Evaluating Particle Size Differences of Suspension-based Nasal Sprays Through In Vitro and Pharmacokinetic Approaches

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1601, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

For questions on the content of the draft document contact Wallace Adams, 301-594-5618.

Draft Nasal BA BE Guidance 2003

Regulatory Landscape for Bioequivalence (BE) Assessment of Nasal Sprays

- Solution-based Nasal Sprays: *In vitro* alone is sufficient
- Suspension-based Nasal Sprays:
  - Drug **particle size distribution (PSD)** in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation
  - *In vivo* studies (**PK** and comparative **clinical Endpoint Studies**) are recommended due to an **inability**, at the present time, **to adequately characterize PSD in aerosols and sprays**

Draft Nasal BA BE Guidance 2003

Challenges (as stated in Draft Nasal BA BE Guidance 2003)

- "Clinical studies are at times **incapable of showing a dose-response** relationship and **may not be consistently reproducible**. However, a showing of dose-response is not necessary for BE studies with a clinical endpoint, as these studies **are intended only to confirm the lack of important clinical differences** between T and R suspension formulation nasal aerosol and nasal spray products (Advisory Committee for Pharmaceutical Science, 2001 in FDA, 2003 Guidance)." (page 21)
- " Clinical endpoints **may be highly variable** (Welch et al., 1991; Meltzer et al., 1998) and relatively insensitive to dose differences over an eightfold or higher dose range (Advisory Committee for Pharmaceutical Science, 2001), thus **insensitive in detecting potential differences between products**. However, clinical studies can **unequivocally establish effectiveness** of the drug product." (page 4)

Regulatory Overview

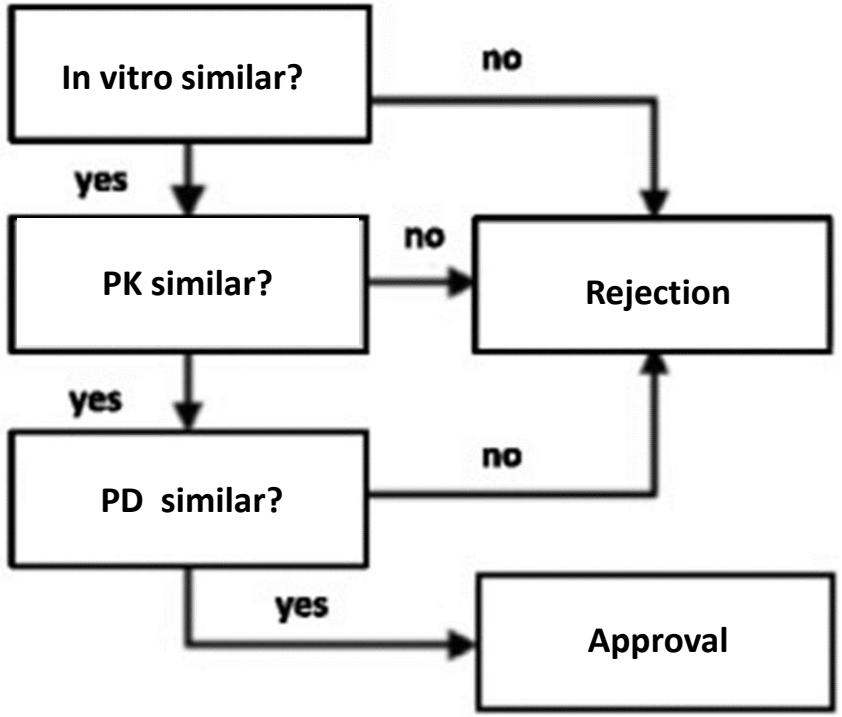
Solution-based nasal sprays

→In vitro studies are sufficient

Suspension

→Weight-of-Evidence Approach

→Alternative Approaches



Comparison: Systemic vs local

STEP	SYSTEMICALLY ACTING DRUGS (e.g., Oral tablet)	LOCALLY ACTING DRUGS (EMA)	WEIGHT OF EVIDENCE APPROACH (FDA)
Step 1	Biowaivers based on BCS or dosage forms in solution	In vitro comparison OR	In vitro comparison AND
Step 2	Conventional PK BE Surrogate of PD	PK BE for safety and lung deposition OR	PK for systemic safety AND
Step 3	PD / Clinical endpoints (Therapeutic equivalence)	Relative potency PD / Clinical endpoints for efficacy or safety	Relative potency PD / Clinical endpoints for efficacy

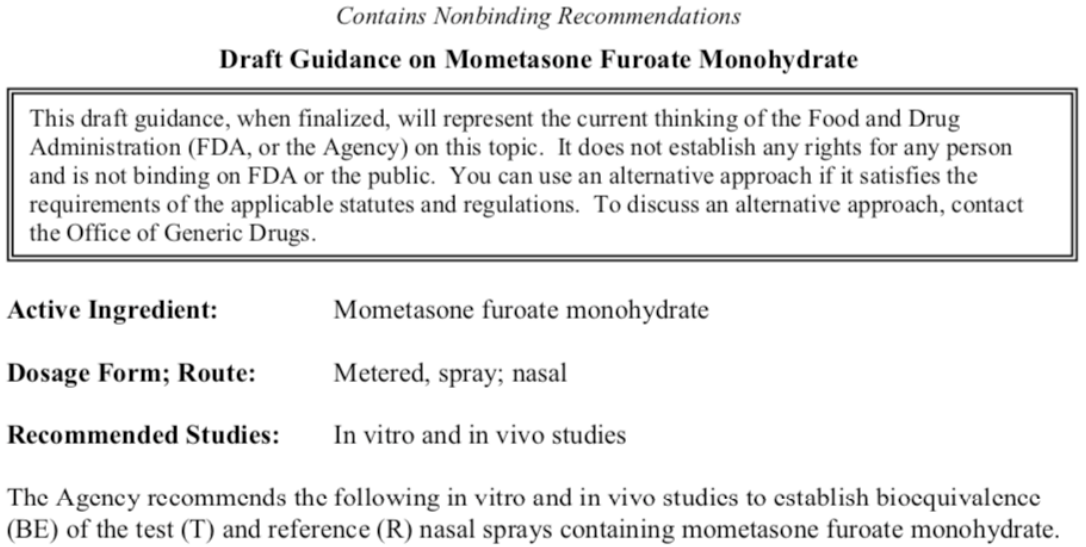
Adapted from Lee et al., AAPS Journal, 2015, 17:1285-1304

