Complex Drug-Device Generic Combination Products

October 9-10
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Enhanced Analytical Tools for Bioequivalence Evaluation of Nasal Spray Drug Products

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Proactive Science and Research Approach

- The OTR science program is designed to maintain preparedness.
  - Consumer complaints
  - Public health issues
- The OTR research program is “forward looking”.
  - New and emerging technologies
  - Advanced analytics (instrument and modelling)
  - Complex drugs

OTR's Role in Generic Drug Science

- Laboratory Consults
  - Method evaluation (verification)
  - Product quality
  - Pharmaceutical equivalence
- Guidance and Standard Development
  - Provide laboratory data
  - Develop improved testing protocols
- Training
  - Laboratory (hands-on) training for assessors

Background

- Particle size of active pharmaceutical ingredient (API) is a critical attribute in evaluating nasal spray suspension products.
  - Quality
  - Effectiveness
  - Bioequivalence (BE) for evaluating generic drugs
- Traditional particle sizing techniques, such as sieving, laser diffraction, and microscopy cannot distinguish particles with different chemical identities.

Challenges in Analyzing Nasal Sprays

- API and excipient particles co-exist in the formulation
- More than one API may be present in formulation
- API may have one or more polymorphic forms

Morphology Directed Raman Spectroscopy (MDRS)

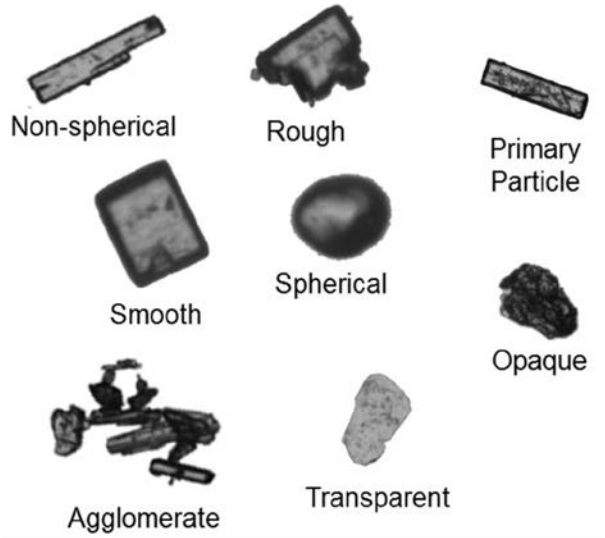
- MDRS, as an emerging technology, shows potential to solve the abovementioned problem
- Commercially-available integrated platform

- Malvern Morphologi G3-ID
  - May be used to screen formulation profile (physical and chemical)
  - Classification of particles based on size, shape and other physical characteristics
  - Chemical Identification based on library spectra

Morphology Screening

Morphology Measurement

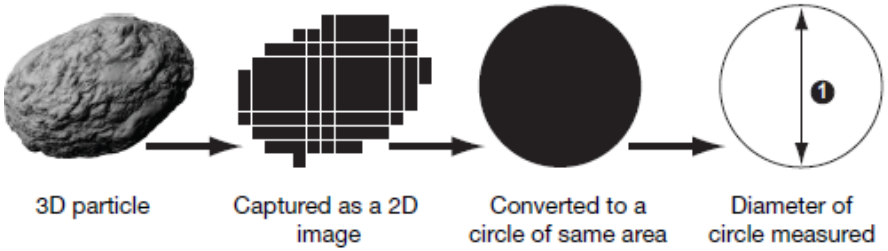
- Automated microscope scan
- Image analysis
  Image binarization: using intensity threshold to define the edge of a particle



Particle Morphology

Size:

- Circular equivalent (CE) diameter: Diameter of a circle with the same area as the 2D image of the particle



Morphology Attributes

Shape:

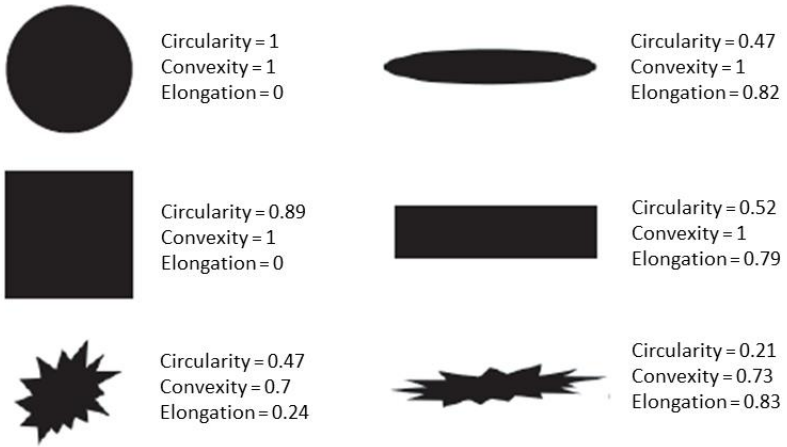
- Aspect Ratio: width / length
- Elongation: defined as [1-aspect ratio] or [1-width/length]
- Circularity: ratio of the perimeter of circle with the same area as the particle divided by the perimeter of the actual particle image
- Convexity: perimeter of a particle divided by its convex hull perimeter
- Solidity: area of a particle divided by its convex hull area.

