Analytical Method Development for Ingredient-Specific Particle Sizing of Nasal Spray Suspensions

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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)

Challenges:

- **API and excipient particles coexist in the formulation**
- **More than one APIs in the formulation**
- **API may have more than one polymorphic form**

Traditional particle sizing techniques, such as sieving, laser diffraction, and microscopy cannot distinguish particles with different chemical identities.

Morphologically-Directed Raman Spectroscopy (MDRS)

MDRS, as an emerging technology, shows potential to solve the abovementioned problem.

Malvern Morphologi G3-ID →

Automated imaging & Raman spectroscopy combined in one integrated platform

- Morphology Screening

  Classification based on particle morphology: separate particles based on their similarities in size, shape, and other physical features.

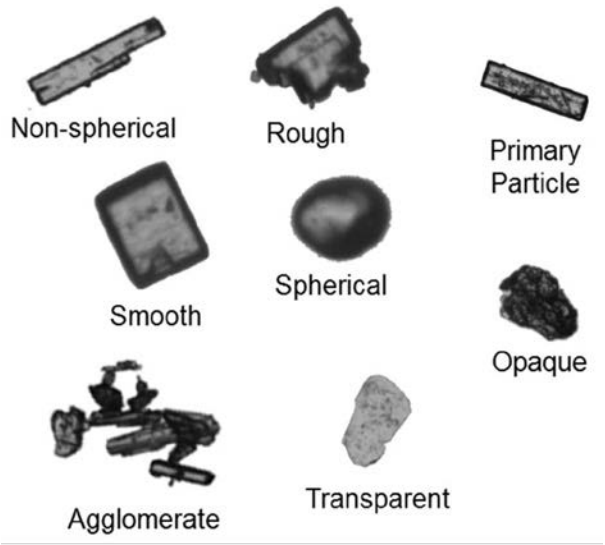
- Raman Confirmation

  Chemical identity of individual particles based on spectral matching to library spectra of API

Morphologically-Directed Raman Spectroscopy (MDRS)

Morphology Measurement

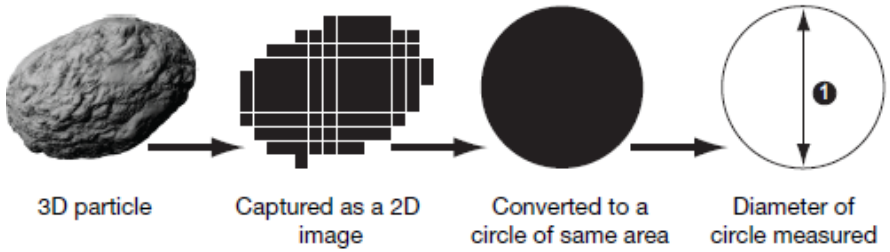
- Automated microscope scan
- Image analysis
  Image binarization: using intensity threshold to define the edge of a particle



Particle Morphology

Size:

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



Morphologically-Directed Raman Spectroscopy (MDRS)

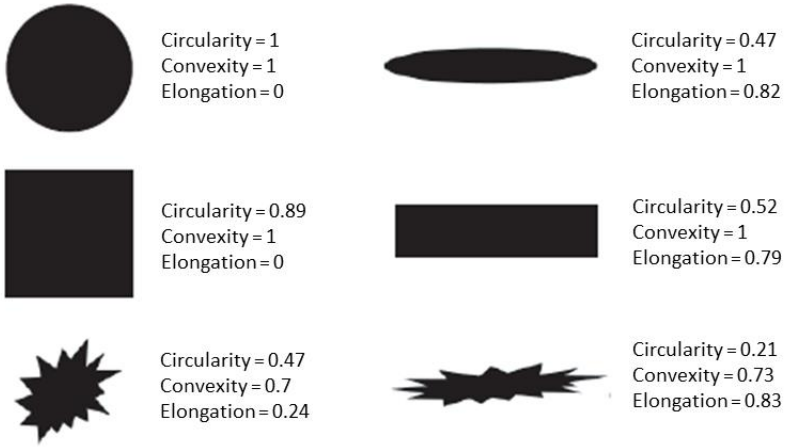
Shape:

- 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

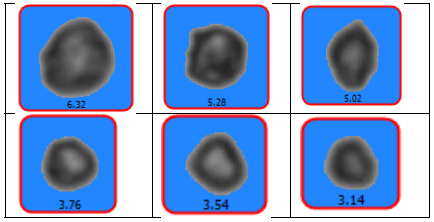
Measurements of light transmission or light reflection of the particles.



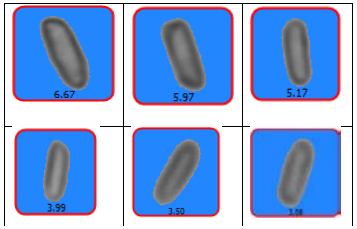
Morphologically-Directed Raman Spectroscopy (MDRS)

Why Morphology Measurement?

API and excipient particles may have different morphologies.



API



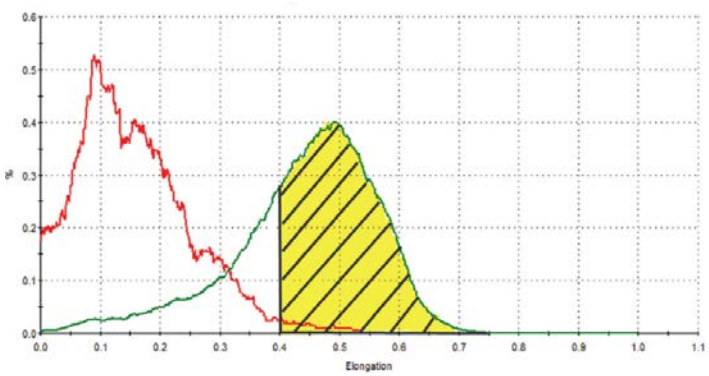
Excipient

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.

Morphologically-Directed Raman Spectroscopy (MDRS)

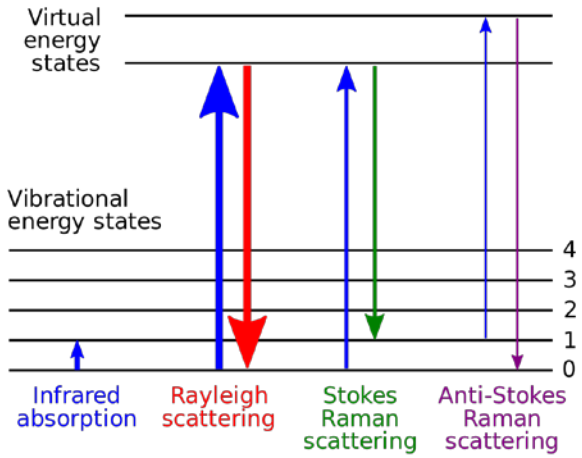
Raman Measurement

Raman spectroscopy provides information on molecular vibrations and crystal structures.

Raman Spectra - "finger-print" of molecules

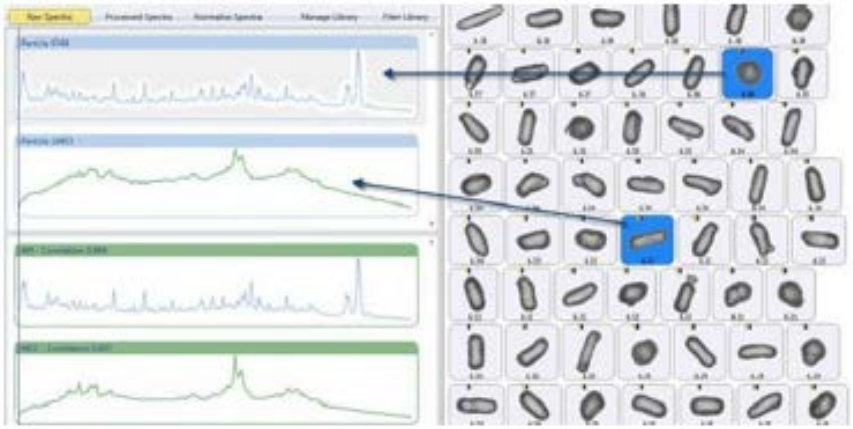
--- Each molecule has its own unique spectrum.

