Advanced Characterization Approaches to Demonstrate Bioequivalence of Nasal Suspension Drug Products

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Nasal Suspension Sprays

Factors affecting nasal drug absorption

API
PSD
Solid State,
Dissolution

+

Formulation
Excipients
Process,
Rheology

+

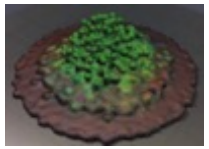
Device
Pump design,
Spray pattern,
Droplet size

+

Patient Activation
Force to fire
Orientation,
Priming,

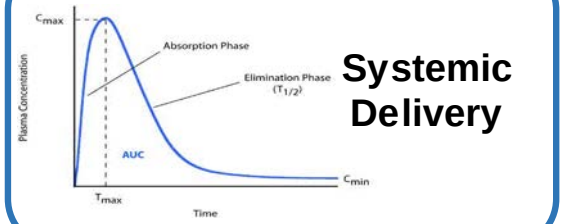
Nasal deposition
Droplet size
Regional Dep,
Nasal Drip

+



Dissolution & Permeability
Physiochem,
fluid volume,
retention time

Site of Action
(Local Effect)



Systemic Delivery

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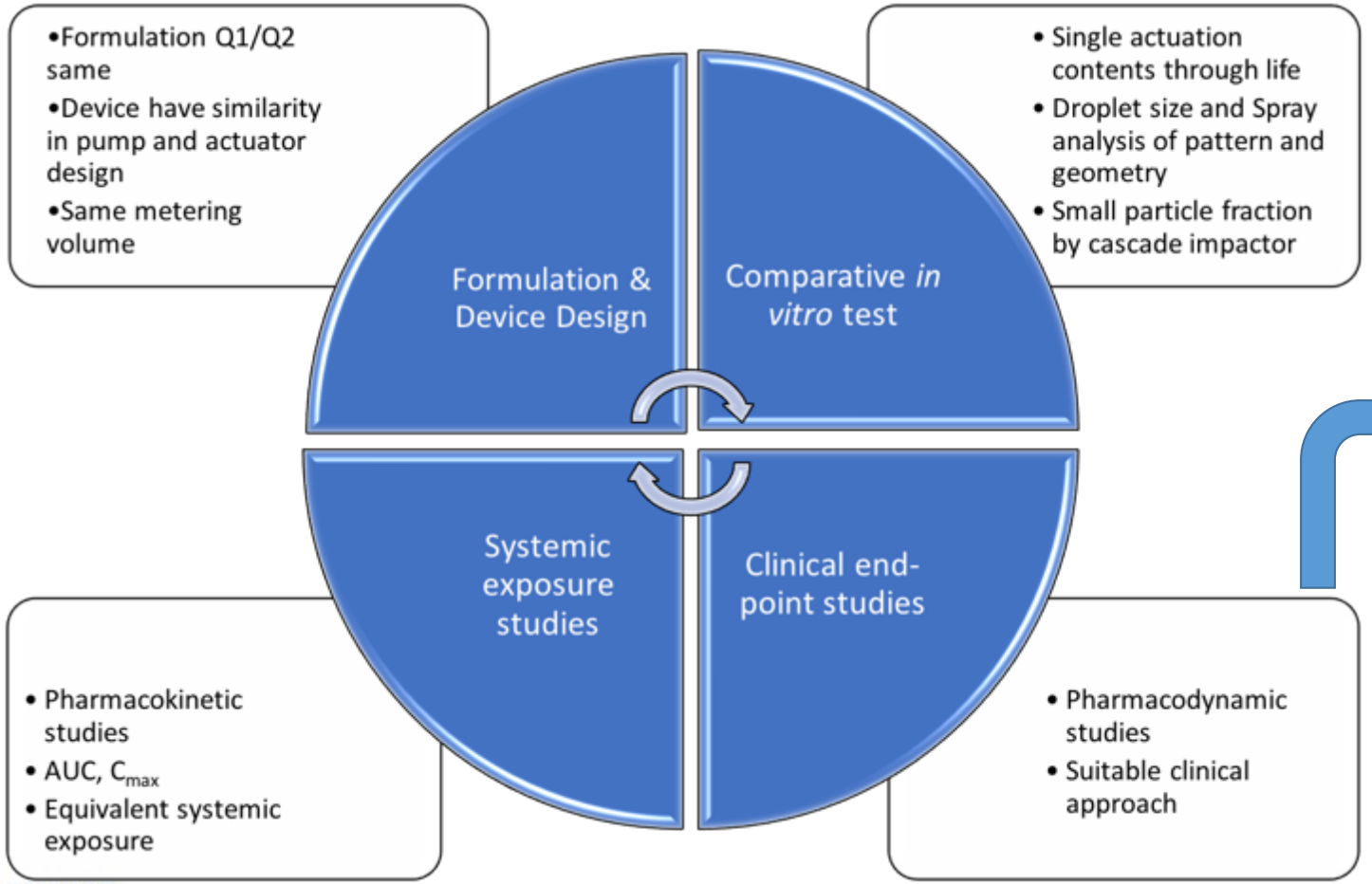
Weight of Evidence Approach for Demonstrating Bioequivalence of Nasal Suspensions



- Required since pharmacokinetic (PK) studies and current *in vitro* studies may not fully describe the fate of the drug in the nose with high resolution. Limited IVIVC.
- Designing and executing clinical end-point studies for nasal suspensions is difficult.
- Methods to assess local equivalence with high resolution and lower costs are urgently needed.

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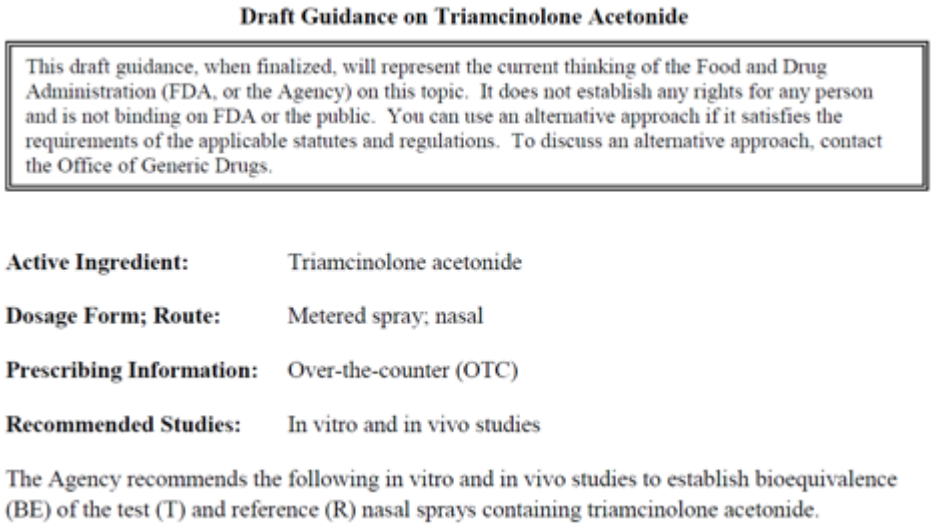
Alternate Approach to the Comparative Clinical Endpoint Study

API Particle Size in Nasal Sprays

- "*A clinical endpoint BE study is recommended… because of an inability to adequately characterize drug particle size distribution (PSD)… using commonly used analytical methods*".
- "*Drug PSD in suspension formulations influence rate and extent of drug availability to nasal sites of action and to systemic circulation*".
- **If drug PSD in the T and R products can be accurately measured using a validated analytical method such as Morphology Directed Raman Spectroscopy** or any other advanced methodology, sponsors may submit comparative particle size distribution data as part of their drug characterization within their ANDA application.
- "*An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range*".



Draft Guidance on Triamcinolone Acetonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

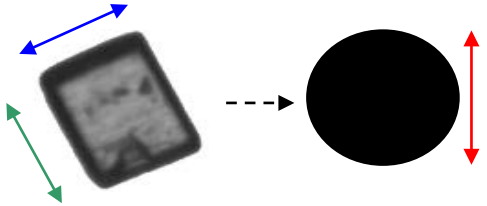
Active Ingredient:	Triamcinolone acetonide
Dosage Form; Route:	Metered spray; nasal
Prescribing Information:	Over-the-counter (OTC)
Recommended Studies:	In vitro and in vivo studies

The Agency recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing triamcinolone acetonide.

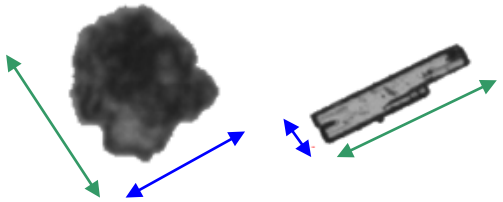
Morphology-Directed Raman Spectroscopy

- MDRS combines automated image analysis and Raman Spectroscopy to measure 3 key particle parameters:

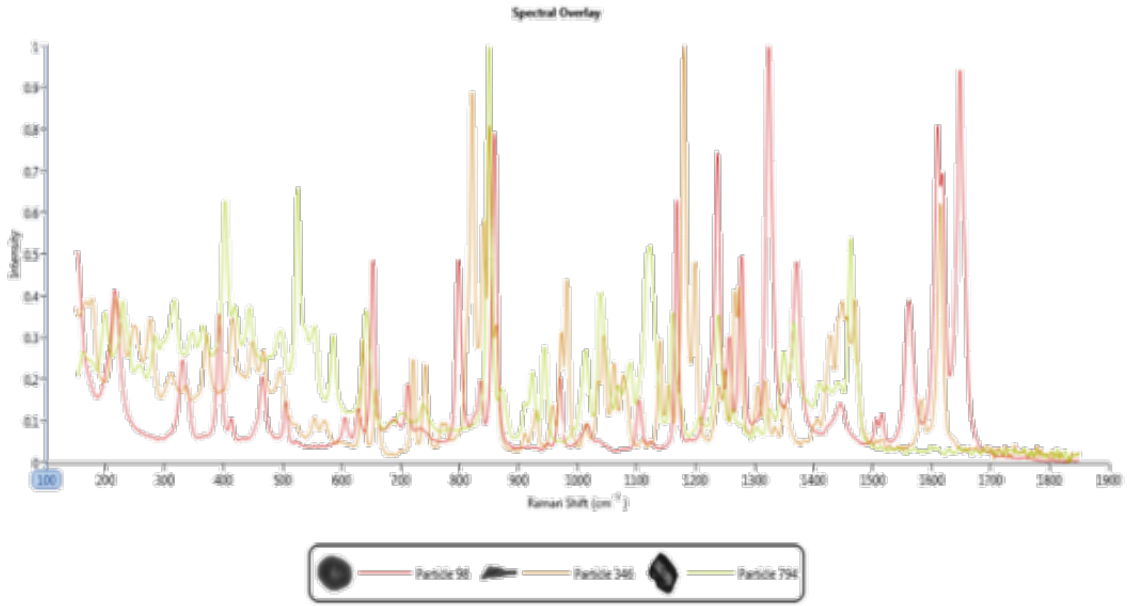
Particle size



Particle shape



Chemical identity



Morphology Directed Raman Spectroscopy (MDRS) Approach to Characterize Nasal Suspensions