Other physical features:

- Intensity Mean
- Intensity SD

Measurements of light transmission or light reflection of the particles.

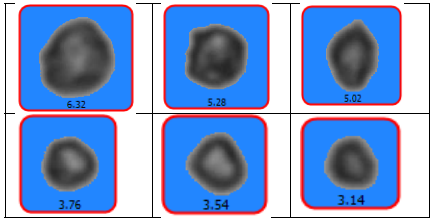
Opaque



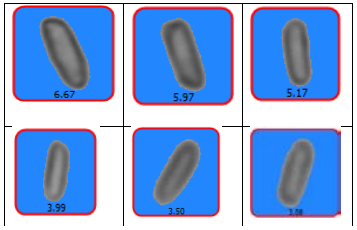
Capabilities of Morphology Screening

Why Morphology Measurement?

API and excipient particles may have different morphologies.



API



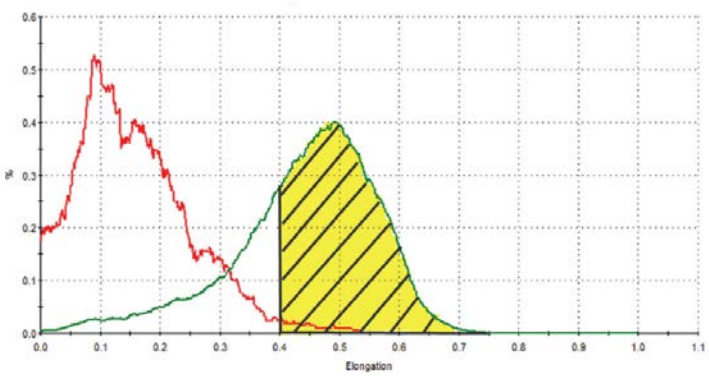
Excipient

Advantage:

- ✓ Fast measurement.
- ✓ Fast data processing.

Disadvantage:

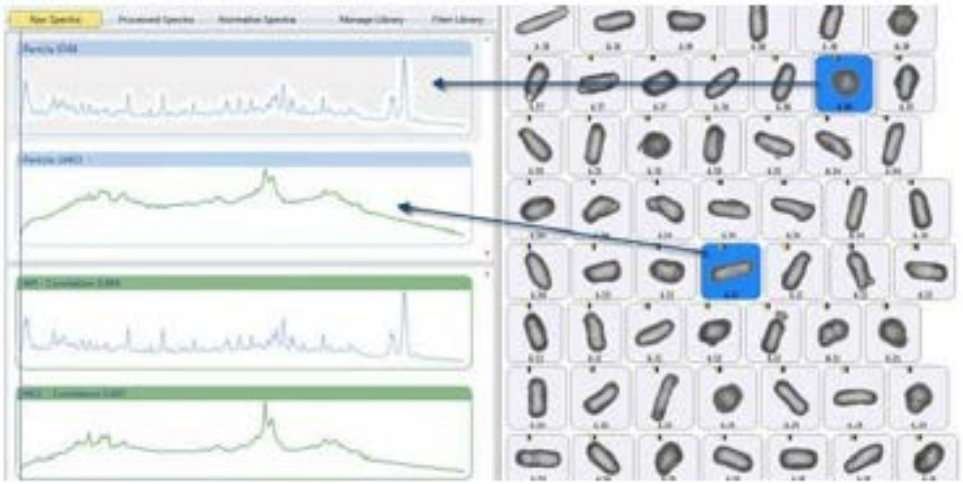
- ❖ Cannot completely separate API and excipient particles due to particles with overlapping morphological feature.



Morphology measurement is a great screening tool, but not good enough to provide conclusive results.

Chemical ID by Raman Spectroscopy

- **Raman spectroscopy** provides information on molecular vibrations and crystal structures.
- Complementary method with IR and provides a finger print of molecules.
- Each molecule has a unique spectrum.
- API/Excipient Particles typically show different Raman profiles.



