Foreign Particle Size Distribution and Characterization in Pharmaceutical Drug Products Using a High Throughput Electron Beam Analyzer

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Agenda

- Review of Techniques for Particle Analysis
- Objective and Goals
- Automated SEM-EDS Technology
- Method Development:
  - Sample Preparation
  - Data Mining
  - Rule File Development
  - Sample Report
- Summary
<table>
<thead>
<tr>
<th>Technique</th>
<th>Capabilities</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTIR Microscopy</td>
<td>Identification of organic, polymeric and inorganic materials.</td>
<td>For identification, particles must be harvested individually.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Labor intensive.</td>
</tr>
<tr>
<td>Raman Microprobe</td>
<td>Identification of organics, polymers, and inorganics.</td>
<td>No particle enumeration.</td>
</tr>
<tr>
<td></td>
<td>Automated analysis is now available with some new systems.</td>
<td>Identification of organics, polymers, and inorganics.</td>
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<td>Automated analysis is now available with some new systems.</td>
</tr>
<tr>
<td>Light Obscuration/Particle Counting</td>
<td>Counting capability at the low-micron levels (e.g., 2 mm and larger).</td>
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<tr>
<td></td>
<td>Short analysis times (e.g., approx. 10 min).</td>
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</tr>
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</table>
## Technique

**Optical Microscopy**

### Capabilities

- Direct observation and measurement of:
  - Morphology
  - Size & Number
  - Color
  
  Particles can be isolated and harvested for analysis by other methods (e.g., FTIR, SEM/EDS, etc.).
  
  Automated counting is currently available.

### Limitations

- Labor intensive.
  
- Not practical for size ranges less than 5mm where it becomes very labor intensive and potentially inaccurate.
  
- Analyst skills and training is crucial.
  
- Rather limited identification capabilities.
<table>
<thead>
<tr>
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<th>Capabilities</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEM/EDS</td>
<td>SEM can perform analysis of particles at low-micron (e.g., less than 10mm) and even sub-micron size ranges.</td>
<td>Limited utility for identification of organic and polymeric materials.</td>
</tr>
<tr>
<td></td>
<td>EDS can determine elemental composition of particles.</td>
<td>Labor intensive when performed manually.</td>
</tr>
<tr>
<td></td>
<td>Automated enumeration and identification is currently available.</td>
<td>Requires high level of skills and training for the analyst.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relatively long analysis times even with automation particularly when EDS is performed.</td>
</tr>
</tbody>
</table>
Objectives and Goals

- Overview of SEM-EDS for particle analysis
- Overview of automated feature analysis
- Characterize particulate material on inhalable product
- Method development: manual particle characterization
- Method development: automated enumeration and characterization
- Data mining and analysis
- Summary
Product Information: PSEM 3025

**SED**
Topographical imaging

**BSED**
Atomic number based contrast

**SDD for X-Ray Detection**
Chemical Composition

**Perception Software Suite**
Integrates hardware and software components

**Audit and Authorization Software**
Comply 21 CFR Part 11 requirements
GMP facilities
Backscattered Electrons

- Backscattered electrons are elastically scattered.
- Minimal energy loss.
- Large directional change.
- \( >50 \text{ eV} \)
- Strong correlation with atomic number.
Backscatter Electron Signal

- **Heavy Metals**: Ta-W-Pt-Au-Hg-Pb
- **Intermediate**: Zr-Mo-Ag-Cd-In-Sn-Sb-Te
- **Steel/brass**: Cr-Mn-Fe-Co-Ni-Cu-Zn
- **Minerals**: Na-Mg-Al-Si-P-S-Cl-K-Ca
- **Organics**: C-N-O

![Graph showing the relationship between backscatter coefficient and atomic number for various materials.]
Characteristic X-Rays

Characteristic X-Rays are generated in a multi-step process.

- An inner shell electron is knocked out by incoming electron.
- An outer shell electron drops down to fill vacancy.
- Energy difference is emitted as a photon.
Energy Dispersive Spectrum

- Energy of emitted X-Ray is characteristic of chemical element.
- The X-ray detector collects the X-rays and results are displayed in a histogram.
<table>
<thead>
<tr>
<th>PSEM Response Signals</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SED</strong></td>
<td><strong>BSED</strong></td>
</tr>
<tr>
<td>Detectors</td>
<td>SED, Quad BSED &amp; SDD EDS</td>
</tr>
<tr>
<td>Accelerating Voltage</td>
<td>0.2 to 25 KeV</td>
</tr>
<tr>
<td>Stage Movement</td>
<td>80mm x 100 mm XY Motorized with Manual Z</td>
</tr>
<tr>
<td>Vacuum System</td>
<td>High Vac and Variable Pressure</td>
</tr>
<tr>
<td>Imaging Resolution</td>
<td>7nm</td>
</tr>
<tr>
<td>Lightest Element Detection</td>
<td>Bornon</td>
</tr>
<tr>
<td>EDX Resolution</td>
<td>133 eV</td>
</tr>
</tbody>
</table>
Why Use Automated SEM-EDS Technology?

