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?
Is it a material characterization issue?

Is it a particle characterization issue?

Yes

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

Which technique is most appropriate?

Particle size distribution is most common problem/interest

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

- 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

- 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

<table>
<thead>
<tr>
<th>Dynamic (Flowing-Gas)</th>
<th>Static (Volumetric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faster</td>
<td>Slower</td>
</tr>
<tr>
<td>Easy to use</td>
<td>Easy to use</td>
</tr>
<tr>
<td>Increased sensitivity to low SSA materials</td>
<td>Low SSA longer measurement times</td>
</tr>
<tr>
<td>Higher throughput</td>
<td>Lower throughput</td>
</tr>
<tr>
<td>Lower operating costs</td>
<td>Higher operating costs</td>
</tr>
<tr>
<td>Lower service costs</td>
<td>Higher service costs</td>
</tr>
</tbody>
</table>

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SA-9600 Surface Area Analyzer

- 0.1 - >2000 m²/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 HORIBA Technique

DYNAMIC RANGE OF THE HORIBA PARTICLE CHARACTERIZATION SYSTEMS

LA-950
LASER DIFFRACTION

LA-300
LASER DIFFRACTION

SZ-100
DYNAMIC LIGHT SCATTERING

PSA300
IMAGE ANALYSIS

CAMSIZER
IMAGE ANALYSIS

CAMSIZER XT
IMAGE ANALYSIS

1nm

1μm

1mm

10nm

100nm

0.3nm

0.5μm

30μm

1μm

8μm

30μm

1000μm

3mm

600μm

30mm

3mm
From PQRI Group*

<table>
<thead>
<tr>
<th>Technology</th>
<th>Optimal Particle Shape</th>
<th>Size Range (µm)</th>
<th>Distribution</th>
<th>Sample</th>
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<tbody>
<tr>
<td>Acoustic spectroscopy</td>
<td>○</td>
<td>0.01-10</td>
<td></td>
<td>Wet</td>
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<tr>
<td>Chord-length measurement</td>
<td>○</td>
<td>1-10000</td>
<td></td>
<td>Wet</td>
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<tr>
<td>Disc centrifuge</td>
<td>○</td>
<td>0.005-100</td>
<td></td>
<td>Wet</td>
</tr>
<tr>
<td>Dynamic image analysis</td>
<td>○</td>
<td>0.05-3500</td>
<td></td>
<td>Wet &amp; dry</td>
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<tr>
<td>Elliptically polarized light scattering</td>
<td>○</td>
<td>0.05-10</td>
<td></td>
<td>Wet</td>
</tr>
<tr>
<td>Electrical sensing zone</td>
<td>○</td>
<td>0.4-1600</td>
<td></td>
<td>Wet</td>
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<tr>
<td>Hydrodynamic chromatography</td>
<td>○</td>
<td>0.01-50</td>
<td></td>
<td>Wet</td>
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<tr>
<td>Laser diffraction</td>
<td>○</td>
<td>0.01&gt;5000</td>
<td></td>
<td>Wet &amp; dry</td>
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<tr>
<td>Light obscuration</td>
<td>○</td>
<td>0.5-5000</td>
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<td>Wet</td>
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<td>Photon correlation spectroscopy</td>
<td>○</td>
<td>0.003-3</td>
<td></td>
<td>Wet</td>
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<tr>
<td>Polarization intensity differential scattering</td>
<td>○</td>
<td>0.04-0.4</td>
<td></td>
<td>Wet</td>
</tr>
<tr>
<td>Sieve analysis</td>
<td>○</td>
<td>5-10000</td>
<td></td>
<td>Wet &amp; dry</td>
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<tr>
<td>Scanning electron microscopy</td>
<td>○</td>
<td>0.001-5</td>
<td></td>
<td>Wet &amp; dry</td>
</tr>
<tr>
<td>Static image analysis (optical microscopy)</td>
<td>○</td>
<td>1-10000</td>
<td></td>
<td>Wet &amp; dry</td>
</tr>
<tr>
<td>Time of flight</td>
<td>○</td>
<td>0.3-500</td>
<td></td>
<td>Wet &amp; dry</td>
</tr>
</tbody>
</table>

○, 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

More information available through www.retsch.com
Sedimentation

- **Stokes Law**

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

- **Symbols and Definitions**
  - \(D\): Diameter of discrete particle
  - \(\mu\): Viscosity of Carrier Fluid
  - \(V_p\): Settling velocity of discrete particle
  - \(G\): Gravity constant
  - \(A\): Density of Particle
  - \(B\): Density of Carrier Fluid