The Raman Measurement

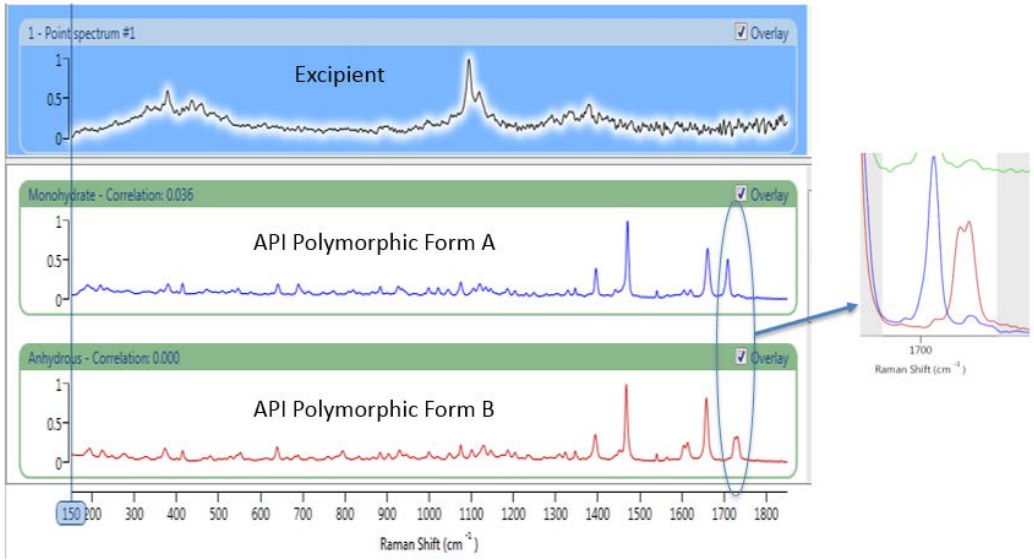
- The MDRS instrument automatically performs Raman measurement after morphology screening.
- The instrument automatically finds the selected particles and collect a Raman spectrum form the center of each one.
- Chemical identification of individual particles by comparison with standard.

Raman Advantages

- ✓ Chemical identification for each individual particle.
- ✓ Identify different polymorphic forms of an API.

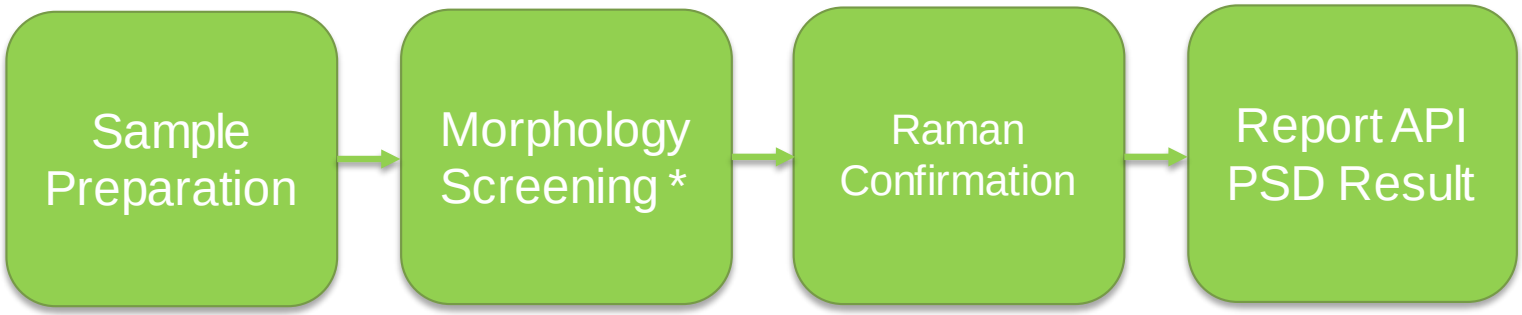
Raman Disadvantage:

- ❖ **Slow measurement, time-consuming.**



Raman microscope is a powerful tool for chemical ID, and appears to provide an ultimate solution for ingredient-specific PSD. However, by applying Raman microscope alone for PSD is not practical due to extraordinary amount of time required to perform the measurement.

