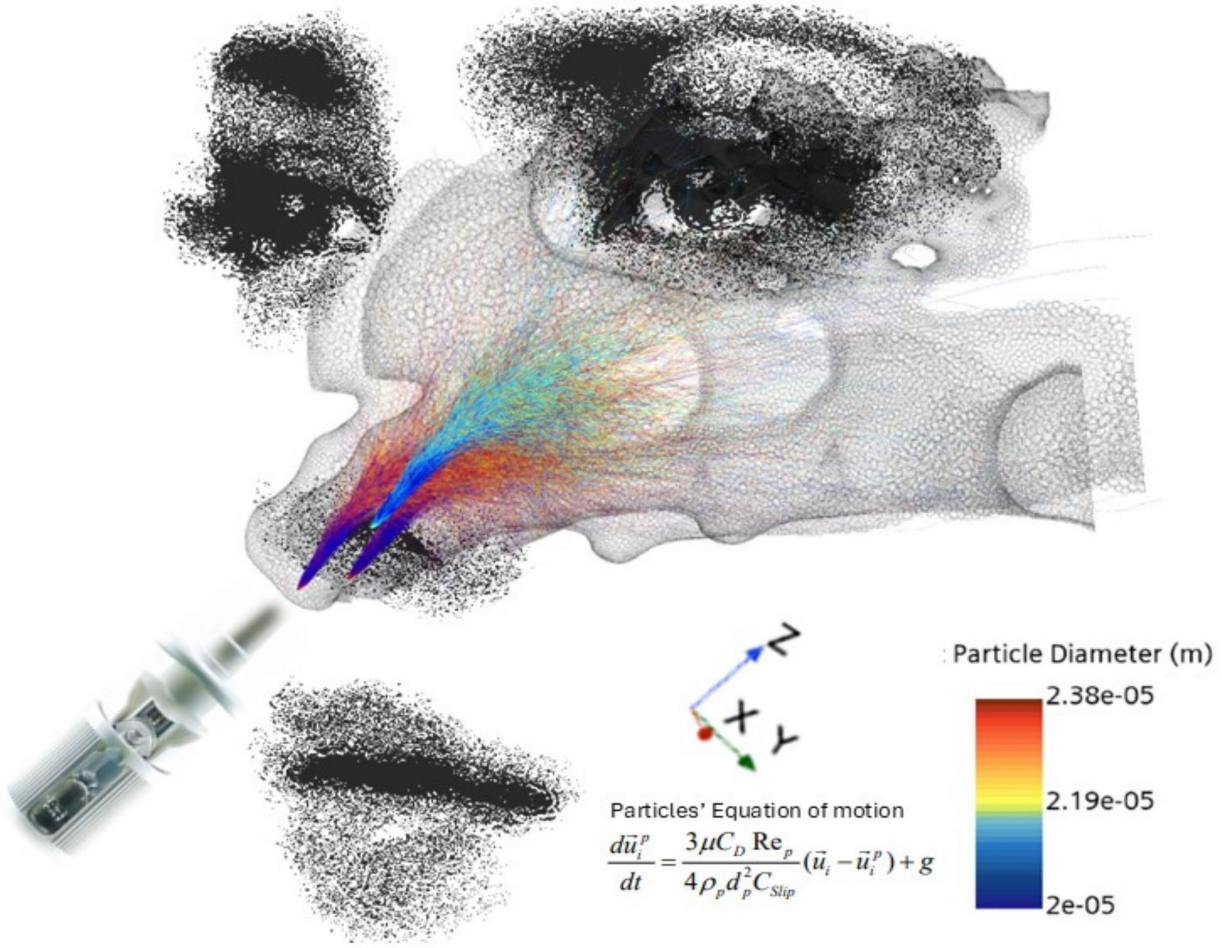
Global R&D - Consumer Health Innovation Center

ROAD TO BILLIONS

IPAC-RS International Pharmaceutical Aerosol Consortium on Regulation & Science

NASAL INNOVATION FORUM

"A Novel Modified-Release Nasal Self-Nanoemulsifying Drug Delivery System (n-SNEDDS) for Enhanced Solubility, Retention, and Brain Targeting"



By: Deb Das.

[Senior Associate Director & Bayer Science Fellow, Formulation Development, Global R&D, Bayer Healthcare US]

September 18th, 2025

R&D Innovation Centers have an Expansive Global Footprint

Morristown Innovation Center
// Therapeutics, VMS, Digestive Health

Alcala Innovation Center
// Soft gelatin capsules (all categories)

Gaillard Innovation Center
// Dermatology

Darmstadt Innovation Center
// Phytomedicines

Singapore R&D Center
// CDMO Innovation for APAC

Global R&D Innovation Center – MOR, NJ // Leading the future of Self-care

1. **Main Innovation Team** – all categories ex. Derm
2. **~ 60** Scientists & Project Leaders
   > 50% Female Talent at all levels
3. Reaching > 50% of US Households
   5 million products sold each week **
4. > 50 launches in the last 5 years

*By Y5 Pipeline Value
** IRI 52 we 3/7/2023

Global Brands for Nasal Sprays (Therapeutic)

Your Nose, Our World!

Oxymetazoline Nasal Spray

Azelastine Nasal Spray.
Rx-OTC switch.

Oxymetazoline Nasal Spray

Mometasone Intranasal spray

Oxymetazoline Nasal Spray

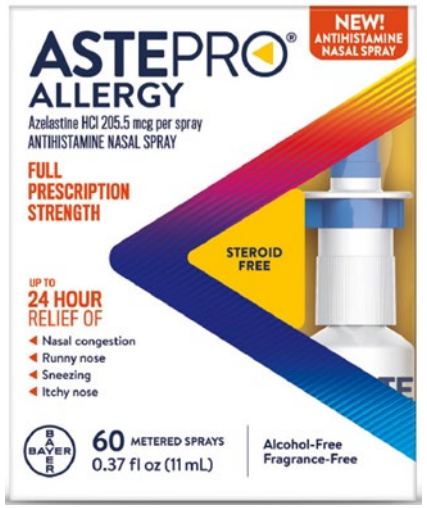
Mometasone Intranasal spray

Oxymetazoline nasal spray
for Zone IVB

Mometasone Intranasal spray

World's leading brands for nasal relief against cough, cold & allergy-related illnesses

Bayer's Nasal Spray Portfolio Focus



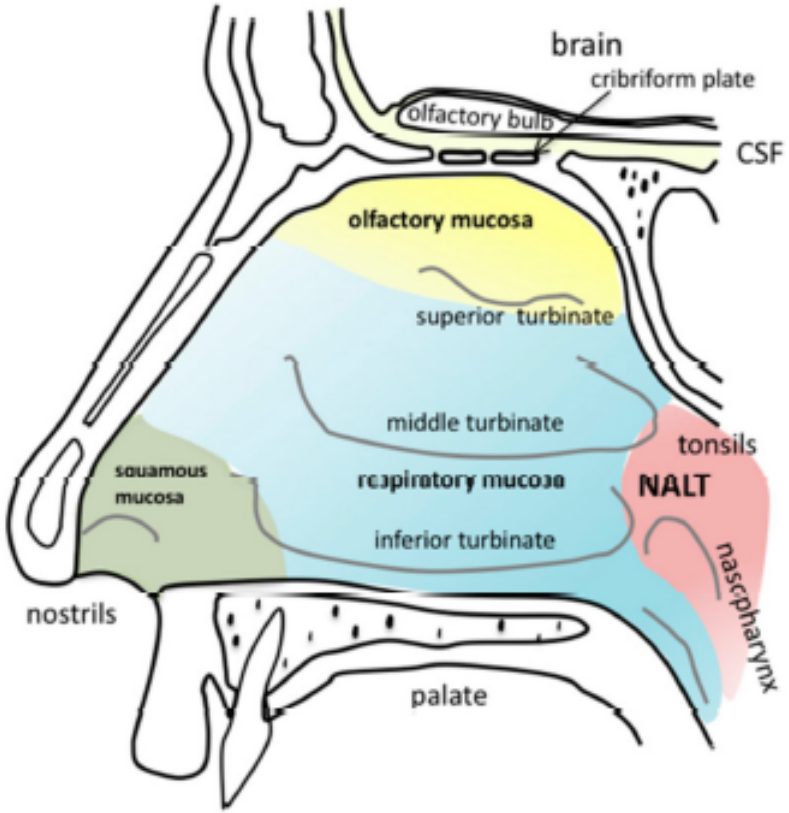
- The launch of Astepro Allergy
- OTC allergy category; Steroid free
- The combination of the MOA (antihistamine) plus delivery mechanism (intranasal) result in fast relief **(30 mins).**

- Line extensions: Allergy + Cough/Cold symptoms.
- Benefits of a nasal antihistamine vs. other OTC options
- Relief of most bothersome allergy symptom (nasal congestion, headache, stuffiness)
- Not needing several days of continuous use to build to full efficacy
- **No-Drip platform – UNIQUE ADVANTAGES**
- *(keeping the dose - in the nose!)*

Designing enhanced nasal sprays: Long lasting products with better bioavailability & targeting

Overview

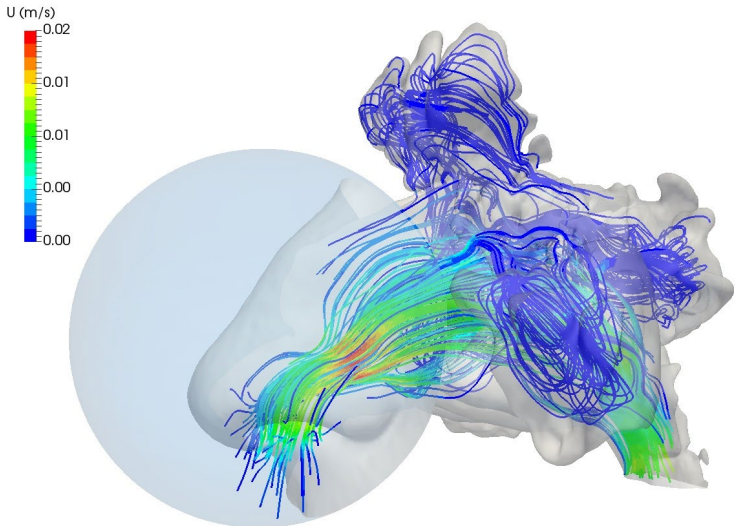
Nasal Drug Delivery: Multipurpose & Non-Invasive

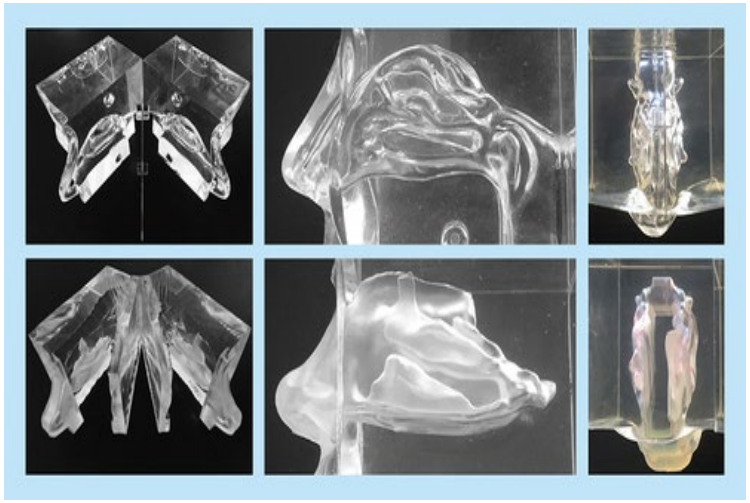


Source:
https://doi.org/10.3390/pharmaceutics1003011

Route of Delivery	Nasal Mucosa	Clinical Examples	References
Local	Squamous & Respiratory	Decongestants, Anti-allergic, Local anesthetics, Glucocorticoids	Allergy Clin Immunol . 2001 Jul;108(1 Suppl):S26-31. ; Clin. Ther. **2008**, 30, 1–13.
Systemic	Respiratory	Calcitonin, Sumatriptan, Desmopressin	Prim. Care Respir. J. **2006**, 15, 58–70.; Cephalalgia **1998**, 18, 487–489.
Intra Nasal Vaccination	Nasopharynx associated lymphatic tissue; Immune cells in mucosa	Seasonal flu vaccine	Am. J. Respir. Crit. Care Med. **2011**, 183, 1595–1604
CNS Delivery	Olfactory & Trigeminal nerve endings	Oxytocin, Insulin	Nutrition **2010**, 26, 624–633. Mol. Pharm. **2018**, 15, 1105–1

Complexities of nose: Variable nasal anatomy





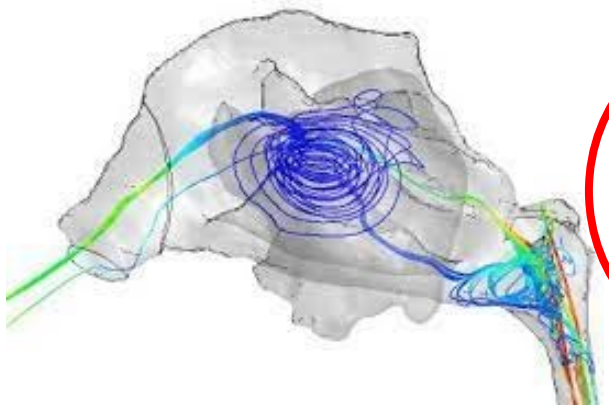


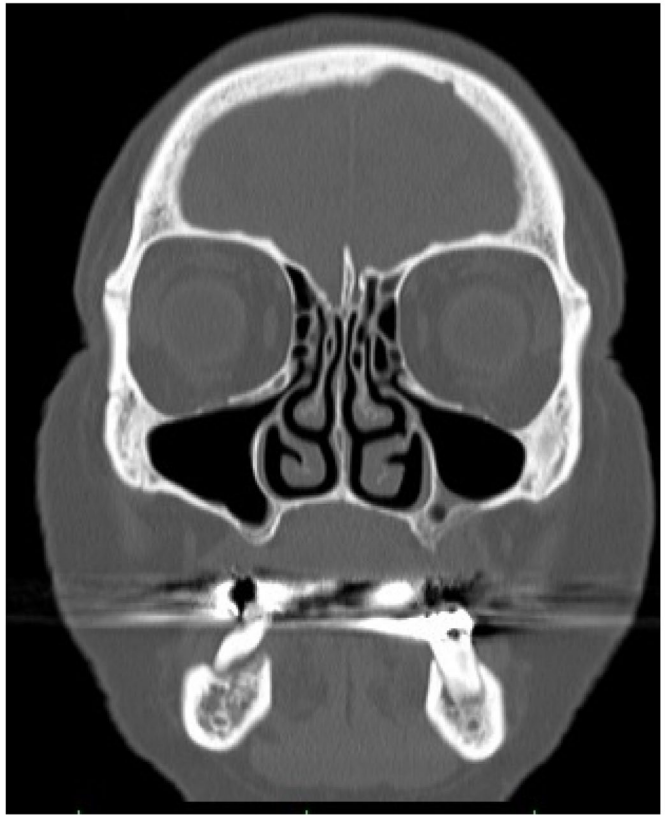
Table 2. Nasal volumes (V_1, V_2 and V_3) established by acoustic rhinometry in 60 nasal cavities from 30 male and female adults with no evidence of nasal obstruction, according to gender and nasal cavity (right-D and left-E), before and after applying nasal vasoconstriction (VC).