--- API / excipient particles show significant different Raman profiles.



MDRS performs Raman measurements 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.



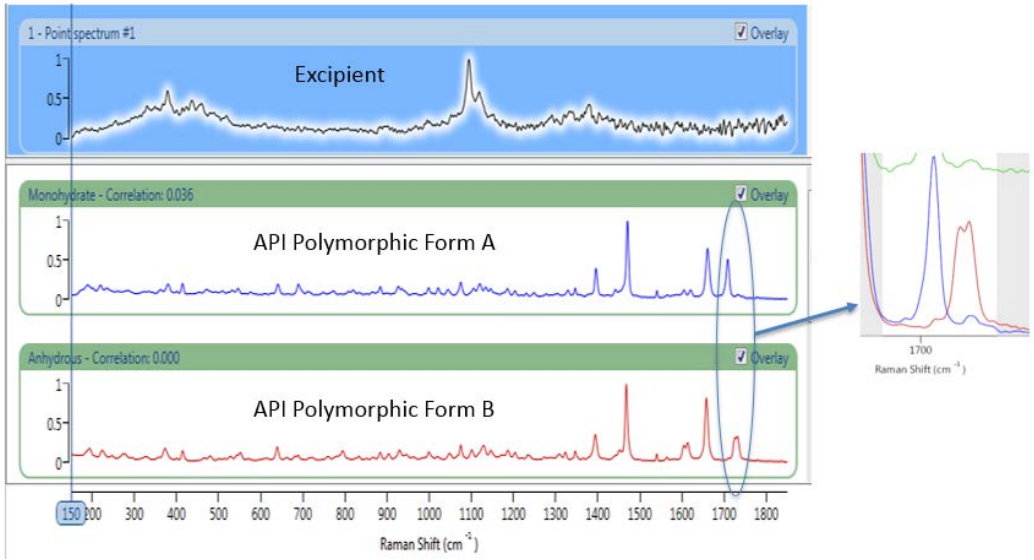
Morphologically-Directed Raman Spectroscopy (MDRS)

Raman Advantages:

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

Raman Disadvantage:

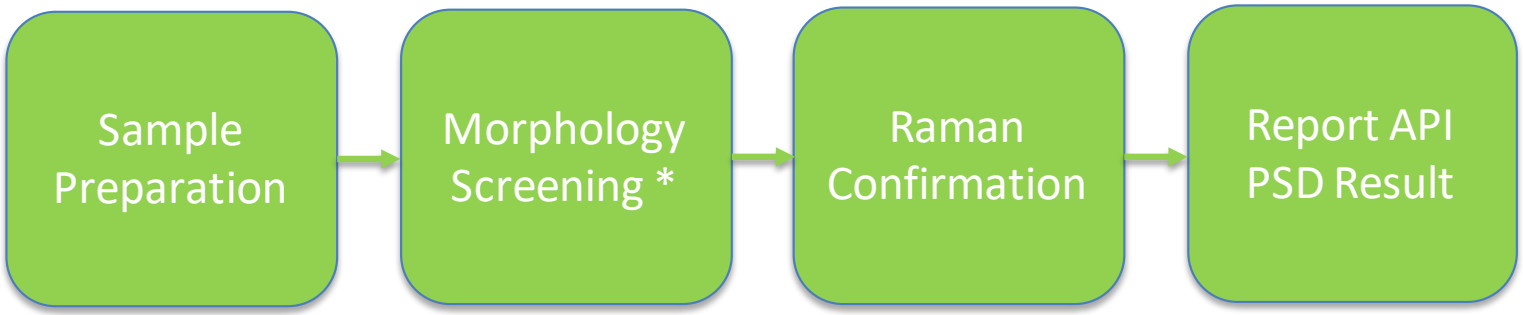
- ❖ **Slow measurement, time-consuming.**



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.

Morphologically-Directed Raman Spectroscopy (MDRS)

Typical MDRS protocol

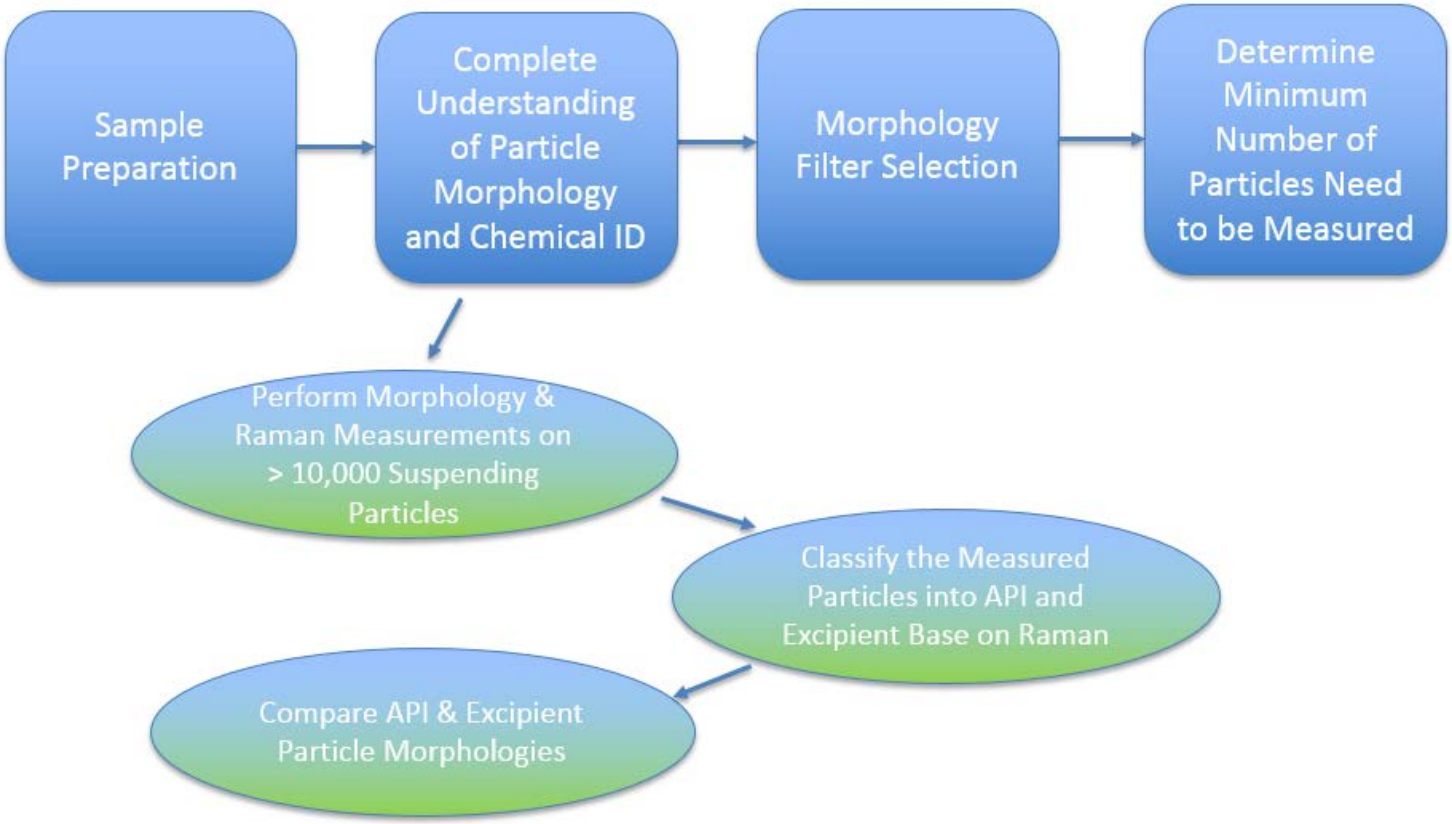


- Since majority of particles in a formulation are excipients, it is important to apply **appropriate** morphology filters to exclude as many excipient particles as possible before performing time-consuming Raman measurements.
  - Be alert: morphology filters will also discard API particles with overlapping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

Method Development is the key to success.