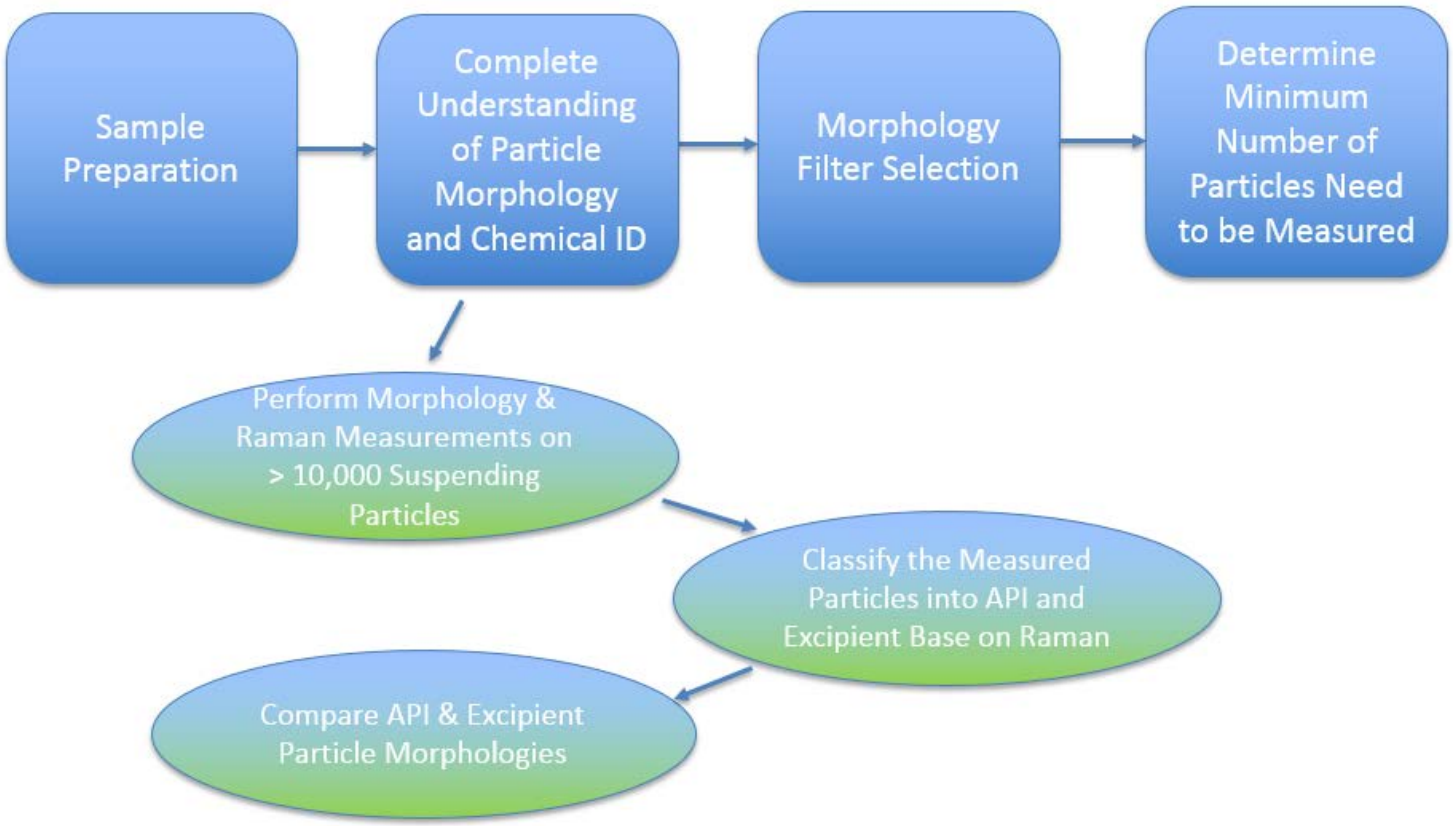
Typical Protocol



- Since majority of particles in a formulation are excipients, it is important to apply **appropriate** morphology filters to exclude as many excipient particles as possible before performing time-consuming Raman measurements.
  - Be alert: morphology filters will also discard API particles with overlapping morphologies. A loose morphology filter selection will cause biased API PSD results.

Method Development is the key to success.