Volume (cm^3)	Before VC	After VC	Percentage variation
V_1 (valve)	1,68±0,32 (n=60)	1,82±0,30 S (n=60)	8%
V_2 (turbinates)	3,98±1,21 (n=60)	5,53±1,03 S (n=60)	39%
V_3 (nasopharynx)	17,67±3,57 (n=30)	22,72±4,06 S (n=30)	29%

average ± standard deviation

n = number of nasal cavities analyzed

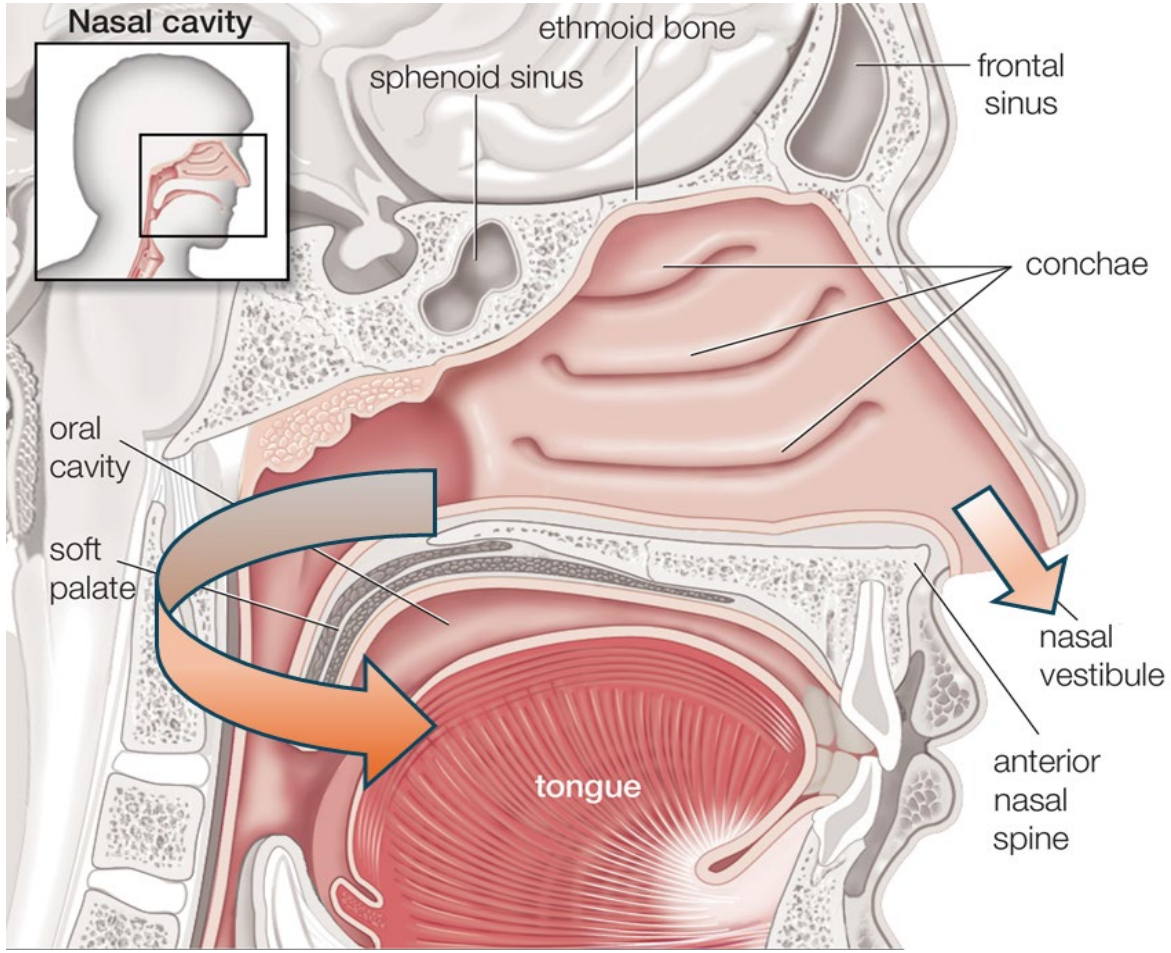
S $p<0.05$: statistically significant difference (before vs. after VC)



https://doi.org/10.1016/S1808-8694(15)31119-8

Practical Challenges: Loss of Dose from Nasal Delivery

Most of the delivered dose either flows out from the front of the nose or drips back from the back of the nose to the throat and mouth region



Source: https://www.britannica.com/science/soft-palate

Formulation challenges to develop a nasal spray:

- ❑ Drugs with very high aqueous solubility and/or potent drugs
- ❑ Volume limitation of 200 µl or 0.2 ml per dose per nostril
- ❑ Mucoadhesion to avoid mucociliary clearance
- ❑ Mucolysis to penetrate mucus thereby aid in absorption.
- ❑ Prevent dose loss due to flowing out of nasal cavity (front & back)
- ❑ Deposition in target area (Olfactory region)
- ❑ Irritation in nasal mucosa

Can strategic use of polymers and/or solubilizers address these challenges?

Formulation targets: QTTP (Quality Target Product Profile) for product performance:

Modified release + Bioavailability

OTC products: Time & Price Limitations!

Viscosity – Longer retention (Thixotropy + Elastic Modulus)

+

Muco-Retentive

Use of mucoadhesive & ciliostatic agents

+

Solubility & Permeation enhancement - Strategic use of surface-active agents to enhance BA

+

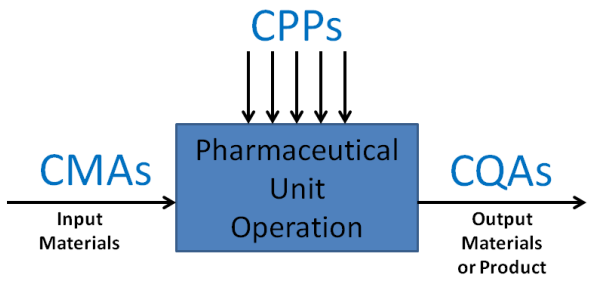
Area of Deposition

Targeted delivery at site of absorption

→ **Modified release + Superior bioavailability**

OGD's View of CMA/CPP/CQA Relationship

In his talk at the GPhA workshop, OGD's Yu presented a pictorial representation the relationship between critical material attributes (CMAs), critical process parameters (CPPs), and critical quality attributes (CQAs).



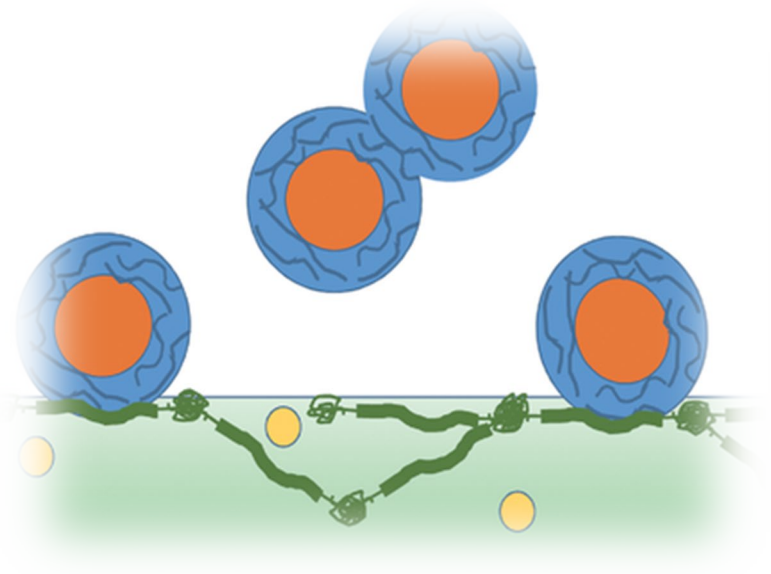
$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$

❑ The ask (QTTP):

- ✓ Generate a **universal model** for solubilization of drugs for ALL BCS classes
- ✓ **Maximize solubilization** power with adequate **permeation**
- ✓ Mucoadhesive (Long acting) , and mucolytic (fast acting) > **Modified Release**
- ✓ Limit to a small volume of **200 µl or 0.2 ml** per dose per nostril
- ✓ Allow solubilization of other **necessary excipients** such as buffers, preservatives, antioxidants to maintain pH, osmolality & drug stability
- ✓ **Targeted delivery** & deposition on olfactory area (for brain targeting)
- ✓ Can be delivered **without any specialized delivery device** is required (price sensitive) if suitable device is not available for delivered specialized formulation (usually thick suspension or solution)
- ✓ Must be **scale-up friendly** with **QbD** manufacturing

Addressing challenges

Thixotropic & mucoadhesive polymeric systems to achieve sprayability & longer retention time in nose



STATE OF ART: THE PROPULSION OF MUCUS BY CILIA

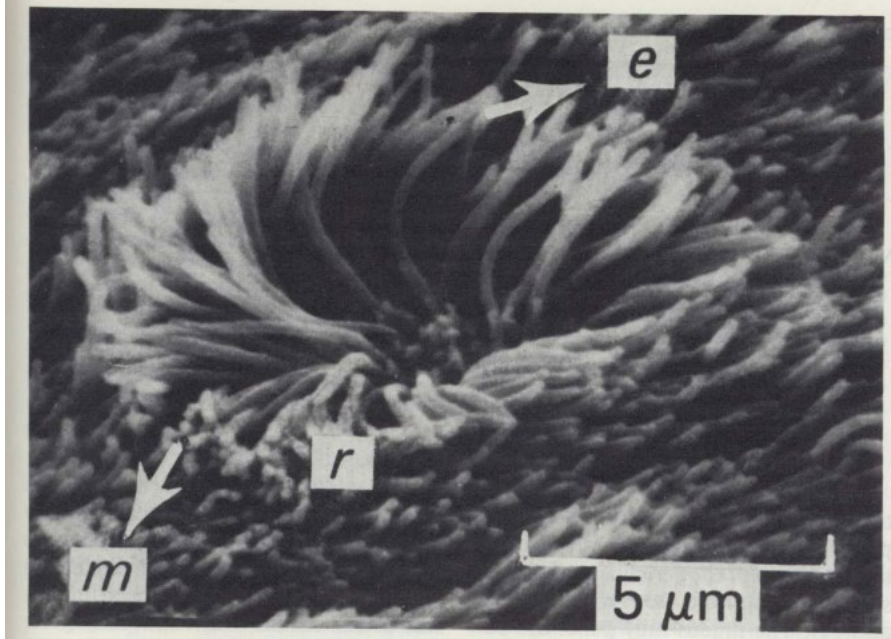


Fig. 6. Scanning electron micrograph of a metachronal wave on rabbit tracheal epithelium fixed in 2% OsO_4 and postfixed in 4% glutaraldehyde. Cilia that move to the left close to the cell surface in their recovery stroke (*r*) then swing over towards the right in the more erect effective stroke (*e*). The metachronal wave moves in the direction indicated by the arrow (*m*). Micrograph by M.J. Sanderson, from reference 22.

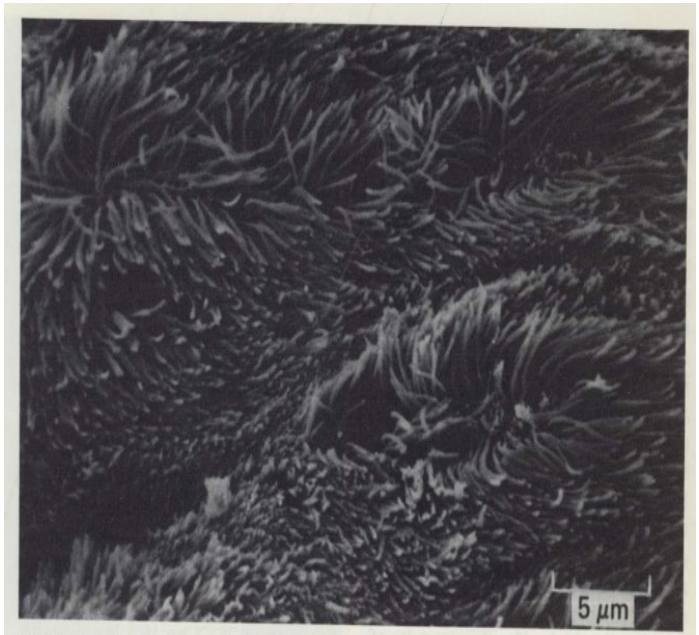


Fig. 4. Scanning electron micrograph of rabbit tracheal epithelium fixed in 2% OsO_4 and postfixed in 4% glutaraldehyde. The 2 active patches contain cilia that would propel mucus towards the right, and cilia between these active patches lie at rest with their tips directed towards the right. Micrograph by M.J. Sanderson, from reference 22.

