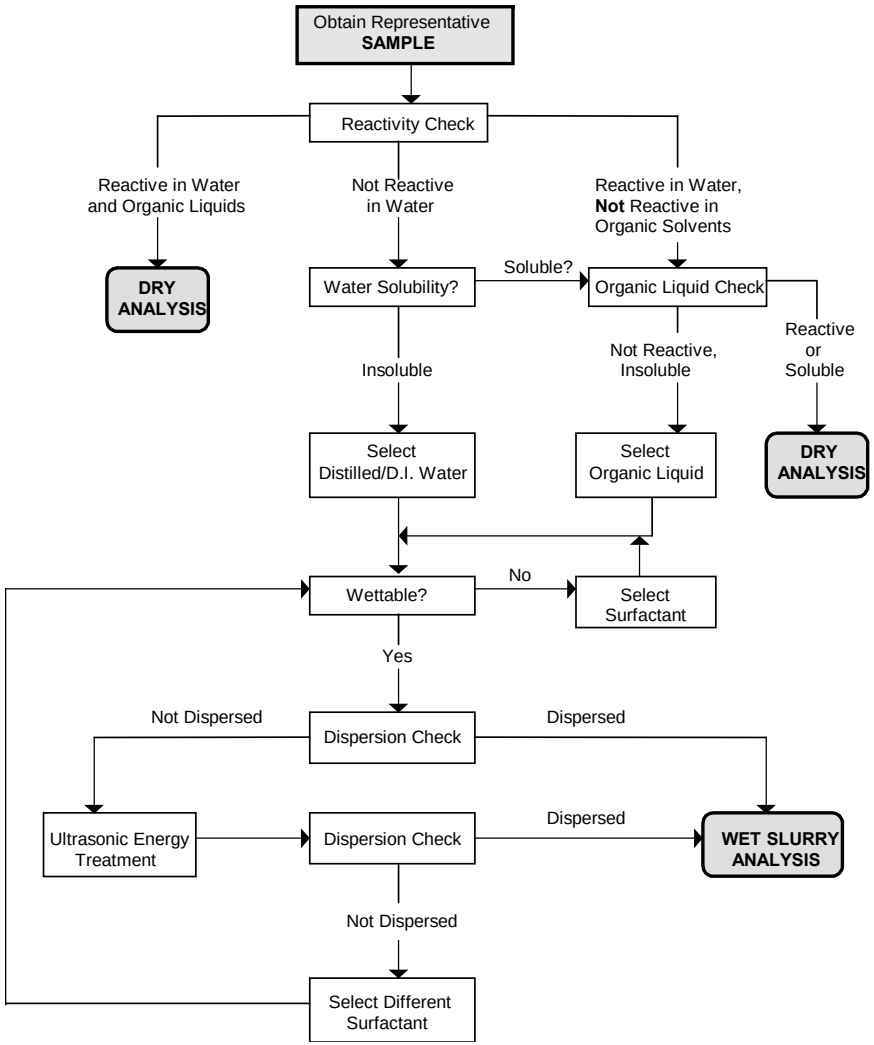
Unique to HORIBA

# Dry Powders

- Measure as dry powder using dry powder feeder
  - Measure in natural state
  - Quick, easy, no clean up
  - Solves solubility problems
  - Increase air pressure to aid dispersion
  - Minimum size 100 nm
- Disperse powder in liquid
  - Liquids reduce surface tension, add surfactant, use U.S. to aid dispersion
  - Lower detection limit (< 30 nm)

# Powder: Wet vs. Dry?

POWDER DISPERSION PROCEDURES




# HORIBA Diffraction Systems

- LA-950: 10 nm – 3,000 µm wet or dry
  - Modular, range of samplers, advanced software including Method Expert

