Developing Nasal Powder Products:

Formulation, Delivery and Characterization

Alan Watts Ph.D.

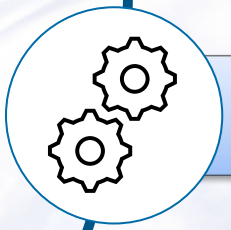
Director, Technology & Innovation, Pulmonary & Nasal Products

IPAC-RS Nasal Innovation Forum, Sep 18-19 2025

Overview

Physiology, Justification and Pipeline

Spray Drying for Powder Manufacture



Other Manufacturing and Devices

Characterization, Route-specific considerations

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Benefits and Challenges

Benefits of Nasal Route

- Needle-free route to systemic
- Rapid-onset, avoid first pass
- Safety/tolerability concerns are less compared to pulmonary
- CNS via Nose-to-Brain

Benefits of Nasal Powder

- Improved stability over aqueous, preservative-free
- High loaded dose (10-25 mg), not solubility dependent
- Reduced loss due to running/dripping, mucoadhesive, longer residence time

Challenges of Nasal Route

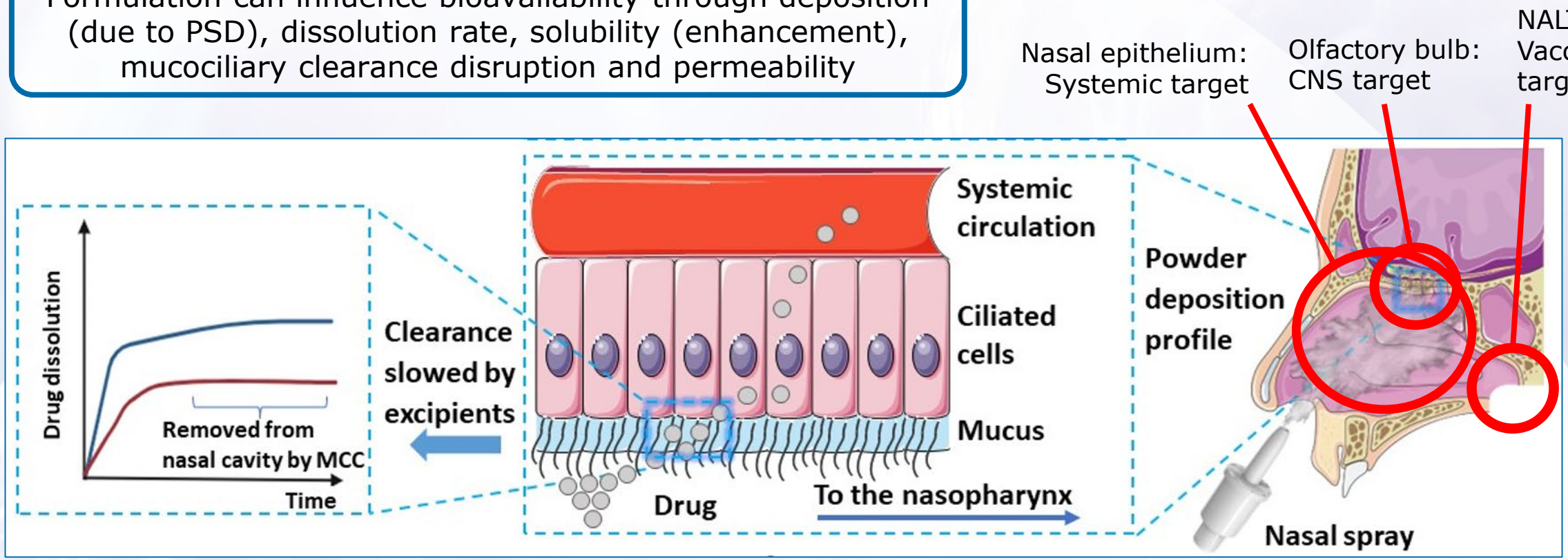
- Less surface area than lung: ~150 cm^2
- Mucus barrier: penetration and clearance
- Regional targeting: anatomical and human factor differences

Challenges of Nasal Powder

- Requires some particle size control: d_{50}~25-50 µm, limited <10 µm
- Powder flow, moisture control
- Nasal irritation?
- Sneezing?

Route and Formulation Considerations

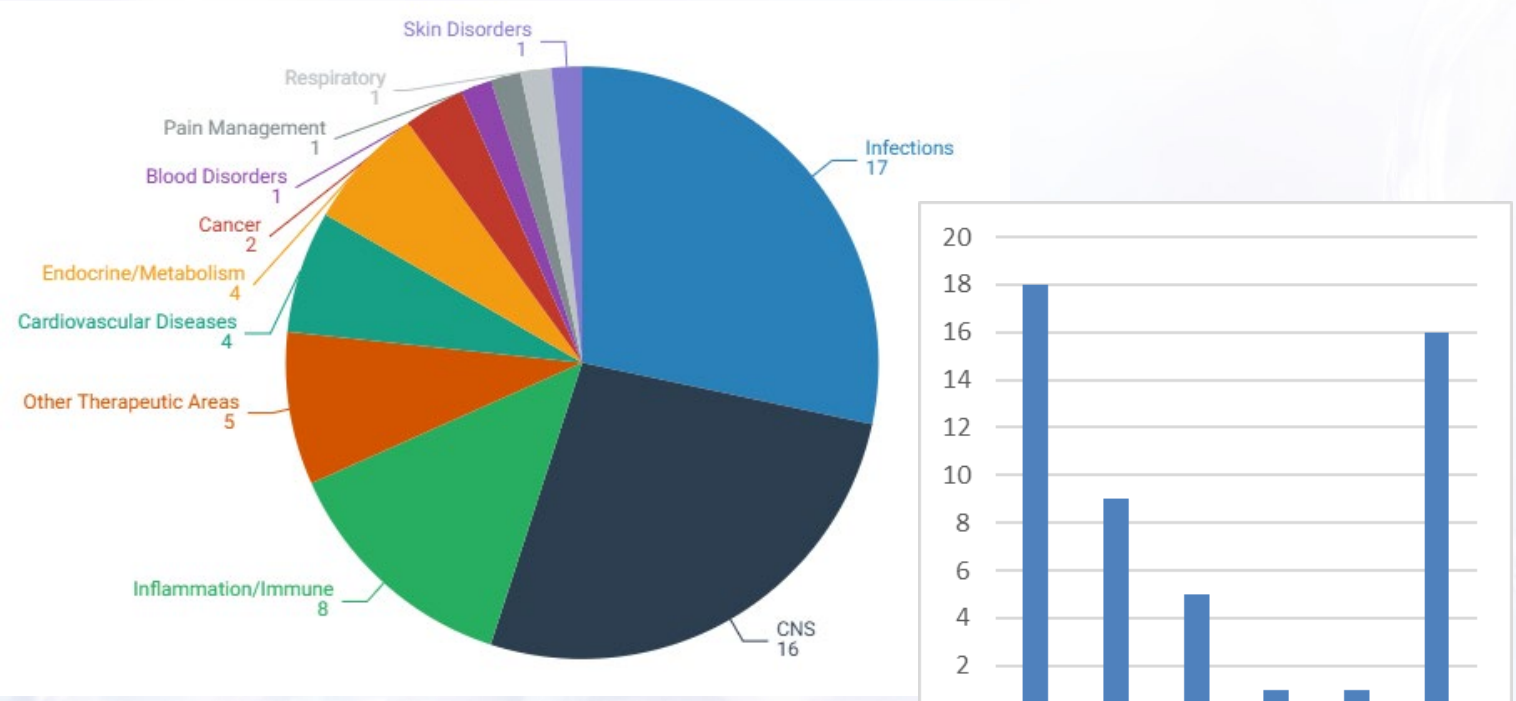
Formulation can influence bioavailability through deposition (due to PSD), dissolution rate, solubility (enhancement), mucociliary clearance disruption and permeability