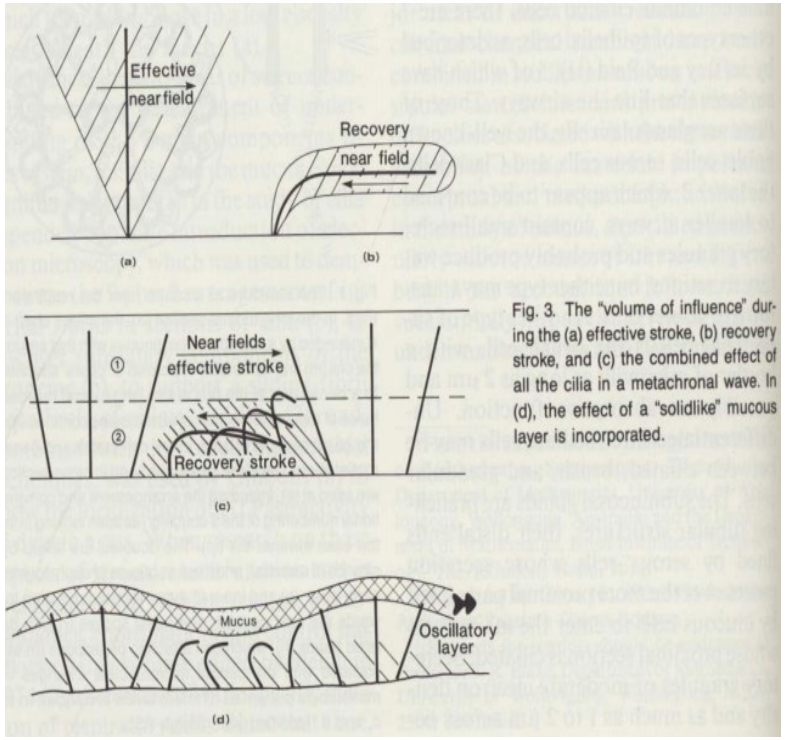


Fig. 3. The "volume of influence" during the (a) effective stroke, (b) recovery stroke, and (c) the combined effect of all the cilia in a metachronal wave. In (d), the effect of a "solidlike" mucous layer is incorporated.

Ref: The propulsion of mucus by cilia.
https://pubmed.ncbi.nlm.nih.gov/3278666/

Use of polymers to achieve sheer thinning systems

- Formula is modified into a specialized delivery vehicle which is thixotropic or shear thinning system
- Provides the product a “no-drip” function which prevents it from “dripping” after nasal delivery
- GEL to SOL to GEL
- Bayer has a similar “no-drip” product in the Afrin line
- Suspension formulation with NaCMC & MCC (in market)
- Solution formula with HPC, HEC, HPMC etc.

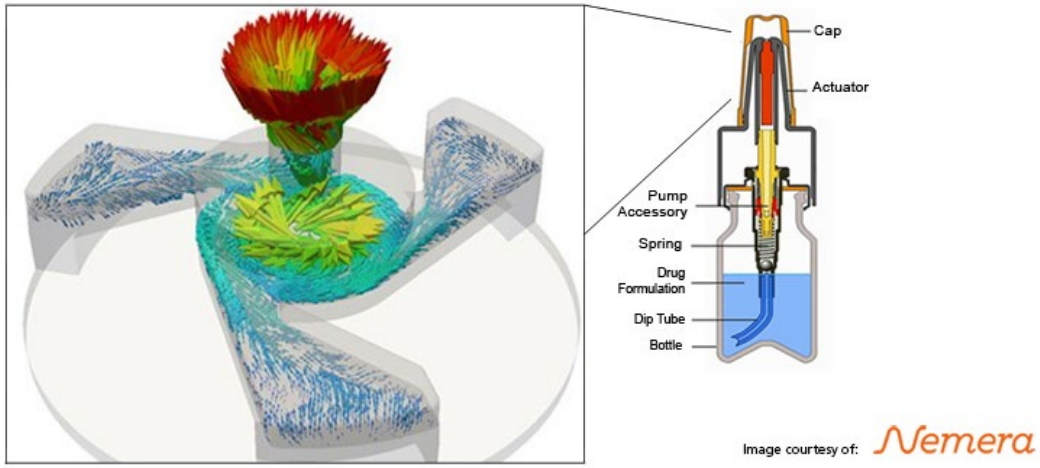
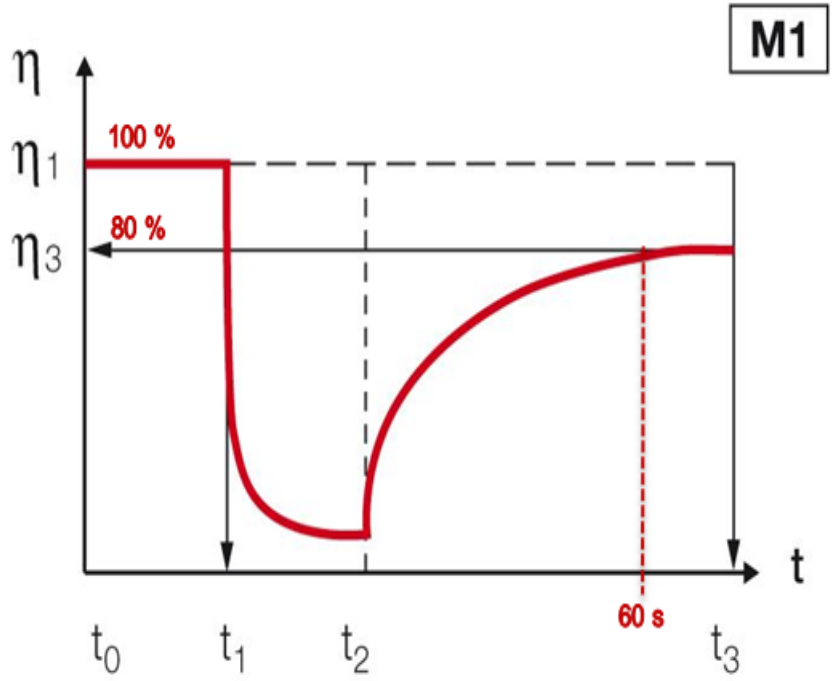


Image courtesy of: Nemera



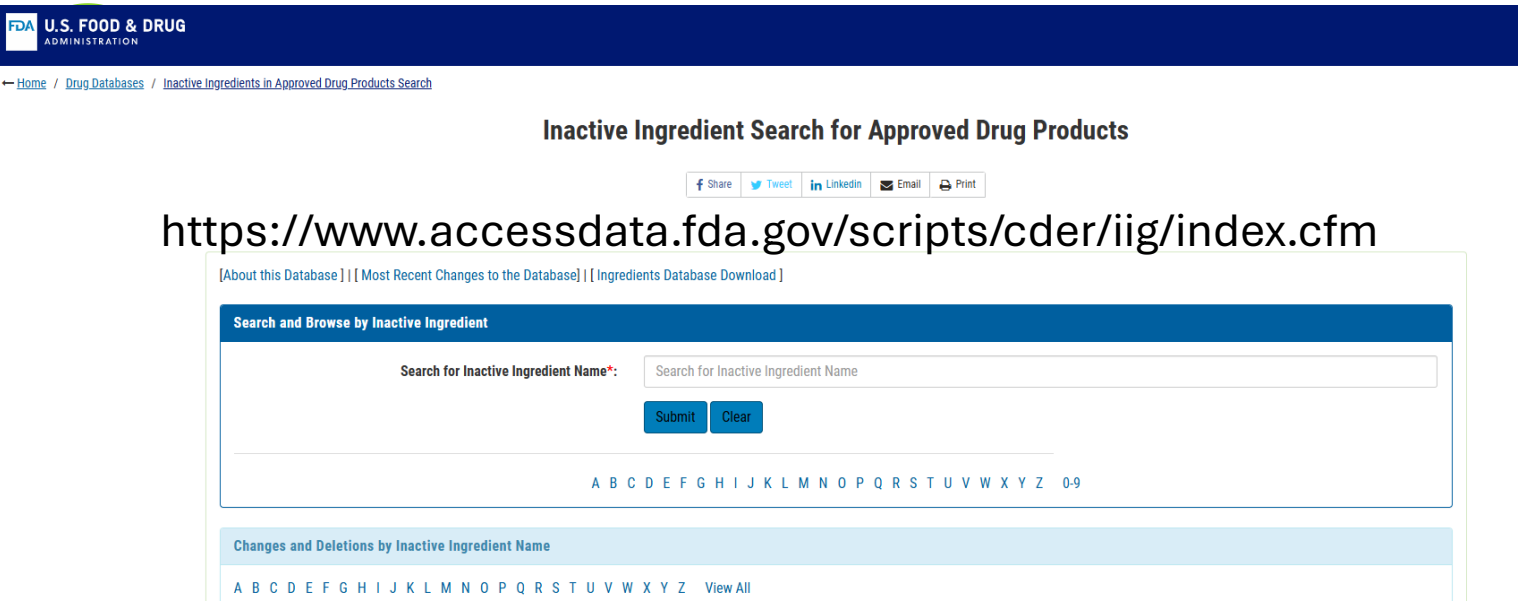
Step test (3 intervals thixotropy test, 3ITT)

Time-dependent viscosity of a sample with thixotropic behavior. η = viscosity, t = time

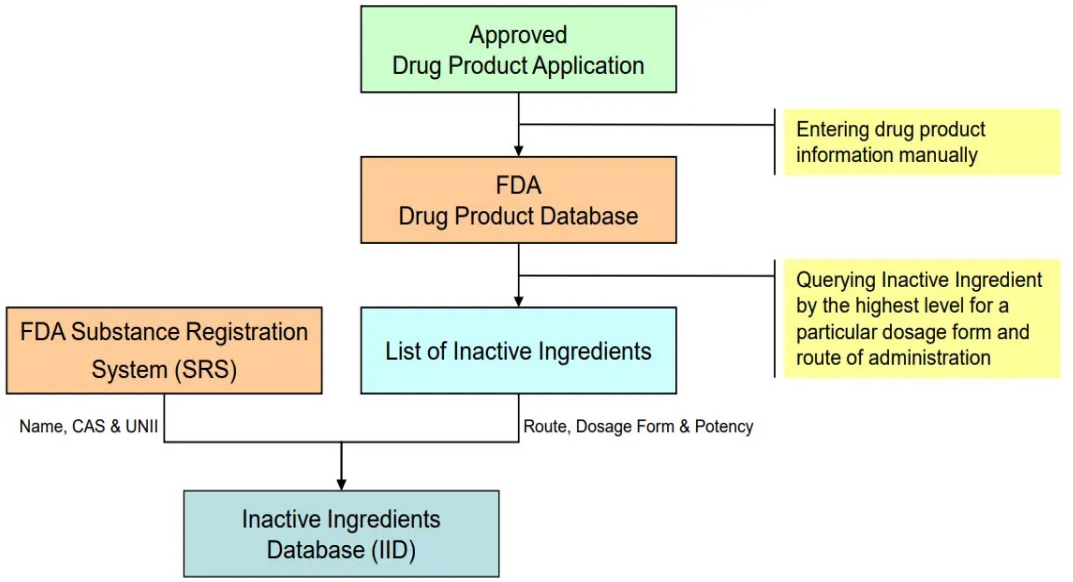
Variation due to Mol. Wt. causing differential internal friction

Analyzing the recovery ratio after a given time. η = viscosity, t = time

Current FDA's IID polymers for nasal use (Need for novel polymers)

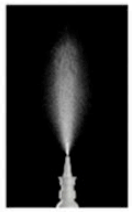


INGREDIENT_NAME	ROUTE	DOSAGE_FORM	CAS_NUMBER	UNII	POTENCY_AMOUNT	POTENCY_UNIT	MAXIMUM_DAILY_EXPOSURE	MAXIMUM_DAILY_EXPOSURE_UNIT	RECORD_UPDATED
CARRAGEENAN	NASAL	POWDER	9000071	5C69YCD2YJ		NA			
CELLULOSE MICROCRYSTALLINE/CARBOXYMETHYLCELLULOSE SODIUM	NASAL	SPRAY, METERED		NA			60	mg	
HYDROXYETHYL CELLULOSE (2000 MPA.S AT 1%)	NASAL	SPRAY	9004620	S38J6RZN16	0.1	mg/0.2 ml			
HYPROMELLOSE 2910 (4000 MPA.S)	NASAL	SPRAY	9004653	RN3152OP35			1	mg	
HYPROMELLOSE 2910 (5 MPA.S)	NASAL	SPRAY	9004653	R75537T0T4	1	mg/1ml			
METHYLCELLULOSE	NASAL	JELLY	9004675	Z944H5SN0H		NA			
PECTIN	NASAL	SPRAY	9000695	89NA02M4RX	10	mg			
POLYETHYLENE GLYCOL 3350	NASAL	SOLUTION	25322683	G2M7P15E5P	40000	mg/100 ml			
POLYETHYLENE GLYCOL 400	NASAL	SPRAY, METERED	25322683	B697894SGQ	200	mg/1ml			

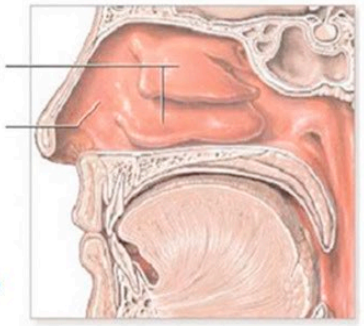


- *Published ones (only 7)* Most polymers will not work with ionic drugs or produce viscosity in prescribed amounts
  - Carrageenan, MCC, NaCMC, HEC, HPMC, Pectin, PEG (3350 & 400)