Current Weight of Evidence Approach for Nasal Suspension Sprays

- Single Actuation Content, begin (B) and end (E) of lifestages, population BE (PBE)
- Droplet Size Distribution (Laser Diffraction, B and E, 2-7 cm, PBE on D50 and Span)
- Drug in Small Particles and Droplet, B, cascade impactor, droplets less than 9 µm (PBE)
- Spray pattern, B, 3-7 cm, qualitative spray shape, PBE on Ovality
- Plume geometry, B, photography, laser light sheet, high speed digital camera, plume angle and width, three batches, ratio of geometric mean within 90-111%
- Priming Repriming through emitted dose, PBE of emitted dose
- **Pharmacokinetics**
- **Comparative clinical endpoint studies**

Regulatory Landscape for BE Assessment of Nasal Sprays has changed

- **Alternative Approaches are possible:**
  - **Azelastine HCl; Fluticasone propionate 2020**
  - **Beclomethasone dipropionate monohydrate 2021**
  - **Budesonide 2020**
  - **Ciclesonide 2021**
  - **Fluticasone furoate 2020**
  - **Fluticasone propionate 2019**
  - **Mometasone furoate 2019**
  - **Triamcinolone Acetonide 2020**
- **Pharmacokinetics**
- **Advanced tests for PSD: MDRS or other approaches**



Contains Nonbinding Recommendations

Draft Guidance on Mometasone Furoate Monohydrate

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: Mometasone furoate monohydrate

Dosage Form; Route: Metered, spray; nasal

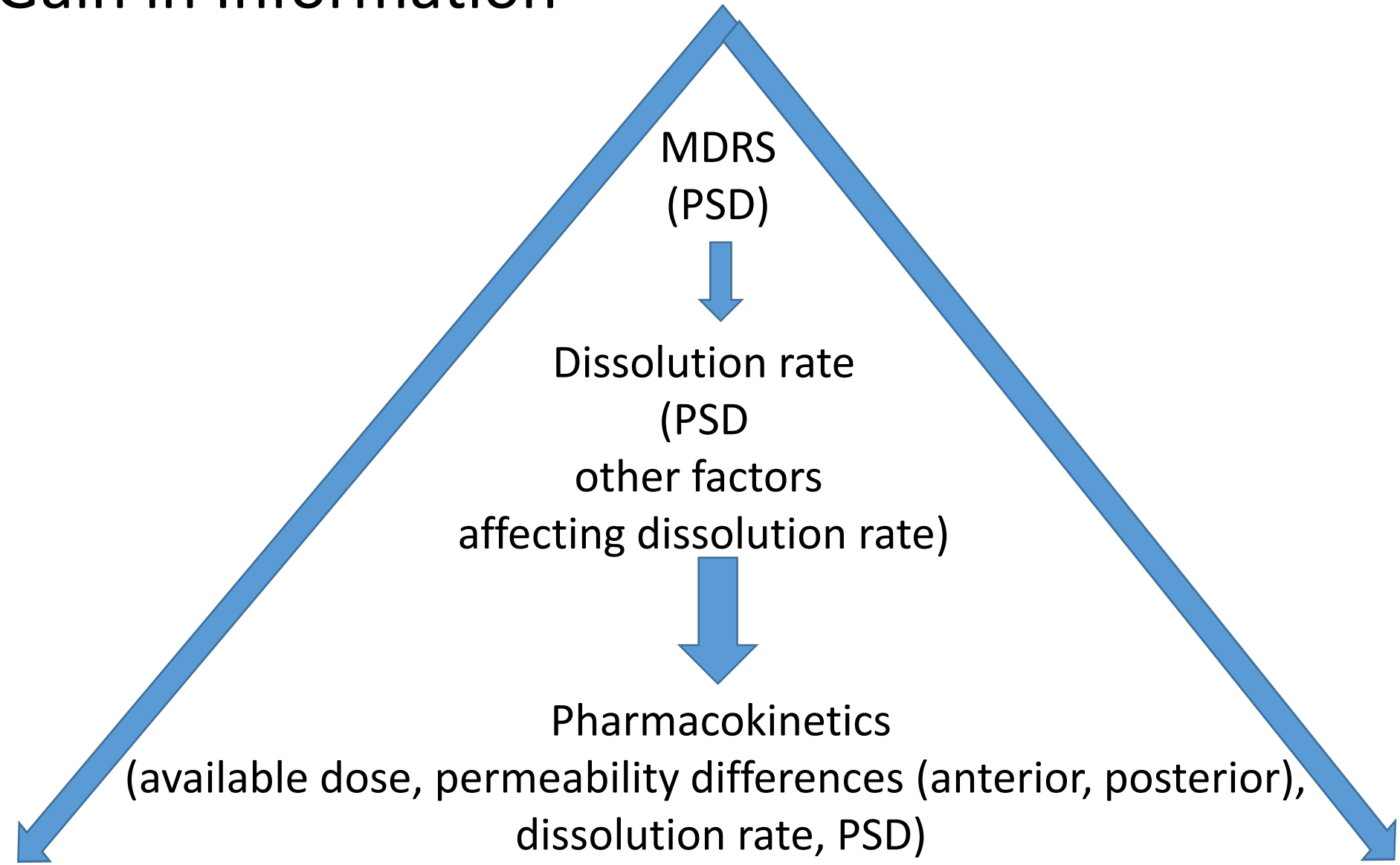
Recommended Studies: In vitro and in vivo studies

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 mometasone furoate monohydrate.