Watts 2024, Nasal Powder: A Stable, Rapid-Onset Strategy for Systemic Therapy Inhalation Magazine, May 2024

Market and Pipeline

50 marketed and development programs*



*approx. 10 double counted in disease area (e.g. epinephrine is Inflammation and Cardiovascular)

Infections

- **Approved – HPMC barriers, IFN for reconstitution**
- **Clinical - Powder vaccines, novel anti-infectives**

CNS

- **Approved – Migraine**
- **Clinical – opioid dependence, Parkinson's, depression, brain injury**

Immune

- **Approved – HPMC barrier for Rhinitis, steroid for allergy**
- **Clinical – epinephrine for anaphylaxis**

Current Landscape – Marketed and late-stage

Molecule	API	Indications	Country/ Region
Small Molecule	Beclomethasone Dipropionate	Allergic Rhinitis	Japan
	Sumatriptan Succinate	Migraine	USA
	Dexamethasone Cipecylate	Allergic Rhinitis	South Korea, Japan
	Dihydroergotamine mesylate	Migraine	USA
Protein	Allergen, extract	Allergic Rhinoconjunctivitis	Europe
	Glucagon	Diabetes, Hypoglycemia	USA, Canada, Europe, Japan
Carbohydrate	Hydroxypropyl Methylcellulose	Infections	Europe, Asia, Canada, Africa

ONZETRA® Xsail Sumatriptan powder, micronized, FDA approved 2016

Baqsimi®
Glucagon powder, lyophilized, FDA approved 2019

Alzair®,micronized HPMC FDA approved as a medical device (510(k)), 2017

Nasdepi
Epinephrine powder, spray dried, emergency use for allergic reaction

OX124
Naloxone powder, SD amorphous, more rapid onset than Narcan®

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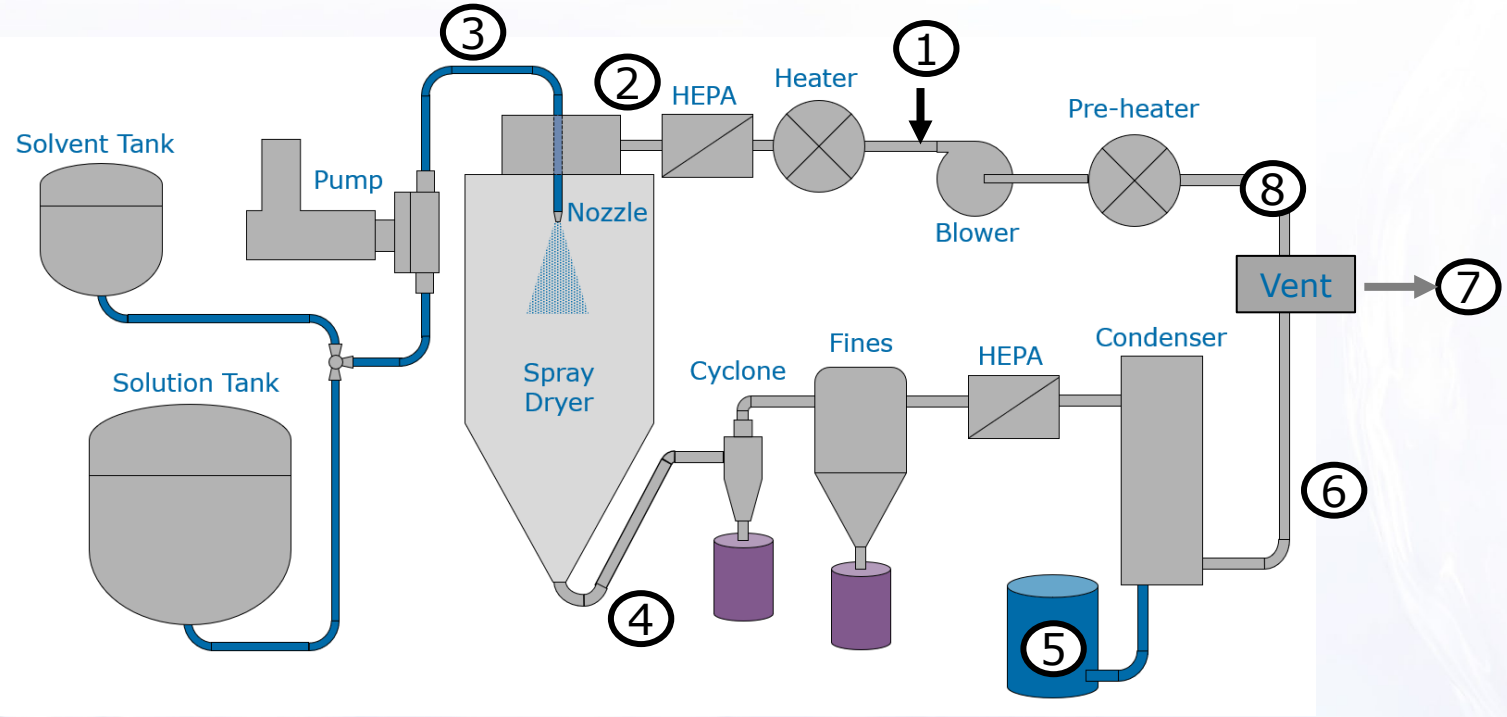
Spray Drying Nasal Powders



Stream	Description
1	Fresh N2 Feed
2	Dryer Gas Feed
3	Dryer Liquid Feed
4	Dryer Outlet
5	Condensate
6	Condenser Vapor
7	Vent
8	Recycle Gas

Benefits of Spray Drying for Nasal Powders

- Control of particle size, morphology, composition
- Scalable, well-established pharmaceutical process
- Control over moisture during manufacture

Considerations for spray drying nasal powders

- Increase feed stock viscosity can be used to increase particle size
- Low ALR will lead to larger droplets but reduced drying, particularly at lab scale

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Excipients for SD Inhalation Powders

Pulmonary

	Spray Drying Excipient	Purpose
Approved	DPPC	Carrier, dispersibility, bulking
	DSPC	Carrier, dispersibility, bulking
	Mannitol	Osmolality
	Glycine	Buffer, stabilizer
	Buffer Salts	Buffer, glass stabilizer
Clinical Development	Leucine	Dispersibility
	Trileucine	Dispersibility
	Trehalose	Glass stabilizer, bulking agent
	FDKP	Carrier
Literature	PLA, PLGA	Controlled release
	Polysaccharides	Dispersibility, bulking
	Cyclodextrins	Dispersibility, bulking

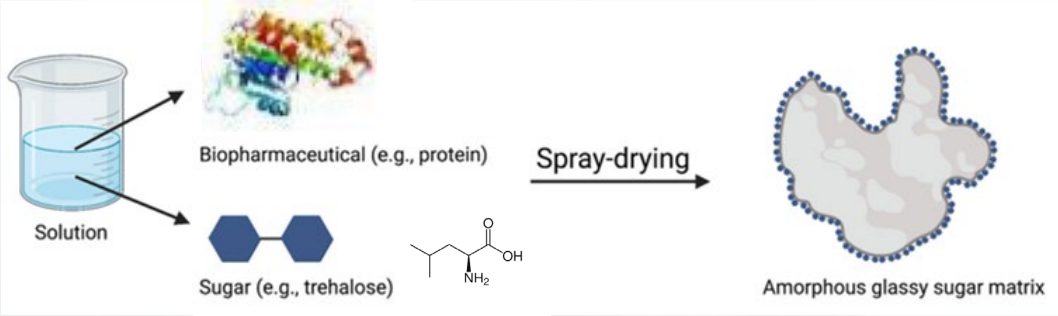
Nasal

Excipient		Function
FDA Approved Nasal Product	HPMC	Suspending agent mucoadhesion, viscosity enhancer
	Beta-cyclodextrin	Bulking agent, solubility, absorption enhancer
	DPC	Absorption enhancer
	Carrageenan	Mucoadhesion, viscosity enhancer
	Mannitol	Bulking agent
	MCC	Bulking agent, viscosity enhancer
Commonly Used in Development	Chitosan	Mucoadhesion, absorption enhancer, adjuvant
	Alginate	Absorption enhancer
	Lactose	Bulking agent
	Trehalose	Bulking agent, verifying agent
	Dextran	Bulking agent, verifying agent
	Cyclodextrins	Absorption enhancer
	Hyaluronic acid	Absorption enhancer
	PVP	Mucoadhesion
	Cellulose derivatives	Mucoadhesion, viscosity enhancer
	Leucine	Dispersion enhancer, moister protection