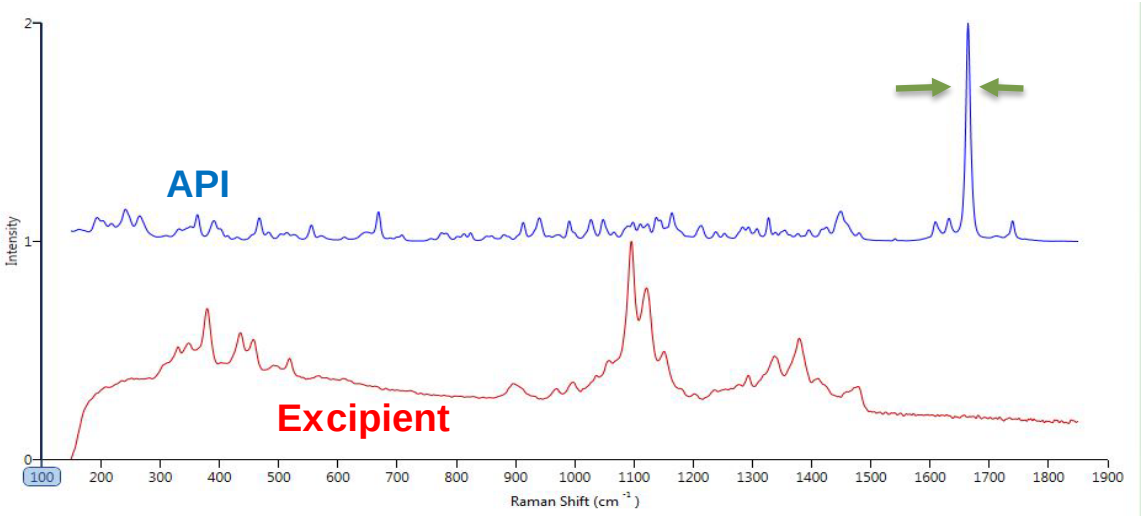
Method Development Example



Method Development Example

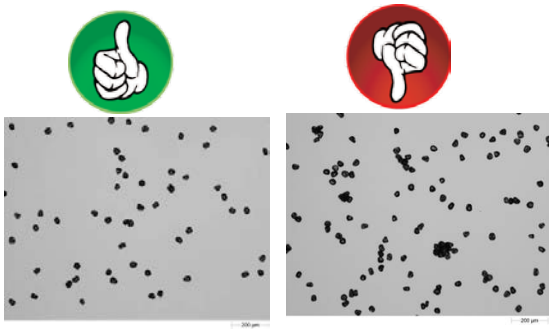
- Sample: A commercial available nasal spray suspension product.
- Suspending particles: one API and one excipient with known chemical IDs.

Normalized Raman spectra of API and Excipient standards (bulk sample)



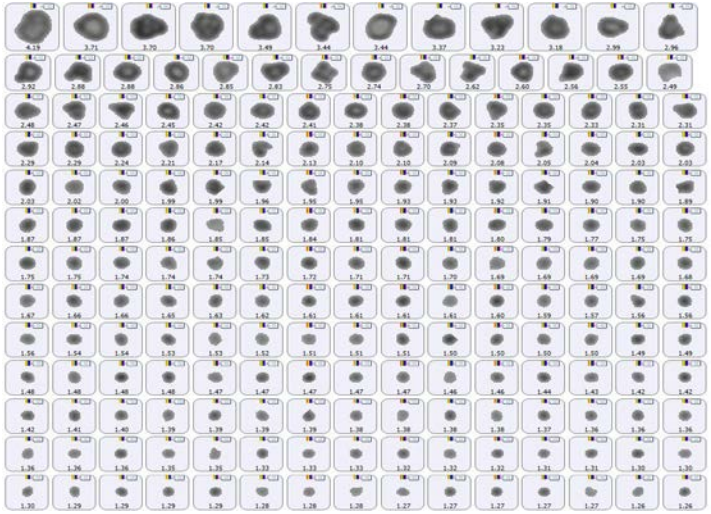
Sample Preparation (Wet Method/post-spray)

- Gently shook nasal spray bottle (per user instruction).
- Primed the nasal spray pump by delivering 2 – 5 actuations to waste.
- Delivered next 2 actuations into a small glass vial (post-spray).
- Transferred 5 µL of the post-spray sample to a quartz microscope slide.
- Covered sample with a quartz coverslip & applied petroleum jelly to the coverslip edges to prevent sample evaporation
- Allowed 1 hr for particles to settle.