Goal of study:
Compare in vitro and in vivo methods for detecting differences in PSD

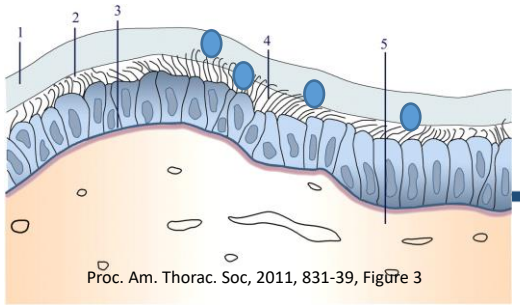
- Evaluate pharmacokinetics as a tool for assessing PSD differences
- Compare with MDRS (Morphologically Directed Raman Spectroscopy)
- Test ability of dissolution tests

Gain in Information



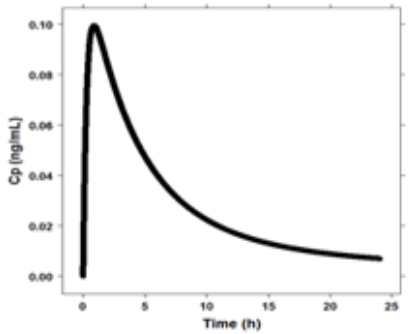
Fate of Intranasal Corticosteroids

Deposition in nasal cavity and pharynx



Proc. Am. Thorac. Soc, 2011, 831-39, Figure 3

Absorption from the nasal tissue

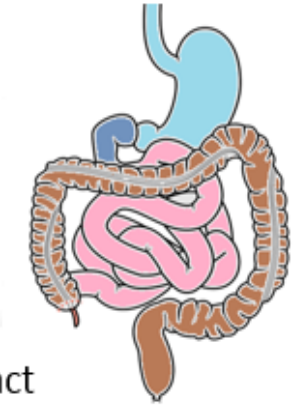


Systemic circulation

Swallowed
+ CL_{muc}

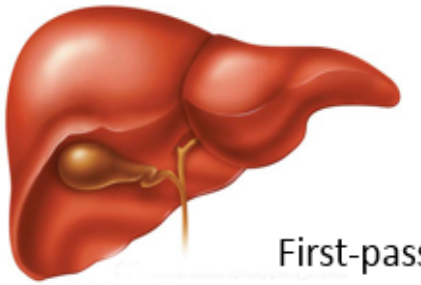
Oral Bioavailability

Systemic side effects



GI-tract

Absorption from gut



Liver

First-pass inactivation

Systemic availability of budesonide after nasal administration of three different formulations: pressurized aerosol, aqueous pump spray, and powder

L. Thorsson,[1,2] O. Borgå[2] & S. Edsbäcker[1,2]

[1] *Department of Clinical Pharmacology, Lund University, S-221 85 Lund, and* [2] *Astra Draco AB, P.O. Box 34, S-221 00 Lund, Sweden*

Formulation	$F_{dose\text{-}to\text{-}subject}$ *(%)*
pMDI	21.0 [16.9; 25.9]#
Aqueous pump spray	31.4 [23.8; 41.3]
Turbuhaler®	40.8 [33.3; 49.8]