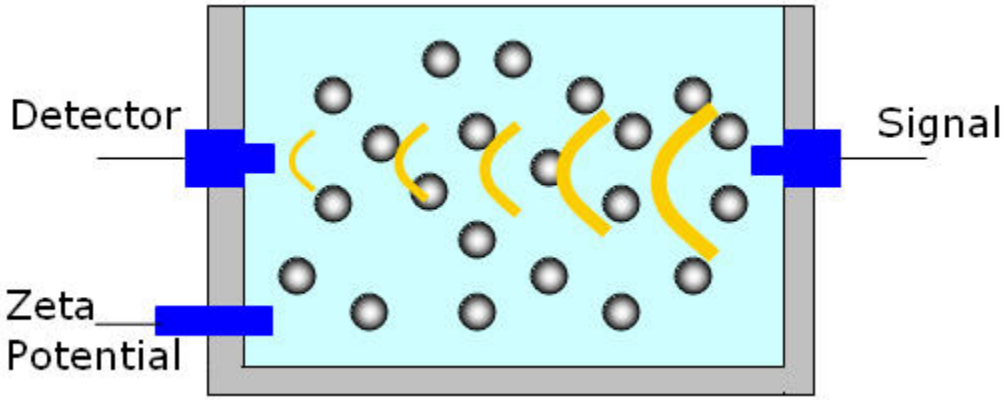

- LA-300: 100 nm – 600 µm wet only
  - Smaller, portable, less expensive


# Measuring at Process Concentration

- Light scattering typically requires dilution
- Does PSD change with dilution?
- Concern when studying dispersion
- Some samples are better analyzed without any alteration
- Implies no sample preparation
- Dispersion stability studies often include zeta potential and other parameters
  - Size, zeta potential, pH, conductivity, temp, surfactant concentration, titration studies

# Acoustic Spectroscopy

- Pulsed electric field applied to sample
- Sound interacts with sample
- Attenuation converted to size




## Advantages

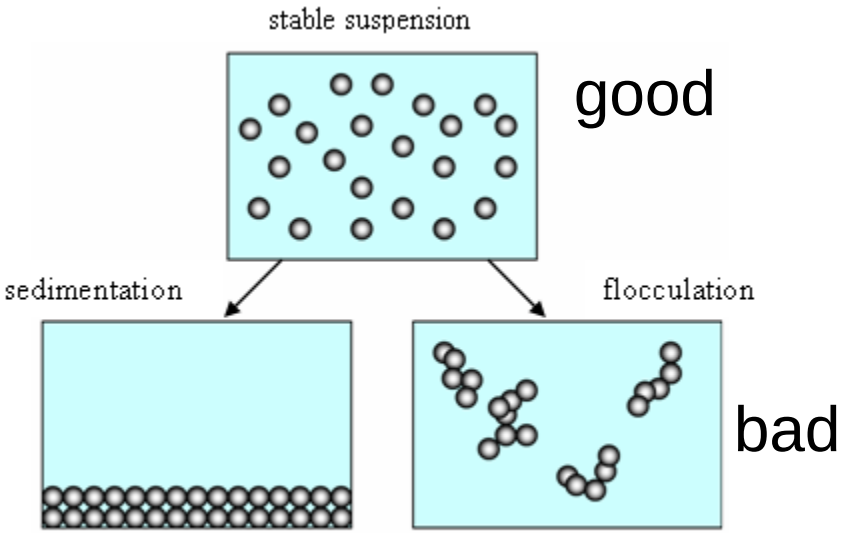
- Can accommodate high sample concentrations
- Also zeta potential, pH, conductivity, conc.