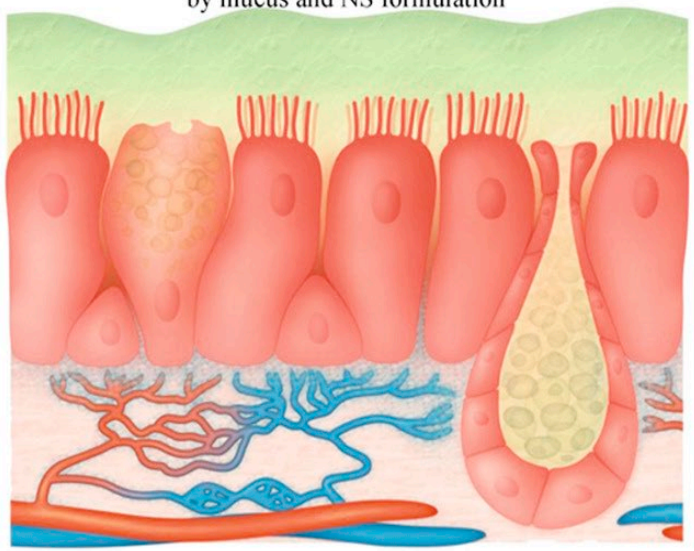
Mucoadhesion for Preventing Loss of Dose

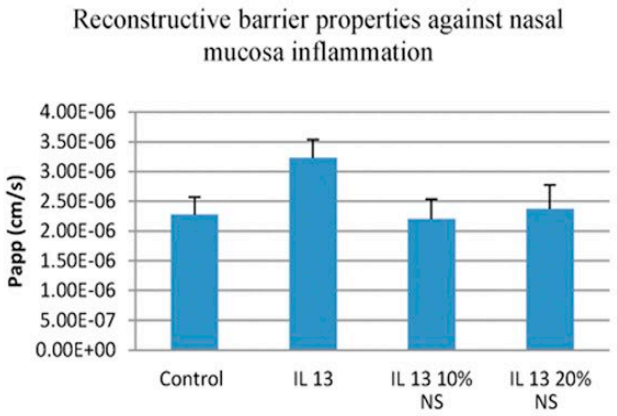


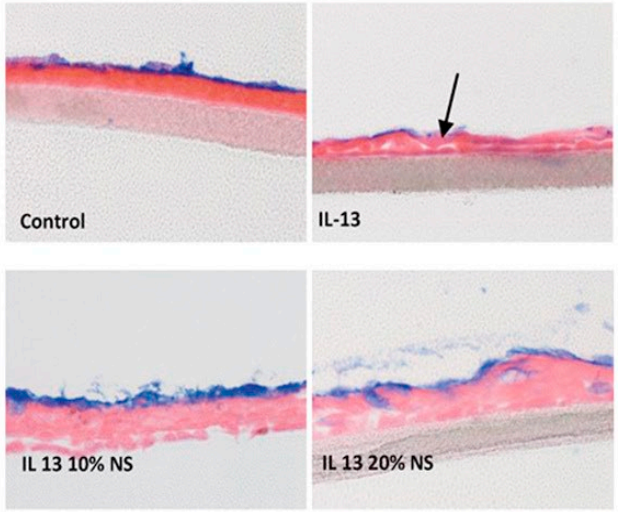
Nasal spray (NS)



Representation of nasal mucosa covered by mucus and NS formulation

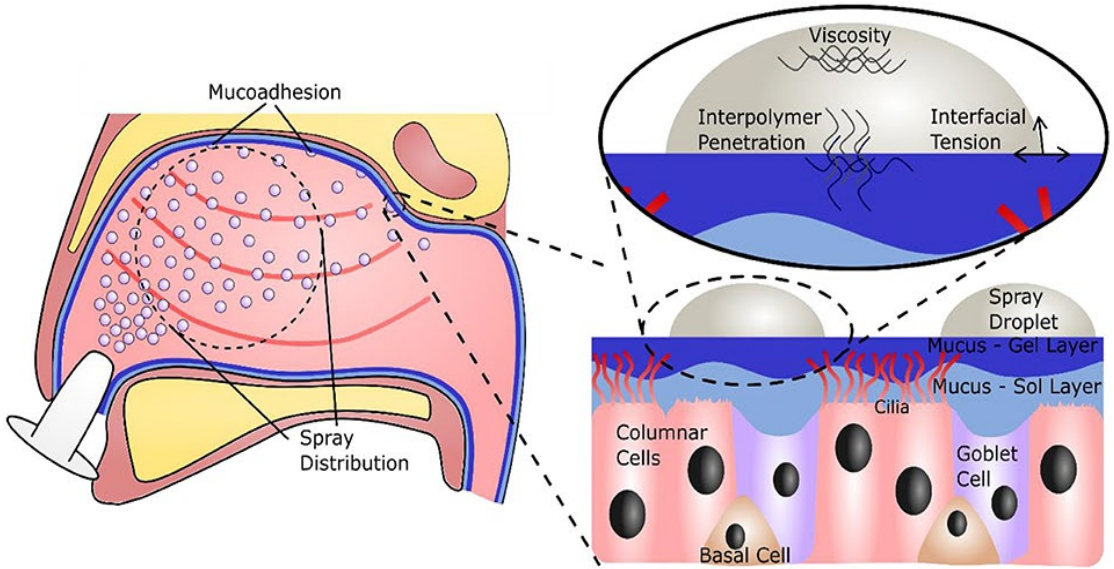






The nasal cavity has a volume of between 15 and 19 ml, and a macroscopic surface area of 150–180 cm^2, However, the presence of microstructures such as microvilli on the columnar cells drastically increase this surface area to around 96,000cm^2 i.e., 600-FOLD!

AMPLE SURFACE AREA FOR MUCOADHESION



Ref: https://doi.org/10.1016/j.jddst.2015.09.013

Ref: https://doi.org/10.3389/fmedt.2021.687681

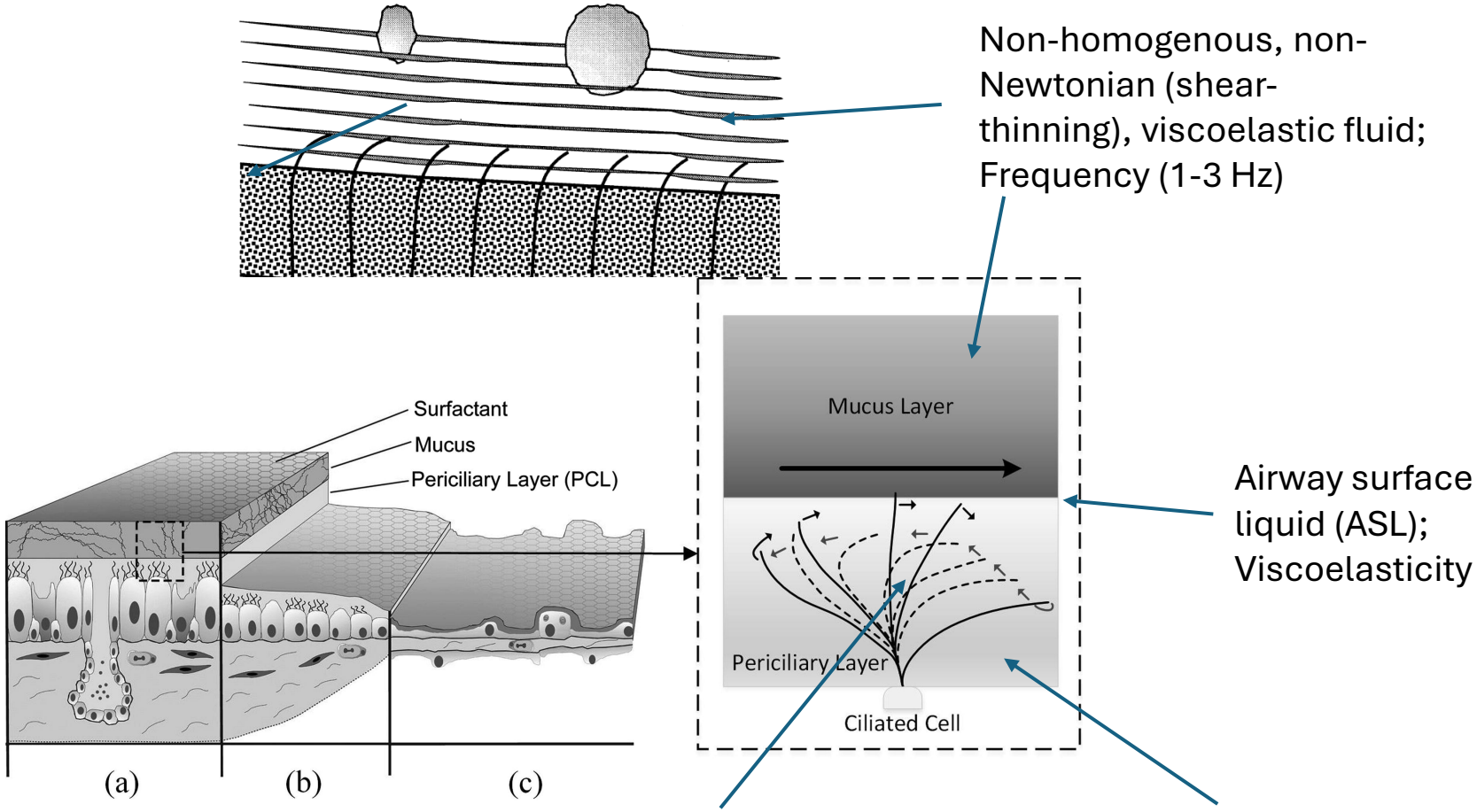
Can mucociliary clearance be modeled with rheology?

Modelling techniques:

I. Continuum cilia:

II. Discrete cilia:
   a) Prescribed beating (PCL+ML)
   b) Fluid structure interaction (Cilia+PCL+ML)

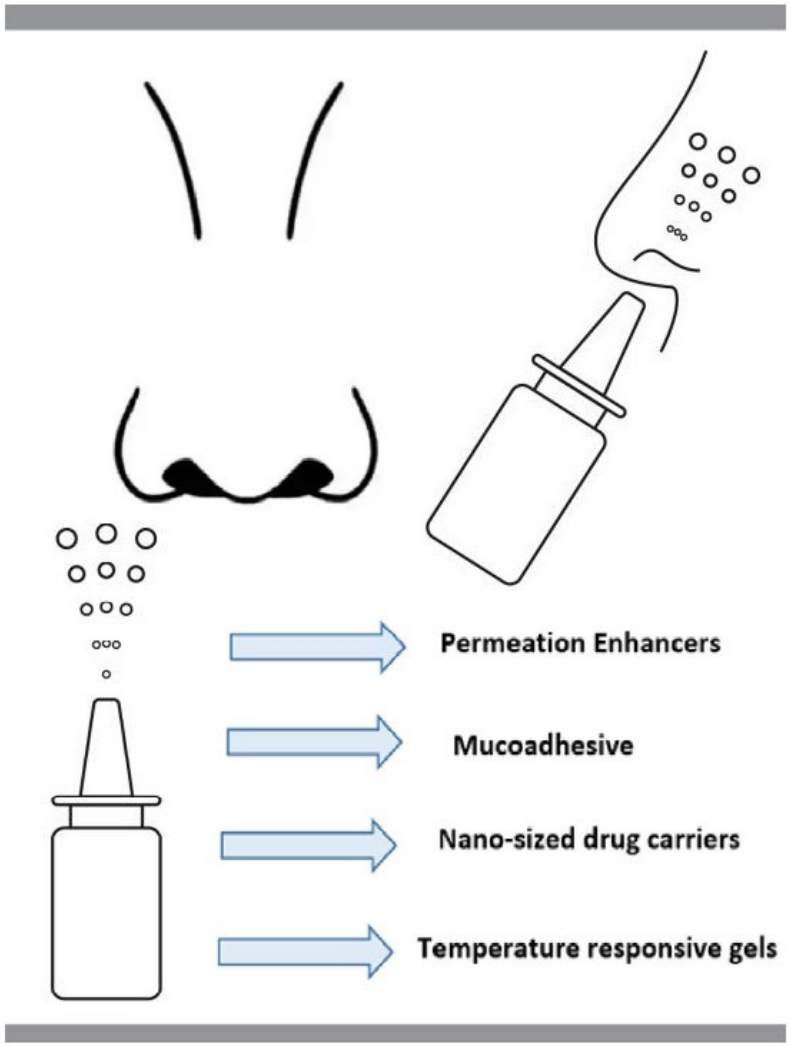
III. Airway surface liquid:
   a) Viscoelasticity (Non-linear, Non-Newtonian, sheer thinning) – use smaller time steps



Mucus viscosity increases by two orders of magnitude (1-10), the mean velocity of mucus can reduce by approximately 40%

Ref: **The propulsion of mucus by cilia.** https://pubmed.ncbi.nlm.nih.gov/3278666/; **The rheology of nasal mucus** https://pubmed.ncbi.nlm.nih.gov/9800075/ ; **Muco-ciliary clearance: A review of modelling techniques** https://pubmed.ncbi.nlm.nih.gov/31916998/ ; **Muco-ciliary transport: Effect of mucus viscosity, cilia beat frequency and cilia density** https://www.sciencedirect.com/science/article/pii/S0045793011001861