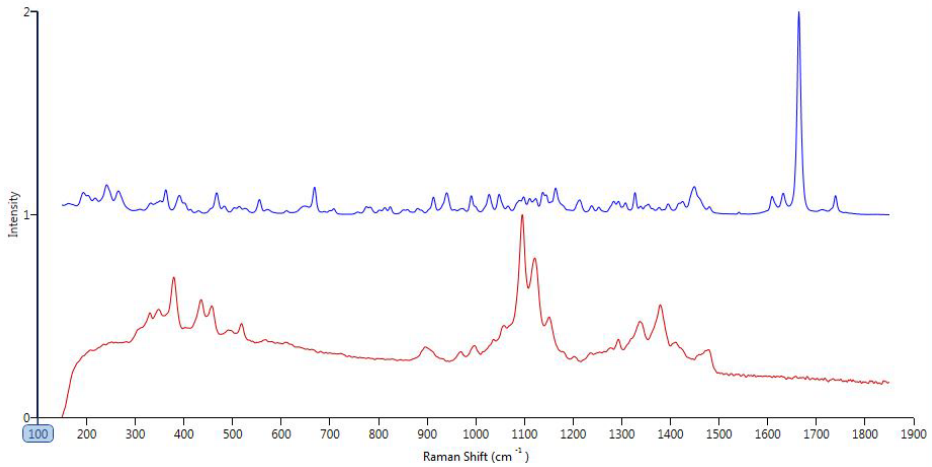
Morphology and Raman Measurements

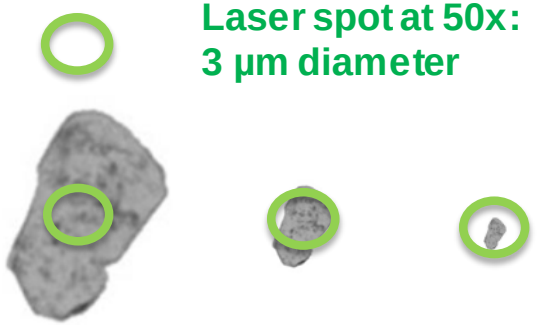
- Target # of particles > 16,000
- Combining results from 9 Experiments in 9 days
- Total Time Spent
  - Morphology Measurement ~ 15 minutes
  - Raman Measurement ~125 hrs (30 s per particle)



Classification of Particles

The API has a unique strong Raman signature peak at 1680 cm^{-1}





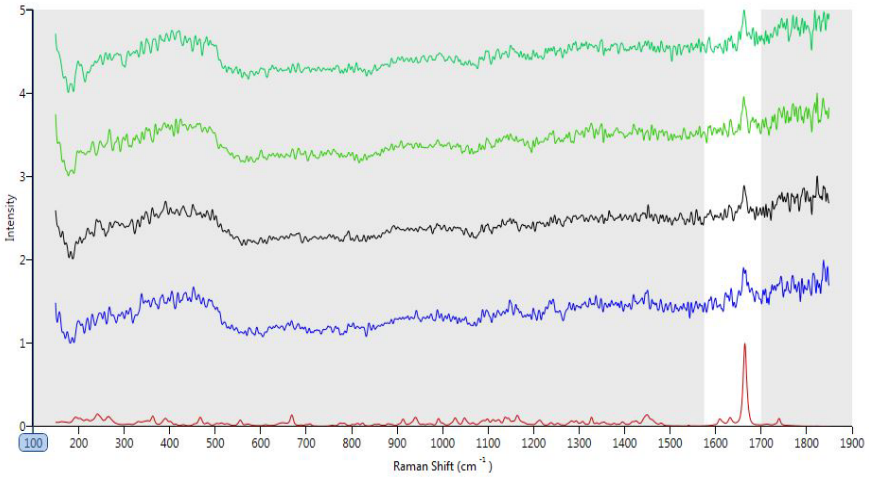
Considerations:

Raman peak intensity of individual particles could be much lower than bulk samples.

- Micron level individual particles vs. bulk sample
  - Individual particle surface properties.
- Laser spot size limitation.
  - Exposure area.
  - Depth of field

Classification of Particles (continued)

The API has a unique strong Raman signature peak at 1680 cm^{-1}



Acceptance criteria: S/N ratio > 3.

Raman range: 1575-1700 cm^{-1}; Raman correlation score: > 0.8

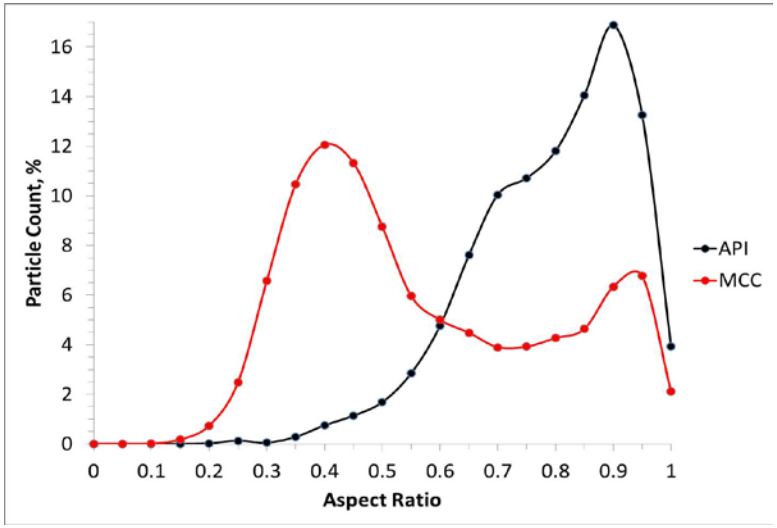
- Raman measurements provided a clear and confirmed separation between API and Excipient particles.
- Out of the total 16,000 particles, 4000 (25%) were identified as API particles by Raman.