Method Development Example

MDRS Method Development Workflow Currently Used at DPA



Method Development Example

Sample:

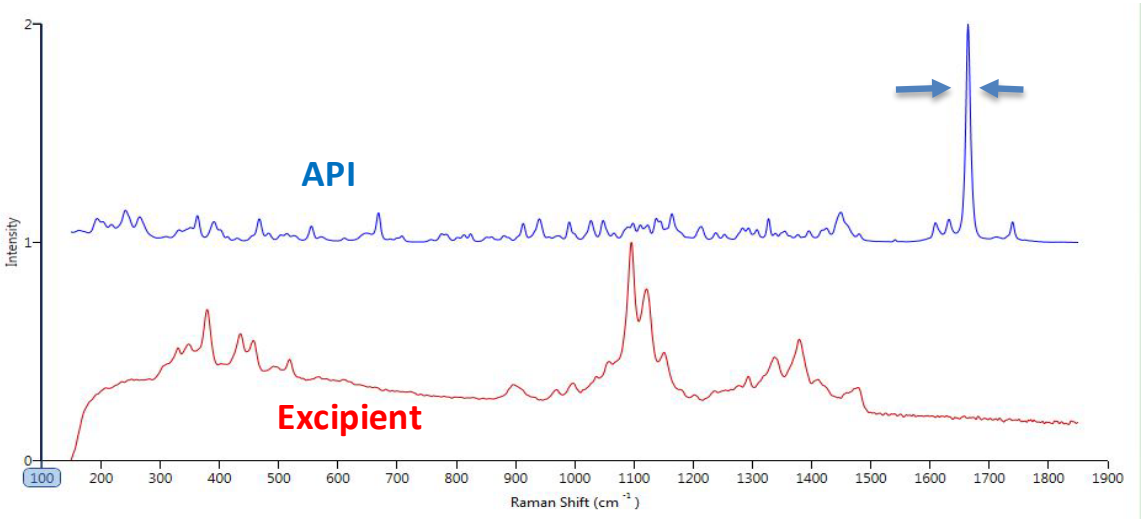
A commercial available nasal spray suspension product.

--- Suspending particles: one API and one excipient with known chemical IDs.

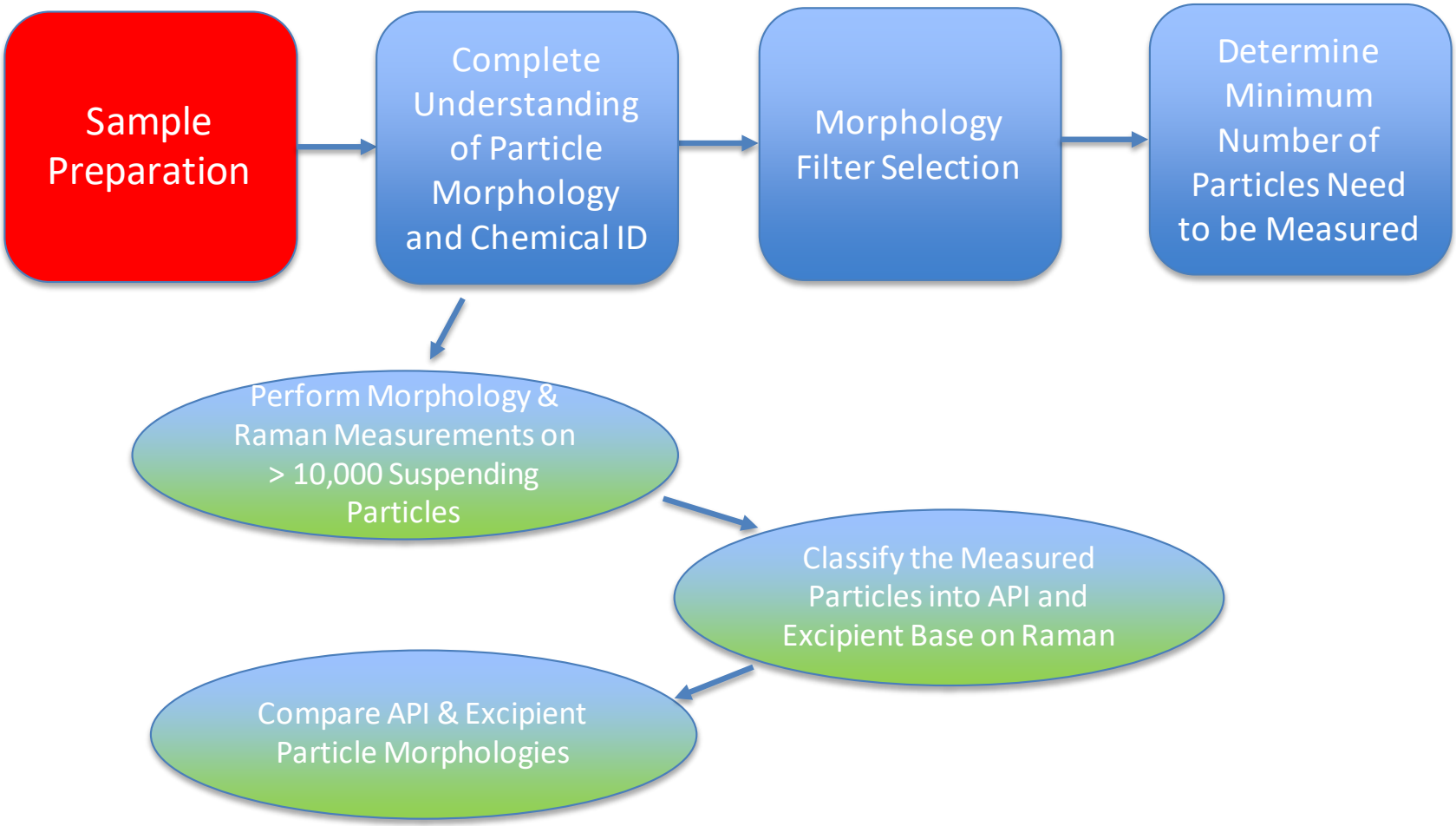
- No background knowledge on API and excipient morphologies.
- No access to the starting materials (API / excipient).

Caution: Morphology information obtained from raw material may not be reliable. Formulation process may alter the morphology of API / excipient.