Lechuga-Ballesteros et al. 2019, in Pharmaceutical Inhalation Aerosol Technology

Strategies for Spray-dried Biologics

Maintaining stability of amorphous respiratory powders

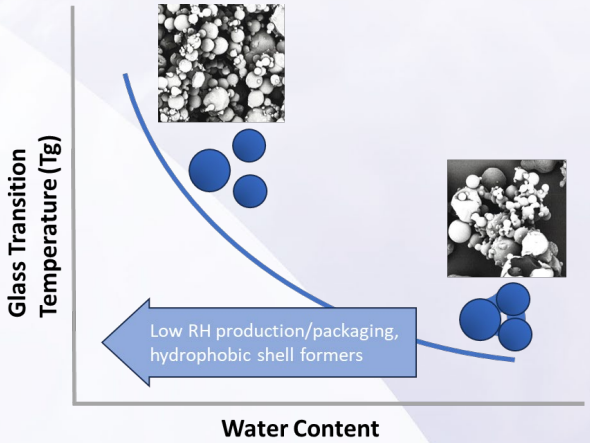


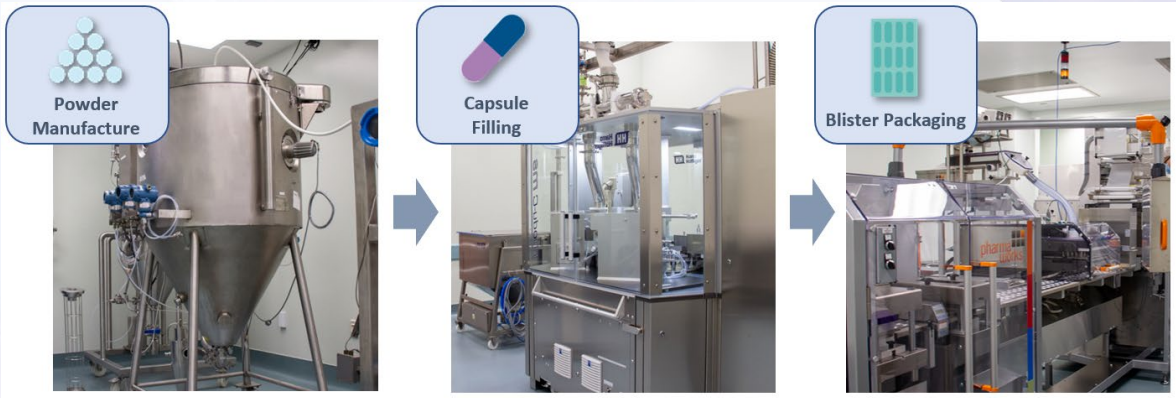
Trehalose and Leucine

Water Replacement – substitution of H2O-protien hydrogen bonds with alternative

Vitrification – reduce molecular movement in a glassy matrix

- Sufficiently dry powder is critical for high Tg and prolonged stability
- Moisture protection during manufacture is often necessary





RH control in closed equipment

RH control within suite where intermediate powder is exposed

DaanZillen et. al., Natural and bioinspired excipients for dry powder inhalation formulations. Current Opinion in Colloid & Interface Science, Vol 56, Dec 2021, 101497

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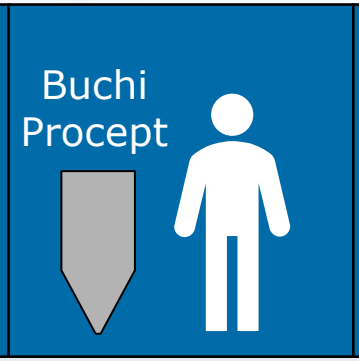
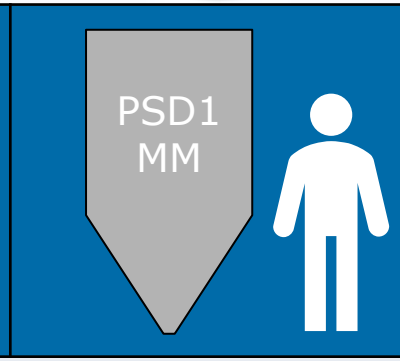
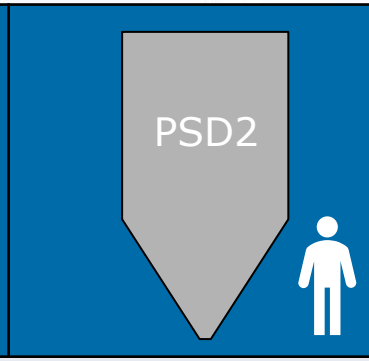
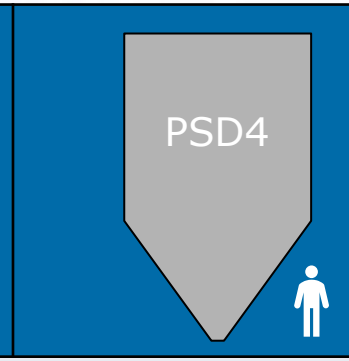
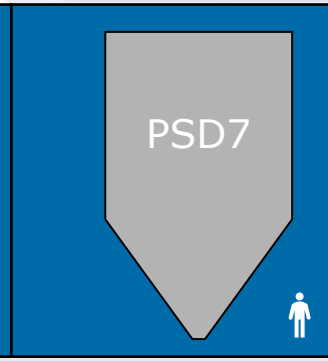
Spray Dryer Scale Comparisons

Relative Size					
Dryer Scale	Feasibility	Pilot	Production	Large Capacity	Industrial
Gas Flow	30 kg/hr	100 kg/hr	360 kg/hr	1600 kg/hr	10000 kg/hr
Typical Gas Loop	Open	Open/Closed	Closed	Closed	Closed
Water Flow	0.6 kg/hr	2.4 kg/hr	9 kg/hr	40 kg/hr	250 kg/hr
Nozzle Config	Single	Single/Cluster	Single/Cluster	Cluster	Cluster