Modified nasal gels/sprays: Use of Enabling Excipients

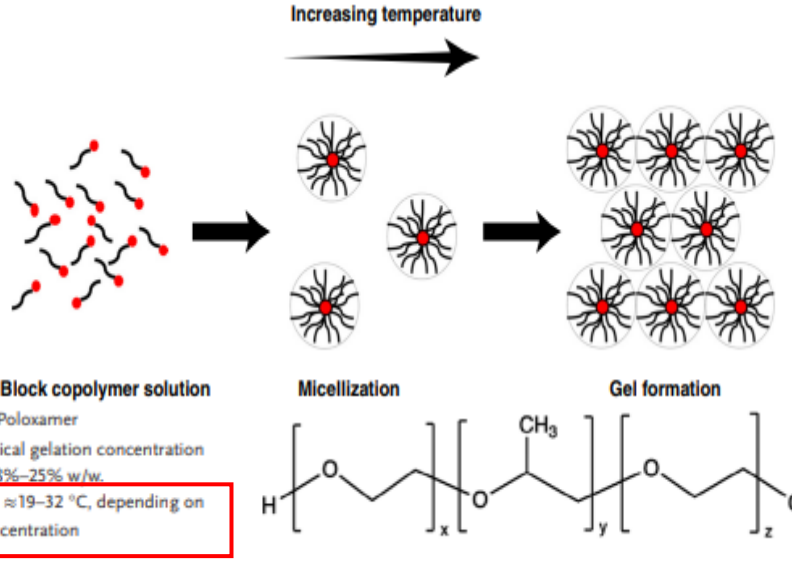


Source: doi: 10.3390/pharmaceutics10030116

- Viscosity builders + Mucoadhesive: Chitosan, Carbopol, Microcrystalline cellulose
- Solubilizers + Permeation enhancers: Surfactants (non-ionic)
- Adsorption enhancers: Cyclodextrins, Bile salts, Fatty acids, surfactants
- High viscosity intra-nasal gels: Hyaluronate, Celluloses, Poloxamer
- Micro/Nanoemulsions: SMEDDS, SNEDDS
- Nanoparticles: PLGA, Chitosan with P-Gp inhibitors
- Liposomes: Mono-di-tri glycerides & PEG

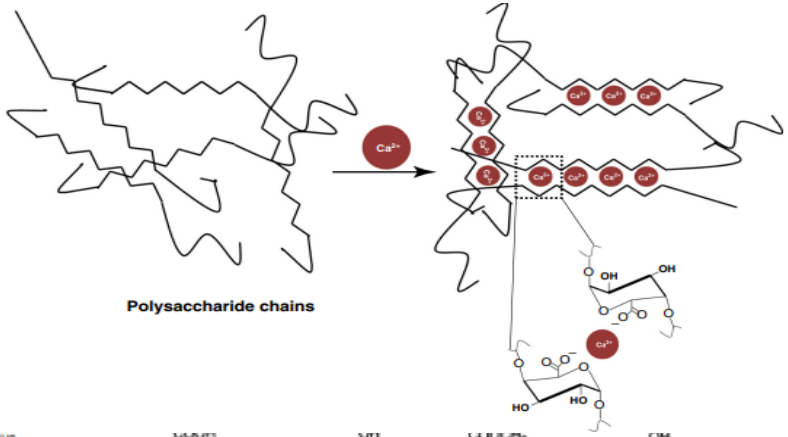
(negatively charged, hydrophilic excipients do not interact with mucus, whereas positively charged, hydrophobic agents display mucus interaction)

Enabling matrix for modified release nasal gels & sprays: Enhanced Performance



Poloxamer

- Critical gelation concentration ≈18%–25% w/w.
- T_{gel} ≈19–32 °C, depending on concentration



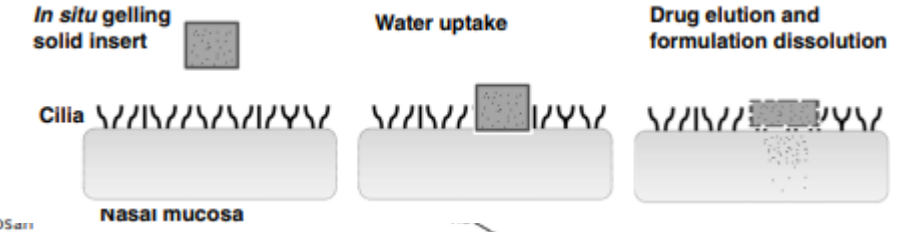
Pectin

Presence of Ca^{2+} ions

- Ion responsive
- Edible
- Natural

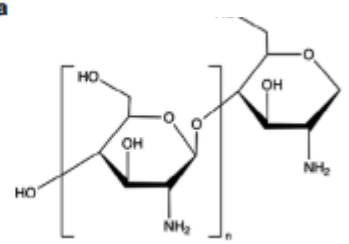
Poloxamers, Pectin, Chitosan, Gellan gum, Carbopol, HPMC, HEC, Pullulan

Same material can have multiple uses: Modified release matrix, viscosity modifier and mucoadhesive



Chitosan

Some chitosan derivatives are thermoresponsive gelators, e.g. PEG grafted chitosan and hydroxypropyl chitin

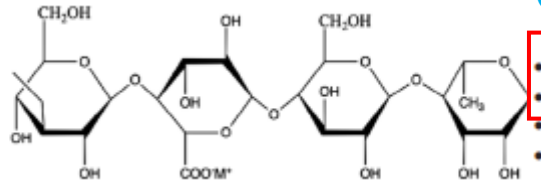


- Biocompatible
- does not gel on its own
- Viscous at low concentration (1%–2% w/w)
- Soluble in acidic conditions (pH < 5)
- Mucoadhesive

Gums

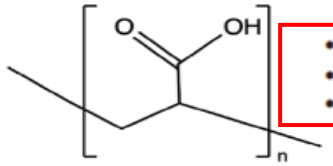
Gellan gum

Critical gelation concentration typically ≈0.3% (depending on ionic concentration)



- Ion responsive
- Gel at low concentration
- Edible
- Natural

Carbopol

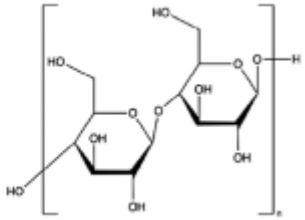


- Hydrophilic
- Mucoadhesive
- pH-responsive

Carbopol is pH responsive and forms a gel when pH > 5.5 pKa.
Carbopol is more often used as a mucoadhesive agent in concentration range 0.1% – 1%

Carbopol

Hydroxypropyl methyl cellulose (HPMC)

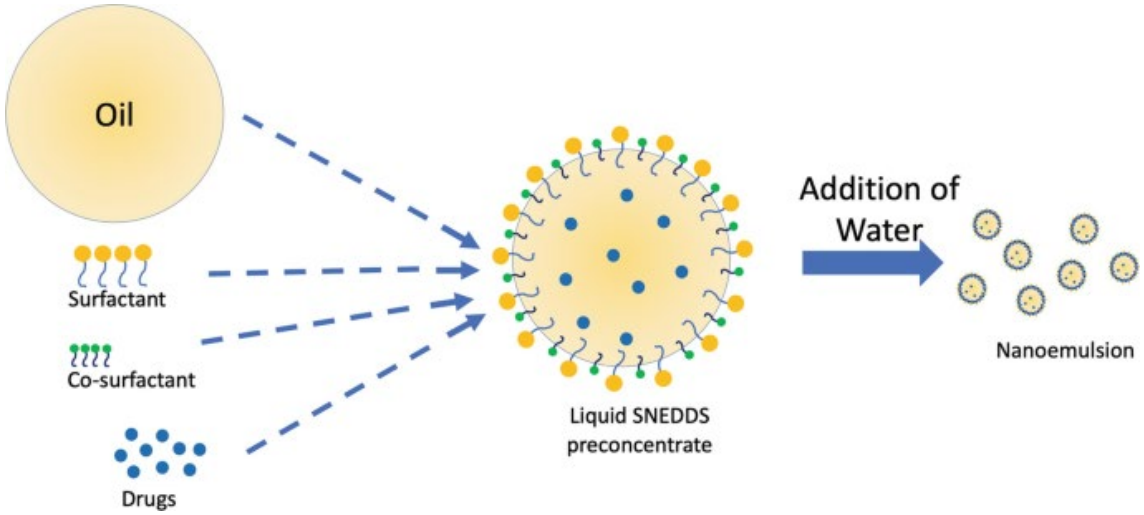


With HPMC as an example:
the typical concentration range added to gelling systems is ≈0.1% – 2%.

- Natural
- Good thickening agent
- Biocompatible
- Shear-thinning
- Mucoadhesive

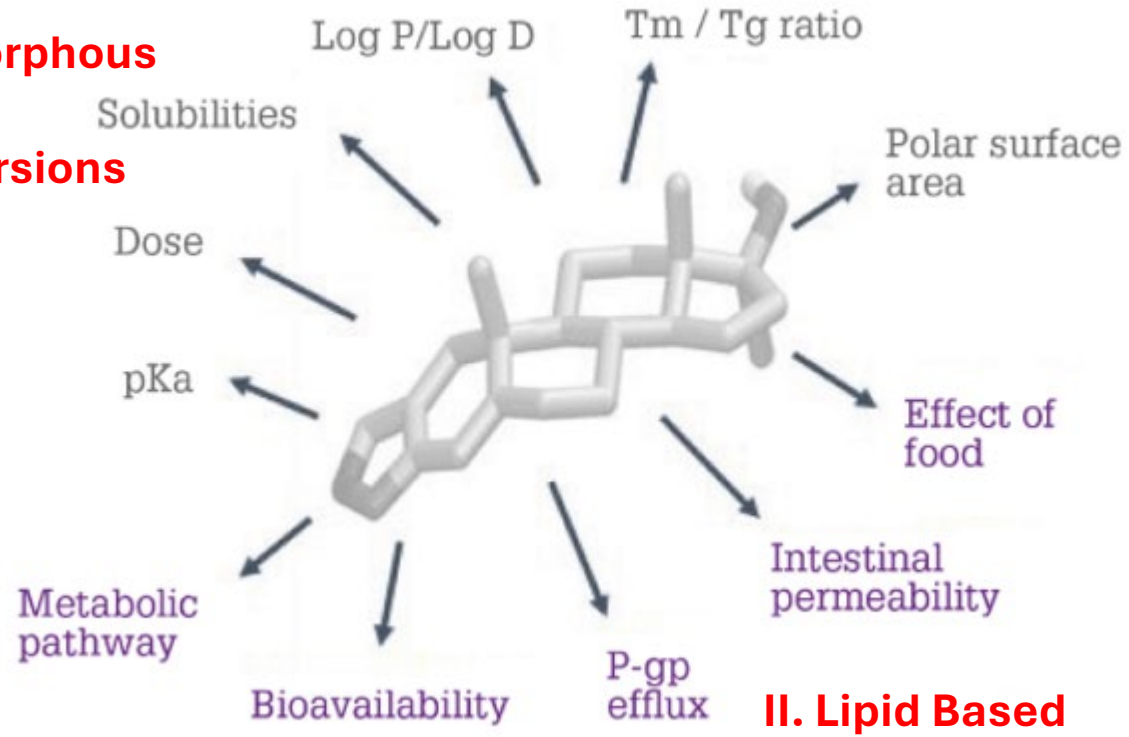
Celluloses

References:
In Situ Gels for Nasal Delivery: Formulation, Characterization and Applications
https://doi.org/10.1002/mame.202400356
Smart materials: *in situ* gel-forming systems for nasal delivery
https://doi.org/10.1016/j.drudis.2015.10.016



I. Amorphous Solid Dispersions

BCS Class IV



II. Lipid Based Formulations

Solubility & permeability challenges in the nasal pathway

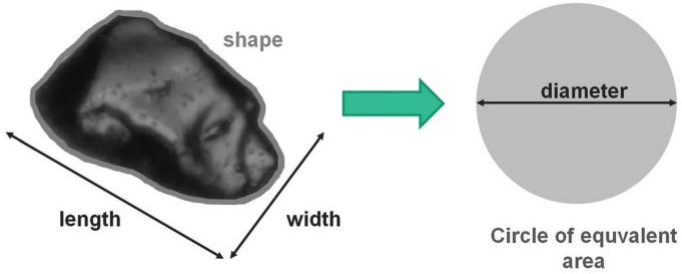
Is “brick dust” to “blockbuster” drug possible by nasal administration?

Which nasal delivery system can address I & II?

References:
1. DOI https://doi.org/10.1007/978-981-33-4497-6_10
2. https://themedicinemaker.com/manufacture/from-brick-dust-to-blockbuster
G Miglierini, “Emerging trends for the pharmaceutical market”, (2019). Available at: https://bit.ly/2Thp8EL

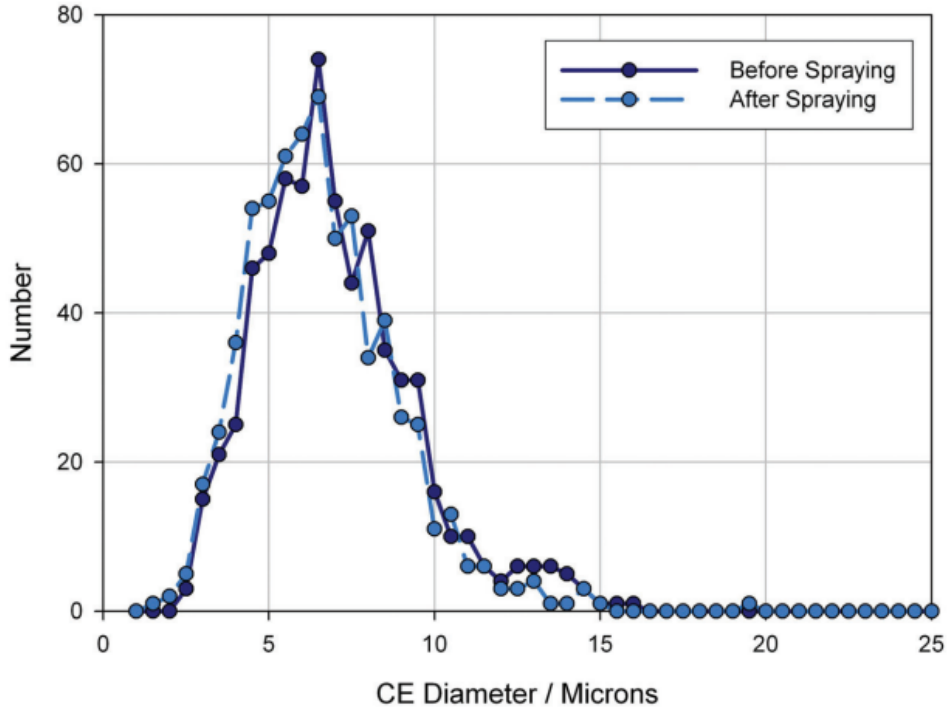
Designing nasal SNEDDS

Complexities with suspensions & other complex modified release products



- Multi-particulate nasal suspensions & gels often suffer from content uniformity & segregation issues
- Supplementary analysis is required to differentiate the API from other suspended solids
- Quantify the impact of the spray process on API morphology & particle size
- Requirement in FDA BE guidance, to measure the particle size of the API pre- and post-actuation - using manual microscopy or DLS
- Added manufacturing steps increasing complexity & costs

Automated morphological imaging captures individual 2D particle images and uses them to determine size/shape distributions. Conversion to a circle of equivalent area enables a spherical equivalent diameter to be calculated.