Sample Preparation
- Wet dispersion – nasal sprays
- Evaporative method – raw API

Threshold
- Defining the particle centre and edge

Filters 1
- Convexity and solidity filters are used to remove very large aggregates and "contaminants"

Morphological Analysis
- Placebo and Nasonex
- Compare and choose new filters

Filters 2
- **Elongation**
- High sensitivity circularity
- Mean intensity
- Distinguish Placebo and API

Chemical ID

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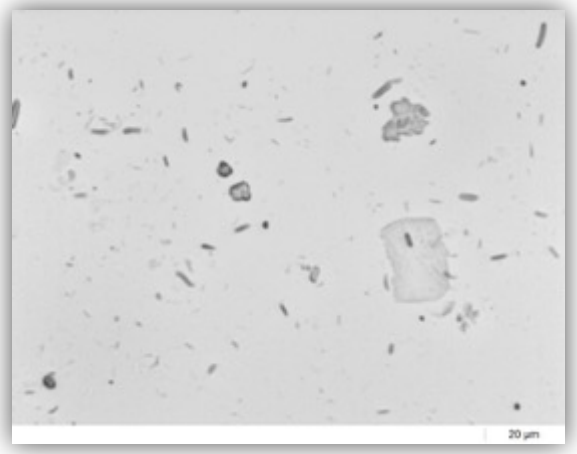
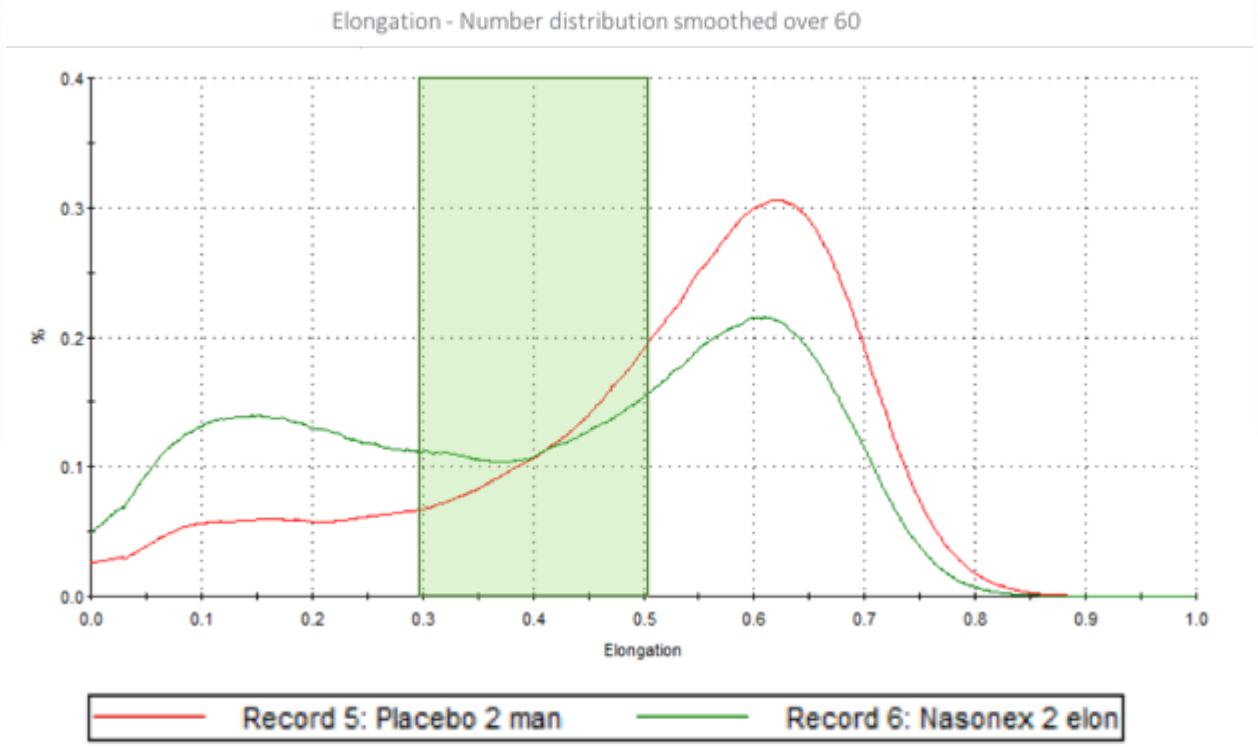
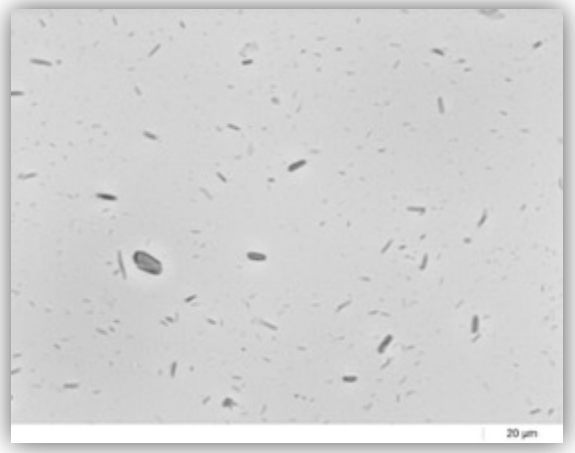
Morphological Analysis of Mometasone Innovator Nasal Spray and Placebo







- Elongation is defined as [1-aspect ratio] or [1-width/length] and has values in the range 0-1.
- Excipent particles are more elongated than drug particles.
- Elongation filter can be applied to differentiate drug particles from excipient particles.

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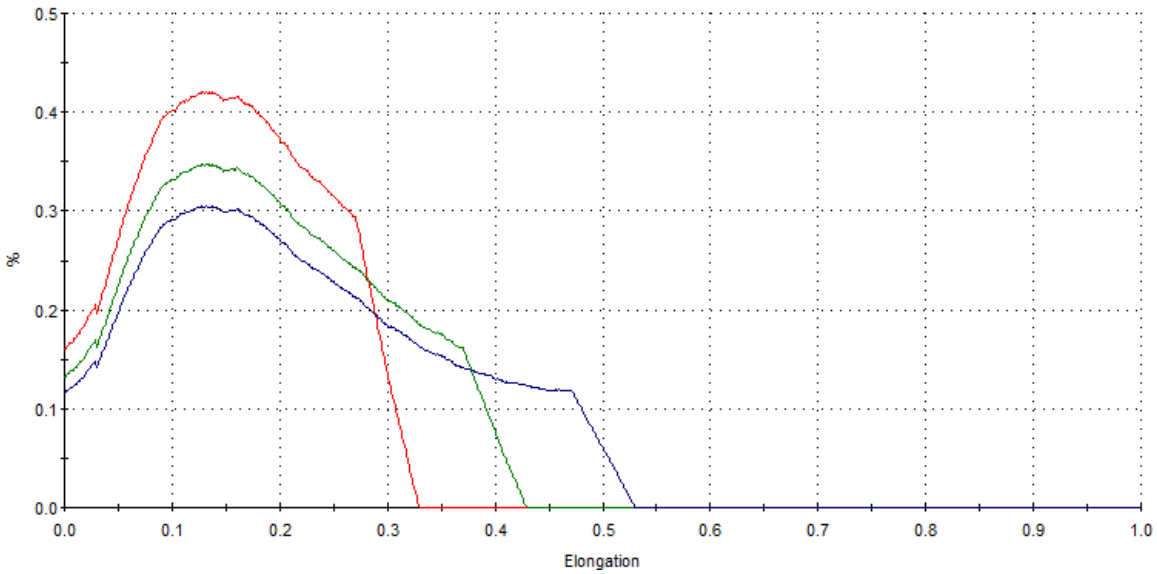
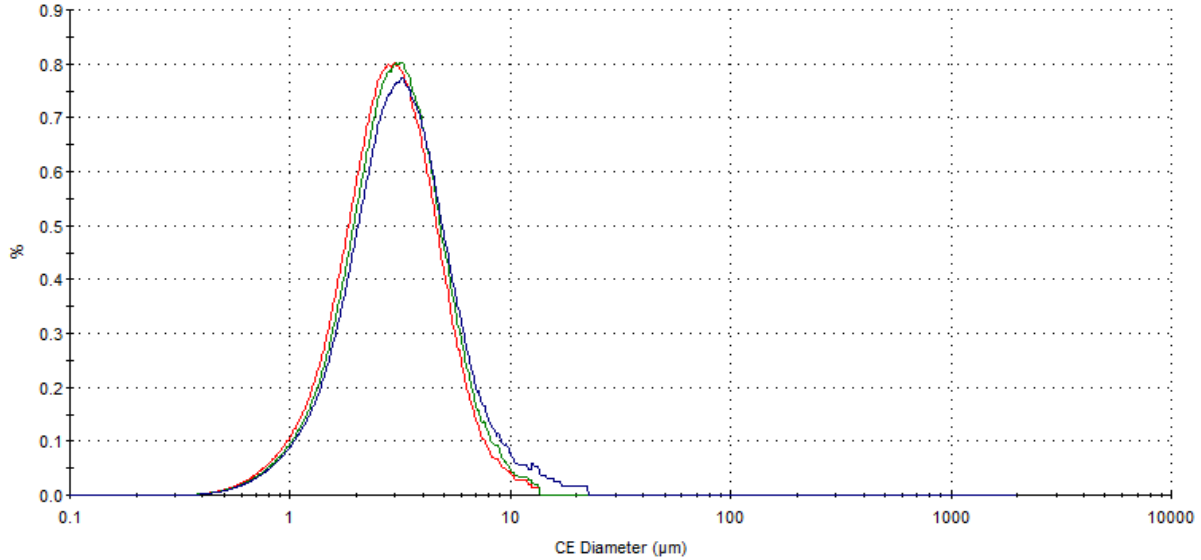
Effect of Morphology Filters on PSD of Mometasone Innovator Nasal Spray Measured by MDRS

- **Elongation filters** – Applying filters between <0.3 and <0.5 **does not effect** the measured PSD significantly