Systemic exposure is formulation dependent

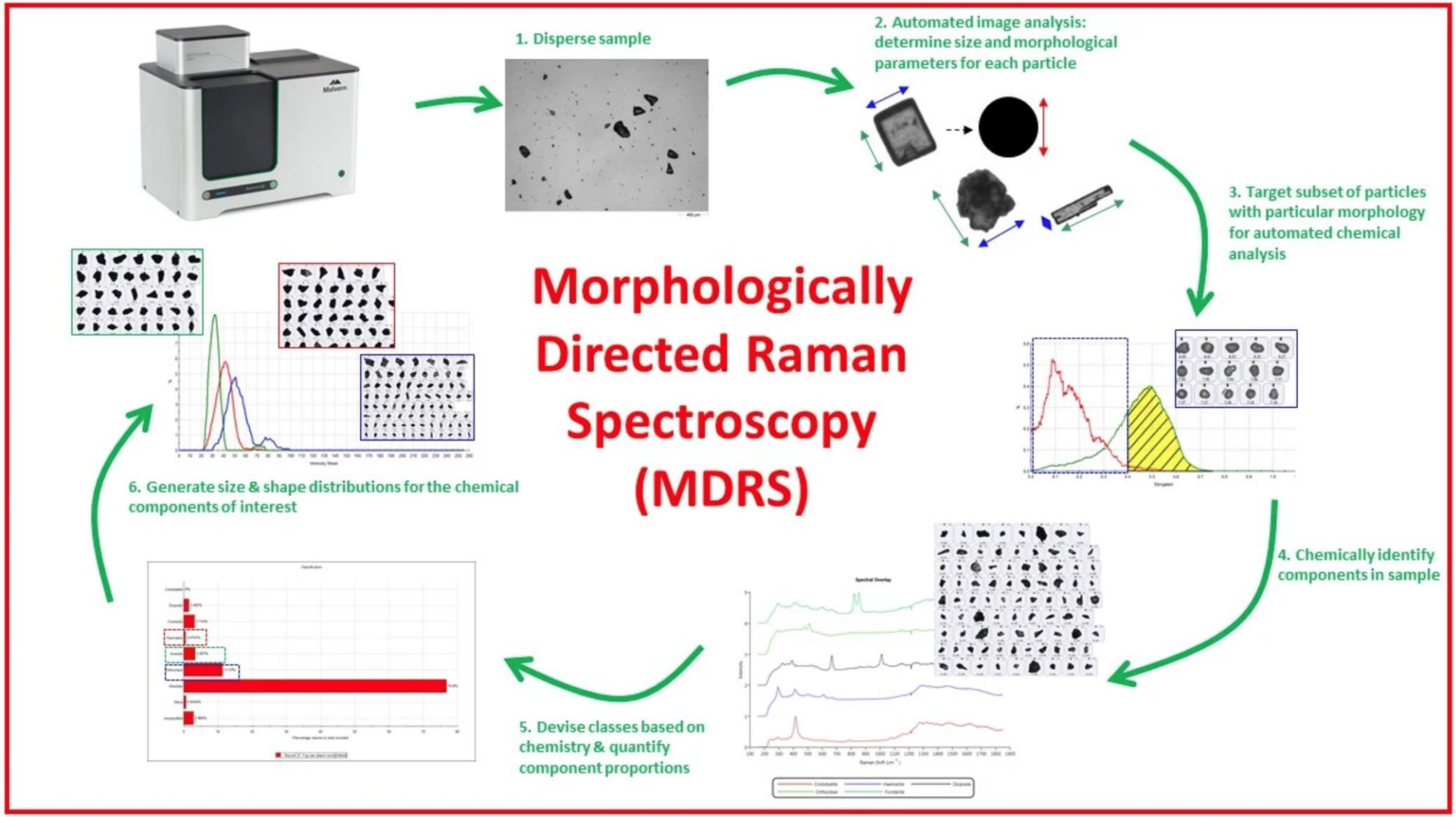
Study Design

- Prepare Mometasone Furoate Formulations that Differ in Particle Size Distribution (MF-I: 1.3 µm. vs MF-II: 3.4 µm, excipients similar to Nasonex)
- Perform detailed *in vitro* characterization (via MDRS), Dissolution test + Standard Evaluation
- Perform human Pharmacokinetic Study

In-vitro Assessment

Formulation	SAC [µg]	DSD d_{50} [µm]	DSD Span	SP Ovality ratio	D_{max} [mm]	Plume Angle (°)
MF-I (~1.3 µm)	44.64	73.9 ± 1.8*	1.64	1.44	28.83	51.33
MF-II (~3.4 µm)	44.55	73.2 ±3 .4*	1.67	1.33	28.39	50.64

***D**SD d50 across all stability tests (1-12 months)



https://www.malvernpanalytical.com/en/products/technology/image-analysis/morphologically-directed-raman-spectroscopy

Results: MDRS

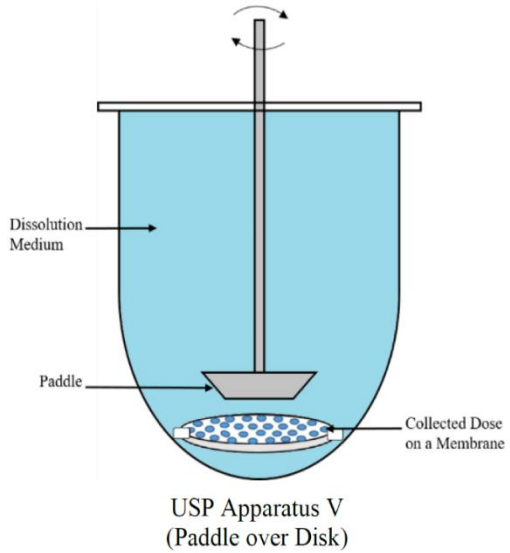
(Malvern Morphologi G3-ID); Jag Shur

	Dv50 Laser [µm]	Dv10 (%CV) [µm]	Dv50 (%CV) [µm]	Dv90 (%CV) [µm]
MF-I	**1.33**	2.25 (2.51%)	**3.17 (4.34%)**	4.59 (4.99%)
MF-II	**3.4**	2.56 (6.63%)	**5.50 (15.58%)**	10.63 (25.41%)
Nasonex®		2.28* (6.14%)	**3.20* (28.75%)**	5.47* (23.40)

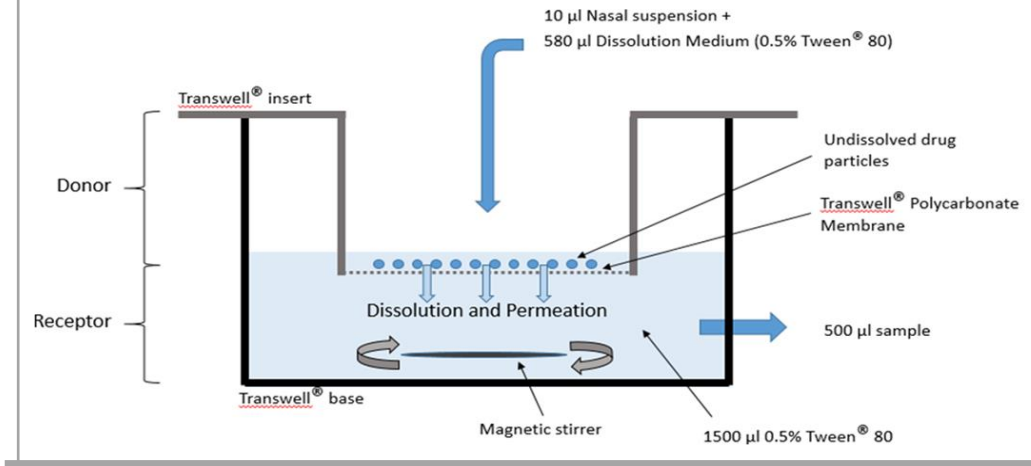
* Data from Farias et al (2021)

Dissolution Tests

Experimental Setup



USP System



Transwell System

Image: E. Amini and G. Hochhaus, “Dissolution and drug release,” in Inhaled Medicines, 1st ed., S. Kassinos, P. Bäckman, J. Conway, and A. J. Hickey, Eds. Elsevier, 2020, pp. 225–266.