The API within a nasal spray suspension shifts slightly to the left following actuation, suggesting particle dispersion.

References:
Statistical Design of Experiment (DoE) based development and optimization of DB213 *in situ* thermosensitive gel for intranasal delivery https://doi.org/10.1016/j.ijpharm.2018.01.032
Quality by design approach for development of suspension nasal spray products: a case study on budesonide nasal suspension https://doi.org/10.3109/03639045.2016.1160108

Nasal Self nano-emulsifying drug delivery systems (n-SNEDDS) system: One potential solution

❑ **Model Drugs:**

Naproxen & Naproxen sodium (BCS Class II, low aq. solubility high permeability);

Promethazine HCl (BCS Class III, high aq. solubility, low permeability);

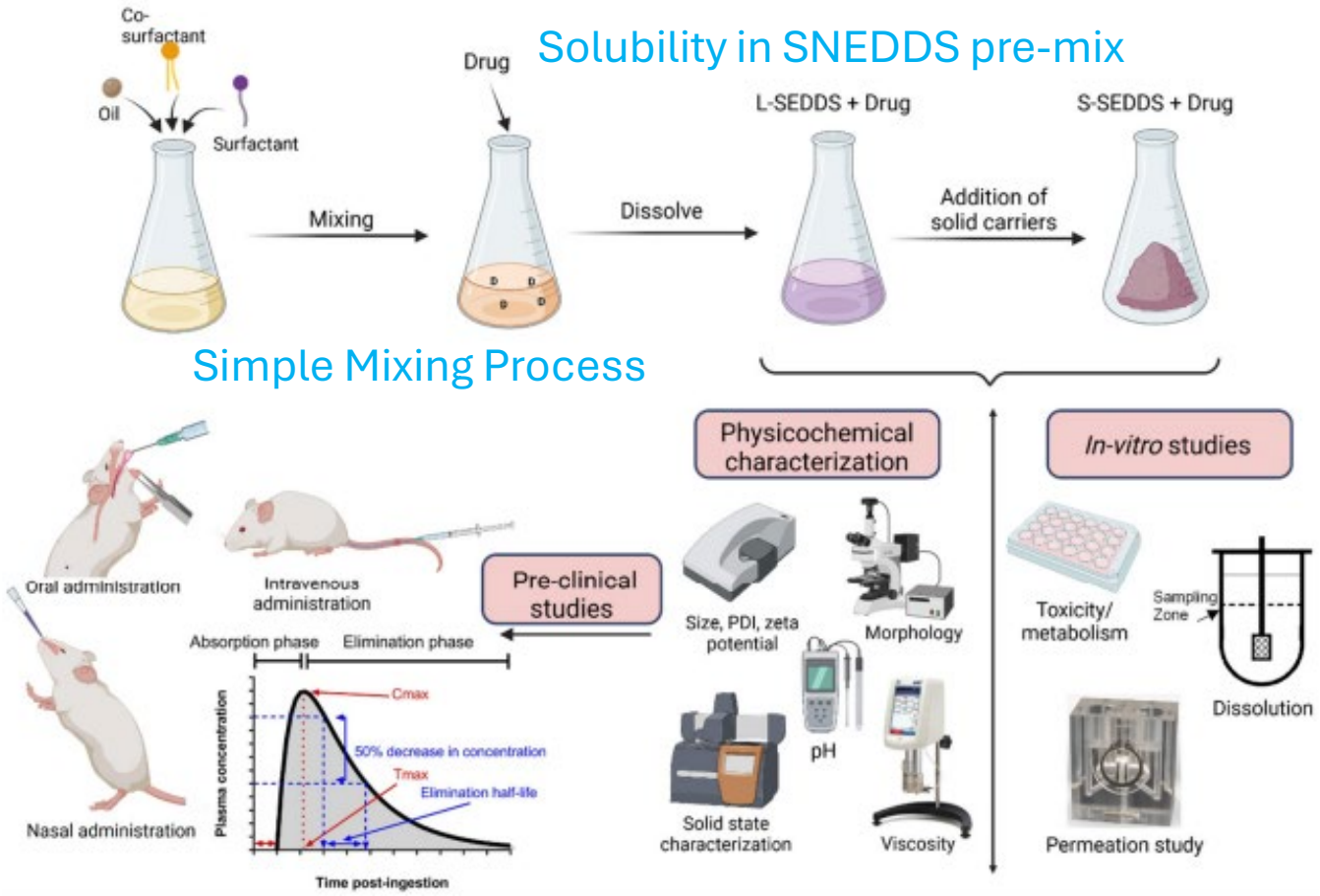
Aripiprazole (BCS Class IV, low solubility, low permeability)

❑ **The ask (QTTP): SNEDDS can answer most of the needs**

- ✓ Generate a **model** for solubilization of drugs using SNEDDS for nasal sprays – **used specialized formulations to carry SNEDDS**
- ✓ **Maximize solubilization** power of the SNEDDS with adequate **permeation**
- ✓ **Modified release,** substantive, mucoretentive, fast and long acting for different BCS classes
- ✓ Limit to a small volume of **200 µl or 0.2 ml** per dose per nostril
- ✓ Allow solubilization of other **necessary excipients** such as buffers, preservatives, antioxidants to maintain pH, osmolality & drug stability
- ✓ Can be delivered without any ***specialized delivery device*** *is required*
- ✓ **Targeted delivery** & deposition on olfactory area
- ✓ **Scale up and QbD friendly** manufacturing

❑ **Aim to Engineer a Universal "incorporation-ready" nasal delivery platform utilizing high solubilizing; high permeating, controlled release, targeted, mucoretentive, SNEDDS nasal system**

SNEDDS in nasal gels & sprays: History of proven Efficacy & Scale-up readiness



- **Advantages:**
  - Solubility & BA enhancement
  - High loading efficiency; can be diluted with water
  - Easy scale-up & transfer
  - Flexibility in matrix selection (sprays or gels)
  - Stability of sensitive drugs
  - pH independent

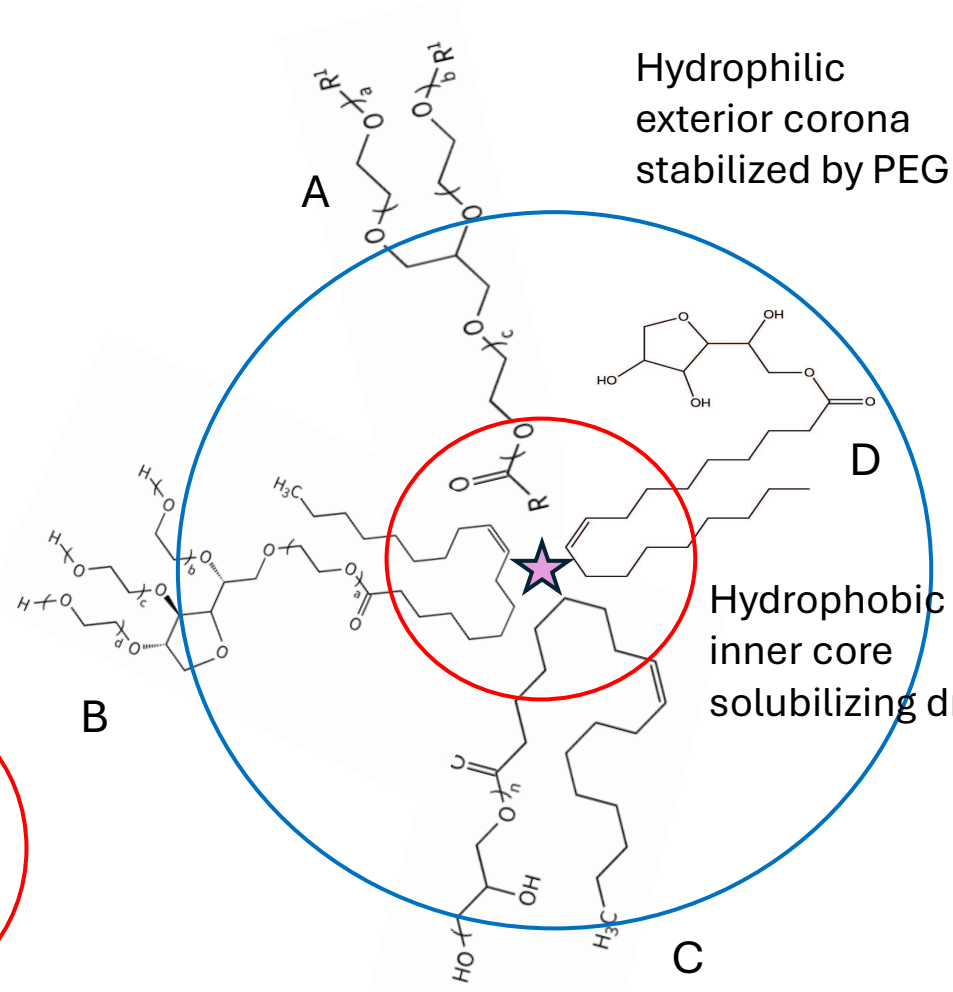
- **Limitations:**
  - API crashing out
  - Very small nasal volume
  - Irritation in nasal mucosa
  - Difficulty to atomize highly viscous formulations
  - Loading limit of 50% surfactants gels liquid media

Reference: **Self-Emulsifying Drug Delivery Systems: An Alternative Approach to Improve Brain Bioavailability of Poorly Water-Soluble Drugs through Intranasal Administration**
https://doi.org/10.3390/pharmaceutics14071487

Which emulsion system to chose? SNEDDS (type IV)

Excipients in formulation	In formulation content (% w/w)				
	TYPE I	TYPE II	TYPE III A	TYPE III B	TYPE IV
Oils: triglycerides or mixed mono- and diglycerides	100	40-80	40-80	<20	- N/A
Surfactants (HLB <12)	-	20-60	-	-	0-20
Surfactants (HLB >12)	-	-	20-40	20-50	30-80
Hydrophilic co-solvent (PEG, PG, Transcutol)	-	-	0-40	20-50	0-50
Particle dimension after dispersion (nm)	Coarse emulsion	100-250	100-250	50-100	<50
Importance upon dispersion in water medium	Limited	Solubilizing capacity remains unchanged	Some loss of solubilizing capacity	Significant phase change and potential loss of solubilizing capacity	Significant phase change and potential loss of solubilizing capacity
Importance of GIT digestion	Significant	Not important, but very likely to occur	Not important, but very likely to be inhibited	Not necessary	Not necessary
Short characteristics	Excellent biocompatibility; digestion via *lipase/co-lipase* in colloidal state.	Surfactants with HLB ~ 11; spontaneously to coarse O/W emulsions.	SMEDDS and SNEDDS; Subgroups in accordance of surfactant and co-surfactant quantity; Clear to slightly opalescenting dispersions		Most hydrophilic type LBDDS; More APIs than TYPE I; very fine dispersions, fast release, increased absorption.

Reference: https://doi.org/10.5272/jimab.2020263.3226



Combination chosen after screening more than 80 oils, surfactants & cosurfactants

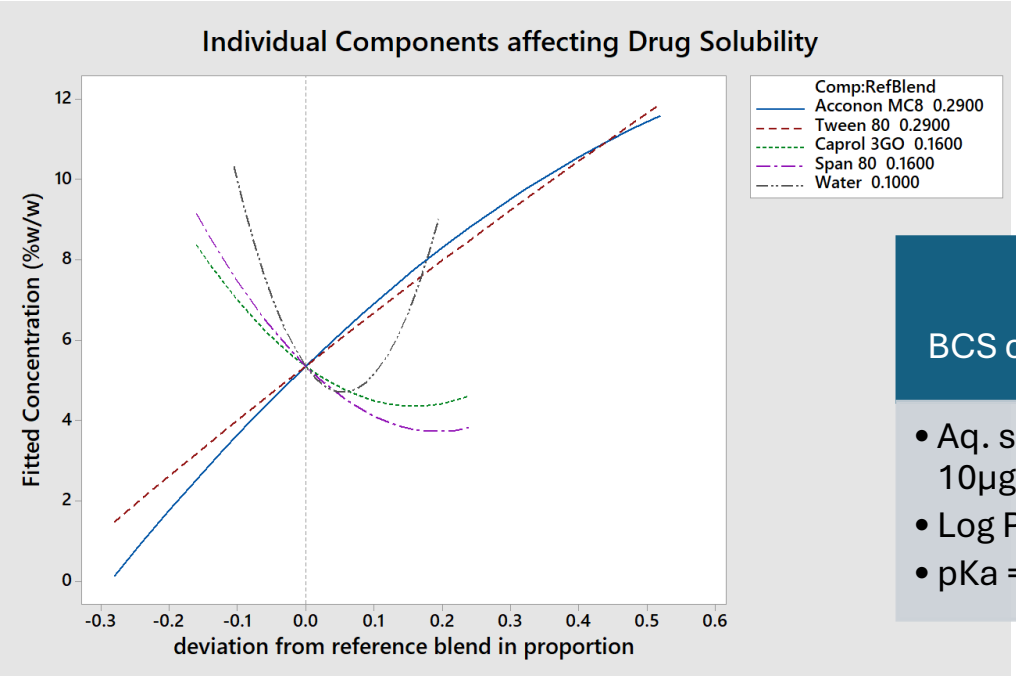
A: Polyoxyethylene 8 caprylic/capric glycerides (Acconon MC8-2; Abitec Corp.)
B: Polyoxyethylene (80) Sorbitan monooleate (Polysorbate / Tween 80)
C: Polyglyceryl-3 monooleate (Caprol 3GO; Abitec Corp.)
D: Sorbitan monooleate (Span 80)