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



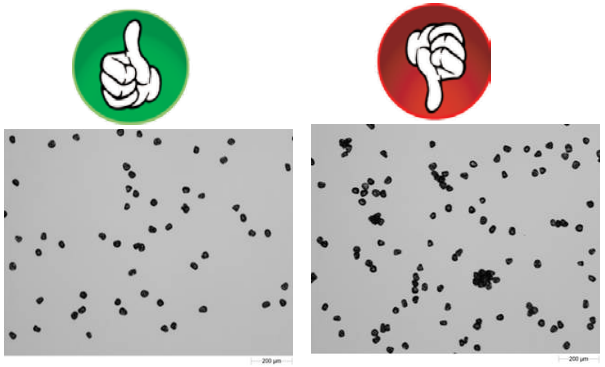
Method Development Example



Method Development Example

Sample Preparation (Wet Method / post-spray):

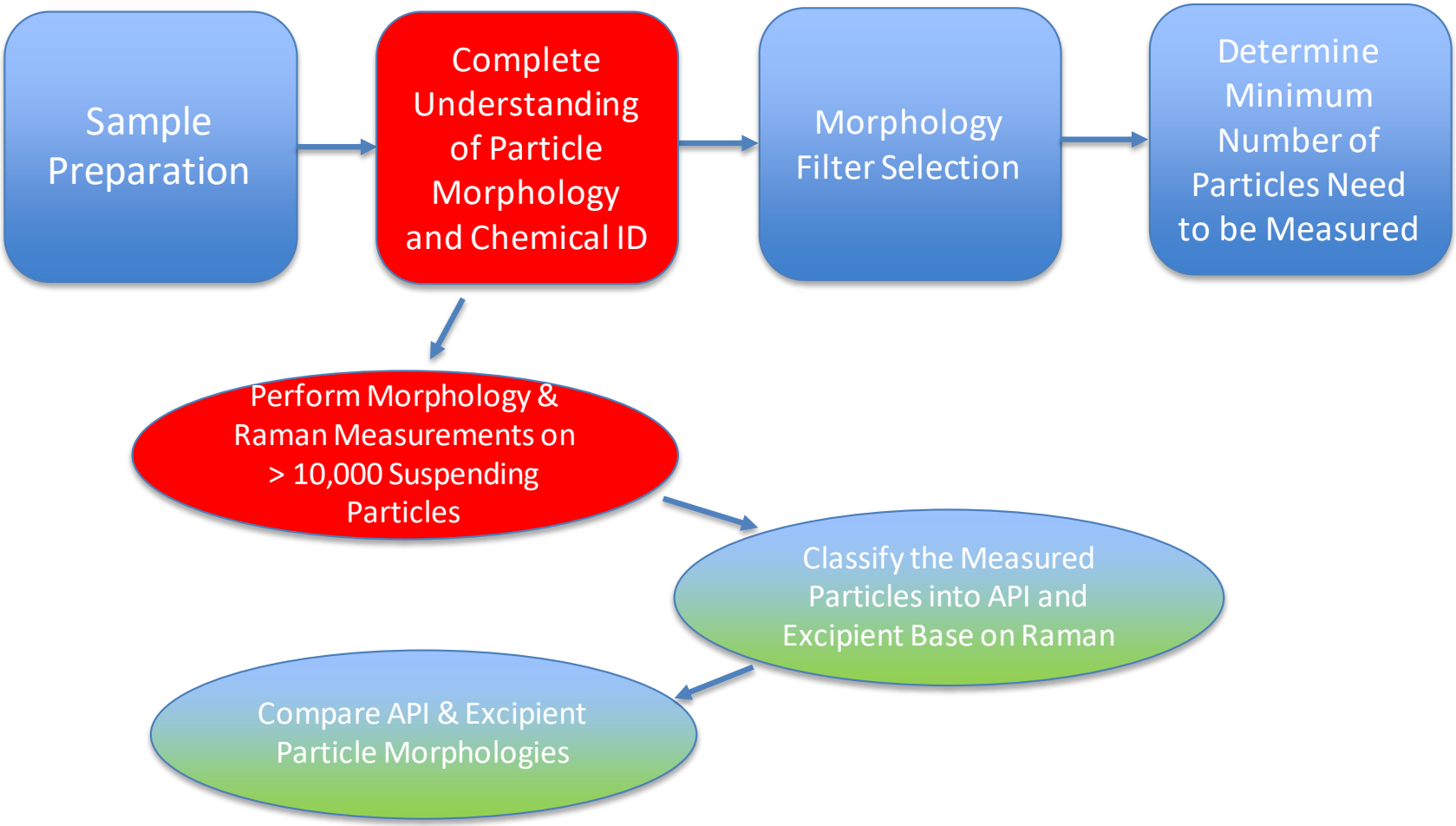
- Gently shook nasal spray bottle (per user instruction).
- Primed the nasal spray pump by delivering 2 – 5 actuations to waste.
- Delivered next 2 actuations into a small glass vial (post-spray).
- Transferred 5 µL of the post-spray sample to a quartz microscope slide.
- Covered sample with a quartz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



Considerations:

- Volume of Sample
  - Possible particle overlapping.
- Time of settlement
  - High viscous formulation: 30 mins to 2 hrs.
  - Low viscous formulation: 12 hrs (Overnight).