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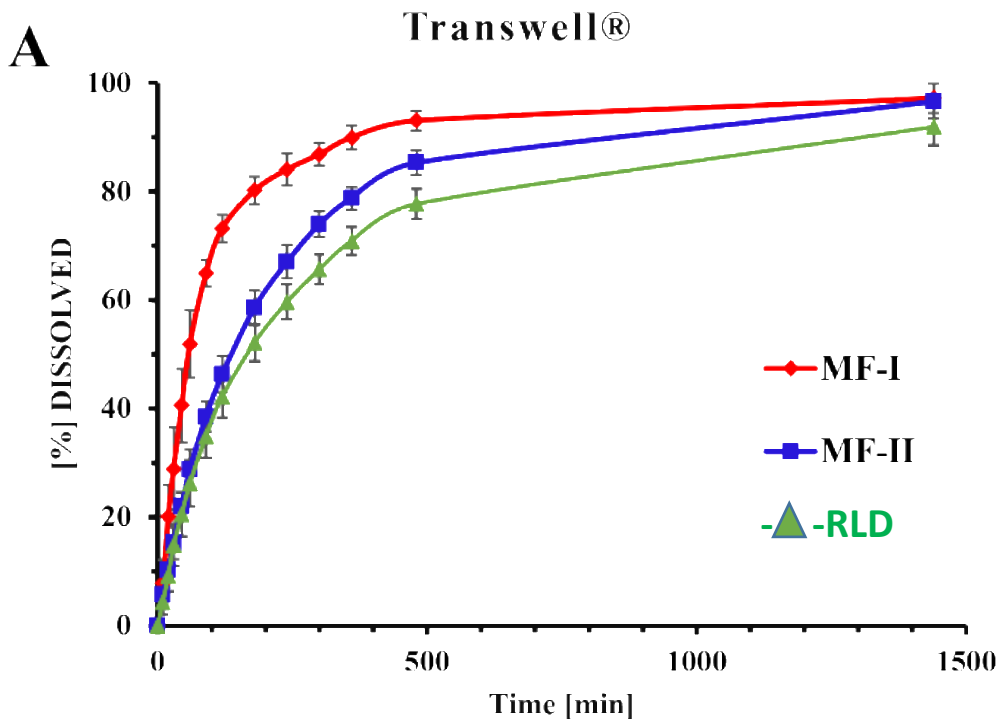
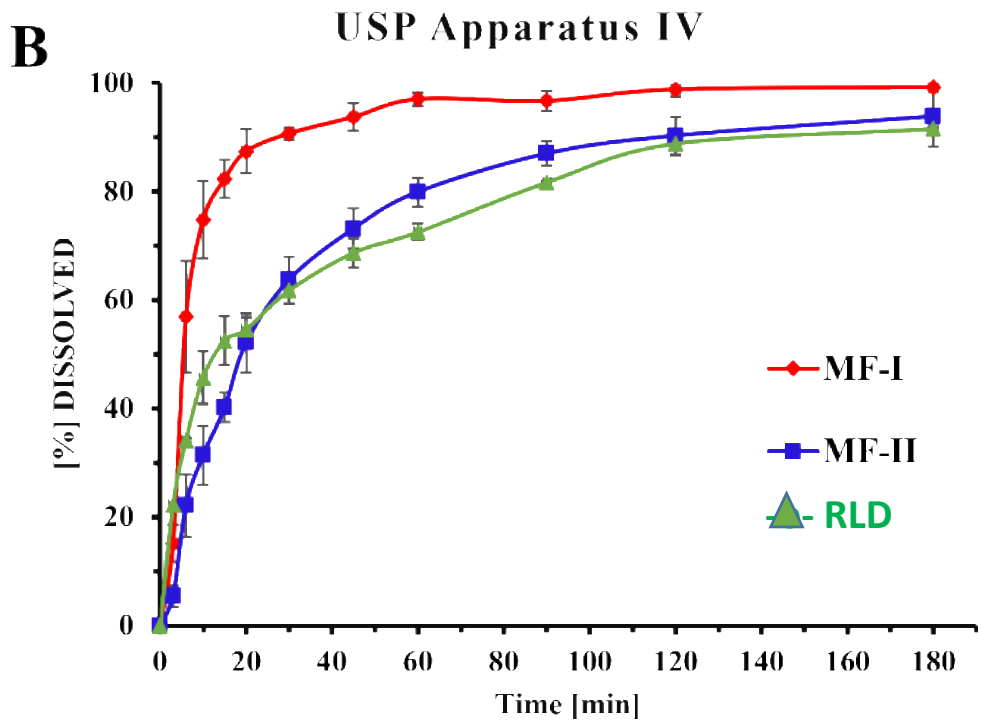
Dissolution sensitive to particle size difference?

- Comparison of Investigational Nasal Suspensions (Small vs Large PSD)
- Dissolution capable of confirming *in vitro* bio-IN-equivalence?





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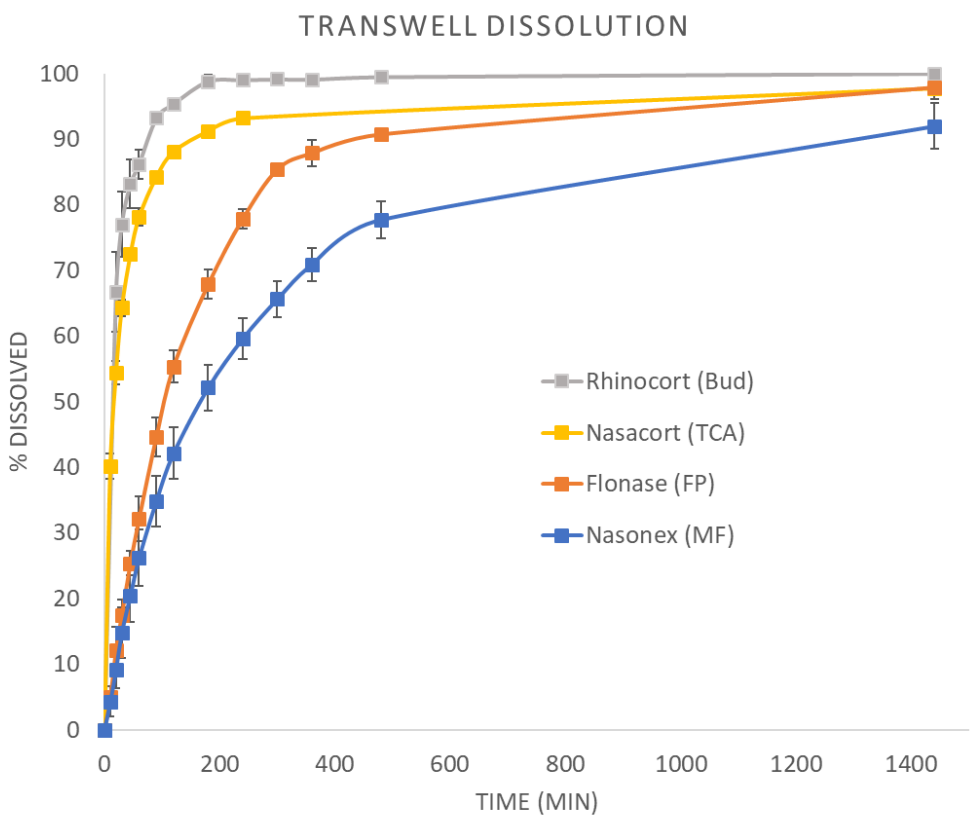
MDRS vs Dissolution