Sedimentation of same density material in a viscous medium

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

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

API’s   Excipients   Lotions   Aerosols   Filters

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

Basic-Camera
Zoom-Camera
Replace Sieve Analysis

**MEASURING DEVICES**

<table>
<thead>
<tr>
<th>Particle Size</th>
<th>1nm</th>
<th>1μm</th>
<th>1mm</th>
<th>10cm</th>
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</thead>
<tbody>
<tr>
<td>Sieve Analysis (dry)</td>
<td></td>
<td>20μm</td>
<td>30mm</td>
<td></td>
</tr>
<tr>
<td>CAMSIZER</td>
<td></td>
<td>30μm</td>
<td>30mm</td>
<td></td>
</tr>
<tr>
<td>Light Diffraction</td>
<td>1nm</td>
<td></td>
<td></td>
<td>3mm</td>
</tr>
</tbody>
</table>

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

CoMo2-0,1%Absch_xc_min_001.rdf

\( x \) [mm]

\( Q3 \) [%]

\( q3 \) [%/mm]

Explore the future
Automotive Test Systems | Process & Environmental | Medical | Semiconductor | Scientific

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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

30 nm silica

40 nm latex
Large Particle Detection

Coffee Results

3mm alumina balls and submicron samples can be measured with only one dry unit.

Dry method: Median diameter 2,700 µm
Non-dispersion measurement
Smaller Sample Volume

- 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.

<table>
<thead>
<tr>
<th>File name</th>
<th>D(v,0.1)</th>
<th>D(v,0.5)</th>
<th>D(v,0.9)</th>
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<tbody>
<tr>
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<td>7.333</td>
<td>9.161</td>
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<td>9.163</td>
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<td></td>
<td>6.216</td>
<td>7.48</td>
<td>9.237</td>
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<tr>
<td>Average</td>
<td>5.992</td>
<td>7.381</td>
<td>9.187</td>
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<tr>
<td>Std. Dev.</td>
<td>0.194</td>
<td>0.086</td>
<td>0.043</td>
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<tr>
<td>CV (%)</td>
<td>3.233</td>
<td>1.162</td>
<td>0.471</td>
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</table>
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

Obtain Representative SAMPLE

Reactivity Check
- Reactive in Water and Organic Liquids
  - DRY ANALYSIS
- Not Reactive in Water
  - Water Solubility?
    - Soluble?
      - Organic Liquid Check
        - Reactive or Soluble
          - DRY ANALYSIS
        - Not Reactive, Insoluble
          - Select Organic Liquid
    - Insoluble
      - Select Distilled/D.I. Water
      - Wettable?
        - Yes
          - Dispersion Check
            - Dispersed
              - WET SLURRY ANALYSIS
            - Not Dispersed
              - Select Different Surfactant
        - No
          - Select Surfactant
      - Ultrasonic Energy Treatment
      - Dispersion Check
        - Dispersed
          - WET SLURRY ANALYSIS
        - Not Dispersed
          - Select Different Surfactant
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: 1x10³ - 2x10⁷ g/mol
- Optional titrator

- Nanoparticles
- Colloids
- Proteins
- Emulsions
- Dispersion 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

Zeta Potential: Dispersion Stability, IEP
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  Nanoparticles  Biomolecules

<table>
<thead>
<tr>
<th></th>
<th>HORIBA</th>
<th>Z ave</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>9.63 nm</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td>Sample 2</td>
<td>10.51 nm</td>
<td>0.19</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Z ave. (nm)</th>
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<tbody>
<tr>
<td>DNT-107</td>
<td>7.6</td>
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<tr>
<td>DNT-189</td>
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</tbody>
</table>
What we’ll talk about

- A Structured Approach
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- 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…)

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Quick Selection Chart

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

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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
<table>
<thead>
<tr>
<th>Particles greater than 1 micron and less than 100 nanometers?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Laser diffraction</td>
</tr>
<tr>
<td>• Acoustic spectroscopy</td>
</tr>
<tr>
<td>• Centrifugal sedimentation</td>
</tr>
</tbody>
</table>

| 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
Thank you

Danke

Gracias

Большое спасибо

Grazie

Obrigado

Thaks

ขอบคุณ

アシクー

Omoshiro Okashiku

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