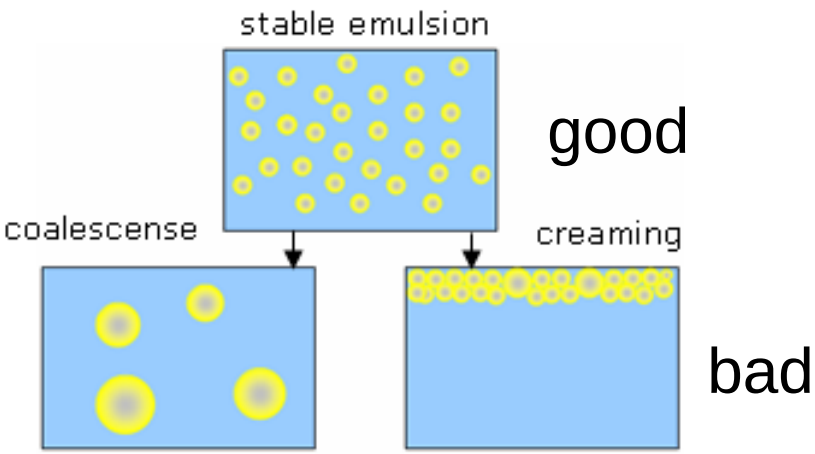
## Applications

- Emulsions & suspensions
- Dispersion stability with zeta potential

# Dispersion Stability

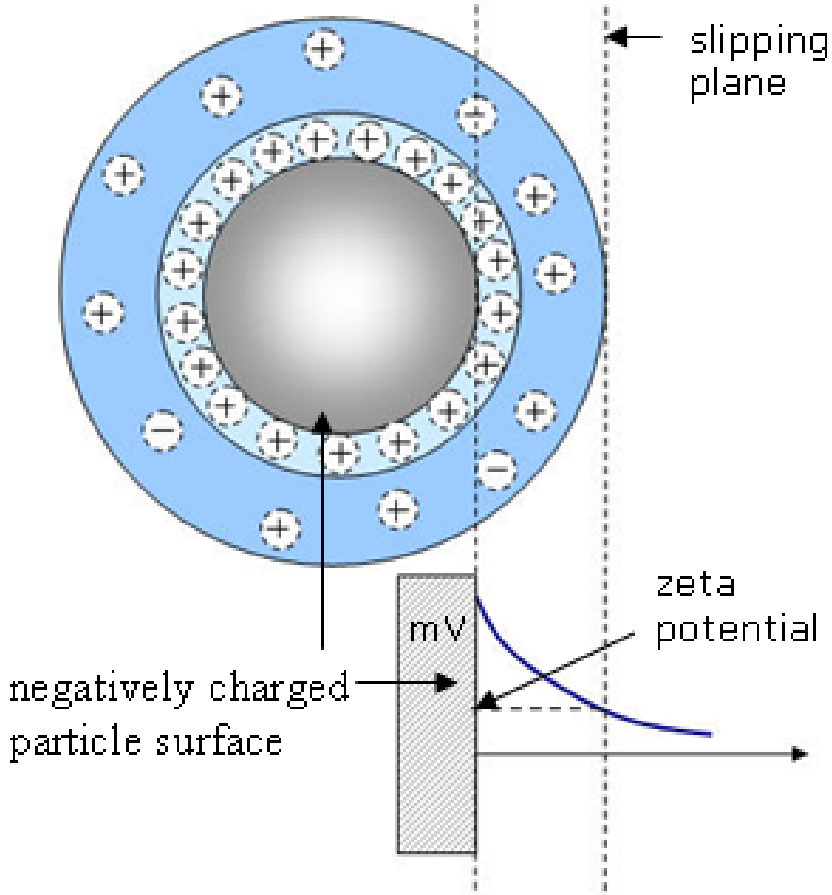
- Want stable dispersion
- Either suspensions or emulsions
- Suspensions sediment & flocculate
- Emulsions phase separate, creaming or coalescence



# Zeta Potential

- If surface has + charge, then - ions attracted to surface
- + ions attracted to – ions, builds electric double layer
- Slipping plane: distance from particle surface where ions move with particle
- ZP = potential (mV) at slipping plane



# SZ-100: Nanoparticle Analyzer

- Size: .3 nm - 8 µm
  - 90° and 173°
- Zeta potential: -200 - +200 mV
  - Patented carbon electrodes
- Molecular weight: $1x10^3$ - $2x10^7$ g/mol
- Optional titrator

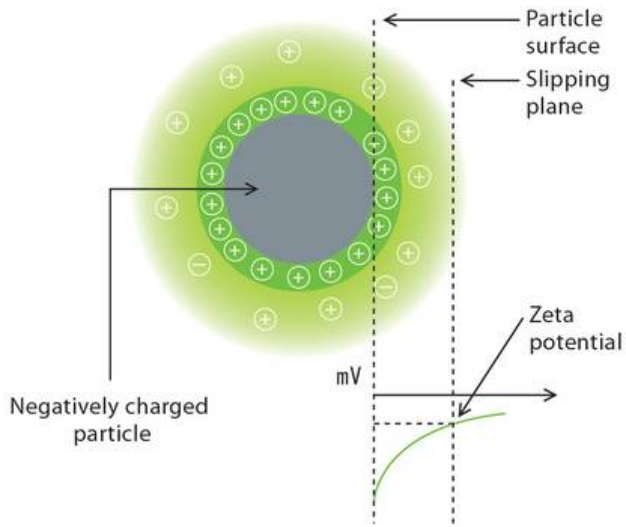
•Nanoparticles
•Colloids
•Proteins
•Emulsions
•Disperison stability