Method Development Example

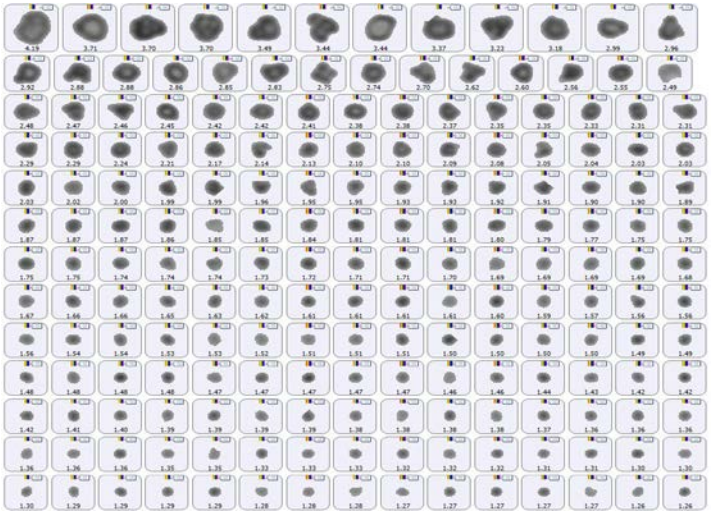


Method Development Example

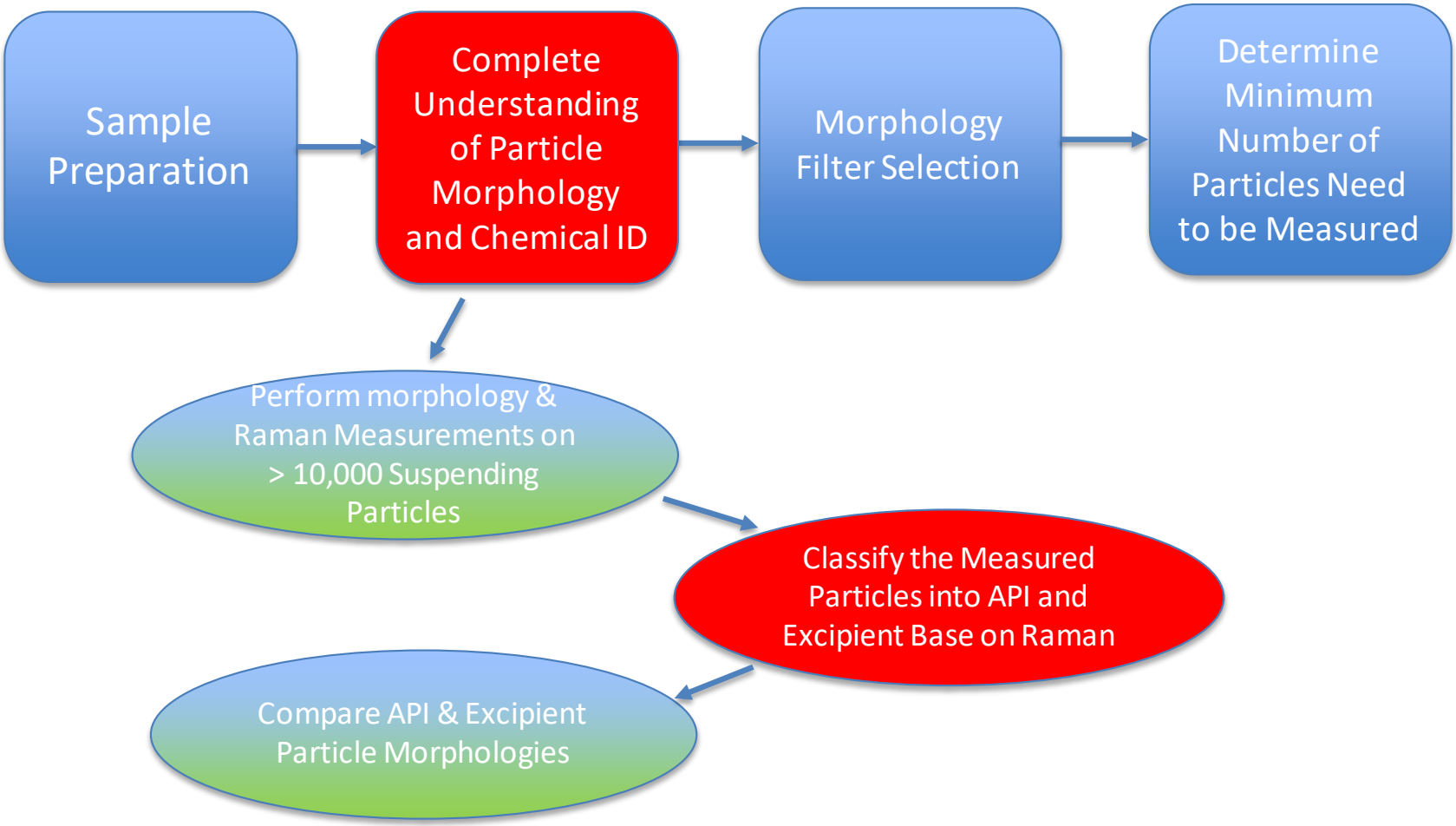
FDA

Perform morphology & Raman measurements on > 10,000 Suspending Particles

- Combining results from 9 Experiments in 9 days
- Total of 16,000 particles were studied.
- Total time spent:
  - ❑ Morphology measurement: ~ 15 mins
  - ❑ Raman measurement: 125 hrs (30 s per particle)



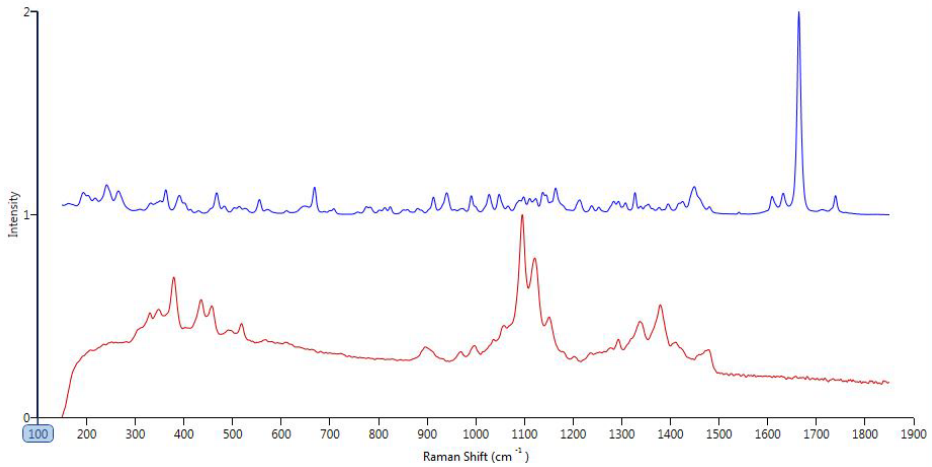
Method Development Example

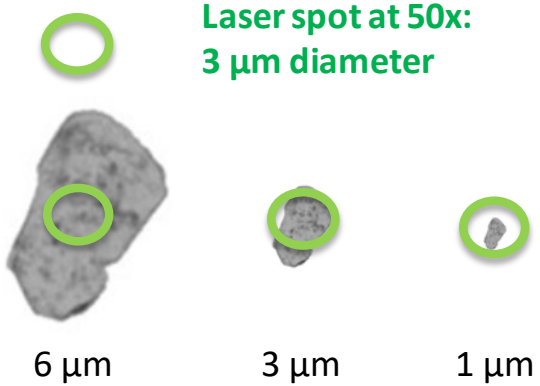


Method Development Example

Classify the Measured Particles into API and Excipient Base on Raman

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

Method Development Example

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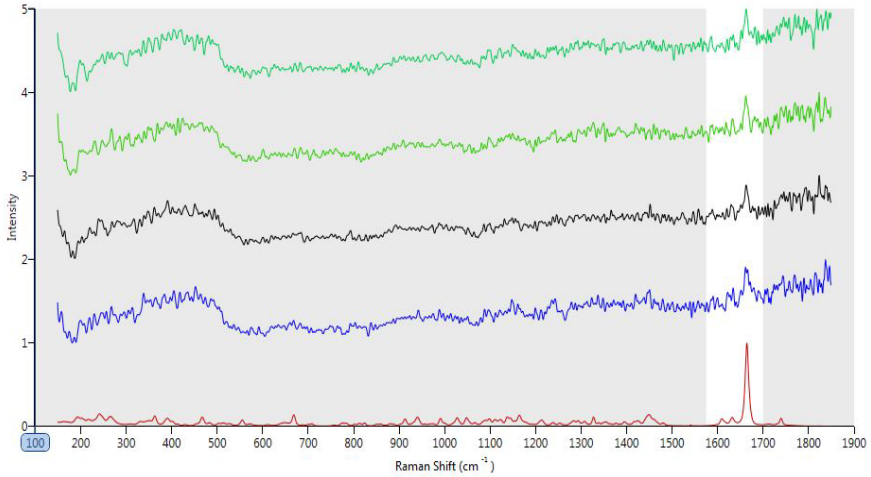


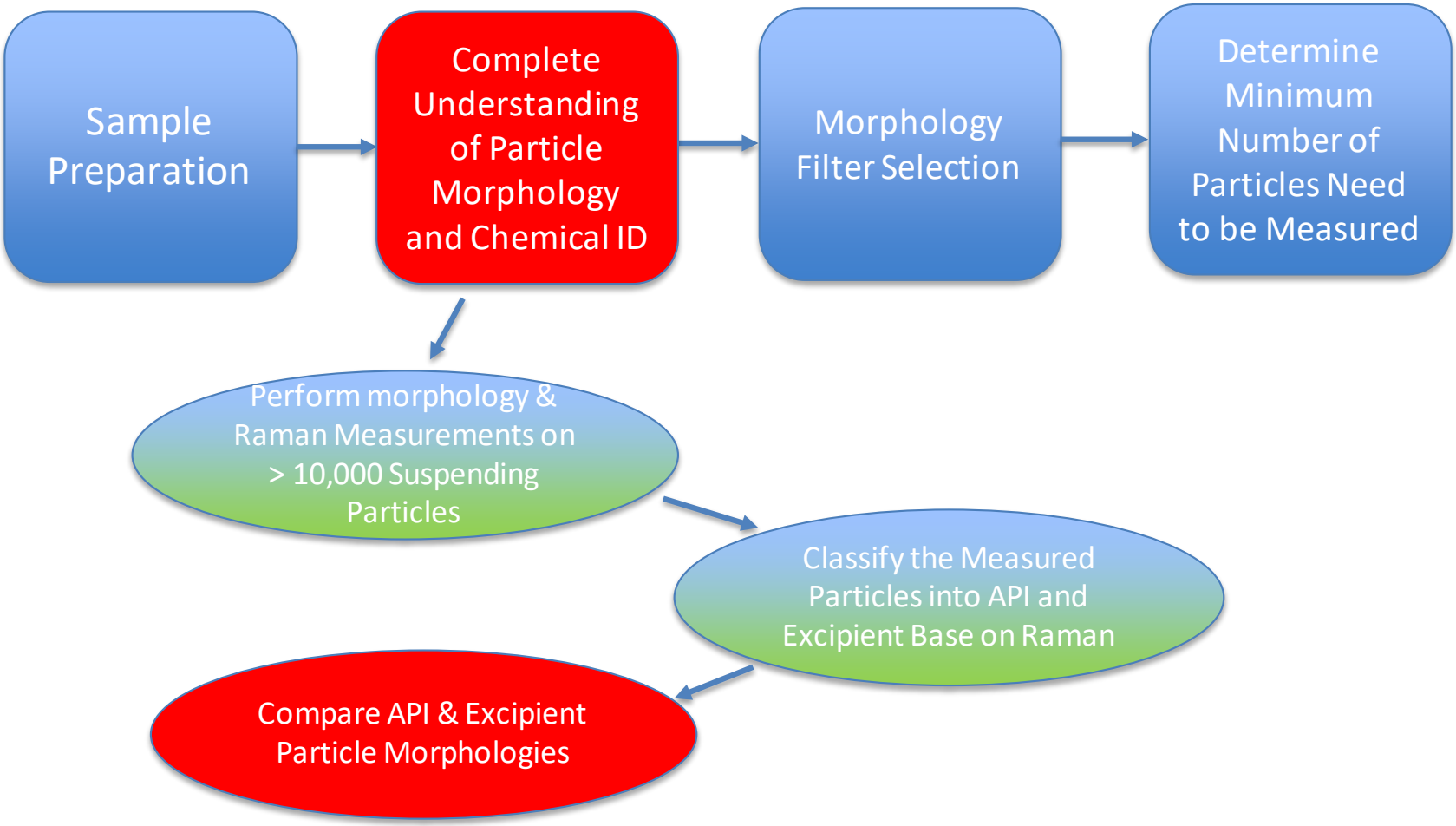
Acceptance criteria: S/N ratio > 3.