• To obtain statistically meaningful metrics.
• To recognize groupings within a population.
• To locate low-probability features (“needle in haystack”).
• To verify absence of contaminants.
• To eliminate subjectivity.
• To improve throughput.
• To reduce labor costs.
What Do You Get From AFA?

For each feature:
- Location on specimen (can be relocated)
- Size (average diameter, area, perimeter)
- Shape (aspect ratio, roughness, etc.)
- BSE contrast level (~average atomic number)
- Elemental composition (if selected)
- Thumbnail image (if selected)
- Classification per rule set (live or post-analysis)

Specimen coverage:
- Total area
- Sampled fields
How Does An Automated E-Beam Systems Work?
Frame-Based Particle Analysis

Software algorithms determine shape parameters:

- Length
- Width
- Aspect Ratio
- Area
- Perimeter
Optimization of E-beam Analysis

Sizing by dynamic beam motion improves speed & precision.

- Electronic sub-fields
- Sampling ‘sieve’
- Dynamic sizing
Automated Particle Analysis

Simple User Interface
What is Used for Characterization?

**Particle Parameters**

- DAVE
- DMAX
- DMIN
- DPERP
- Aspect
- Area
- Perimeter
- Orientation
- Video
- Void Area
- Void Count
- Edge Roughness
- RMS Video
- Roundness
- Formfactor
- ECD

**Elemental Composition**

*Example Rule:*

Vermiculite

Si>Mg and Mg>Al and Si>30 and
Si<65 and Mg>20 and Mg<38
and K<16 and Fe<=12 and Al<=26
and Al>0 and K>0 and Fe+K>6
Advantages of Automated SEM-EDS Analysis

- Relatively short analysis times (e.g., on average 30 minutes per sample compared to 8-10 hrs using manual microscopy).

- Real-time, one-step analysis of particles, i.e., particle enumeration and elemental composition obtained in one run.

- No special preparation (e.g., polishing of a lollipop sample required)

- System is usually optimized for quick installation and use.

- Relatively low operating cost—Unattended Operation.
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- Summary
Research Study

- Active drug processed into a respirable dry powder.
- The product is administered with a hand-held device.
- Determine highest number of particles that a patient could receive from the drug kit.
- Determine origin, profile and number of foreign particle material in drug powder, packaging and device.
Method Development: Filter Membrane Sample Preparation

**Inorganics**
- Polycarbonate Filter Membrane

**Organics**
- Gold-coated Polycarbonate Filter Membrane

Filtration in a Class 100 Laminar Flow Hood
Sample Preparation: Compositional Contrast and Pore Size

**Inorganics (bright-on-dark)**

**Organics (dark-on-bright)**

- **Silver Membrane**
  - 0.2 micron
- **Nickel Membrane**
  - 3 micron
- **Gold Membrane**
  - 0.2 micron
Sample Charging

Non-conductive specimens can build-up charge which:
Alters SE contrast
Deflects the beam

Application of conductive coating is traditional solution for high-resolution imaging

Variable Pressure (VP) method is now widely used for BSE and x-ray analysis
Bonus: VP reduces sensitivity to sample outgassing
Variable Pressure

**Analyze insulating materials**
Filter membranes, plastics, paper, glass, rubber, ceramics...

**No sample preparation**
Examine as received
No coating

High Vacuum Variable Pressure Mode
Collect data on standard sample of features.
Size, shape and elemental composition

Based on preliminary data, select appropriate substrate and optimize instrumental parameters for detection and measurement.
Magnification
Pixel size and density
Dwell time per pixel
EDS scan time
Foreign Particle Data

Carbonaceous on Gold Coated Filters

AFA Thumbnails
- 8 us scan
- 64x64 pixels
- 5 sec EDS

Manual Images
- 15 second scan
- 512x512 pixels
- 30 sec EDS
Foreign Particle Data

Aluminum on Gold Coated Filters

AFA Thumbnails
- 8 us scan
- 64x64 pixels
- 5 sec EDS

Manual Images
- 15 second scan
- 512x512 pixels
- 30 sec EDS
Foreign Particle Data

Glass on Gold Coated Filters

AFA Thumbnails
- 8 us scan
- 64x64 pixels
- 5 sec EDS

Manual Images
- 15 second scan
- 512x512 pixels
- 30 sec EDS
Foreign Particle Examples

- Aluminum
- Iron
- Synthetic Fibers
- Talc
- Stainless Steel
Samples were prepared in triplicates
Data was tabulated in the following detection size ranges
• 20-10 mm, 25-50 mm, 50-150 mm, 150-500 mm
• 0-1 mm, 1-2 mm, 2-3 mm, 4-5 mm, 5-6 mm, 6-7 mm, 7-8 mm, 8-9 mm, 9-10 mm
• >10 mm
• >25 mm

Elemental Composition Data
Total Particle Count
Collect data on standard sample of features and of every category of interest.