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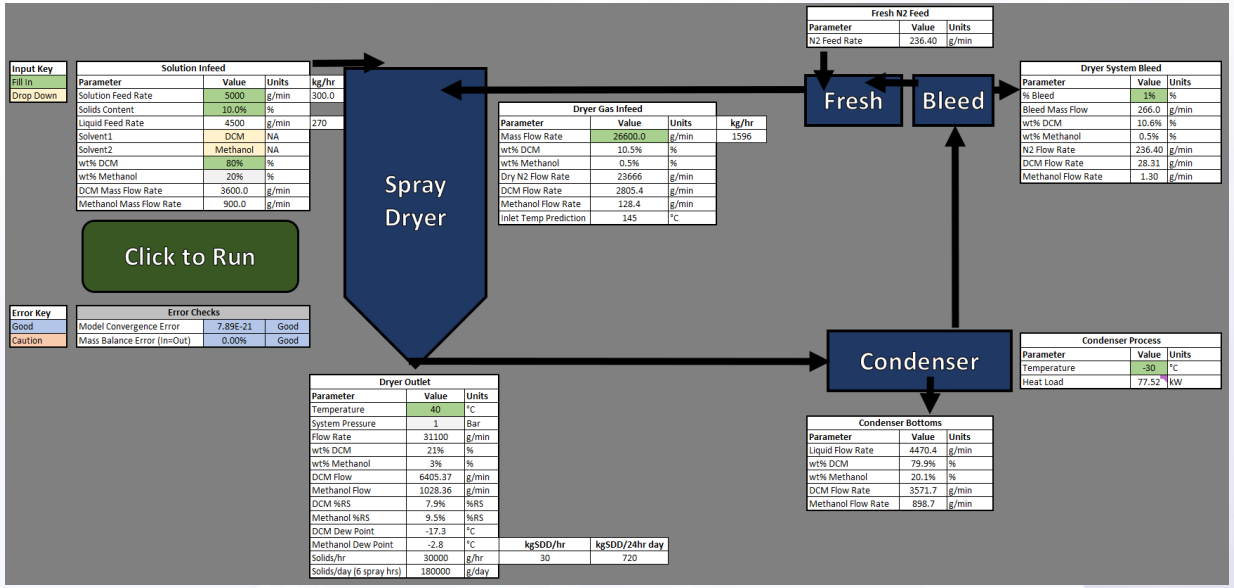
Spray Dryer Thermo-Model

What is it?

Mass and energy balance model of a spray drying system



How does it work?

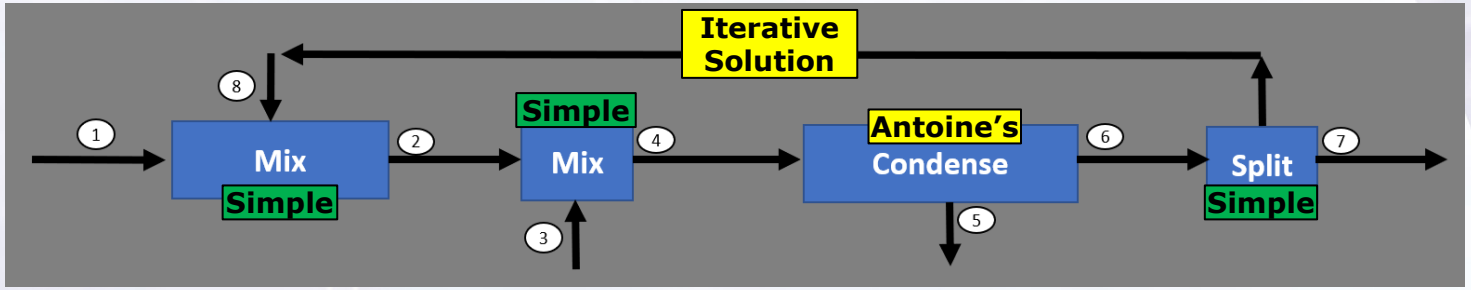
User specifies input parameters
"Guess" of initial recycle gas composition
Antoine's equations for condenser fractions
Compare new recycle composition to initial value
Iterate until results converge

What can it do?

Predict dryer outlet conditions and recycle gas composition
Estimate dryer inlet temperature
Estimate utility energy requirements

What can't it do?

Know if the output makes sense
Directly predict product attributes



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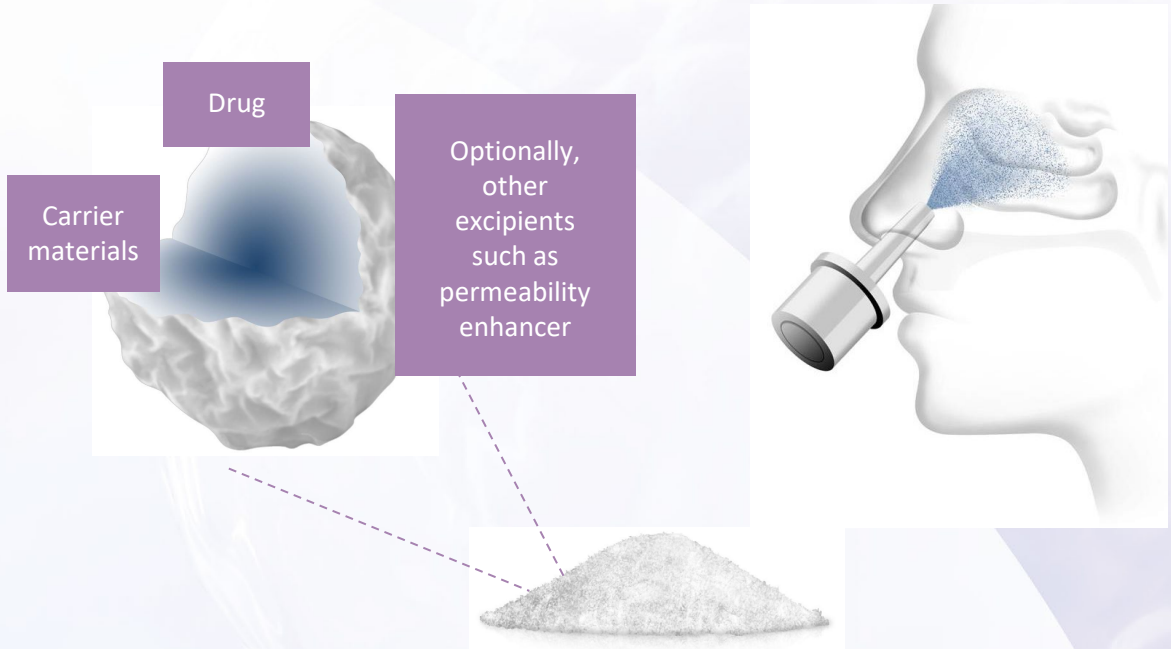
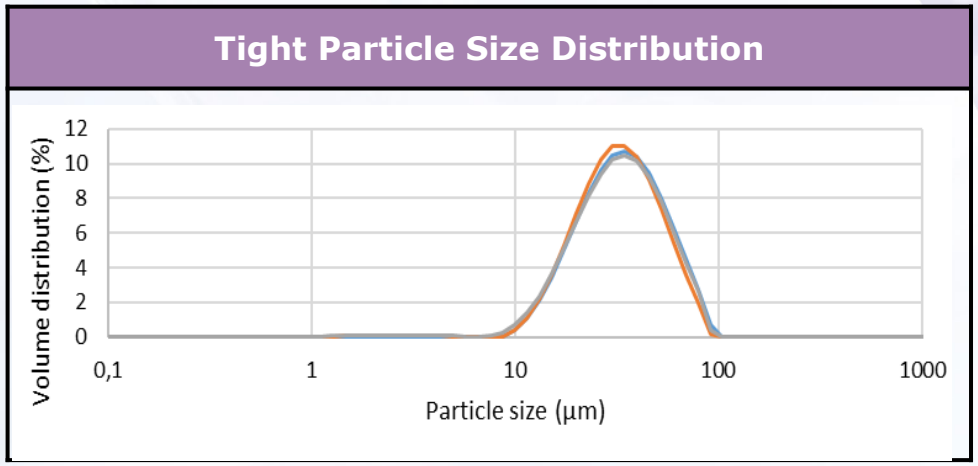
Spray Drying – AmorphOX®

AmorphOX® – a platform for intranasal drug delivery

- **500 batches over 8 years, 21 different APIs, 5 clinical trials**
- **Commerical scale manufacturing is established**
- **1st approval expected as part of OX124 (intranasal naloxone for opioid overdose rescue med)**
- **Spray-dried amorphous powder**
  - Can increase solubility and absorption for greater bioavailability