Elongation - Number distribution smoothed over 60 points



Volume distribution smoothed over 60 points



RLD – Elongation filter < 0,3
RLD – Elongation filter < 0,4
RLD – Elongation filter < 0,5

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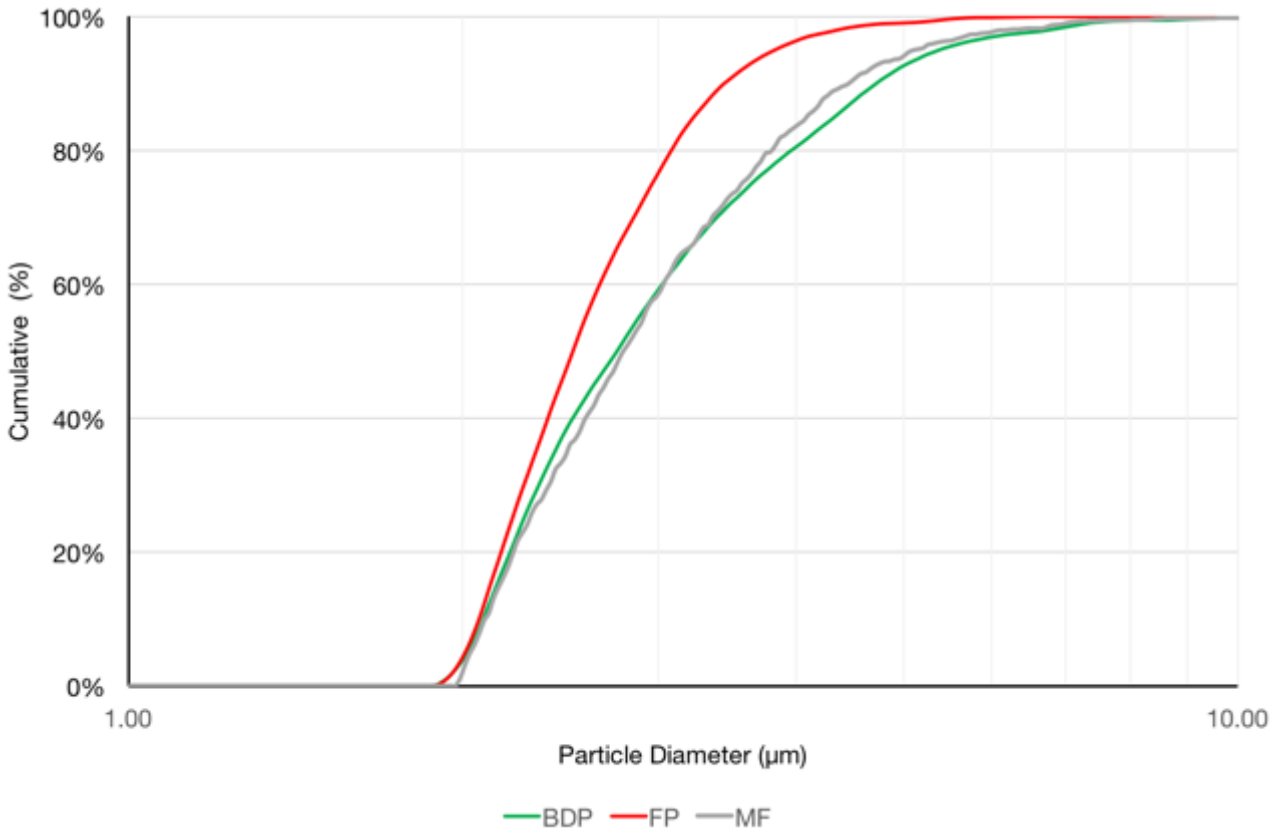
MDRS Analysis of Commercial Innovator Nasal Products



Product	Dv(10) /µm	Dv(50) /µm	Dv(90) /µm
Beclomethasone	2.09 (0.18)	2.75 (0.85)	4.70 (0.56)
Fluticasone Propionate	2.07 (0.17)	2.51 (0.43)	3.45 (0.39)
Mometasone	2.10 (0.03)	2.80 (0.11)	4.37 (0.21)

- Limit of particle size measurement resolution is approximately 1 µm.
- Chemical ID increases sample measurement time, but required for accurate PSD determination.

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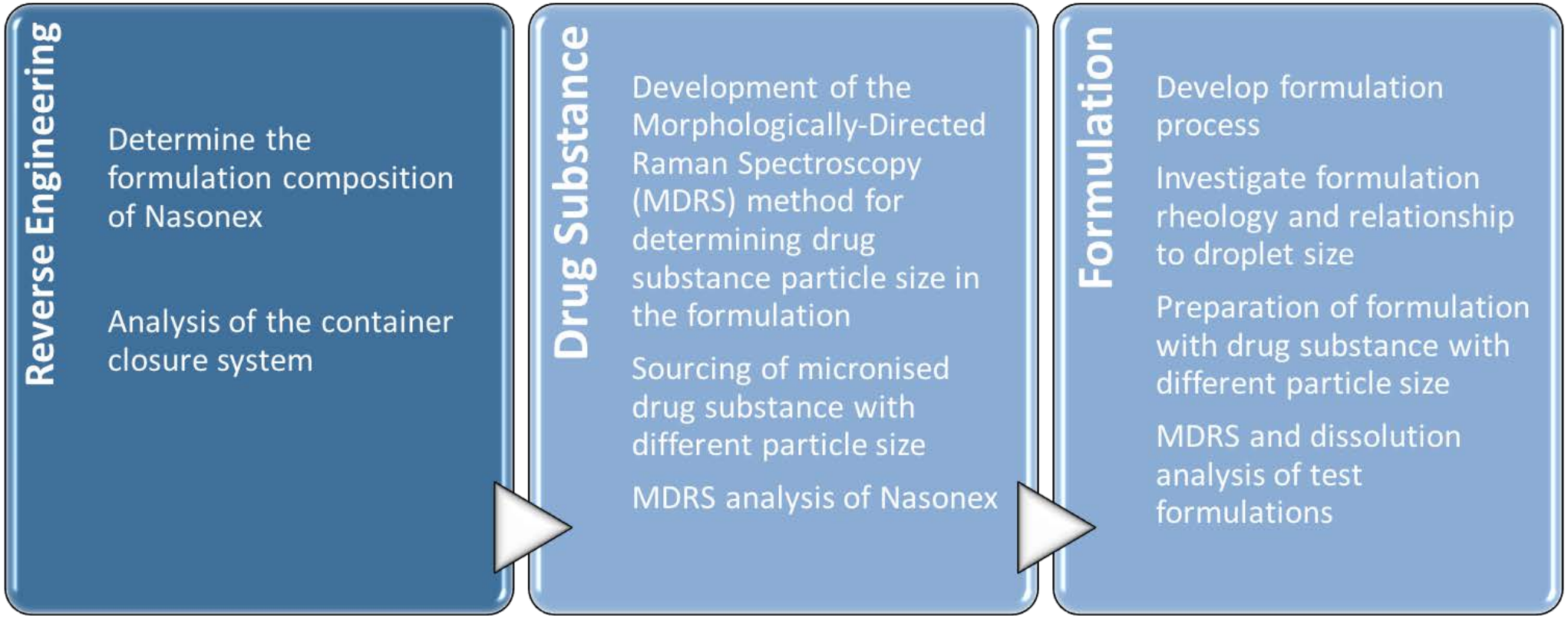
FDA Contract: HHSF223201310220C
Drug Substance and Formulation Investigations at UoB



- **Nasal Pumps utilised**: Screw-on VP3 pump (18/415, Aptar Pharma, France).

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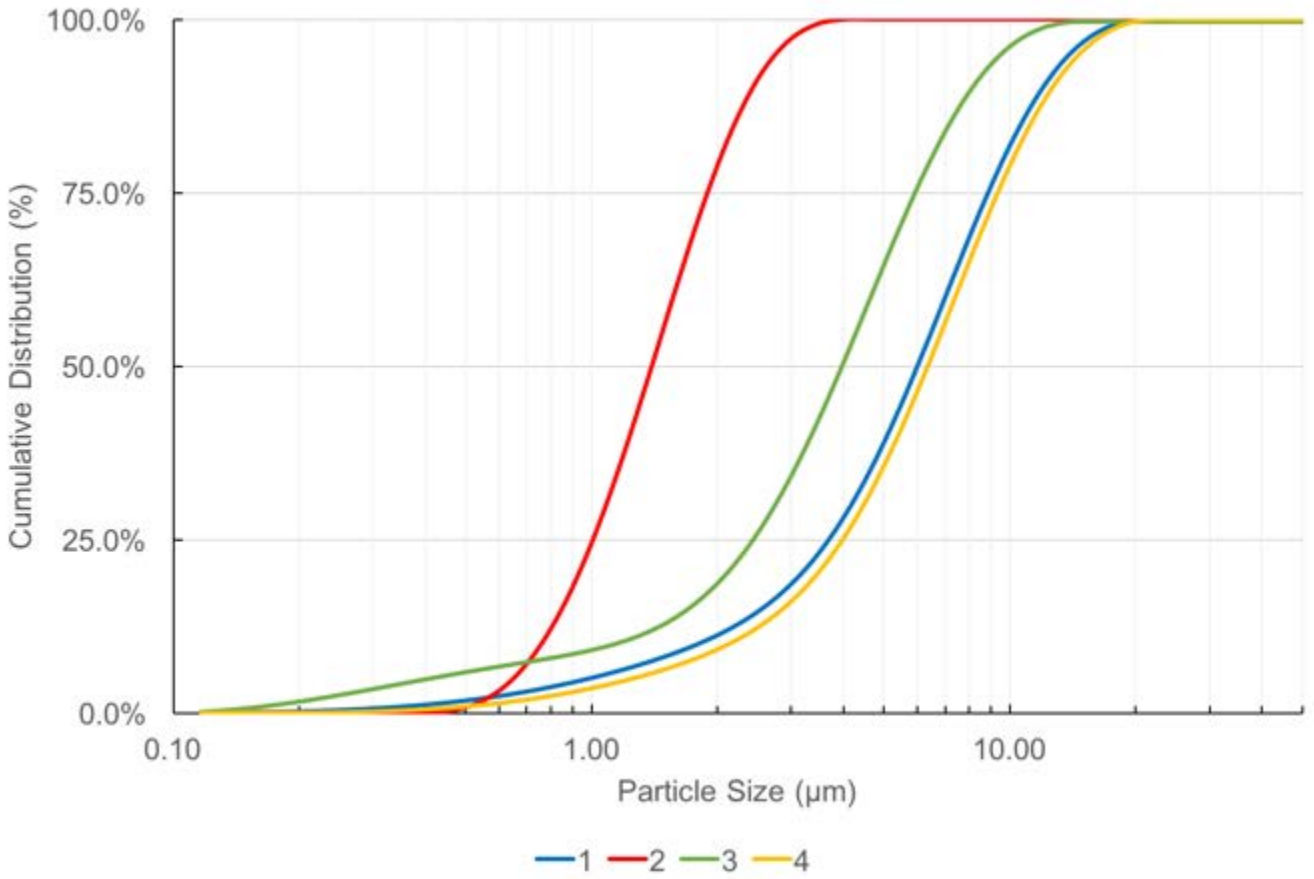
Raw API Particle Size Distribution of Batches of Mometasone Furoate Monohydrate – Laser Diffraction