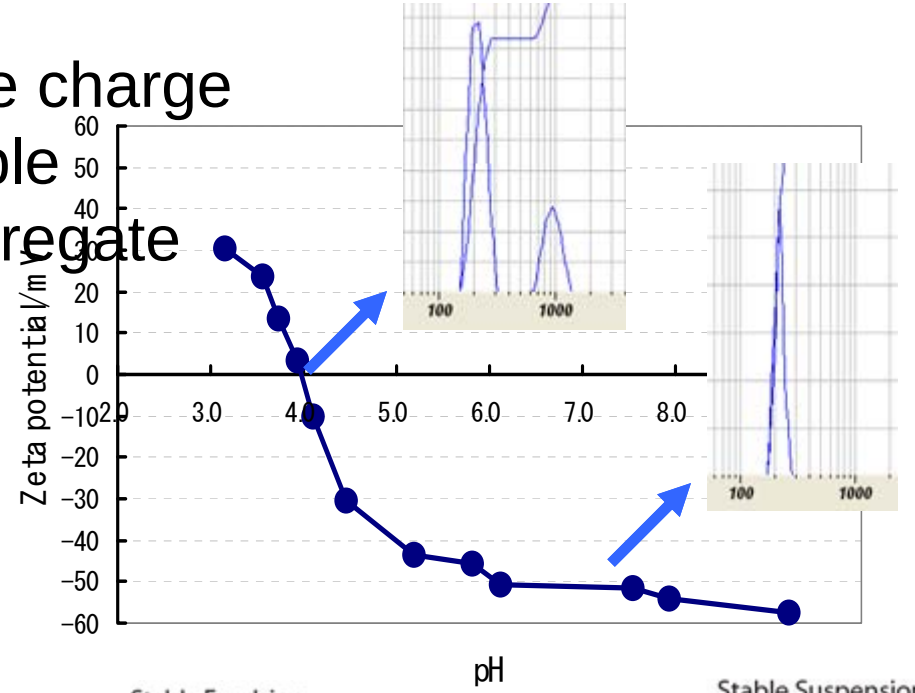
# What is Dynamic Light Scattering?

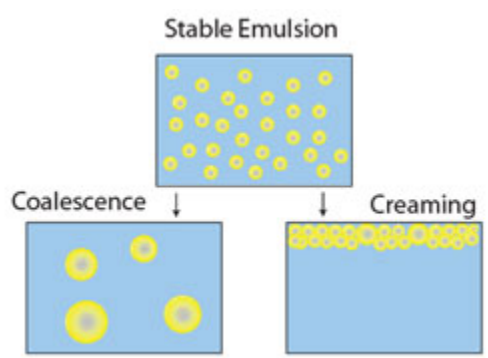
- Dynamic light scattering refers to measurement and interpretation of light scattering data on a microsecond time scale.
- Dynamic light scattering can be used to determine
  - Particle/molecular size
  - Size distribution
  - Relaxations in complex fluids

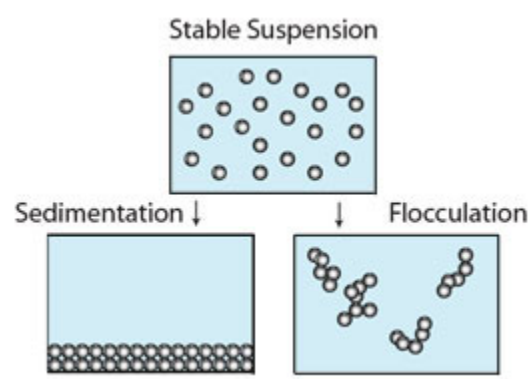
# Zeta Potential: Dispersion Stability, IEP

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



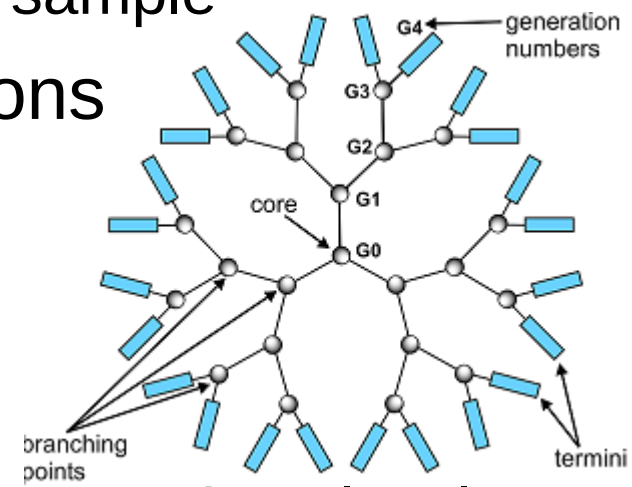



# Why DLS?

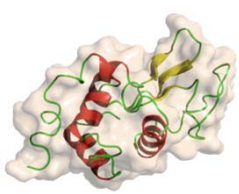
- Non-invasive measurement
- Requires only small quantities of sample
- Good for detecting trace amounts of aggregate
- Good technique for macro-molecular sizing