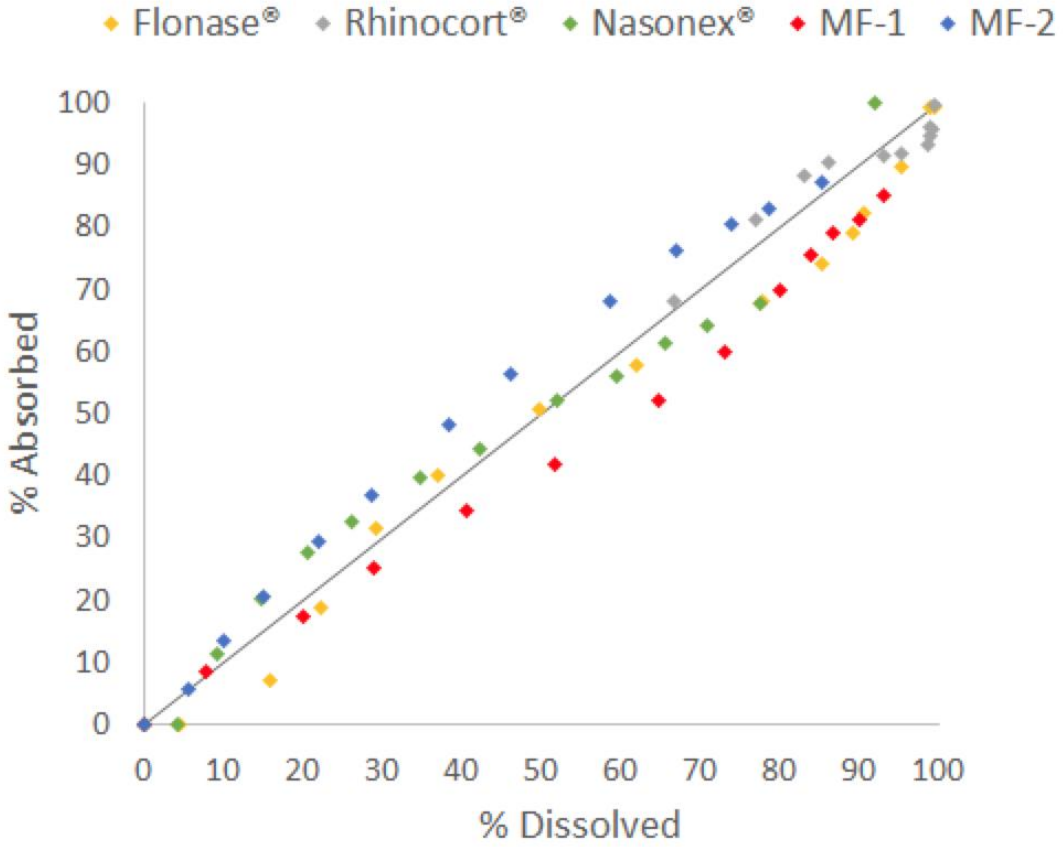
	Dv50 Laser [µm]	Dv50 (%CV) [µm]	VMD (GSD) [µm] USP Apparatus V	VMD (GSD) [µm] Transwell®
MF-I	1.33	3.17 (4.34%)	5.55 (1.44)	9.05 (2.12)
MF-II	3.4	5.50 (15.58%)	10.42 (1.76)	20.84 (1.82)
Nasonex®		3.20* (28.75%)	9.12 (2.56)	23.68 (2.08)

* Farias et al. 2021, AAPS J

MDRS differ from Dissolution Results

IVIVC: % absorbed (after deconvolution of PK) vs % dissolved





Good correlation between Transwell based" % dissolved" and PK based "% absorbed"

Bud=Budesonide, FP= Fluticasone Propionate, MF=Mometasone Furoate, TCA= Triamcincolone Acetonide