Batch Number	Dv(10) /µm	Dv(50) /µm	Dv(90) /µm
1	1.81 (0.05)	6.01 (0.15)	11.94 (0.25)
2	0.76 (0.01)	1.39 (0.01)	2.42 (0.03)
3	1.14 (0.01)	3.97 (0.02)	8.11 (0.1)
4	2.14 (0.05)	6.36 (0.08)	12.57 (0.11)

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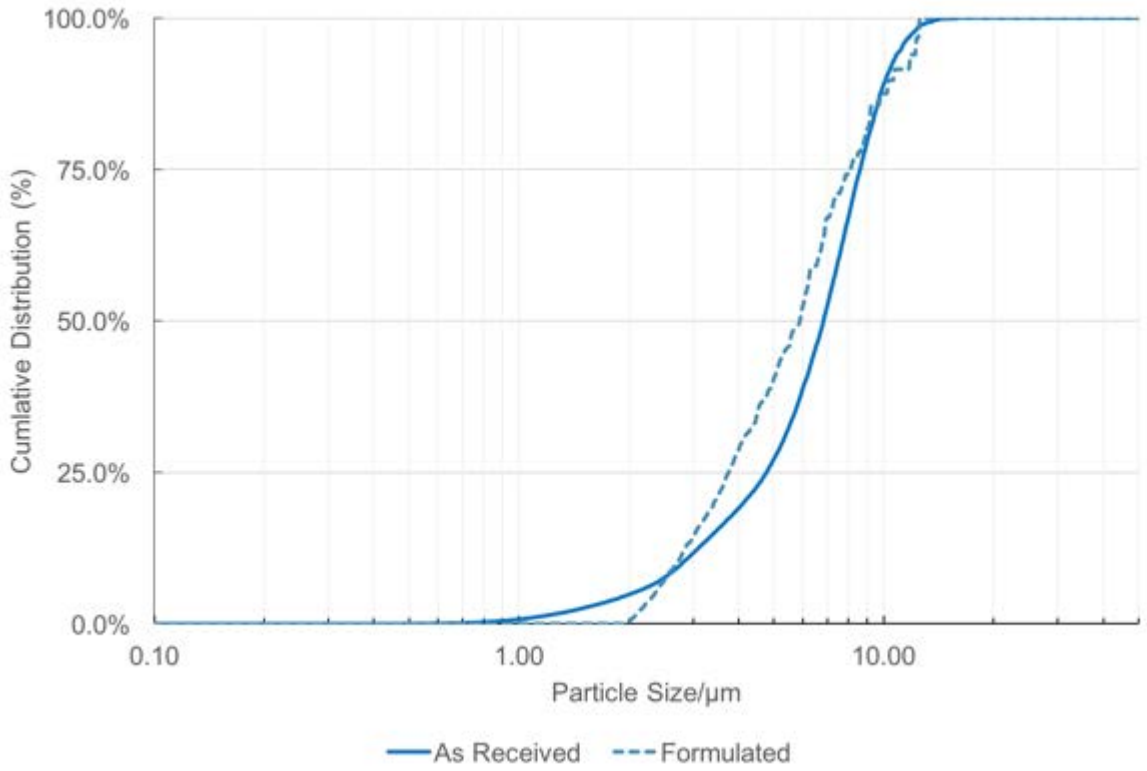
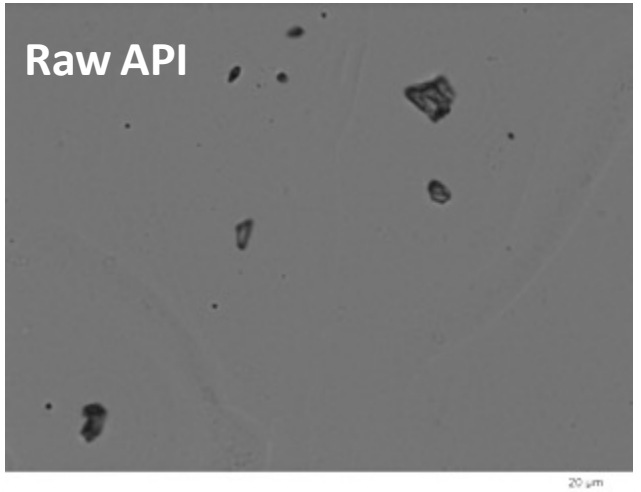
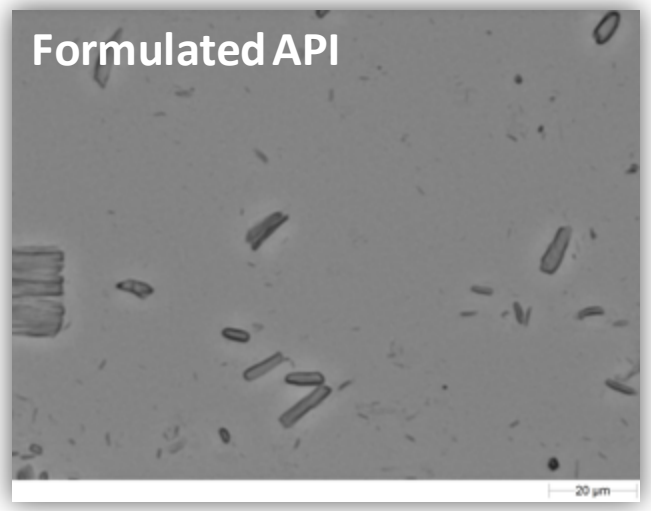
As-received and Formulated API MDRS PSD – Batch 1



Batch	Dv(10) /µm	Dv(50) /µm	Dv(90) /µm
As-received	2.81 (0.05)	6.84 (0.50)	10.09 (0.48)
Formulated	2.72 (0.29)	5.64 (0.62)	10.26 (1.36)





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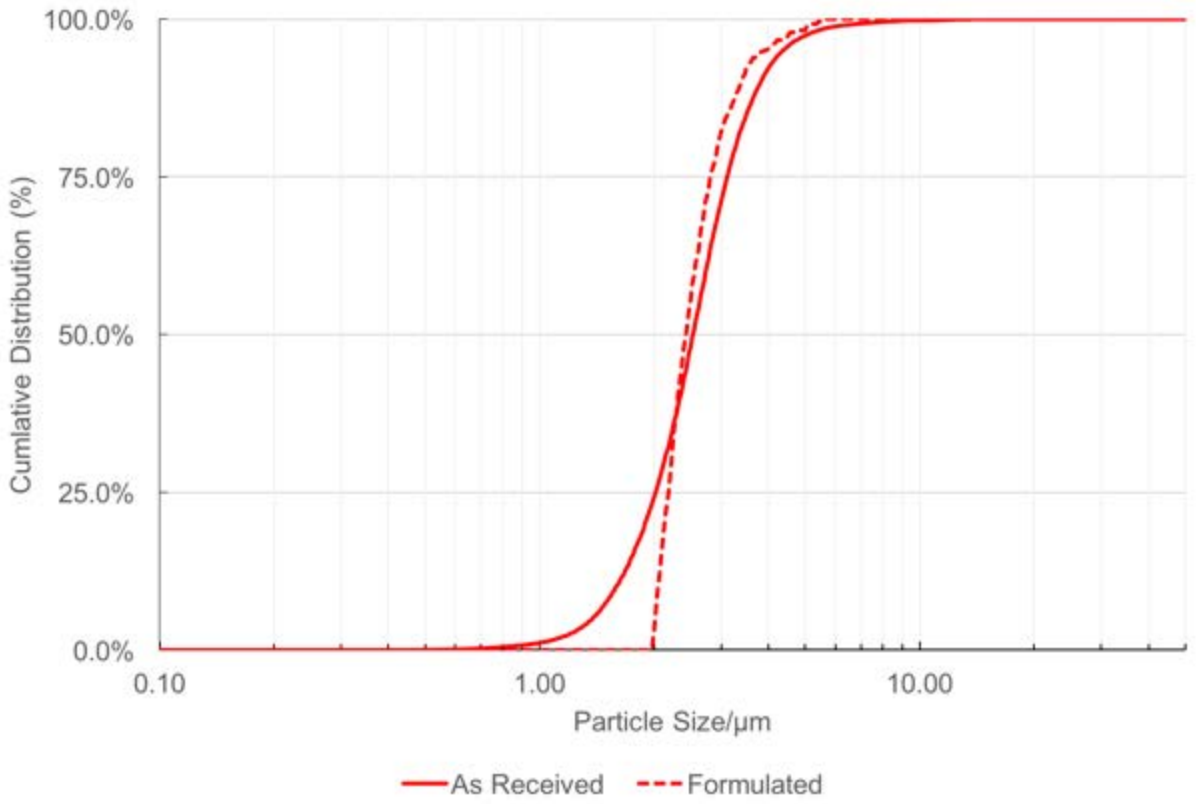
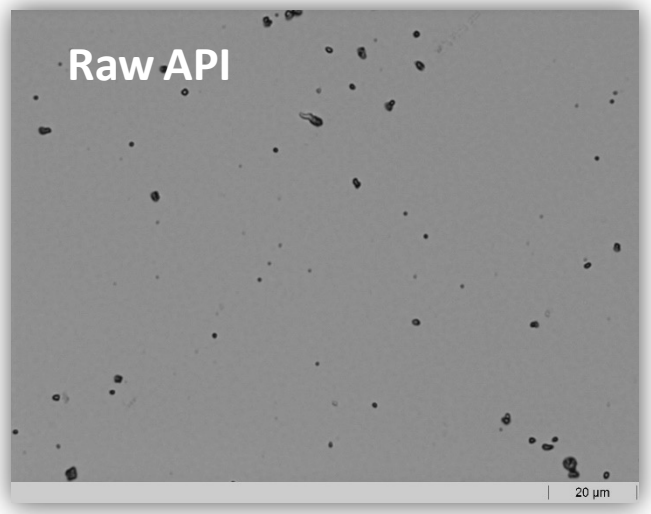
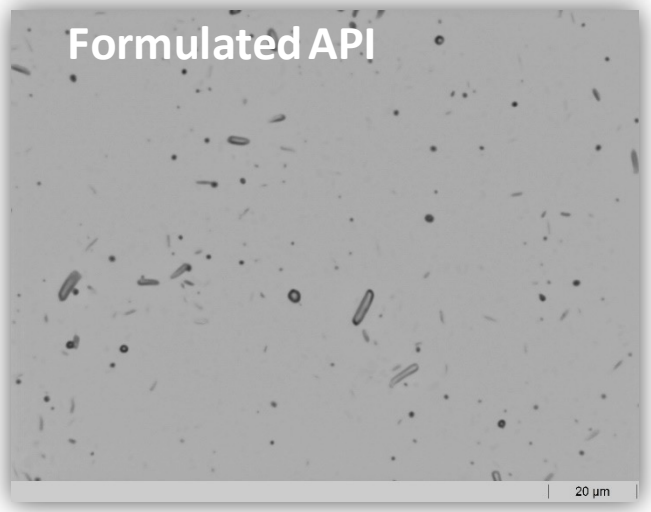
As-received and Formulated API MDRS PSD – Batch 2