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%

Method Development Example

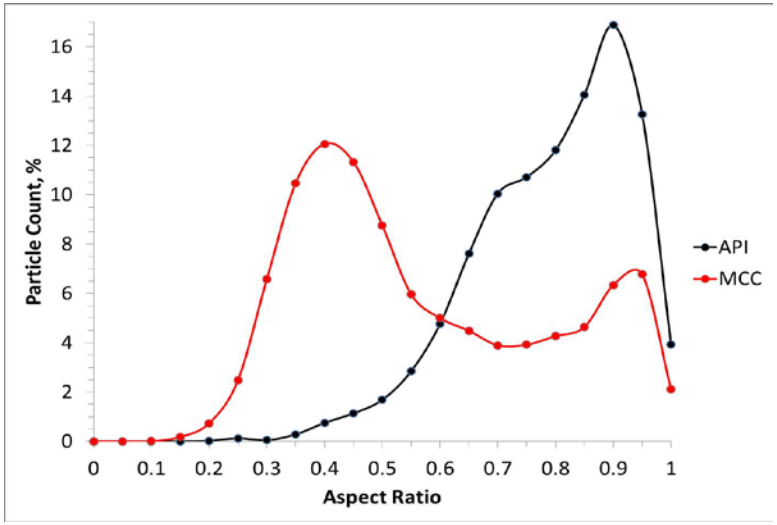


Method Development Example

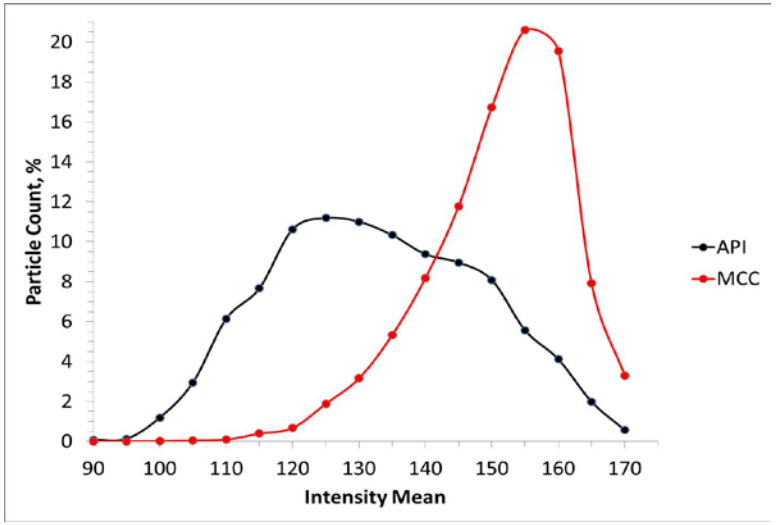
Compare API & Excipient Particle Morphologies

API vs. Excipient Morphology Distribution (Normalized Plots)

Aspect Ratio



Intensity Mean



Method Development Example

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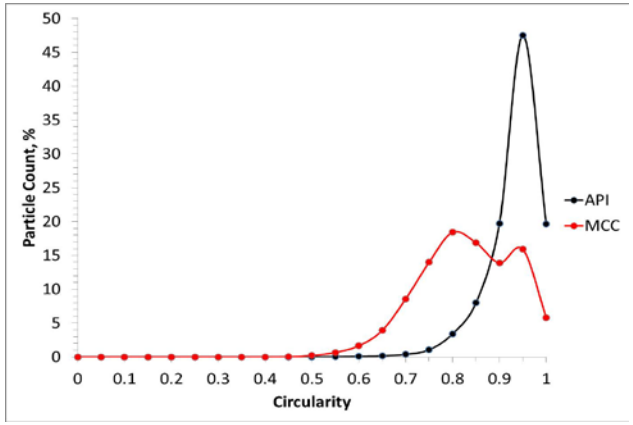
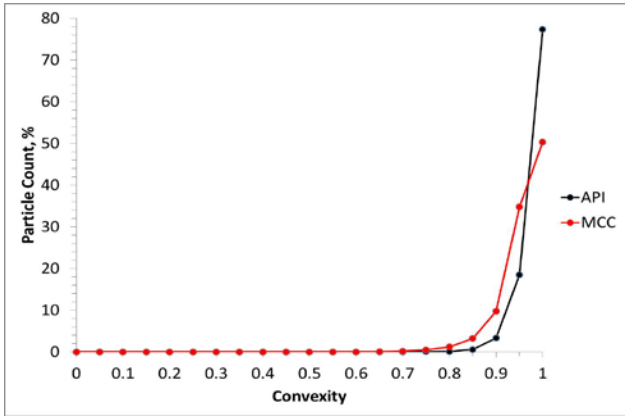
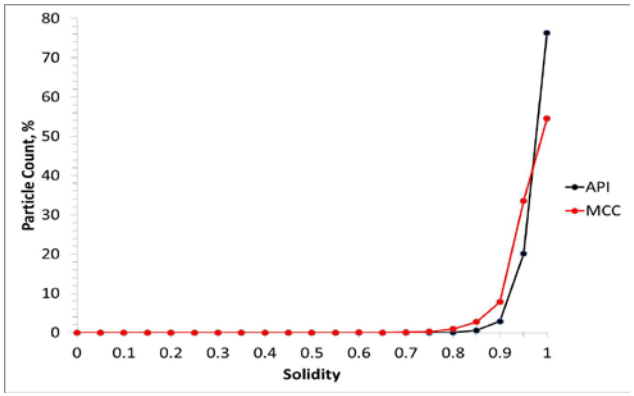
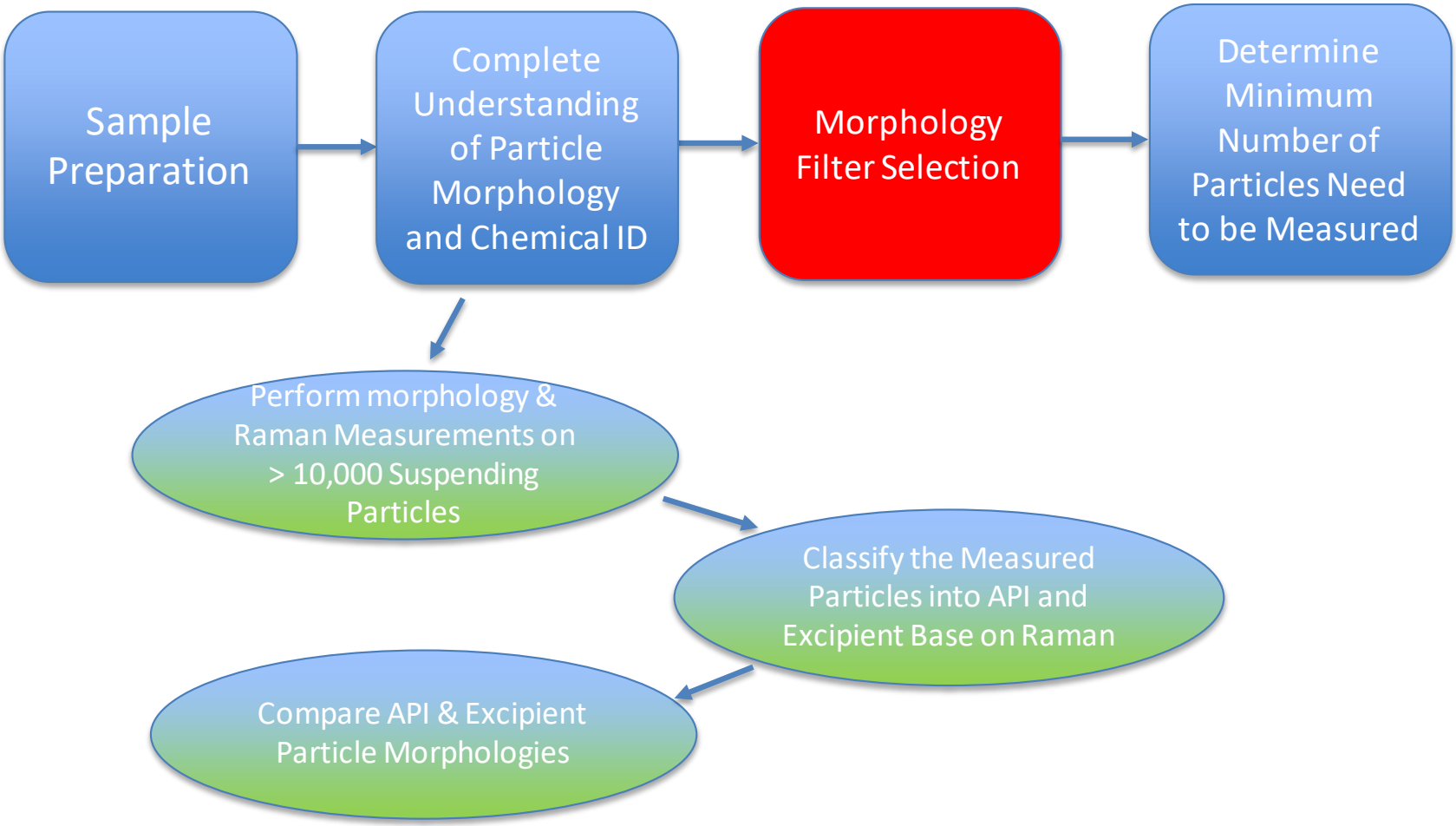