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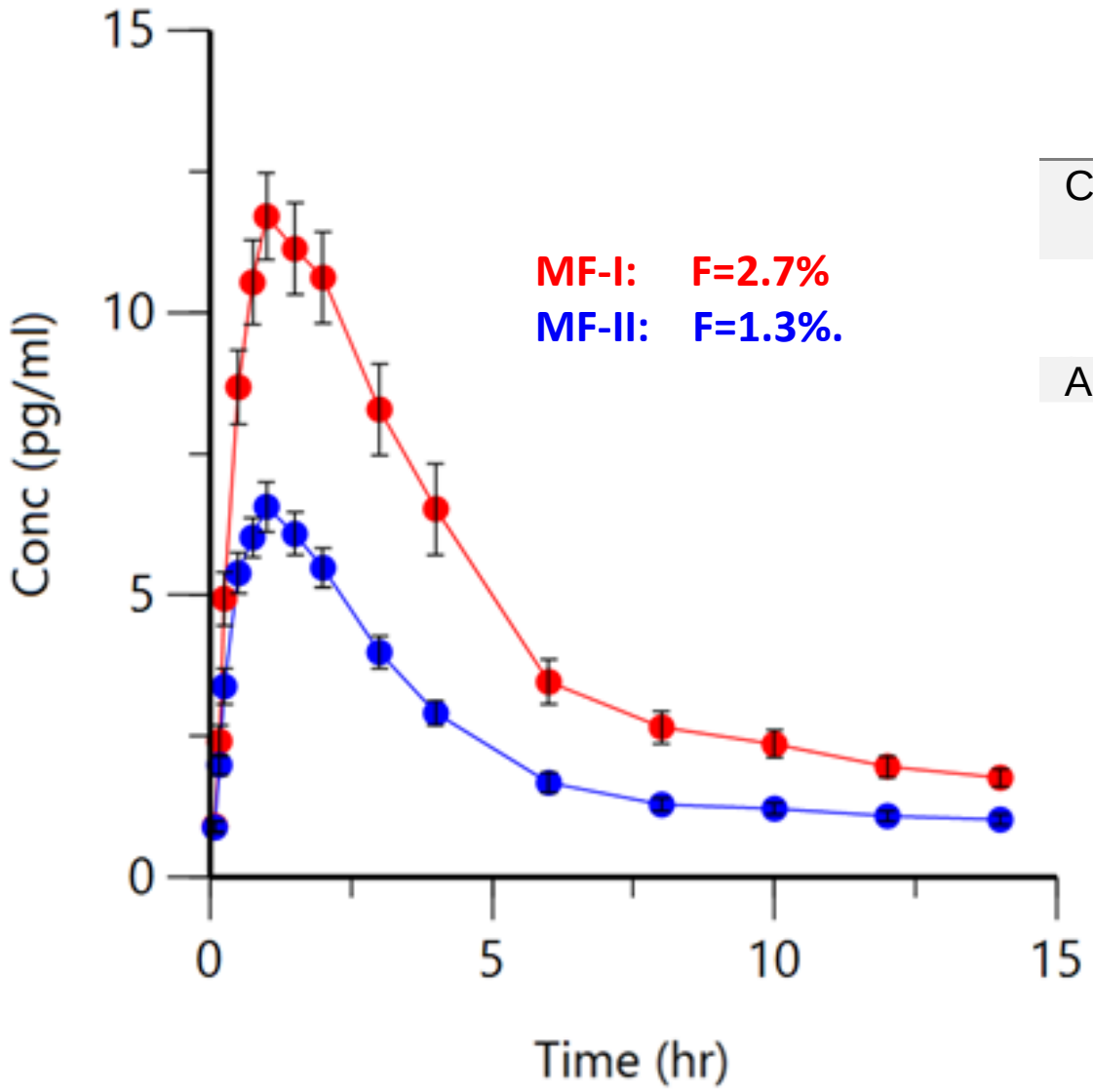
PK Study Design

- 2-way, Cross-over, Double blind
- Carefully standardized Dosing (administered by experienced clinical personnel)
- 44 healthy volunteers with data on both formulations
- Dose: 2 Actuations ('sprays') into each nostril,
  i.e. 4 actuations total, → 200 µg dose
- Non-compartmental PK Analysis (AUC_{0-t}, C_{max})

Non-Compartmental Analysis



Parameter	*Formulation*	*Mean*
C_{max} (pg/mL)	**MF-I (small)**	13.6
	MF-II (large)	7.3
AUC_{last} (pg/ml*h)	**MF-I (small)**	63.4
	MF-II (large)	32.1