Batch	Dv(10) /µm	Dv(50) /µm	Dv(90) /µm
As-received	1.63 (0.19)	2.54 (0.24)	3.77 (0.34)
Formulated	2.05 (0.01)	2.43 (0.03)	3.41 (0.15)





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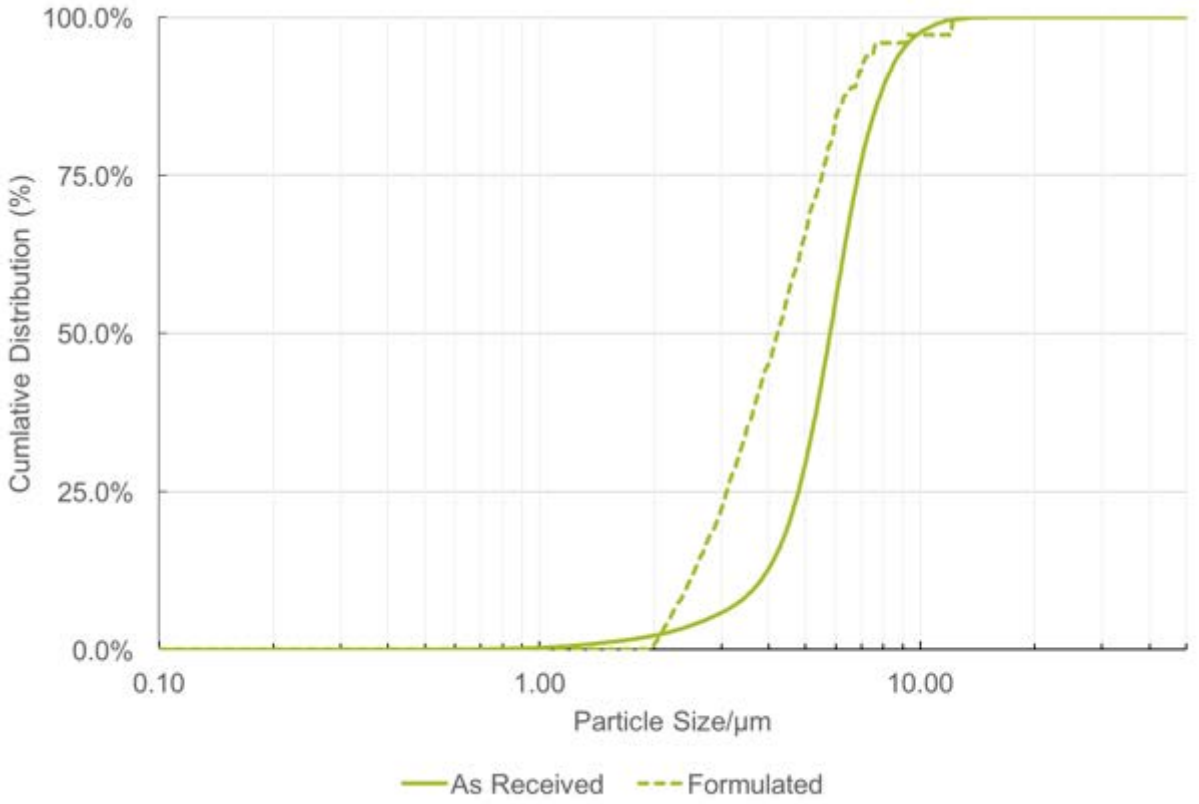
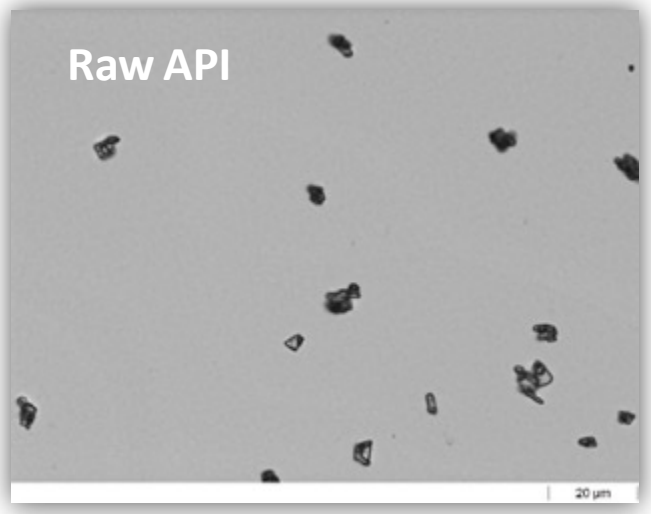
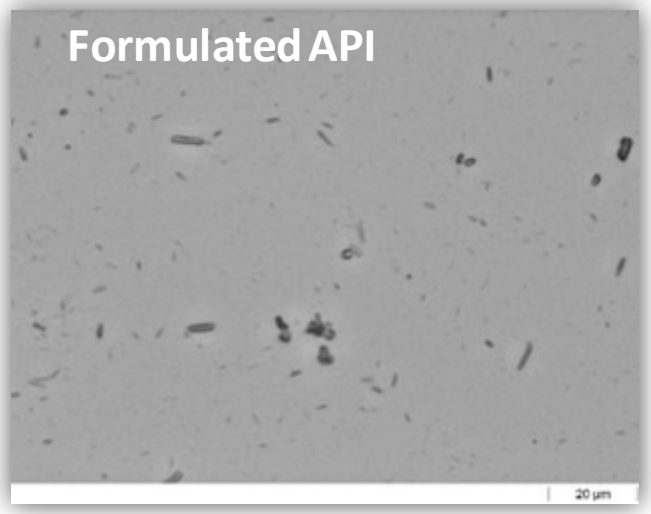
As-received and Formulated API MDRS PSD – Batch 3



Batch	Dv(10) /µm	Dv(50) /µm	Dv(90) /µm
As-received	3.69 (0.15)	5.80 (0.04)	8.14 (0.26)
Formulated	2.47 (0.20)	4.21 (0.46)	6.60 (0.40)





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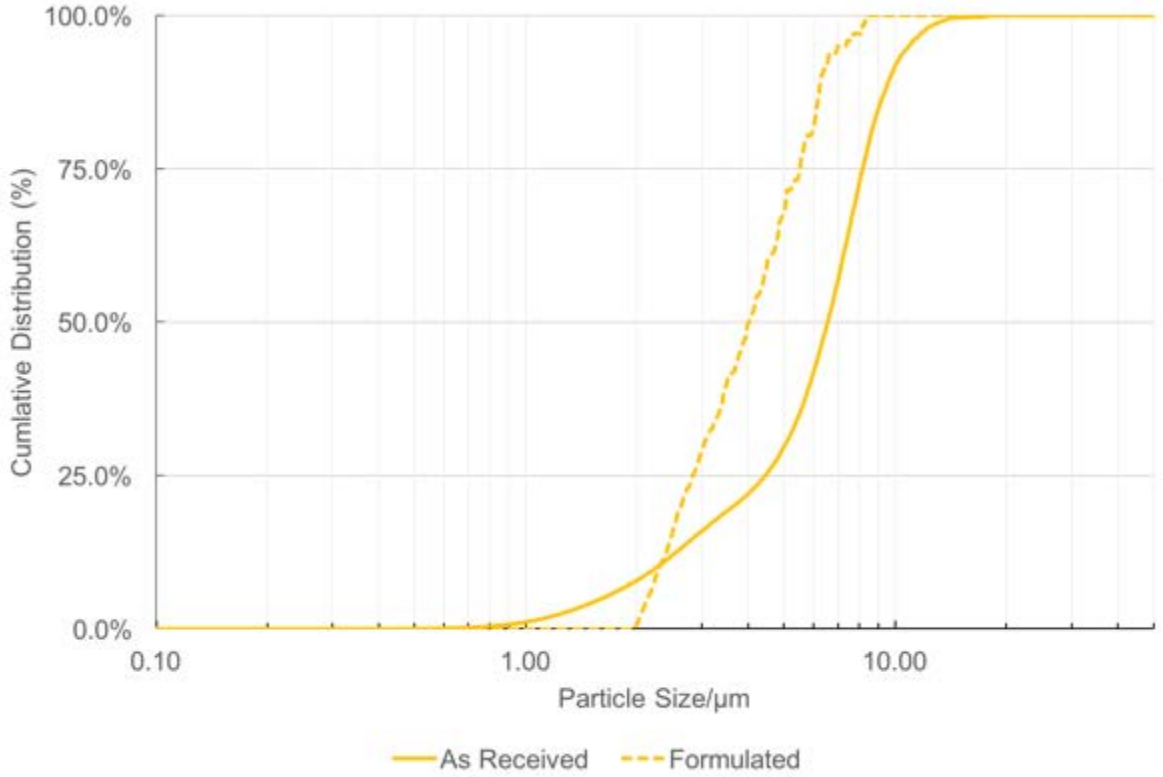
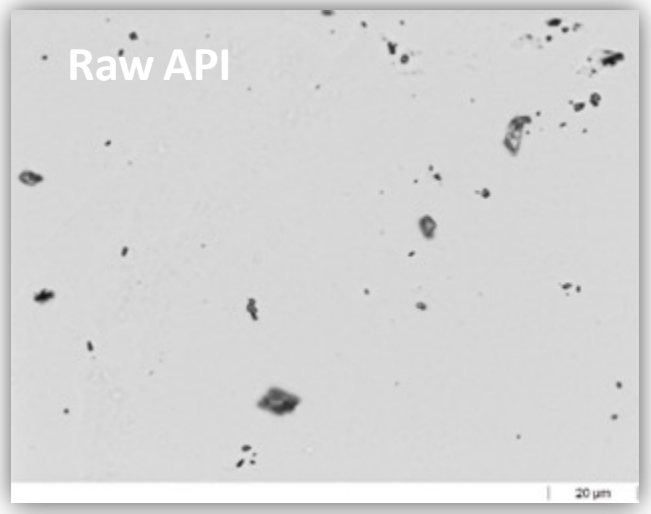
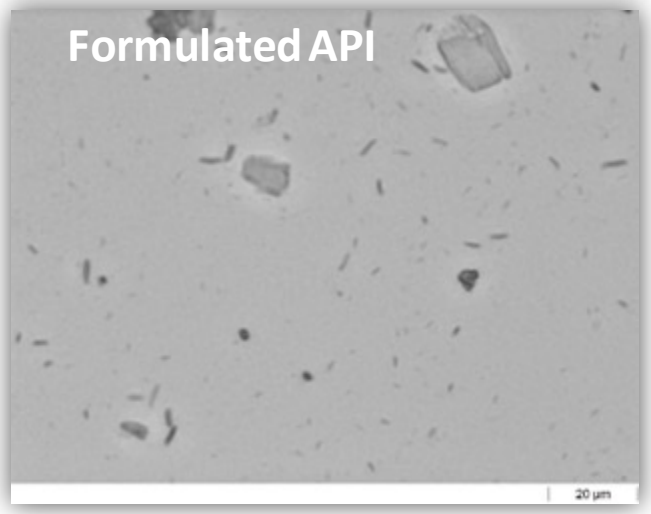
As-received and Formulated API MDRS PSD – Batch 4