# DLS Applications

- Particle size of suspension 1 nm – 1 μm
  - Both ends extended depending on sample
- Zeta potential of dilute suspensions
  - Only suspensions, small particles
- Molecular weight, second virial coefficient




Proteins



| | Results |
|---|---|
| Mean Dia. (nm) | 4.5 |

Nanoparticles

| 8011 HORIBA | Z ave | PDI |
|---|---|---|
| Sample 1 | 9.63 nm | 0.079 |
| Sample 2 | 10.51 nm | 0.19 |

Biomolecules

| | Z ave. (nm) |
|---|---|
| DNT-107 | 7.6 |
| DNT-189 | 8.6 |

# What we'll talk about

- A Structured Approach
- Technique Overviews
- Quick Selection Charts
- Q&A

# Quick Selection Chart

- Need size distribution?
  - Laser diffraction
  - Dynamic light scattering
  - Image analysis
  - Acoustic spectroscopy
  - Light obscuration
  - Nanoparticle tracking analysis
  - Centrifugal sedimentation
  - Scanning mobility
  - Ultra microscopy (statistics…)

# Quick Selection Chart

- Particles greater than 1 micron?
  - Laser diffraction
  - Image analysis
  - Acoustic spectroscopy
  - Light obscuration
  - Centrifugal sedimentation (sample…)

# Quick Selection Chart

- Particles less than 1 micron?
  - Dynamic light scattering
  - Laser diffraction (down to 30 nm)
  - Acoustic spectroscopy
  - Nanoparticle tracking analysis
  - Scanning mobility
  - Ultra microscopy

# Quick Selection Chart

- Particles greater than 1 micron <u>and</u> less than 100 nanometers?
  - Laser diffraction
  - Acoustic spectroscopy
  - Centrifugal sedimentation

- Otherwise you need multiple techniques

# Quick Selection Chart

- Need particle count/number basis?
  - Image analysis (direct)
  - Light obscuration (direct)
  - Electrical sensing zone (direct)
  - Nanoparticle tracking analysis
- Need concentration (particles/mL)?
  - Light obscuration
  - Electrical sensing zone
  - Nanoparticle tracking analysis

# Quick Selection Chart

- Need particle shape (or a leg up)?
  - Image analysis (direct)
  - Ultra microscopy
- Need surface area?
  - Flowing gas (direct)
  - Static volumetric (direct)
  - Laser diffraction (indirect, rough)

# Quick Selection Chart

- Low concentration (read a newspaper)?
  - Dynamic light scattering
  - Light obscuration
  - Electrical sensing zone
  - Nanoparticle tracking analysis
  - Laser diffraction (sample dependent)
- Can’t dilute?
  - Acoustic spectroscopy
  - Dynamic light scattering (sample…)
  - NEVER counting

# Quick Selection Chart

- Need to measure stability?
  - Electrophoretic light scattering (indirect)
    - Usually part of a DLS instrument
  - Nanoparticle tracking analysis (indirect)
  - Electroacoustic spectroscopy (indirect)
  - Multiple scattering (direct)
- Aerosols?
  - Laser diffraction (specialized)
  - Scanning mobility
  - Time of flight

# Quick Selection Chart

- Need to measure powder directly?
  - Laser diffraction
  - Image analysis
  - Ultra microscopy

# Conclusions

- Talk to application experts
  - Manufacturer or colleague
  - Have samples run on system of interest
    - Most vendors do this free of charge
  - It's rare for one application to be equally suited to more than one instrument
- Rank most important factors for you
- Only one technology? **Laser Diffraction**
  - Most flexible, quick & easy, widely accepted

# Value of Multiple Techniques

- Good idea to have several techniques
- If > 1 µm use microscope for reference
- Sieves useful to confirm presence of large particles or to remove particles too large for another technique
- Beware: Use a different technique = get a different answer
- It is important to understand how analysis methods differ in order to know how to compare data

# IRMM Nanoparticle Review

- Joint Research Centre (part of the European Commission)
  - Institute for Reference Materials and Measurements released review of nanoparticle characterization options
  - http://publications.jrc.ec.europa.eu/repository/handle/111111111/26399
- Download directly or e-mail HORIBA

HORIBA

# Thank you

ありがとうございました

ขอบคุณครับ

谢谢

اشكُر

Gracias

Grazie

Σας ευχαριστούμε

धन्यवाद

Tacka dig

Danke

Merci

நன்றி

Obrigado

감사합니다

Большое спасибо

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