Use histogram and ternary plots to separate major constituents. Combine size and semi-quant chemical information to develop classification rules.

Different components require different rule sets. A combined total of 24 types of particles were found on the three components of the kit. 
Minerals (dolomite, mica), talc, stainless steel, organics, etc...
### Data Format Example: Tabular Reporter

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total</th>
<th>DMAX (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[0.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[1.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[2.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[5.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[10.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[25.00]</td>
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<tr>
<td></td>
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<td>[50.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[100.00]</td>
</tr>
<tr>
<td>Talc</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Calcium Rich</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Aluminum Rich</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Si Rich</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Chromium Rich</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stainless</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Iron Rich</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>Misc</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>All particles</td>
<td>244</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total</th>
<th>DAVE (μm)</th>
<th>DMIN (μm)</th>
<th>DMAX (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum Rich</td>
<td>1</td>
<td>15.2</td>
<td>13.4</td>
<td>17.3</td>
</tr>
<tr>
<td>Calcium Rich</td>
<td>16</td>
<td>6.0</td>
<td>4.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Chromium Rich</td>
<td>0</td>
<td>1.4</td>
<td>0.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Iron Rich</td>
<td>49</td>
<td>5.6</td>
<td>3.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Misc</td>
<td>23</td>
<td>3.4</td>
<td>1.7</td>
<td>8.8</td>
</tr>
<tr>
<td>Stainless</td>
<td>106</td>
<td>1.1</td>
<td>0.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Talc</td>
<td>32</td>
<td>3.4</td>
<td>2.2</td>
<td>5.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total</th>
<th>ASPECT RATIO (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[1.00] [1.10] [3.25] [5.50] [7.75] [10.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[1.00] [1.10] [3.25] [5.50] [7.75] [10.00]</td>
</tr>
<tr>
<td>Talc</td>
<td>30</td>
<td>1 1 1 0 0 0</td>
</tr>
<tr>
<td>Calcium Rich</td>
<td>13</td>
<td>2 0 0 0 0</td>
</tr>
<tr>
<td>Aluminum Rich</td>
<td>0</td>
<td>1 0 0 0 0</td>
</tr>
<tr>
<td>Si Rich</td>
<td>75</td>
<td>13 3 2 2 0</td>
</tr>
<tr>
<td>Chromium Rich</td>
<td>0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Stainless</td>
<td>15</td>
<td>1 0 0 0 0</td>
</tr>
<tr>
<td>Iron Rich</td>
<td>38</td>
<td>8 1 0 0 0</td>
</tr>
<tr>
<td>Misc</td>
<td>18</td>
<td>3 0 0 0 0</td>
</tr>
</tbody>
</table>
Data Format Example: Particle Counts

- **Counts**
- **Particle Type**

Legend:
- Capsule
- Device
- Blister
Data Format Example: Maximum Diameter

![Graph showing average Dmax (microns) for different particle types: Capsule, Device, Blister. The x-axis represents particle type, and the y-axis shows average Dmax.](image)
Automated SEM-EDS analysis is a reliable technique to obtain relevant information such as enumeration and characterization of particles from encapsulated powders, packaging and devices.

The type of particulate and the size distribution can be used to develop specifications and controls for production of drugs in FDA regulated environments.

Particle size distribution and morphology data is reliable measured for particles as small as 0.1 microns.

Organic and inorganic materials can be simultaneously analyzed in a single sample analysis.
Other Applications in Pharmaceutical Industries

- Active product ingredient
- Tablets
- Drug powders
- Capsules, blister packaging and inhalers
- Parenteral products
- Coating durability
- Micro-contamination particle identification
  Paints, pigments, syringes, IV bags, tubing ampoules, dropper bottles, product container, packaging material, etc...

All particles > 0.1 μm of a sample are automatically sized, counted, identified and reported.
The FDA is encouraging pharmaceutical manufactures to adopt the **Quality by Design** approach:
“design quality into the product rather than testing quality into the product”

**Quality by Design for management of Foreign Particles (FP)**
- Control and understanding of production processes and materials manufactured in-house and/or from suppliers
- Careful enumeration and characterization of FP during development studies
- Conduct safety evaluation of FP
- Identify potential sources of FP
- Eliminate or minimize the sources of FP
- Establish appropriate specifications for routine control
IPAC-RS recommendation for the control of FP in drug product development and manufacture:

- Enumeration
- Characterization (size, shape and elemental composition)

From: Wolff et al; Pharmaceutical Research, 2007