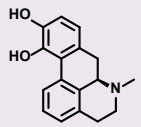




Spray Drying - AmorphOX®

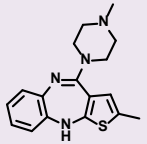
Small — Molecular weight (Mw) — Large

Apomorphine



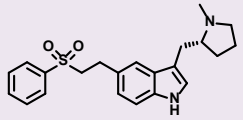
0.2% after 24 months

Olanzapine



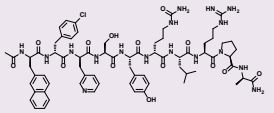
0.2% after 6 months

Eletriptan



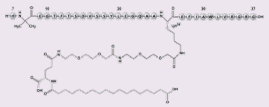
0.5% after 12 months

Cetrorelix



0.6% after 12 months

Semaglutide



0.1% after 6 months

Enzyme

Retained activity after 1 month (40° C)

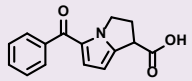
Virus like particle

Retained structure after processing and after 3 months at 40°C

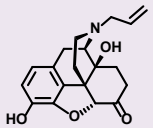
Attenuated Virus

Retained titer levels, resilient to freeze thaw cycles

Ketorolac

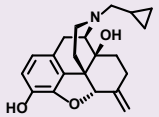


Naloxone



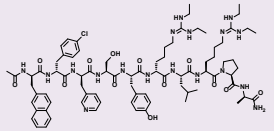
≤0.1% after 24 months

Nalmefene



≤0.1% after 15 months

Ganirelix

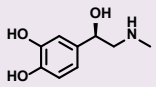


0.7% after 12 months

Covid Spike protein

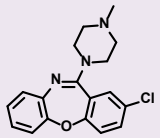
Retained activity after 3 months (40° C)

Epinephrine



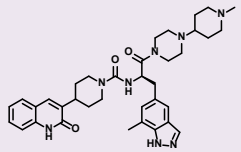
0.3% after 24 months

Loxapine



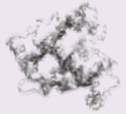
0.3% after 24 months

Zavegepant



≤0.1% after 9 months

Immuno-modulator



99% purity after 1 month (50° C)

Chemical degradation after accelerated stability studies in **40° C/75% RH**

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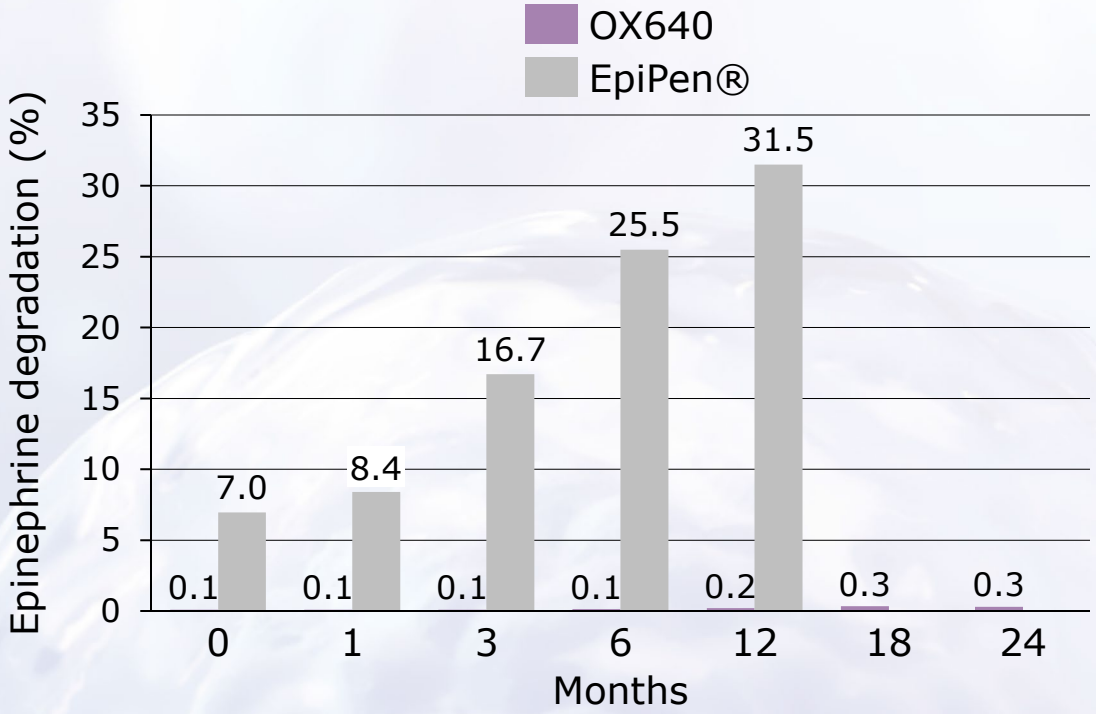
Spray Drying - AmorphOX®

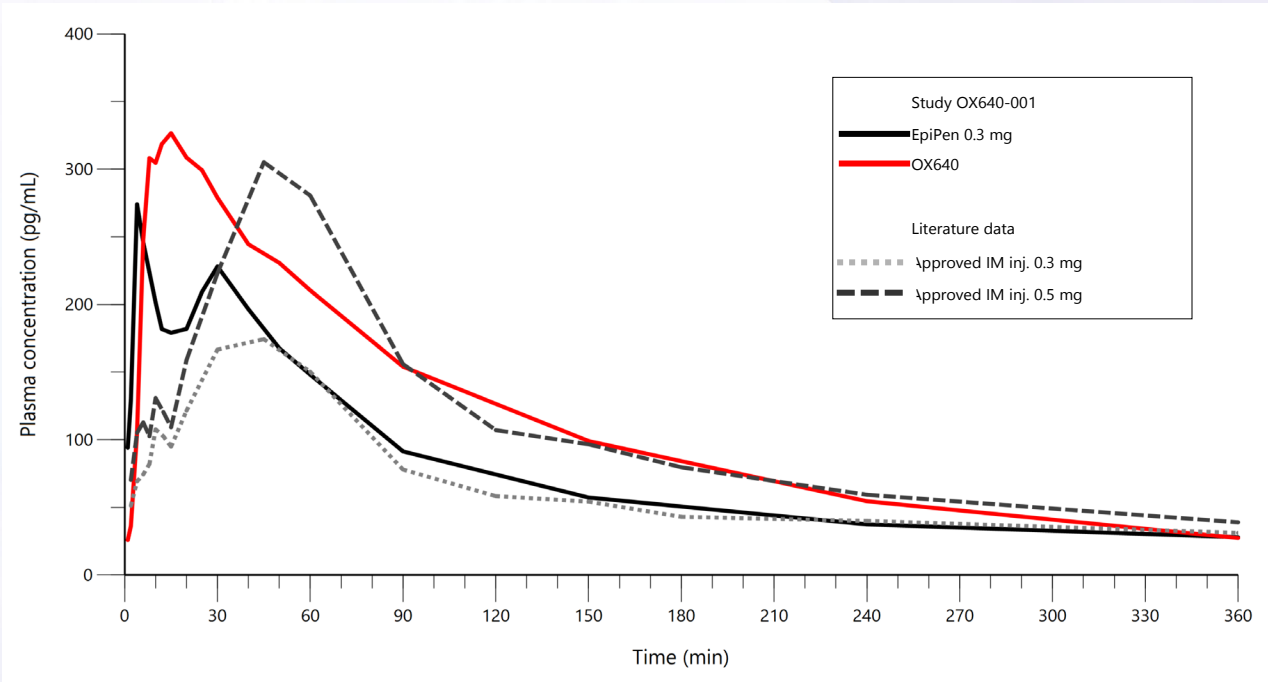
OX640: Nasal Epinephrine Powder – Improved stability over liquid comparitor and PK in humans

Comparative stability study @ 40°C/75% RH



✓ Excellent stability
✓ Preservative-free

Comparative bioavailability study in healthy volunteers



✓ Rapid and extensive absorption

Data from clinical study OX640-001 (n=40)