Selection of surfactants to enhance solubility & bioavailability post-nasal administration

Surface active agents used to create universal solubility model

- PEGylated Caprylic/Capric Glycerides
- Polyoxyethylene-80-sorbitan monooleate
- Polyglyceryl 3-oleate
- Sorbitan monooleate
- Cetearyl glucoside

} Extreme Vertices DOE for developing Type IV SNEDDs



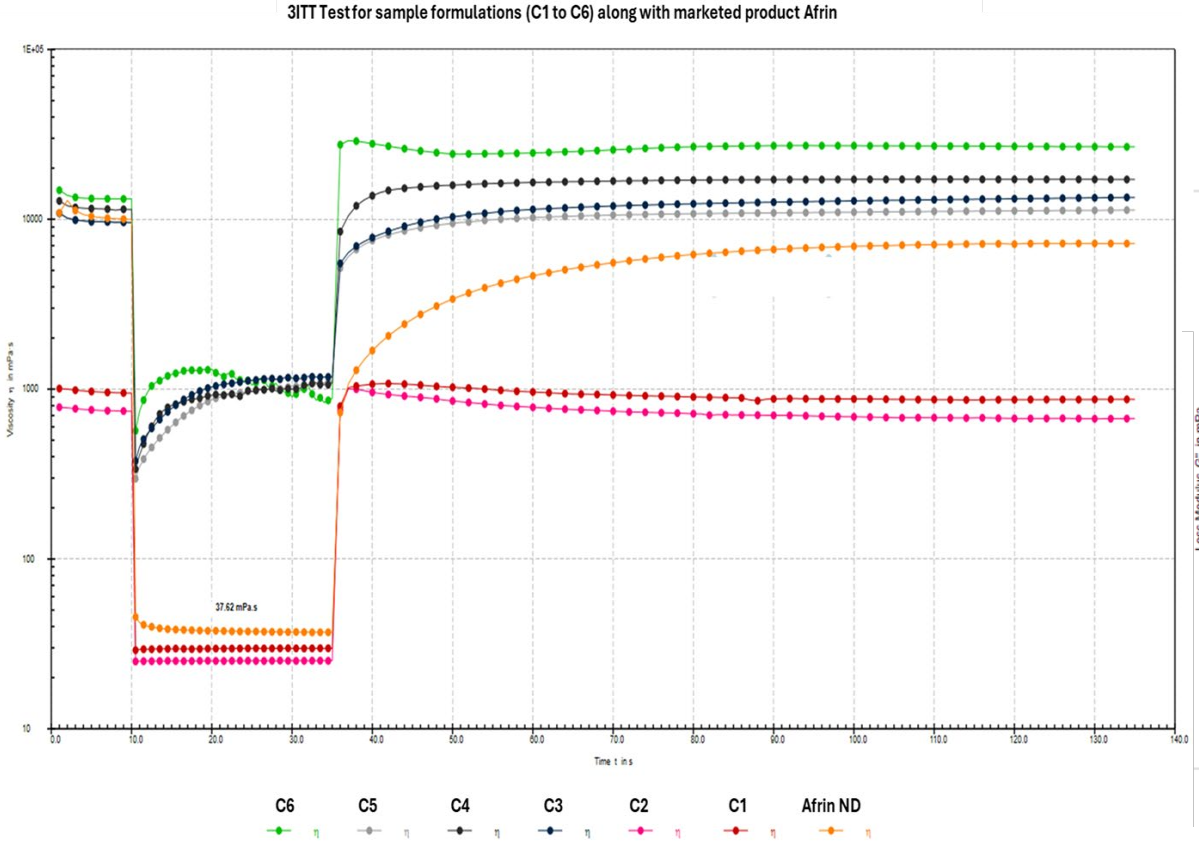
Properties of actives studied BCS II, III & IV

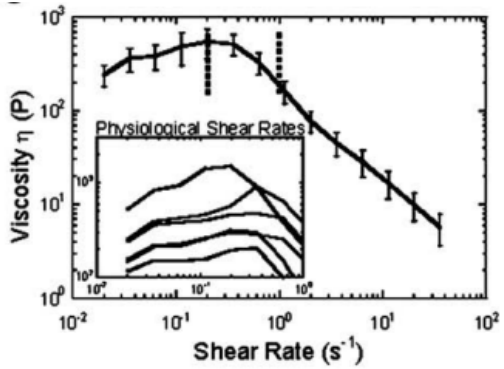
Active 1 BCS class II (Naproxen)	Active 2 BCS class III (Promethazine)	Active 3 BCS class IV (Aripiprazole)
• Aq. solubility ≤ 10µg/ml • Log P = 3.18 • pKa = 4.15	• Aq. solubility > 20mg/ml • Log P = 4.52 • pKa = 6.47	• Aq. solubility ≤ 10ng/ml • Log P = 5.21 • pKa = 7.46

Viscosity optimization: 3ITT tests & Viscoelastic Moduli of Formulations

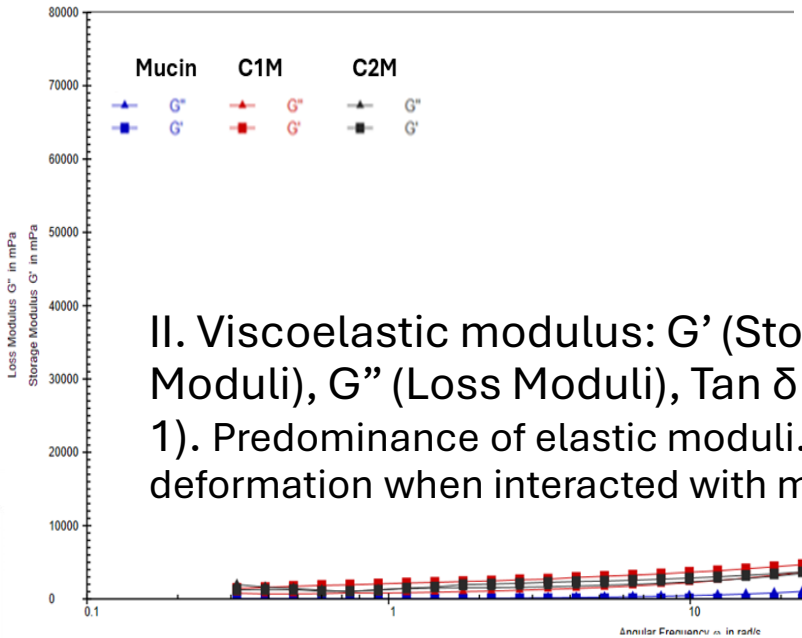
SNEDDS (30 to 50% w/w) + Buffer as formulations. Sprayable and spontaneously interacts with nasal mucus to form a viscous in situ gel.

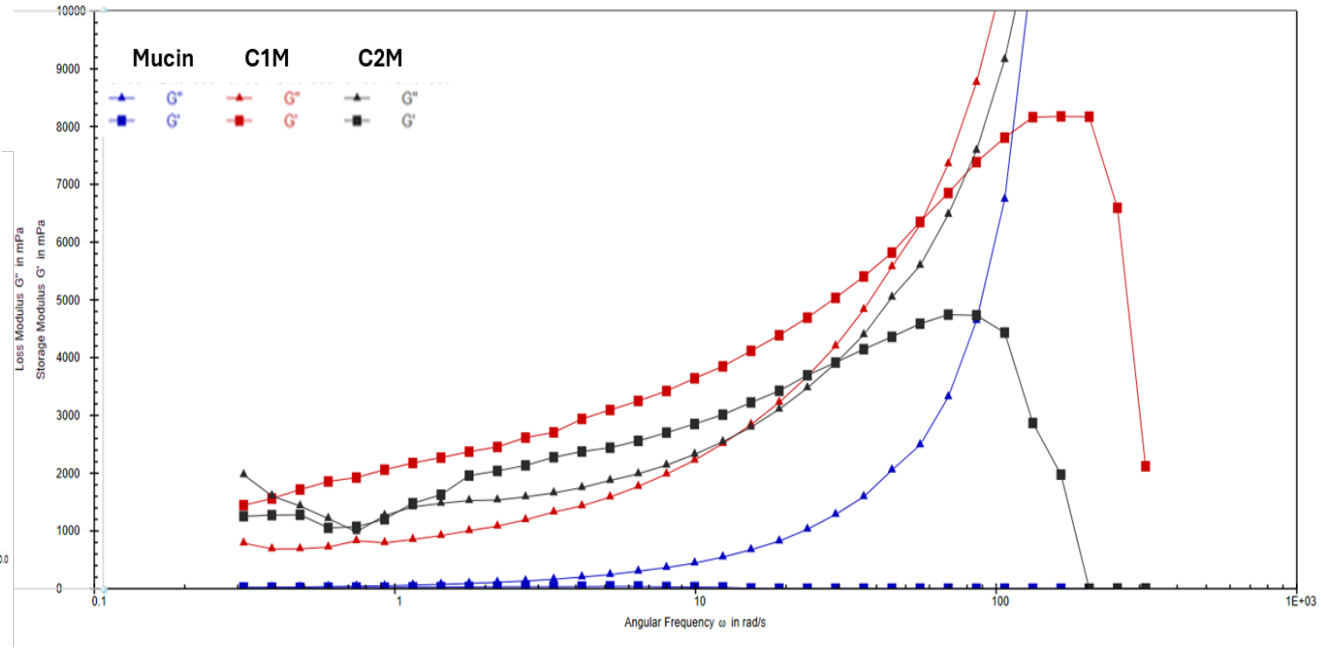
I. Thixotropic test (gel – sol – gel transformation)



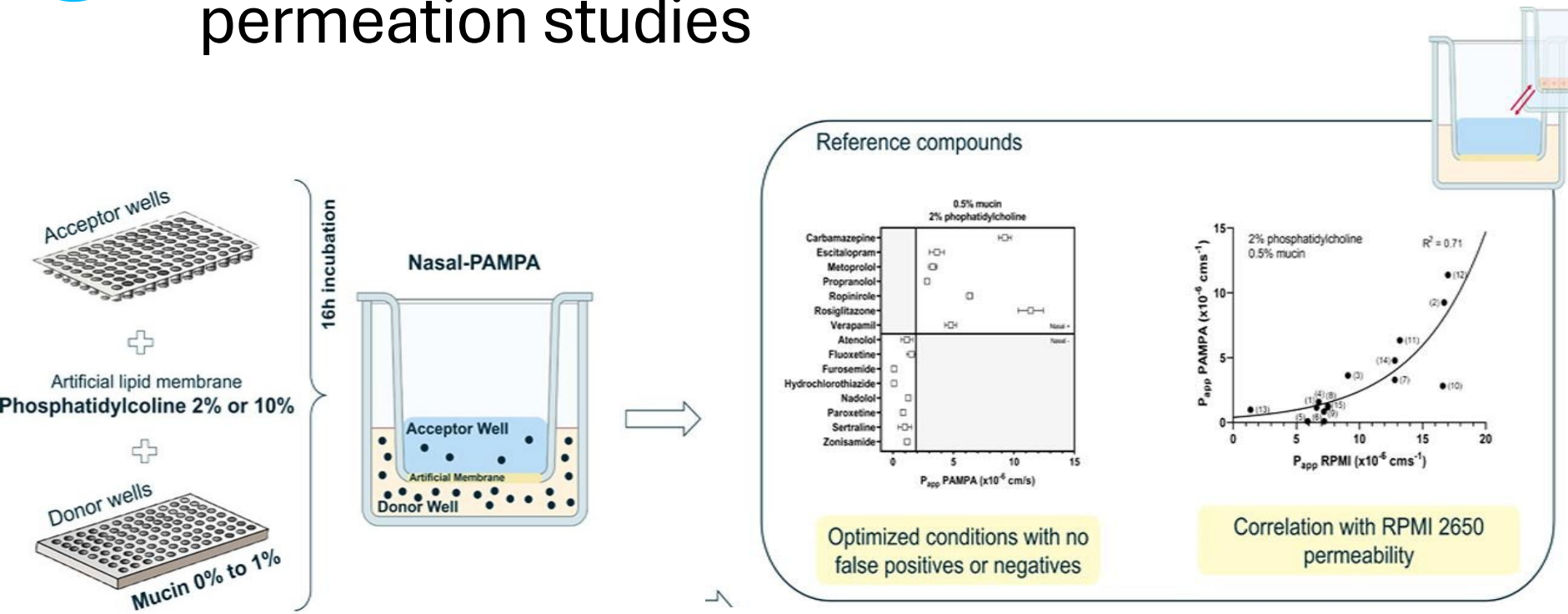


II. Viscoelastic modulus: G' (Storage Moduli), G" (Loss Moduli), Tan δ = G"/G' < 1). Predominance of elastic moduli. Resist deformation when interacted with mucin



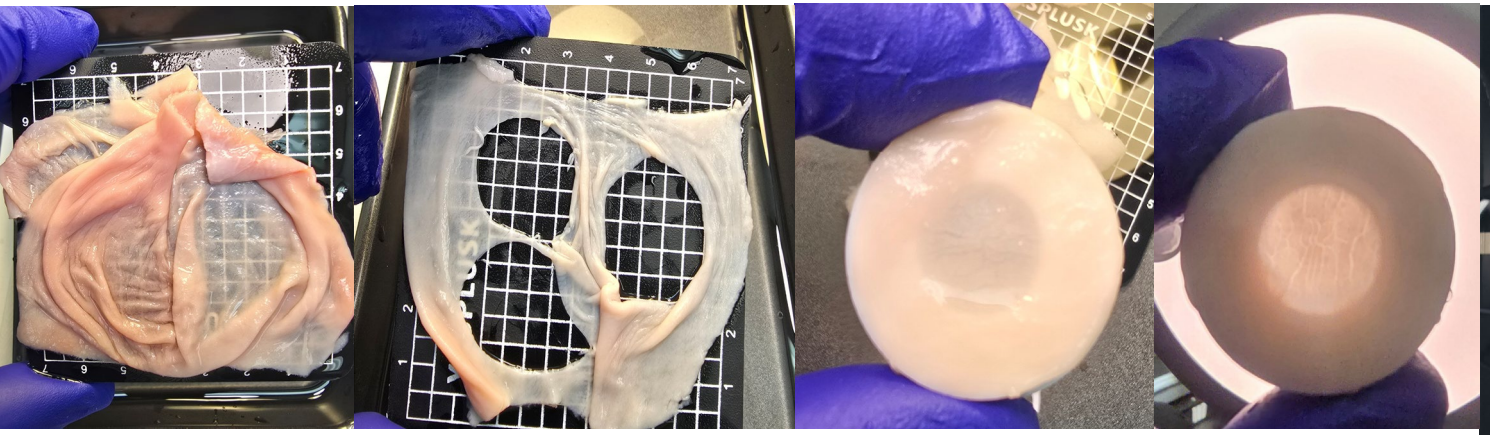


Modified PAMPA & Diffusion cell studies for *in vitro* nasal permeation studies



Modification: For nasal permeation 0.5% (w/v) mucin in the donor compartment; 2% (w/v) phosphatidylcholine in PVDF (polyvinylidene difluoride) membrane. Highest correlation with permeation across human nasal epithelial cells, RPMI 2650 (R^2 = 0.93).