% API particles varies for different products: 4% - 30%

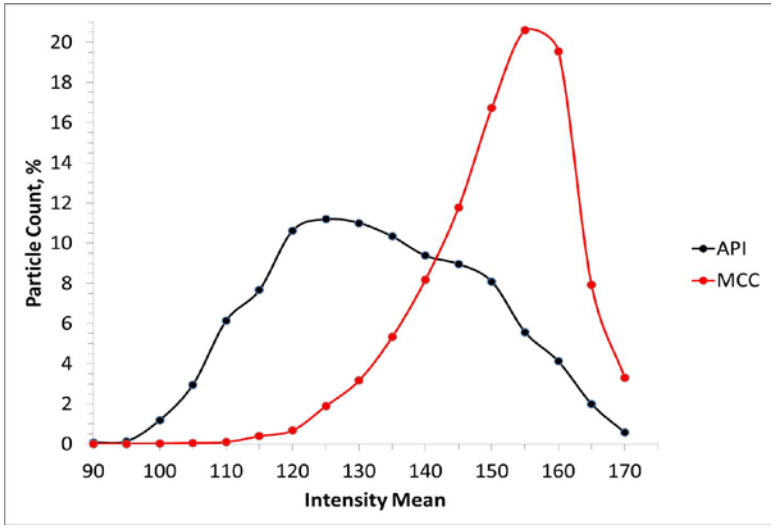
Comparison of API and Excipient Particles

- Once the chemical ID has occurred, the API and excipient particles can be better distinguished.

Aspect Ratio

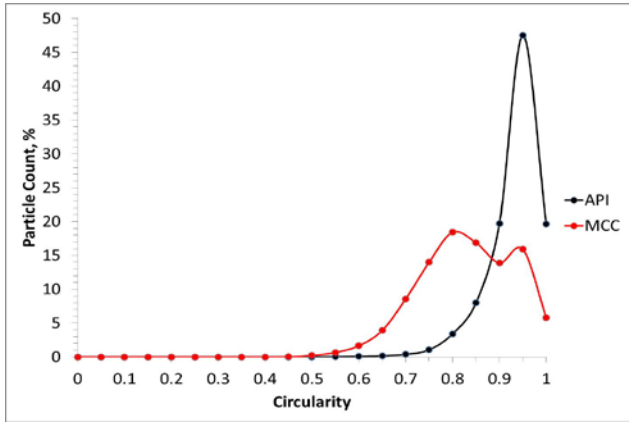


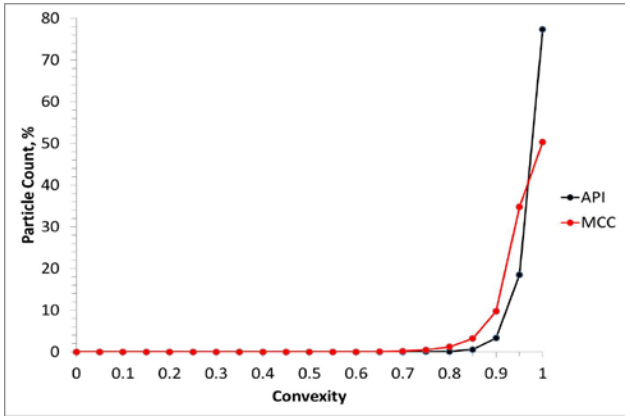
Intensity Mean



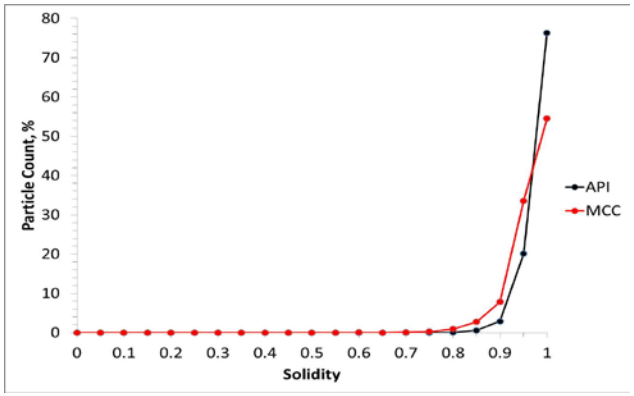
Comparison of API and Excipient Particles

API vs. Excipient Morphology Distribution (Normalized Plots)