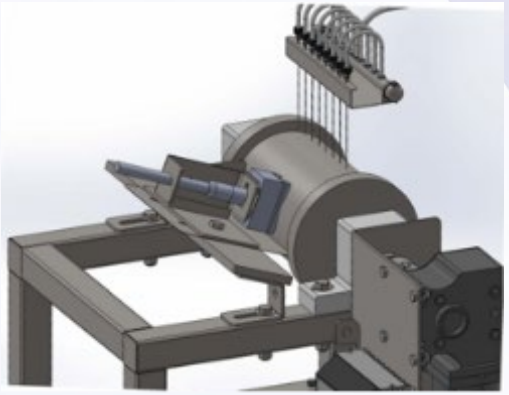
Alternative Manufacturing Approaches

Top-down: Micronization, Milling, Blending

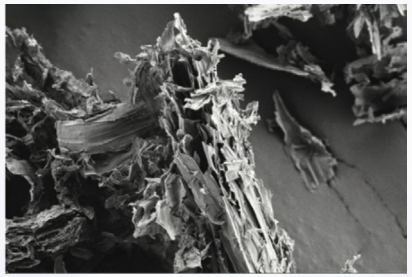
- Advantages – lower cost, established pharma process, scalable
- Disadvantages – Less control over particle size, morphology, not suitable for biologics

Bottom-up: Spray freeze drying, Freeze drying, Thin Film Freezing

- Advantages – suitable for biologics, lyo is an established pharma process
- Disadvantages – limited control over particle size, cost of lyophilization



Manufacturing – Impacts of Drum Filling



Lyophilized (made by TFF)

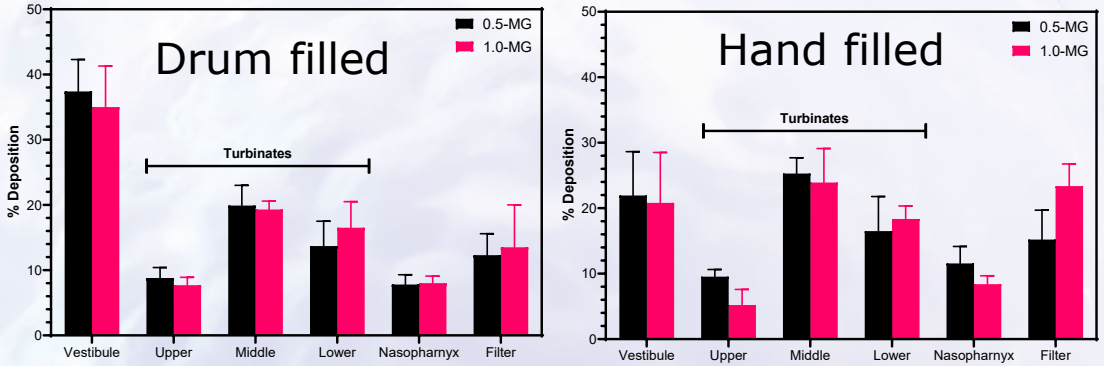
Extremely low density, friable cake

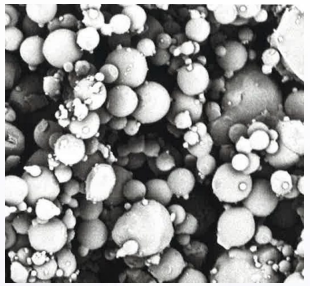
- Bulk density – 0.013 g/cc
- Compress Index – 22.8

LD of Device Emitted

	0.5 mg Fill Weight			1.0 mg Fill Weight		
	Dv(10) µm	Dv(50) µm	Dv(90) µm	Dv(10) µm	Dv(50) µm	Dv(90) µm
Drum	8.6 ± 1.1	40.7 ± 13.0	338.4 ± 174.9	11.6 ± 2.2	48.4 ± 10.6	330.5 ± 58.6
Hand	7.0 ± 0.3	30.0 ± 0.7	161.1 ± 42.8	10.9 ± 1.4	49.4 ± 6.2	251.1 ± 81.9

Cast Depo of Device Emitted



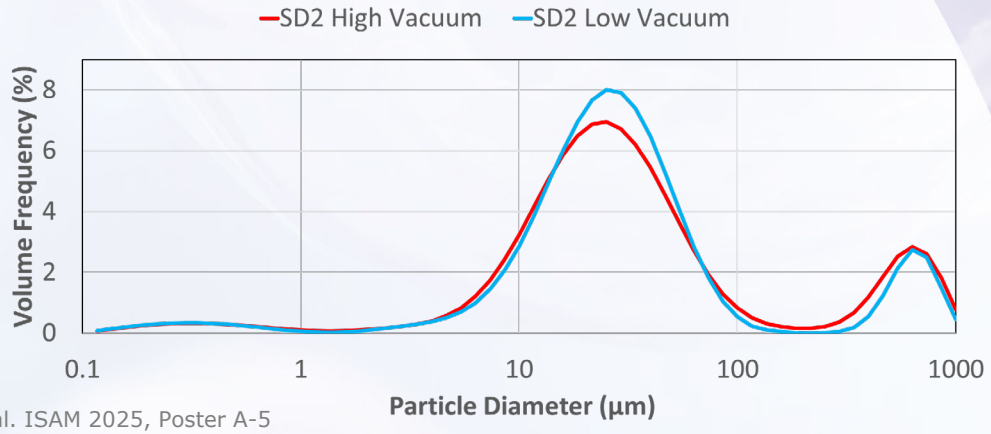


Spray Dried

- Will vacuum pressure effect emitted aerosol?
- Vacuum of 600 (high) and 200 (low) mbar investigated

LD of Bulk and Device Emitted

	Dv(10) µm	Dv(50) µm	Dv(90) µm
Bulk (wet LD)	4.6	17.9	42.1
High Vac	7.7 ± 2.7	25.6 ± 3.6	478.4 ± 231.1
Low Vac	8.3 ± 2.7	24.8 ± 2.3	339.5 ± 227.5



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Sandoval et al., Respiratory Drug Delivery 2024. Volume 1, 2024: 420-423

Owen et al. ISAM 2025, Poster A-5

Nasal Powder Devices

Air-powered, actuated

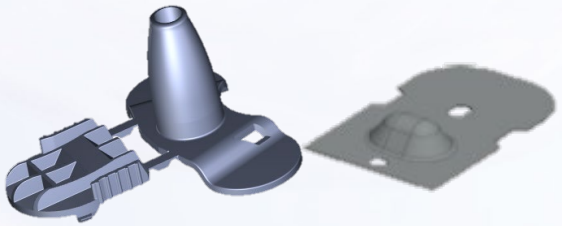
Air-powered, non-actuated

Breath-powered

HFA-powered

We have passive DPIs, why not passive nasal powder devices?