Batch	Dv(10) /µm	Dv(50) /µm	Dv(90) /µm
As-received	2.60 (1.13)	6.54 (0.23)	9.72 (0.20)
Formulated	2.30 (0.01)	4.03 (0.04)	6.33 (0.07)





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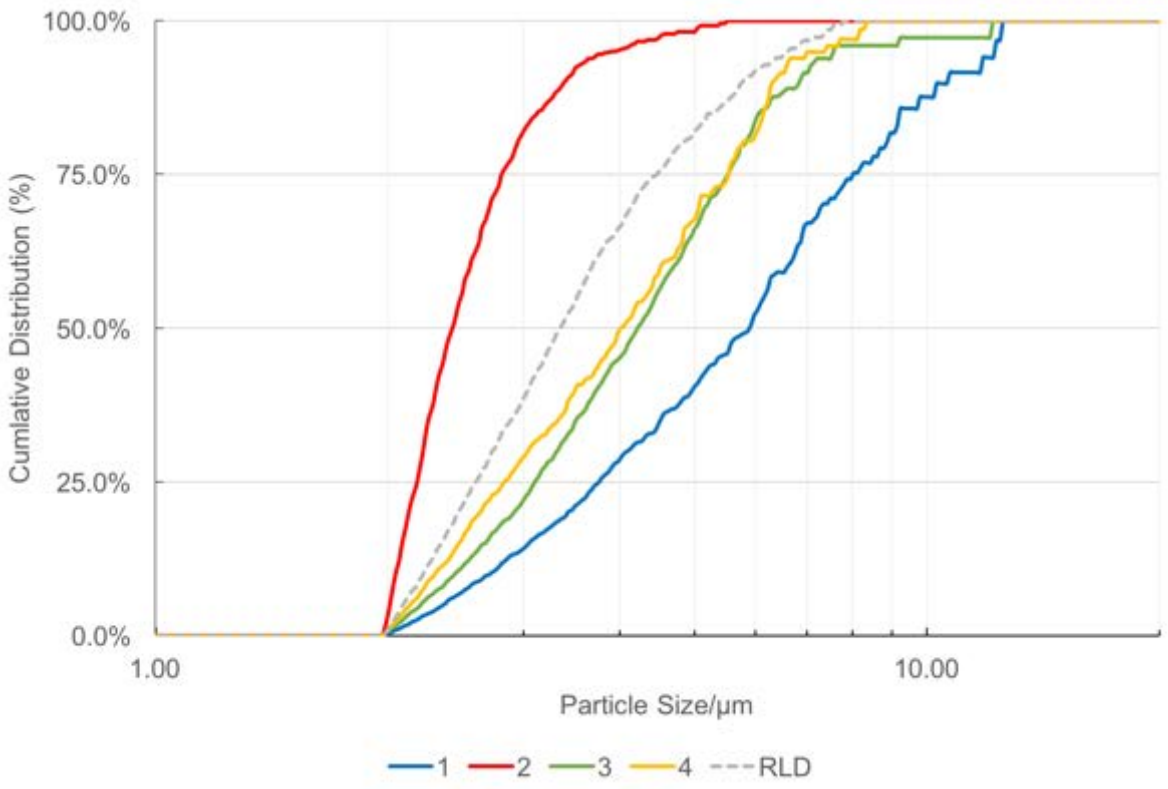
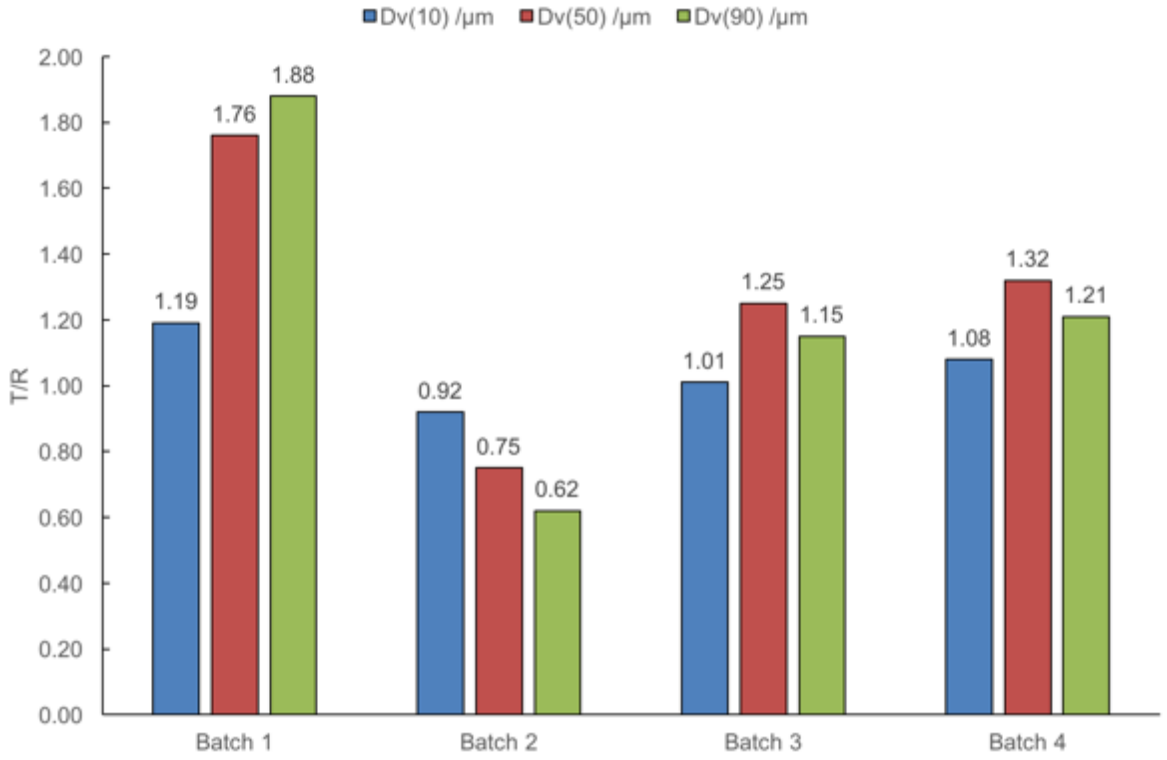
PSD Comparability of Reference and Formulated Drug Substance – MDRS





- With exception of Batch 4, the MDRS PSD of the formulated test products were in line with as-received API PSD measured using laser diffraction.

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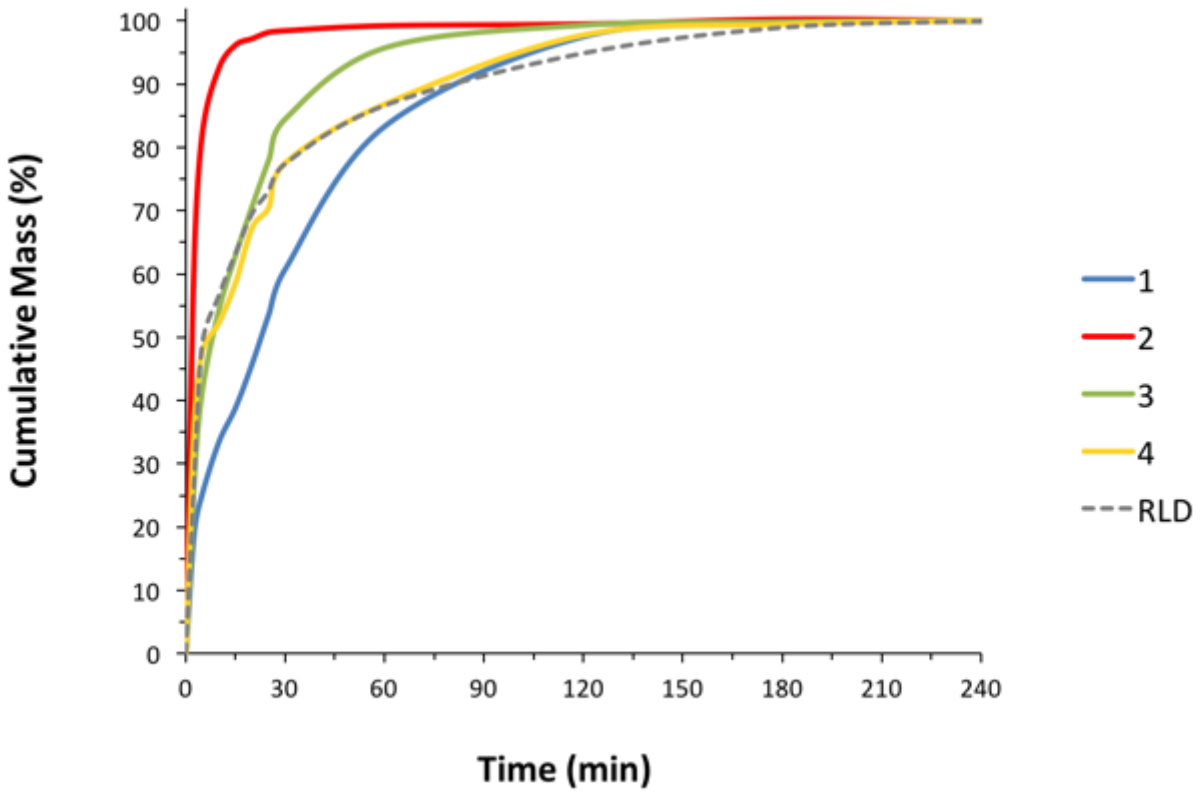
Dissolution Analysis of Drug Product



- Dissolution of the emitted spray from the RLD and test formulations was performed using UniDose.
- Two actuations were emitted into the UniDose system.
- The UniDose collection system has been developed to uniformly deposit the whole emitted spray from a nasal spray onto a glass microfibre filter membrane.
- The filter is placed into disk cassette and Paddle Over Disk (POD) studies were undertaken using 300ml PBS+0.2%SDS in a USP Apparatus II at 37C.
- Differences in the rate of dissolution of the test and reference product were found.