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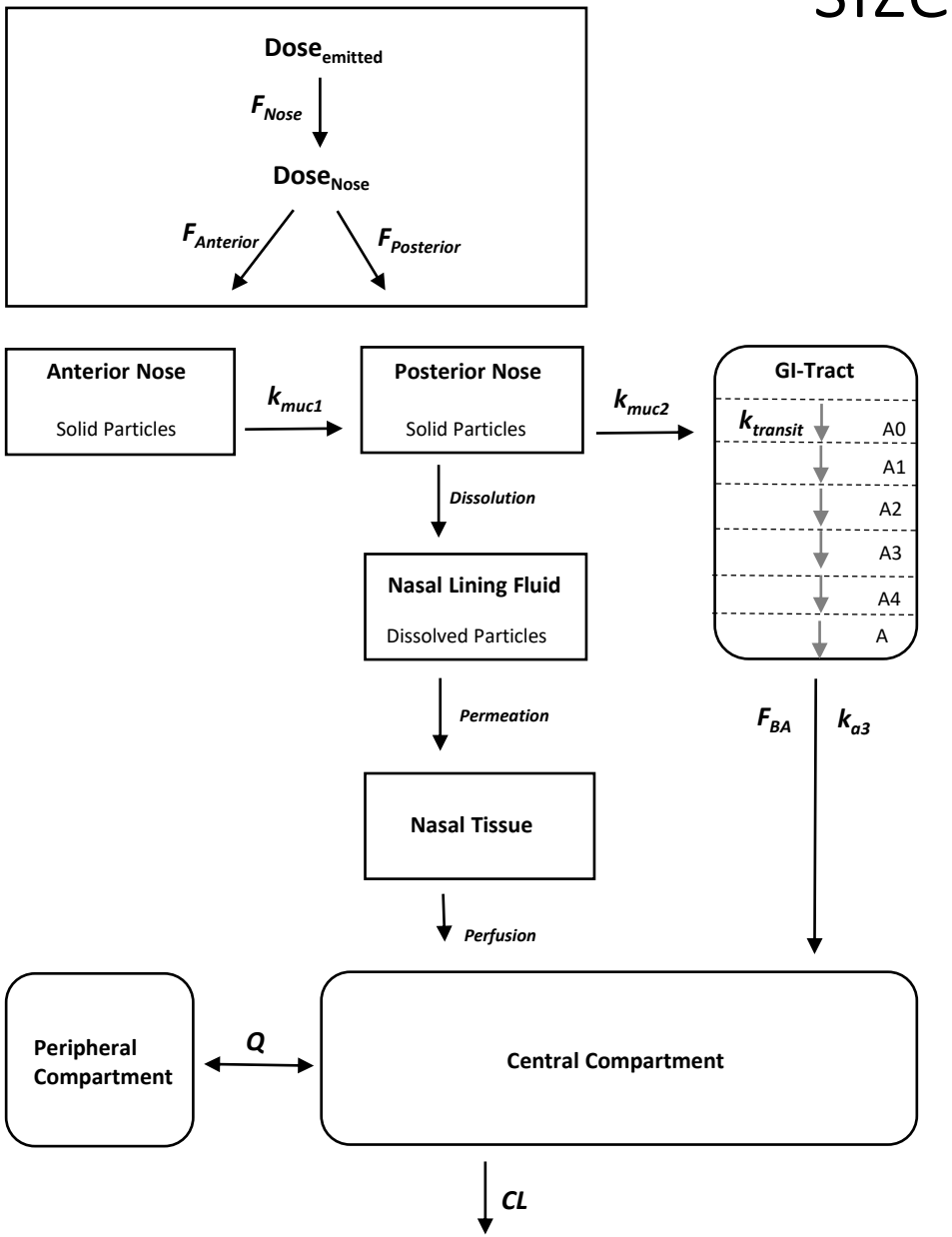
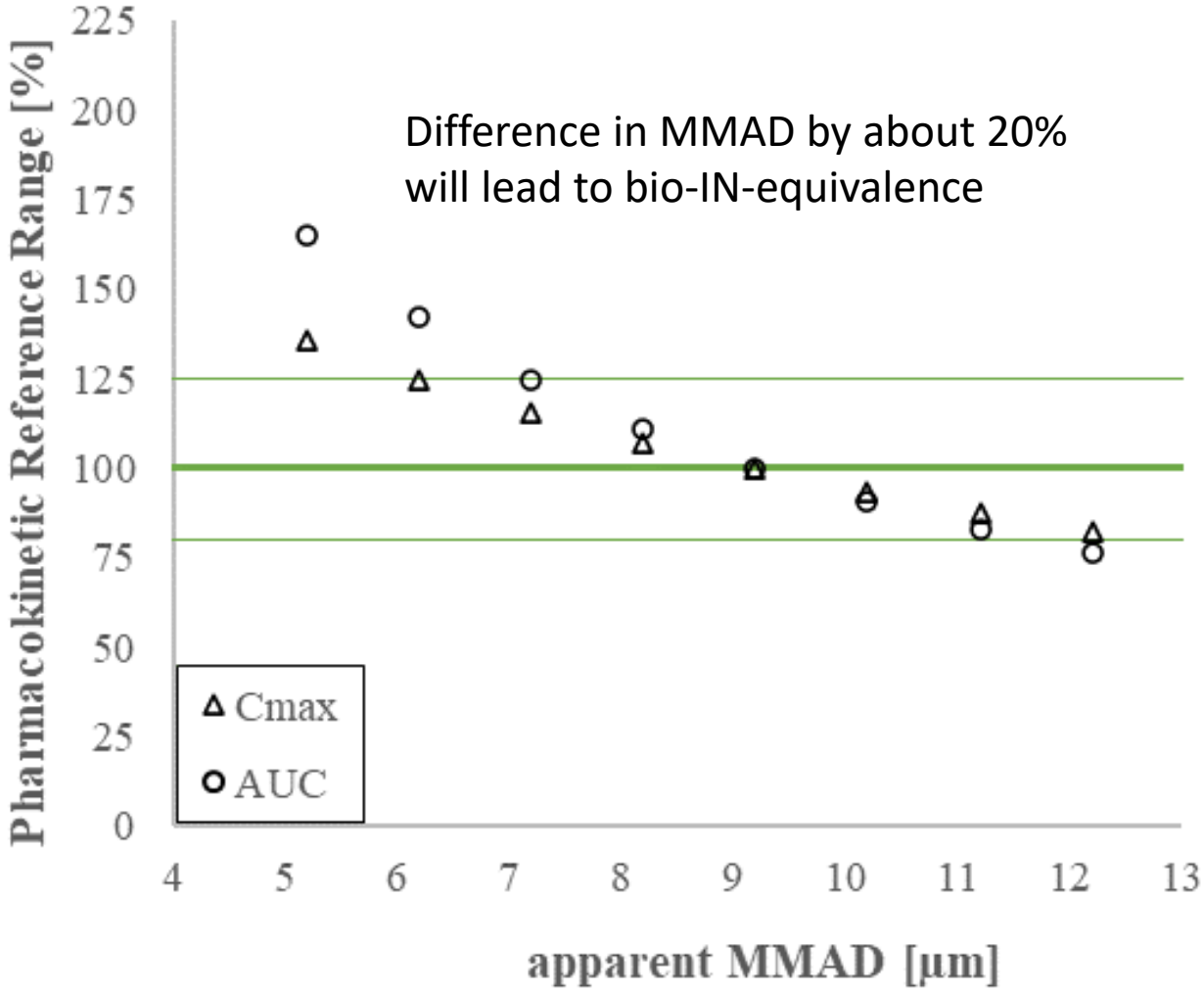
PBPK- Model to evaluate sensitivity of PK to detect particle size differences





Difference in MMAD by about 20% will lead to bio-IN-equivalence

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Conclusion for Pharmacokinetics

- **PK** study was sensitive to detect differences in particle size differences.
  - Formulation with larger Particle size shows **smaller AUC and smaller Cmax**

- Based on PBPK model, a 20 % difference in particle size should yield bio-IN-equivalence in PK study
  - PK is therefore more sensitive to differences PSD than comparative clinical endpoint study

- Dissolution studies showed good correlation to PK parameters and had a similar sensitivity to detect differences in PSD

Author's Overall Conclusion for Suspension Based Nasal Sprays

- PK and Dissolution tests were found to be sensitive in evaluating PSD differences, and may be part of an alternative to comparative clinical endpoint studies
- PK with charcoal as well as dissolution tests, after thorough validation, may be suitable as orthogonal methods to PSD measurements (e.g., MDRS)
- Future consideration:
  - Role of PK studies (no charcoal) in addressing any residual uncertainties; "PK plus comparative clinical endpoint study" was based on inability **to adequately characterize drug PSD in aerosols and sprays** per Draft Nasal BA BE Guidance 2003**.**
  - Roles of MDRS, dissolution tests and PK: Should cards be shuffled?

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WORLDWIDE CLINICAL TRIALS

C Carrasco

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