Passive



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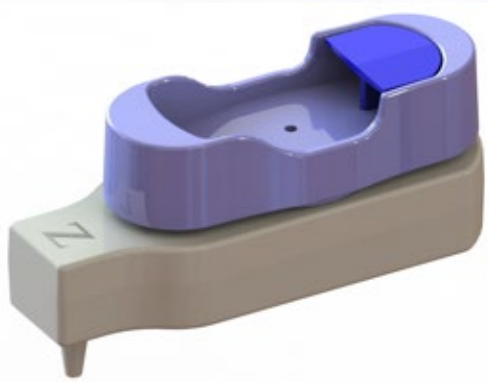
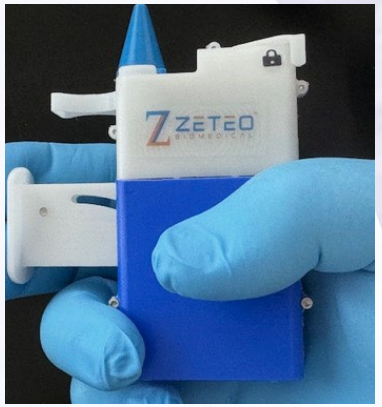
Zeteo devices

- **Active dispersion with ambient air**
- **Primary container is USP class VI cold form blister**
- **No priming, orientation independent operation**
- **Replaceable nasal tips (adult, pediatric and small animal)**
- **CygnusSDX – single dose**
  - 2-16 mg delivered mass
  - Actuated by rotating lever 180°, pressing actuation button
- **CygnusMR – multidose (≤60 dose)**
  - 7-25 mg delivered mass
  - Actuate-> press dosing button

CygnusSDX™



CygnusMR™

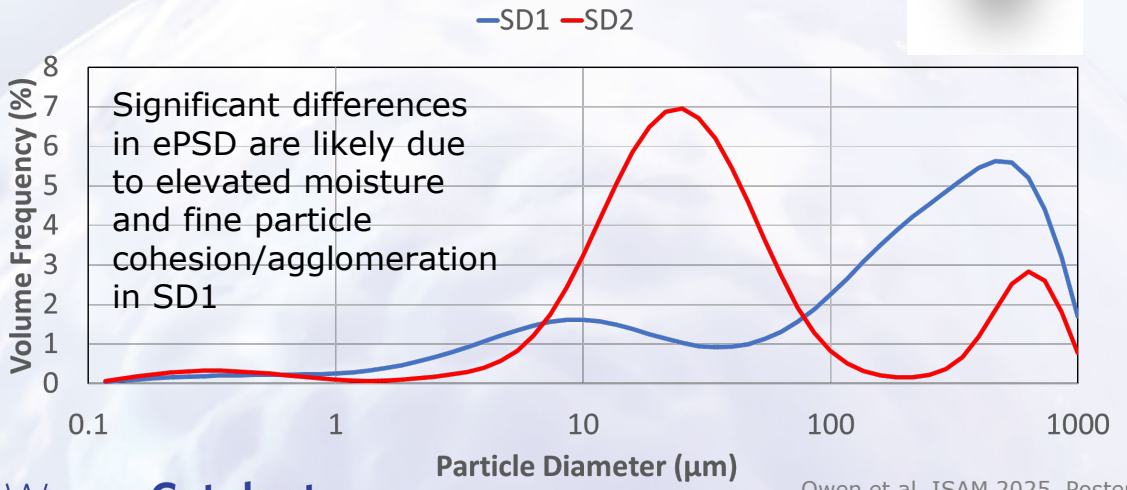


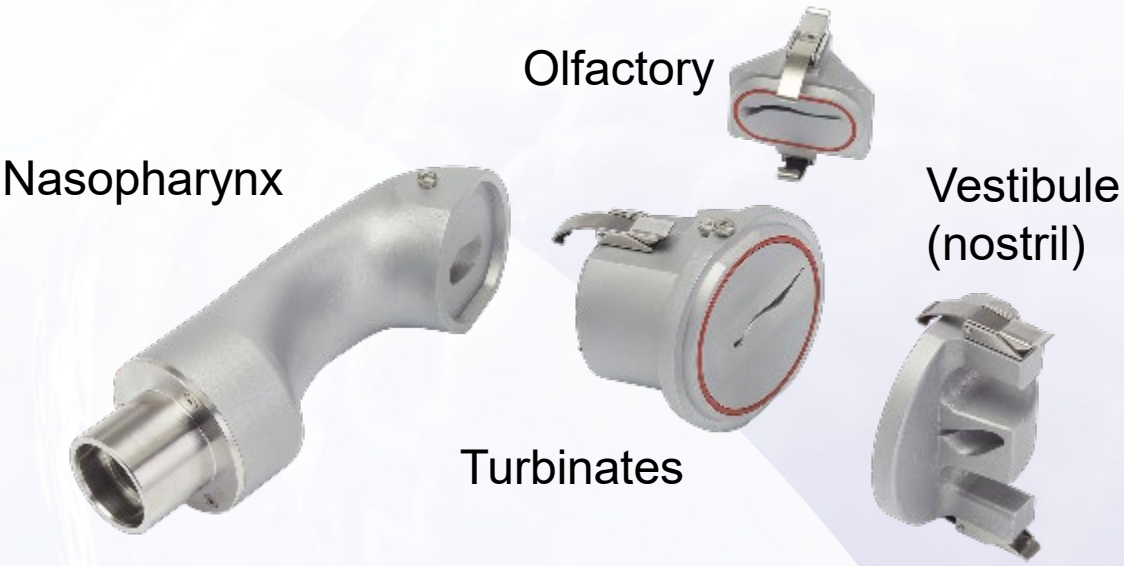
Characterization – Anatomical Models

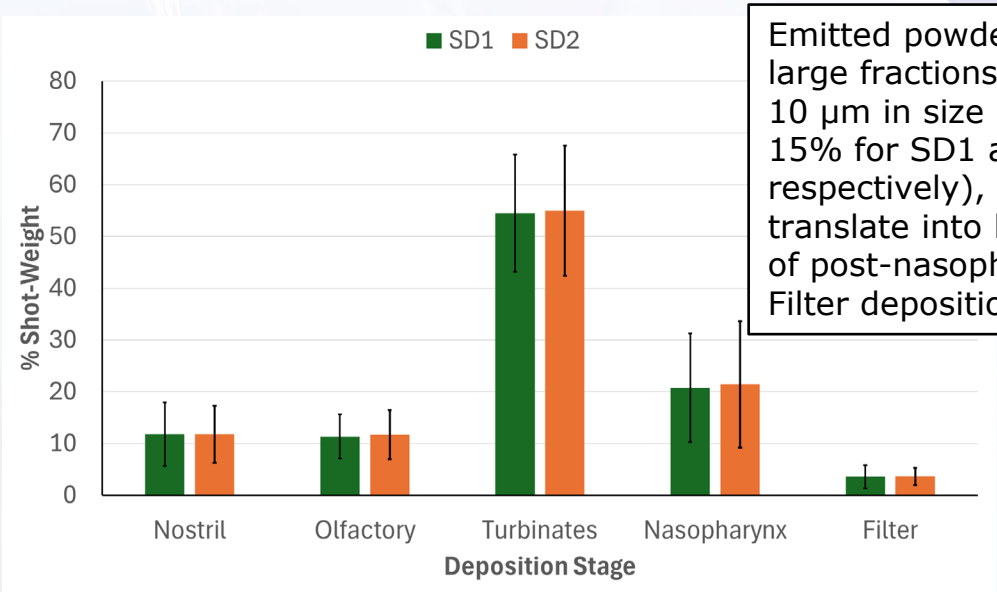
Two distinct bulk intermediate epinephrine powders were filled and tested for emitted PSD and anatomical deposition

LD of Bulk SD Intermediate

	SD1	SD2
Dv(10) (µm)	1.8	4.6
Dv(50) (µm)	5.3	17.9
Dv(90) (µm)	13.4	42.1







Emitted powders had large fractions less than 10 µm in size (17 and 15% for SD1 and SD2 respectively), but did not translate into high levels of post-nasopharynx Filter deposition