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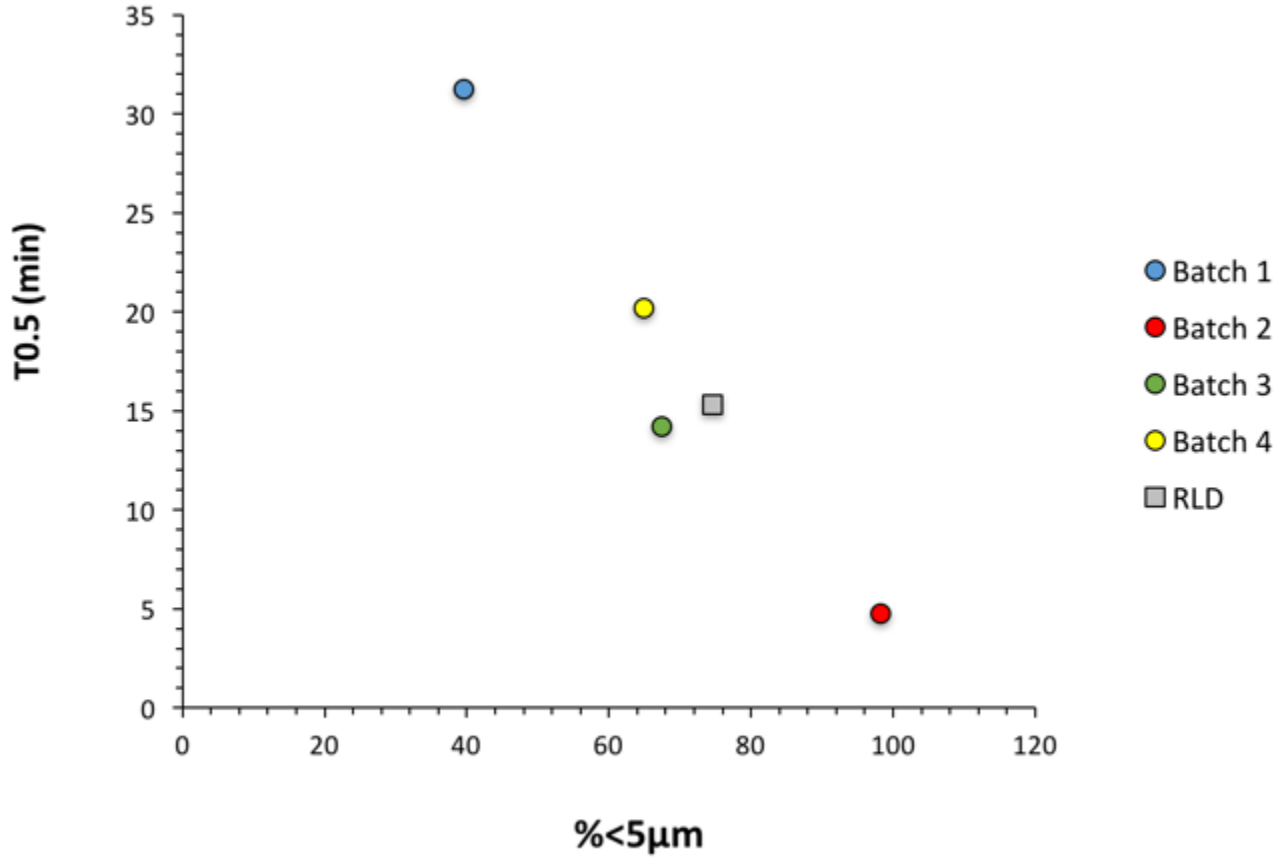
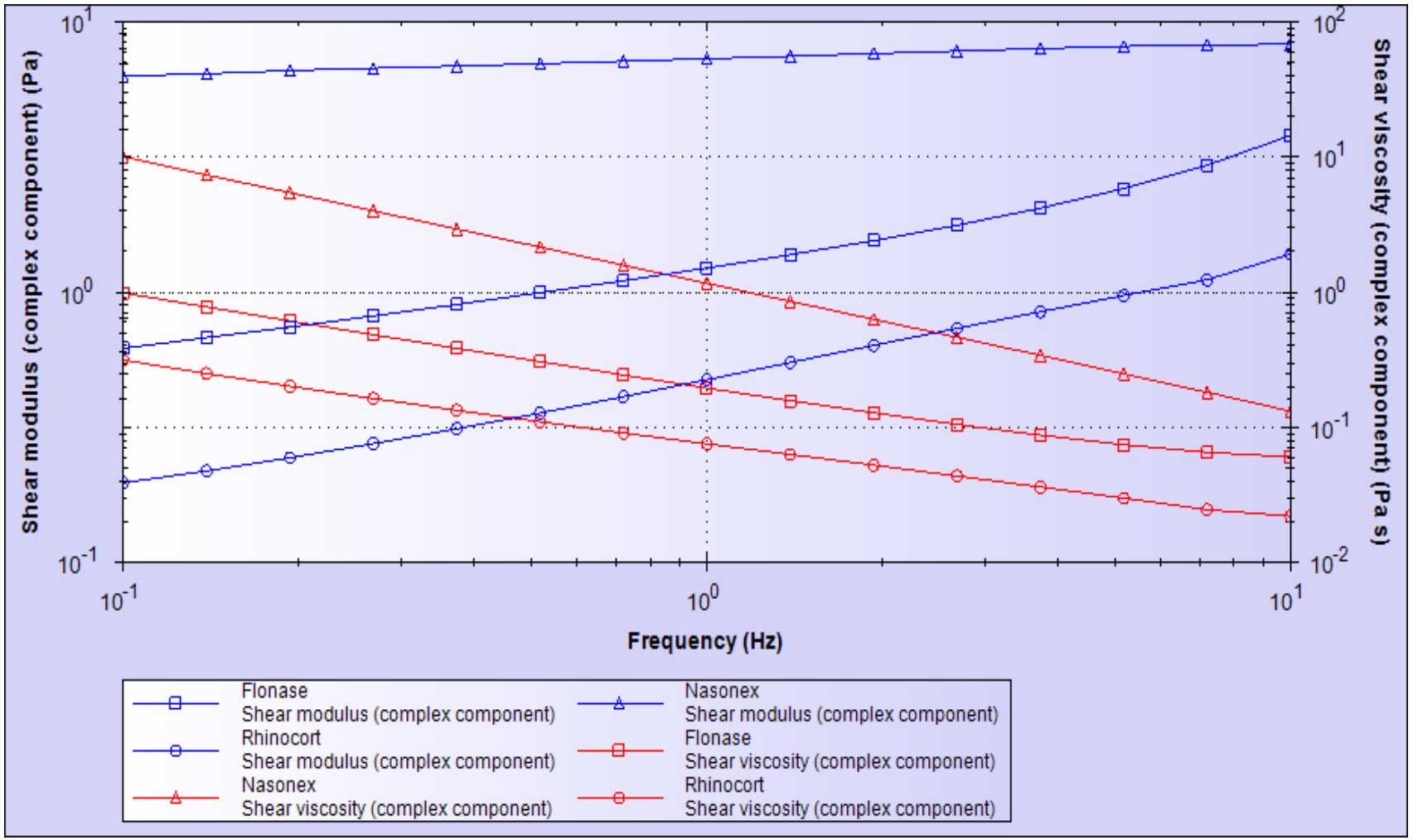
Relationship Between MDRS PSD of Formulated API and Dissolution



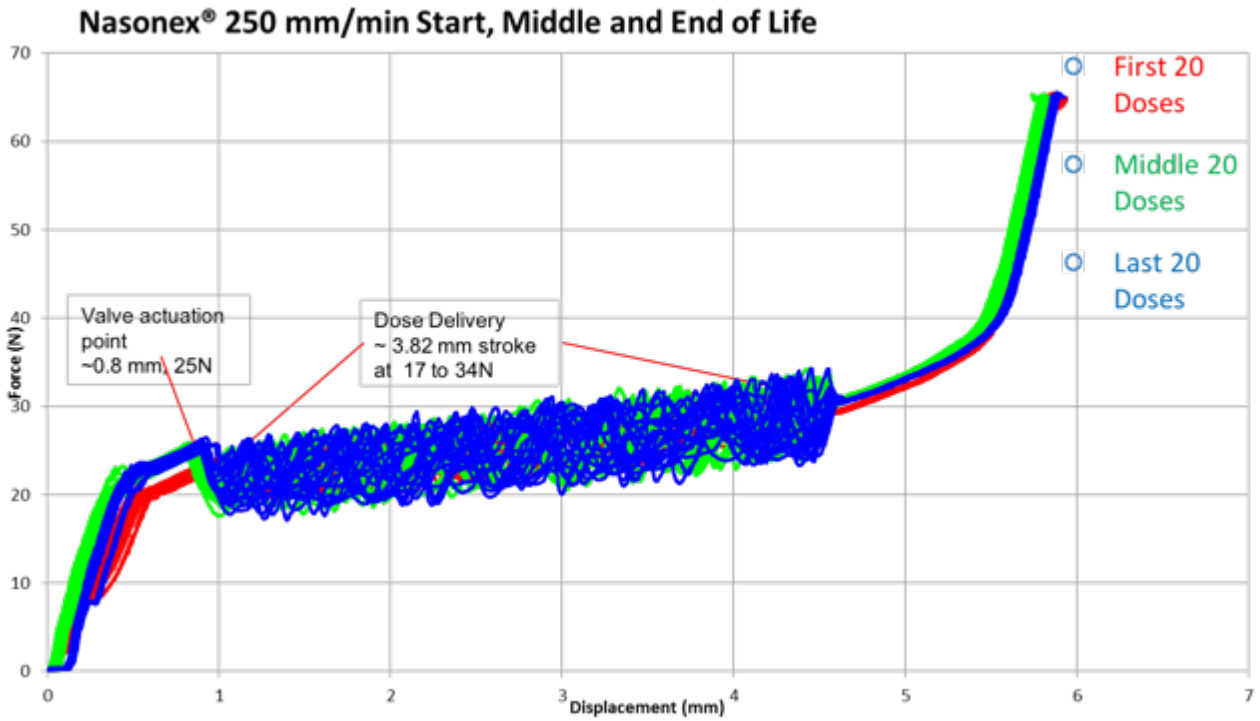
- Good correlation between dissolution half-life and %<5µm.