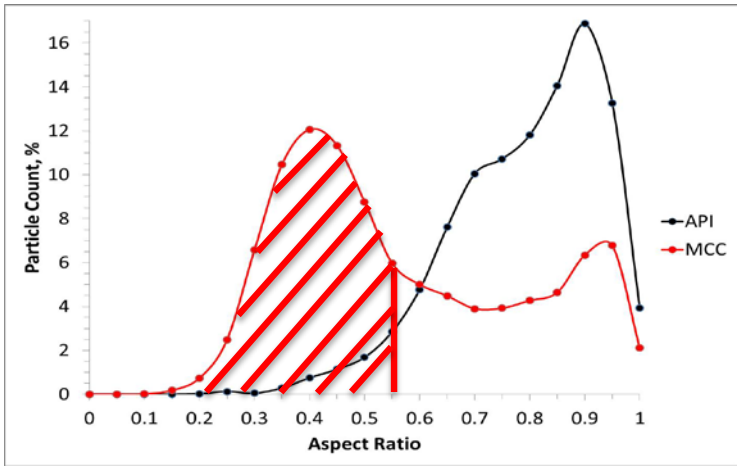
None of the morphology parameters or morphology parameter combinations can provide a clear separation between API and excipient.

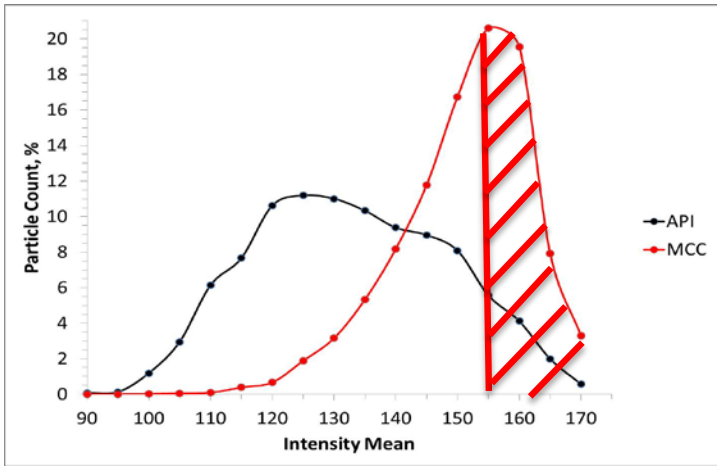


Filter Selection

- Exclude as many excipient particles as possible.
- After applying morphology filters, keep at least 85% API particles. (It is inevitable to discard some API particles due to overlapping morphologies)

Morphology filter selection: aspect ratio + intensity mean
Exclude particles with aspect ratio < 0.55 or intensity mean > 155.





Effects of Filter Selection

- Applying the morphology filters (aspect ratio < 0.55 or intensity mean > 155)

	Before	After	% Excluded
API	4000	3500	12.5%
Excipient	12000	3000	75.0%
Total	16000	6500	59.4%

Validate the morphology filter selection

--- Compare API PSD results before and after morphology filter application.

- Proposed validation criteria: < 10% difference in D_n10, D_n50, D_n90, and D_{mean}.

- If the criteria cannot be met, need to tighten filter selection to include more API particles.

An Example Method

- Optimized MDRS Method

MDRS Experimental Parameters	
Sample volume	5 µL
Particle settling time	1 hr
Aspect Ratio cutoff	< 0.55
Intensity Mean cutoff	> 155
Exposure time, Raman measurements	30 seconds
Spectral correlation range	1575 – 1700 cm^{-1}
Raman spectral correlation score cutoff	> 0.8
Minimum # of API particles to be measured by Raman after morphology screening	**200**
Minimum # of total particles to be measured before morphology screening	**1,000**
Total MDRS measurement time	**~ 6 hrs**

- **The listed MDRS parameters were for this tested product, as an example, only. Not applicable to other products.**

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Summary and Conclusions

- MDRS method must be developed on a product-by-product basis.
- The MDRS parameters and selection criteria need to be scientifically justified.
- The MDRS method is capable of facilitating automated non-destructive physical and chemical profiling of nasal spray samples.
- MDRS method is an emerging technique with room to improve!
- Experience in method development and application needs to be gained and shared.

Acknowledgements

- Research Team
  - Changning Guo, OPQ/OTR/DPA (PI)
  - Brandon Thomas, OPQ/OTR/DPA
  - Latevi Lawson, OPQ/OTR/DPA
- Collaborators
  - Mohammad (Abir) Absar, CDER/OTS/OCP
  - Renishkumar Delvadia, OGD/ORS
  - Sau (Larry) Lee, OPQ/OTR
  - Dhaval Gaglani, OPQ/OLDP
  - Intira Coowanitwong, OPQ/OLDP

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