Owen et al. ISAM 2025, Poster A-5

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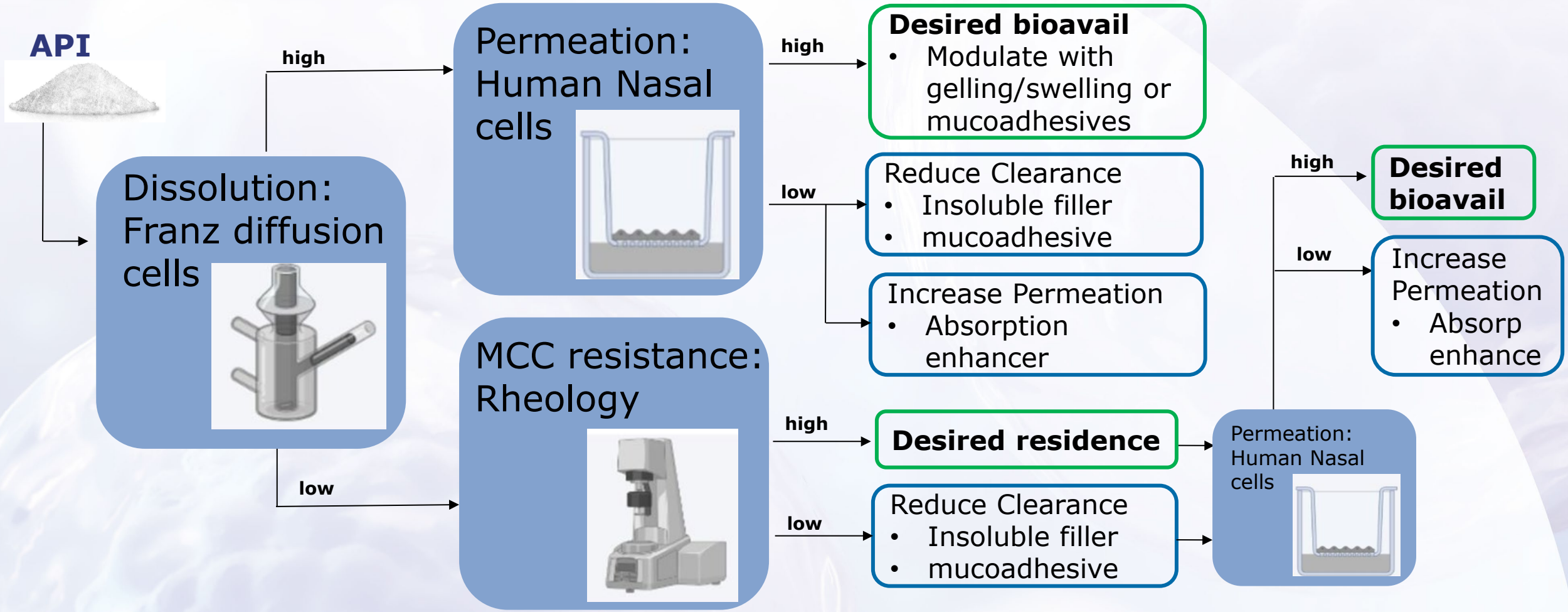
Characterization – Disso, MCC & Absorption

A rationale formulation approach (adapted from Trenkel 2023)



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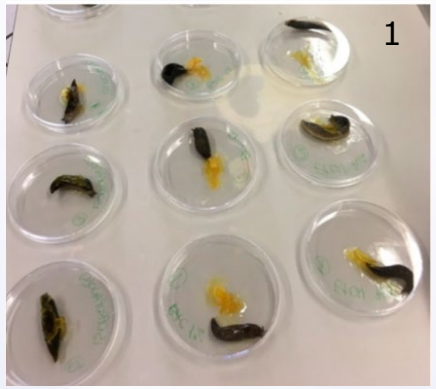
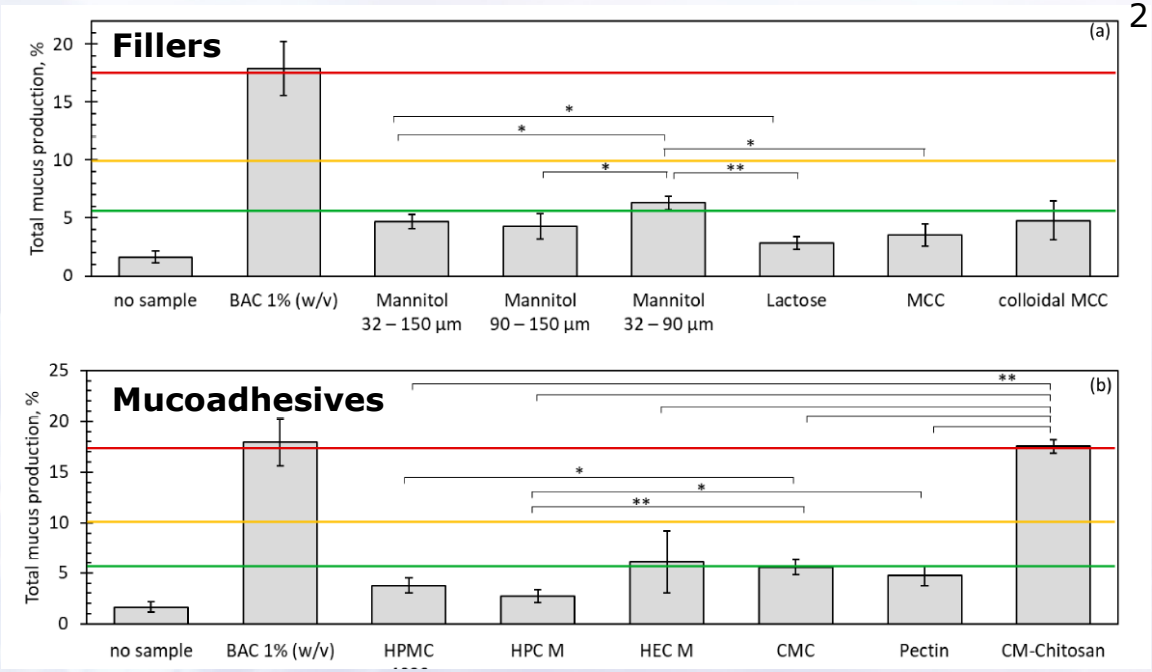
Trenkel et al. Pharmaceutics 2021, 13, 385

Characterization – Nasal Irritation



Slug Mucosal Irritation Assay can be used to determine nasal tolerability

- Smaller particles dissolve more rapidly, increasing osmolarity
- Neutral polymers less irritating than anionic



Baqsimi adverse events in children [3]

Table 3—Adverse events by treatment arm within age cohort

	4 to <8 years old			8 to <12 years old			12 to <17 years old	
Adverse events	IM	2 mg IN	3 mg IN	IM	2 mg IN	3 mg IN	IM	IN
N	6	12	12	6	11	12	12	13
One or more events	5 (83)	6 (50)	5 (42)	6 (100)	5 (46)	6 (50)	7 (58)	9 (69)
Gastrointestinal[a,b]	5 (83)	5 (42)	5 (42)	5 (83)	4 (36)	6 (50)	6 (50)	6 (46)
Headache[a]	0	2 (17)	1 (8)	2 (33)	2 (18)	4 (33)	1 (8)	4 (31)
Nasal[a,c]	0	1(8)	2 (17)	0	0	1 (8)	0	3 (23)
Ocular[a,d]	0	0	0	0	1(9)	0	0	2 (15)
Sensory/pain[a,e]	2 (33)	1 (8)	0	3 (50)	0	0	0	0
Other[a,f]	1 (17)	1 (8)	0	1 (17)	0	0	0	0

Patients (of 59) with Nasal AE

- **Nasal Congestion - 2**
- **Nasal Discomfort – 3**
- **Sneezing -1**
- **Rhinalgia - 1**

1) Cutuli et al. Biomedicines 2021, 9(4), 424
2) Trenkel et al. Pharmaceutics 2021, 13, 385
3) Sherr et al Diabetes Care 2016;39:555–562

In Summary

The nasal route is a needle-free, rapid-onset means for local, systemic or CNS targeted therapies

Nasal powders offer improved stability, high dose and increased residence time compared to liquid

Formulation Design & Development → Process Design & Optimization → Scale-up & Commercial

Development to Commercial

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