Measuring Viscoelastic Properties of Different Commercial Innovator Products

Kinexus, Malvern Instruments.



Force Vs. Displacement Studies of Mometasone Innovator Nasal Spray



- Innovator mometasone nasal spray demonstrated the greatest variation in the user forces experienced.
- The user force during dose delivery increases from around 17.5N for the 400 mm/min to 25N for the 250 mm/min.
- The greater variability of innovator mometasone nasal spray product is in part due to the high viscosity and thixotropic nature of the formulation.
- Behavior may effect emitted droplet size.

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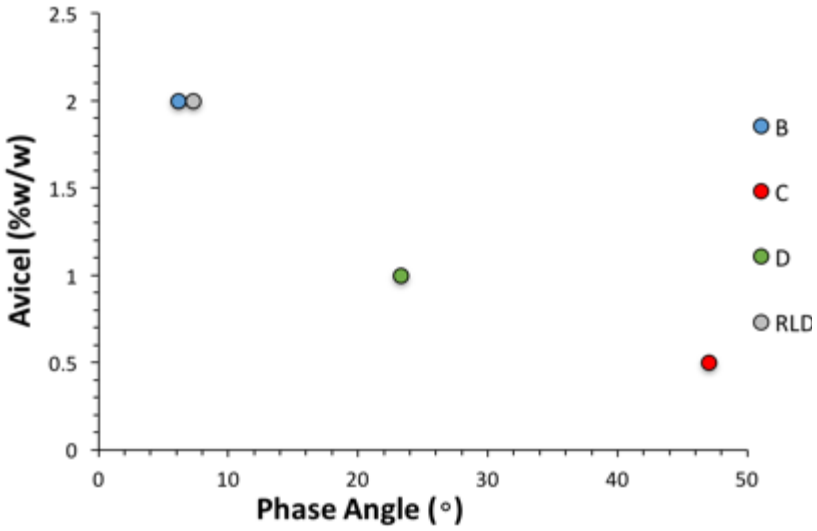
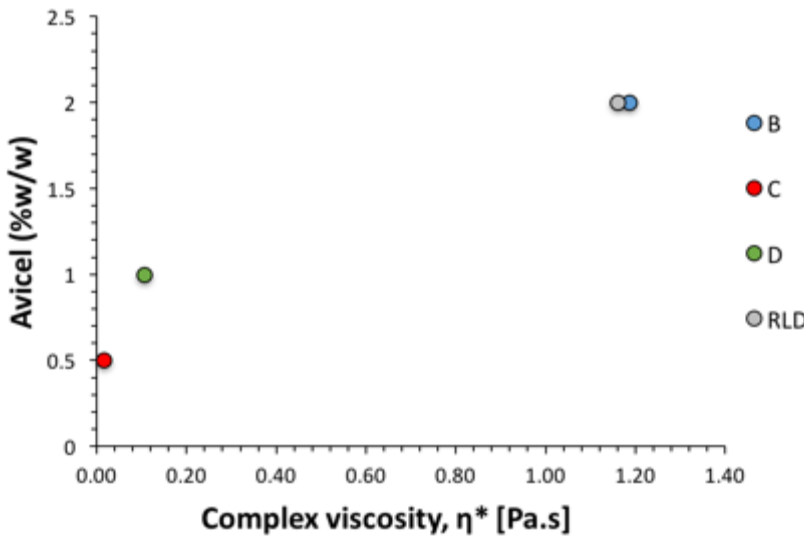
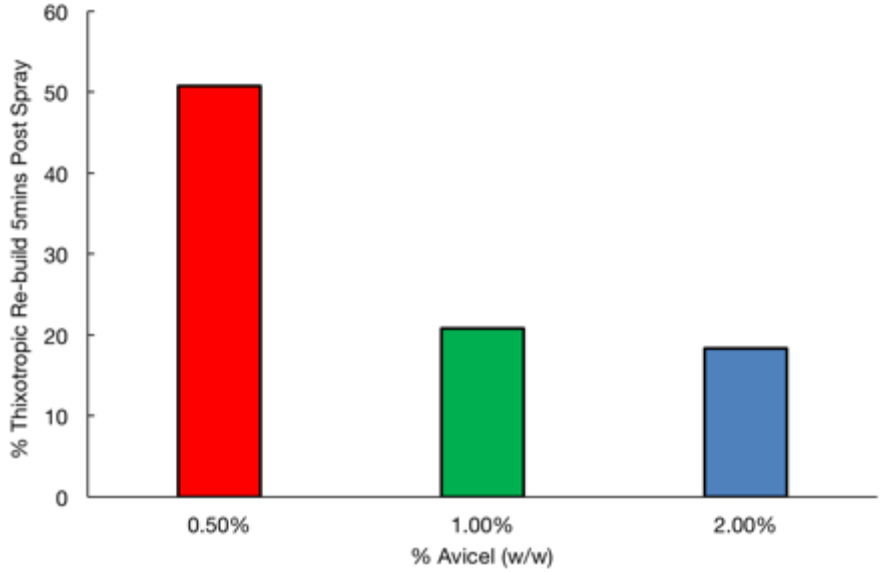
Effect of Avicel Concentration on Formulation Rheology

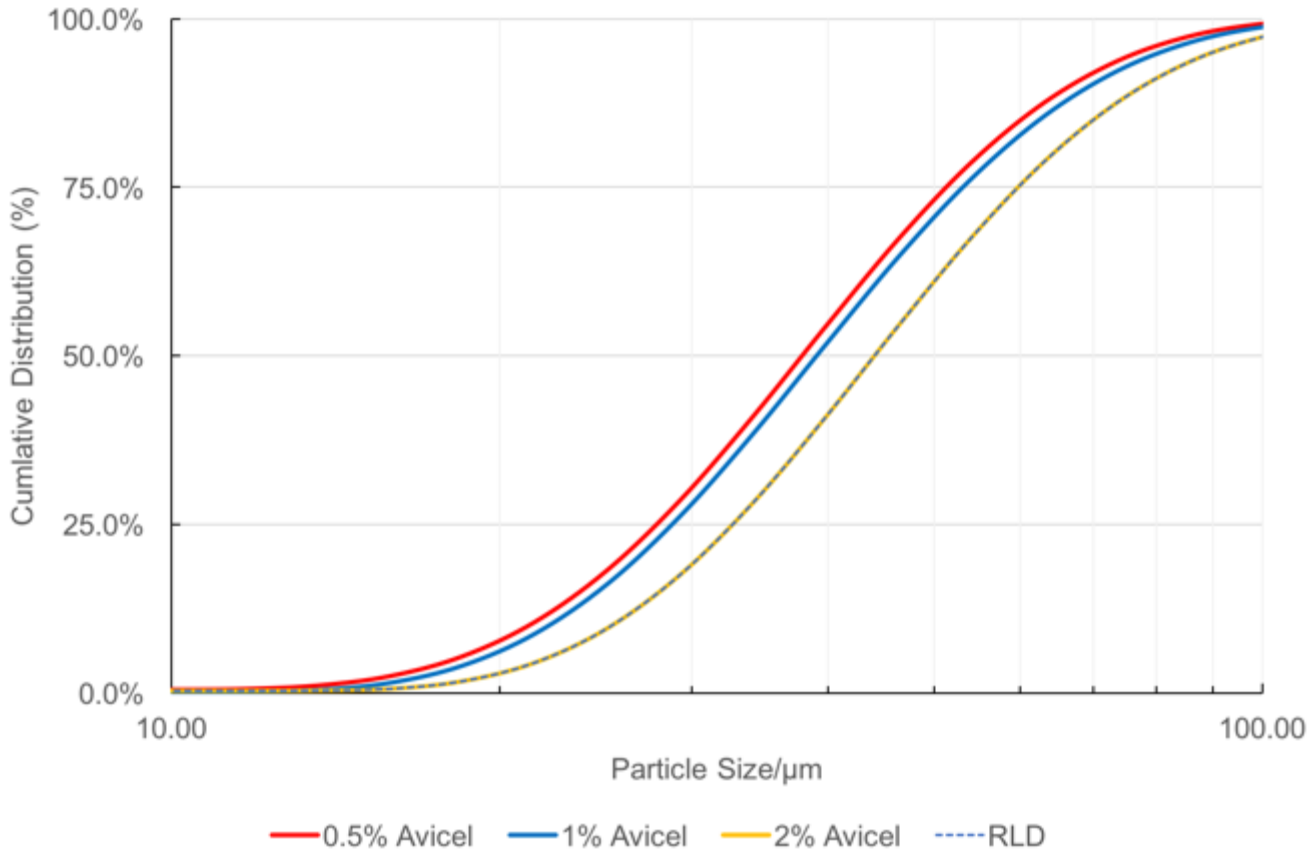






- Avicel content effects formulation rheological properties.
- Increasing Avicel content increases formulation elasticity and viscosity.
- Increase in thixotropic behavior of formulation with increasing Avicel content.

Relationship Between Avicel Content and Droplet Size



Summary

- MDRS methodology was developed for the analysis of particle size of drug substance in the nasal suspension.
- Method was sensitive to detect differences in drug substance particle size and showed similar rank order pattern of size of drug substance in test formulations.
- Good correlation between dissolution half-life of drug delivered from test and reference formulation and MDRS particle size.
- Utility of rheology to provide similar structure to test formulation as RLD to assure similar droplet size and therefore similar regional deposition.
- Potential to utilize dissolution as an orthogonal tool in demonstrating bioequivalence.

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Future Directions

- The FDA have recently funded UoB (Grant No.: BAA-PMQWP#118) – ***Investigating orthogonal analytical approaches to demonstrate bioequivalence of nasal suspension formulations***

- The ultimate aim of the project is to provide the agency a range of validated in vitro based methods to assess the structural equivalence (Q3) of nasal suspension sprays.

- Analytical methods under evaluation include in vitro dissolution/permeability, morphology directed Raman microscopy, nanoparticle characterization and formulation rheology tools.

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