None of the morphology parameters or morphology parameter combinations can provide a complete separation between API and excipient.



Method Development Example



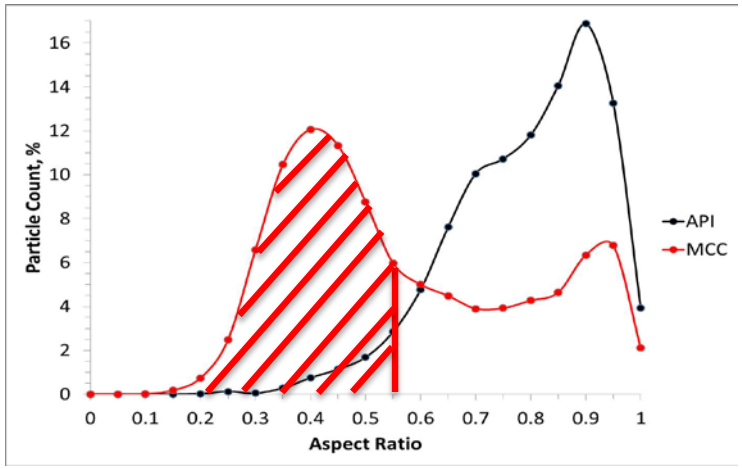
Method Development Example

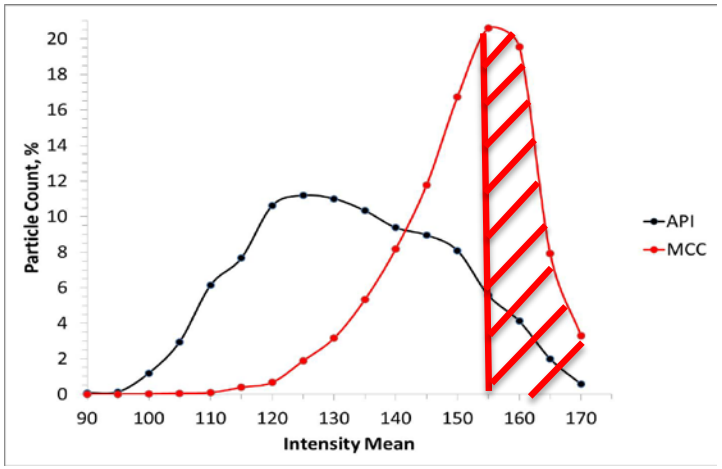
Morphology Filter Selection

Goal:

- 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.





Method Development Example

Morphology Filter Selection

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

Comparison of number of particles analyzed before & after applying morphology filters

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

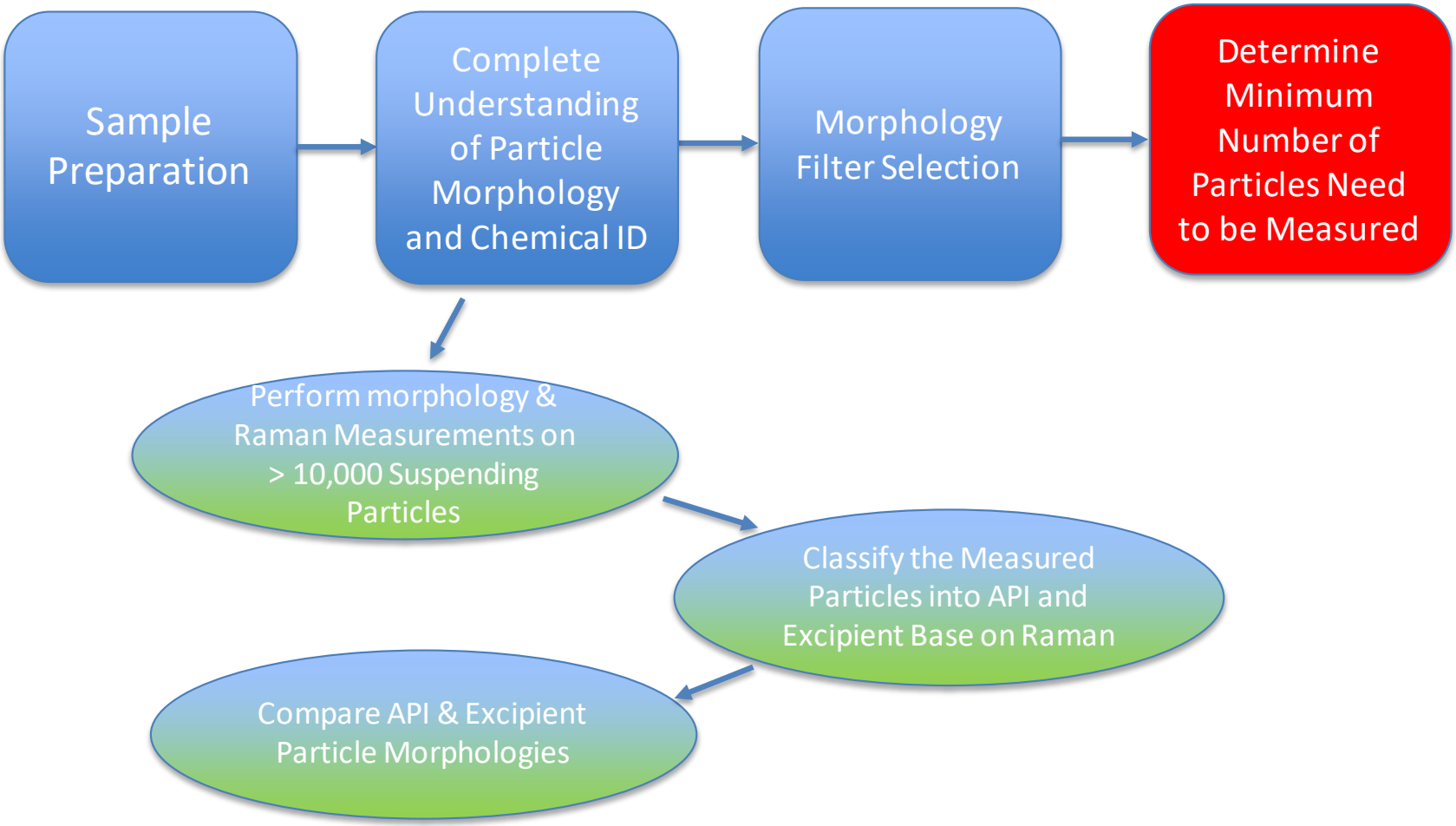
Validate the morphology filter selection

--- 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.

Method Development Example



Method Development Example

Determine Minimum Number of Particles Need to be Measured

Selection rule:

1. Measuring more particles will not result in statistically significant changes in PSD results.
2. The PSD measurement results should be repeatable.

Method:

Perform computer simulation runs to evaluate PSD results when counting number of N (10, 20, 50, 100, 150, 200, 300 …) particles.

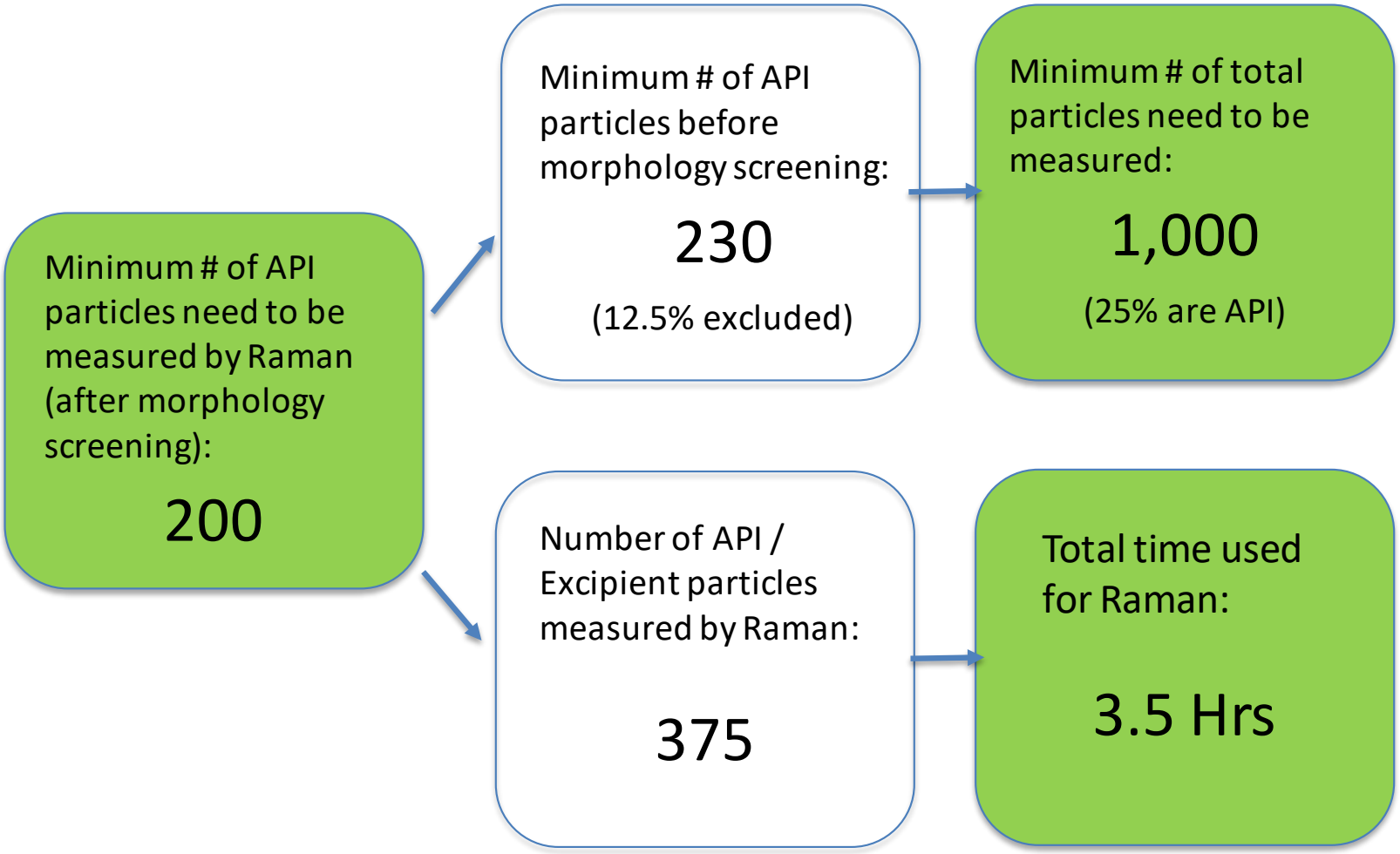
- Randomly pull out number of N particles from the original 4,000 API particles. Five replicates.
- Evaluate PSD results (D_n10, D_n50, D_n90, and D_{mean}) from simulation results.

  Proposed criteria for determining minimum number of particles:

  - Accuracy: < 10% difference compare to PSD result from the 4,000.
  - Repeatability: < 10% in RSD from the 5 replicates.

Method Development Example

Determine Minimum Number of Particles Need to be Measured



Method Development Example

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.**

Summary

The MDRS method in this presentation is an example.

The MDRS parameters and selection criteria used in this presentation may not be applied to other nasal spray suspension products.

MDRS method must be developed on a product-by-product basis. The MDRS parameters and selection criteria need to be scientifically justified.

MDRS method development considerations for different nasal spray suspension products:

- Formulation Viscosity
- API concentration (4% - 30% in total particles)
- API morphology
  - Possible agglomerates / aggregates
- API Raman sensitivity --- possible limit of detection issue for small particles
- API particle size distribution --- influence minimum number of particles
  - Multimodal distribution
  - Single distribution: narrow vs. wide (span)

Summary

MDRS Advantages:

- ✓ Specially designed Raman Microscope system focused on particle sizing.
- ✓ Non-destructive measurements require no change in the formulation.
- ✓ Automatic measurement on particle size, shape, and chemical identity.

MDRS Limitations:

- ➢ Cannot measure particles < 1 µm in diameter.
- ➢ Raman selectivity: some ingredients are weaker Raman scatterers or do not have resolved Raman features.

MDRS is a complex analytical method.

- ➢ Extra effort needed in order to develop a robust MDRS method.

MDRS is an emerging technology.

- ➢ More room to improve.
- ➢ Experience in method development and application need to be gained and shared.

Acknowledgement

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