Reference: **Henriques P, *et al*** Nasal-PAMPA: A novel non-cell-based high throughput screening assay for prediction of nasal drug permeability, Int J Pharm, 643 (2023) 123252.



Freshly excised porcine nasal mucosa for permeation testing

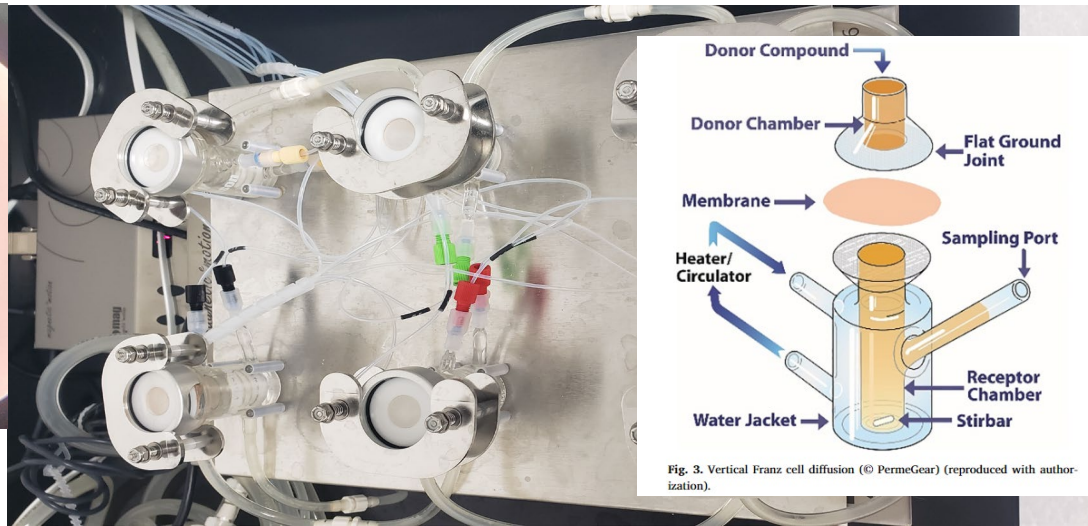


Fig. 3. Vertical Franz cell diffusion (© PermeGear) (reproduced with author-ization).

Solubility & Permeation Enhancements utilizing SNEDDS

The solubility results showed increase of BCS II, III & IV by 6000, 610 & 3896 times respectively

Drug moiety	Average PAMPA* Papp (x10-6 cm/s)	Concentration (µM)		Papp ratio (Acceptor_test /Acceptor_control)	Mass ratio (Acceptor_test / Acceptor_control)
BCS II (control)	0.76 (±0.06)	Donor compartment	0.624	3.83	1.52
		Acceptor compartment	0.023		
BCS II (n-SNEDDS)	2.9 (±0.4)	Donor compartment	0.637		
		Acceptor compartment	0.036		
BCS III (control)	1.4 (±0.1)	Donor compartment	0.369	3.43	3.36
		Acceptor compartment	0.02		
BCS III (n-SNEDDS)	4.8 (±0.7)	Donor compartment	0.373		
		Acceptor compartment	0.0678		
BCS IV (control)	1.8 (±0.1)	Donor compartment	0.062	1.94	2.86
		Acceptor compartment	0.02		
BCS IV (n-SNEDDS)	3.5 (±0.7)	Donor compartment	0.068		
		Acceptor compartment	0.0518		

Fig. 2

Fig 2A. Nasal PAMPA studies with nasal SNEDDS (n-SNEDDS) using PVDF with phosphatidylcholine

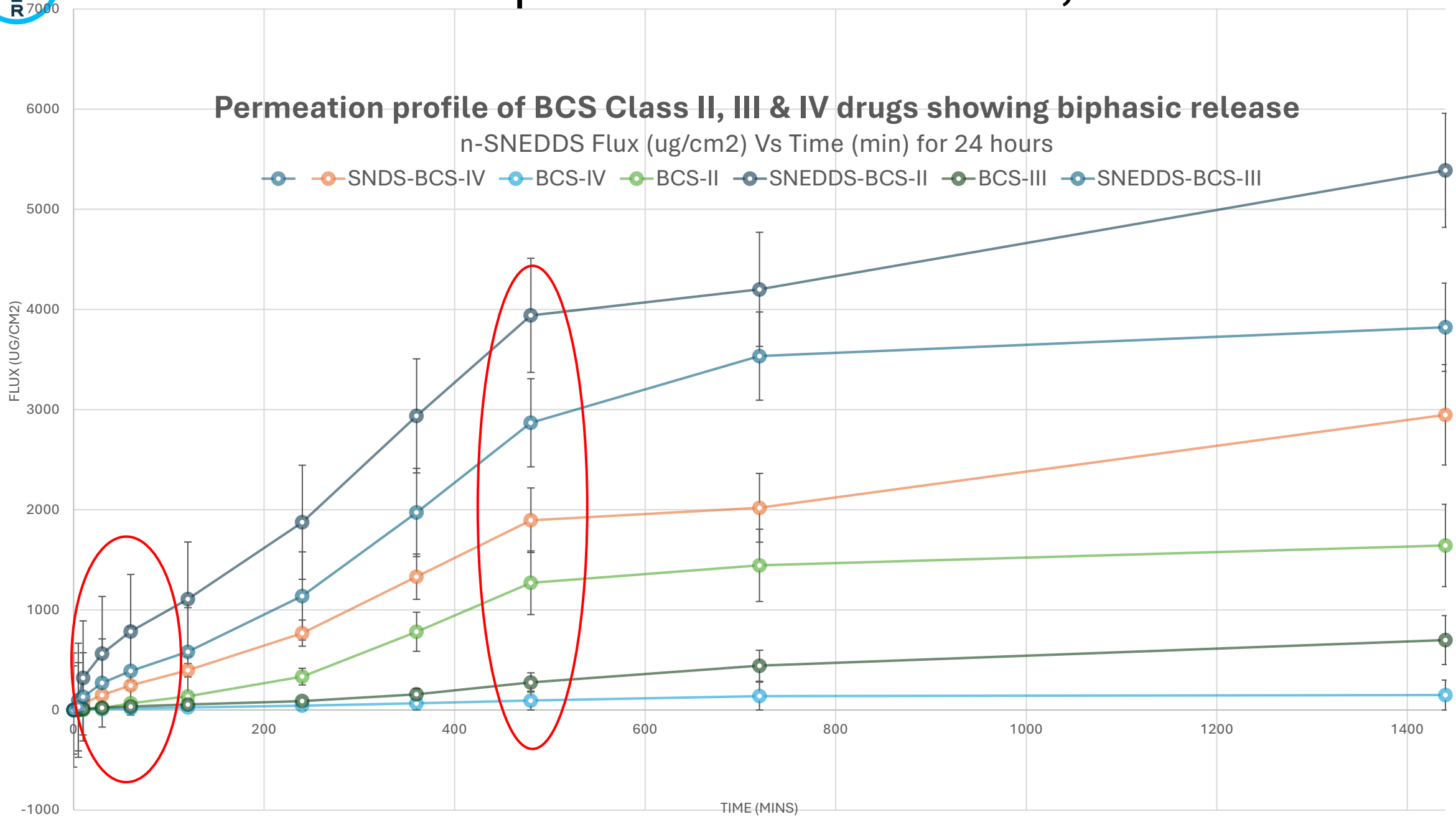
(P_{app}) ratios compared to control for BCS II, III & IV were 3.83, 3.43 & 1.94 times respectively

The flux results showed increase of BCS II, III & IV by 29.67, 6.41 & 46.46 times respectively

Fig 2B. Permeation parameters of n-SNEDDS formulations using Franz diffusion cells

Permeation Parameters	BCS-II	SNDS-BCS-II	BCS-III	SNDS-BCS-III	BCS-IV	SNDS-BCS-IV
Dose (ug)	500	500	500	500	500	500
Jss (15-120) ug/cm²/min	0.2916	8.6536	0.0519	0.333	0.1777	8.256
Lag time (min)	0.445423943	1.874086626	18.11767666	1.109656006	4.085490782	5.901856725
Q60 (ug/cm²)	17.86887389	547.8055694	20	26.04859873	6.67881	456.88032
Q180(ug/cm²)	35.39356433	1065.677225	1.905335032	66.49589809	15.5772	1548.53244
Kp (cm/min)	0.00486428	0.001156119	0.000147186	0.00225295	0.000652716	0.000480075
Dapp (cm²/h)	0.000632356	0.000150295	2.35497E-06	3.37943E-05	1.04435E-05	8.16127E-06
Thickness (cm)	0.013	0.013	0.016	0.015	0.016	0.017

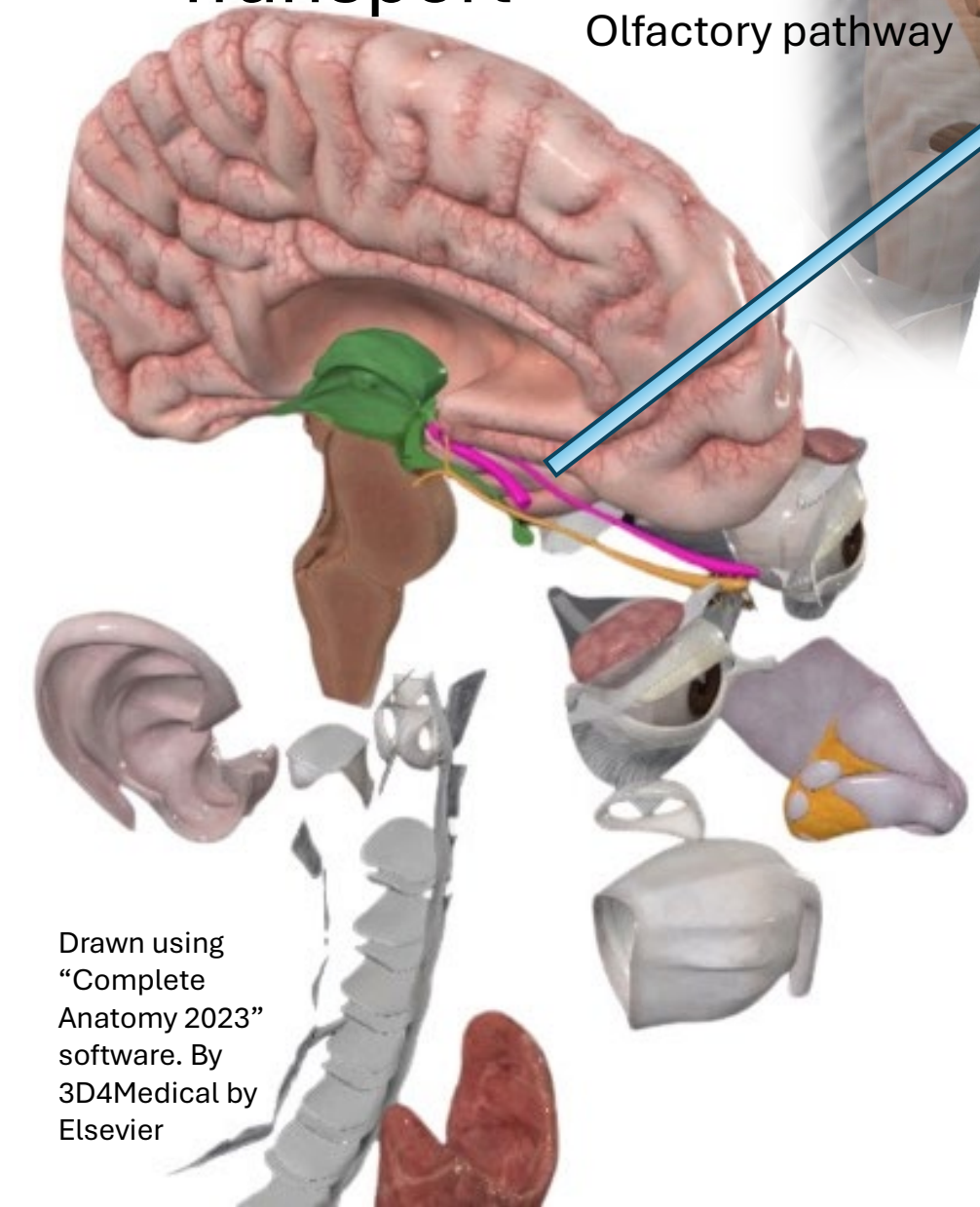
Permeation profiles of BCS Class II, III and IV

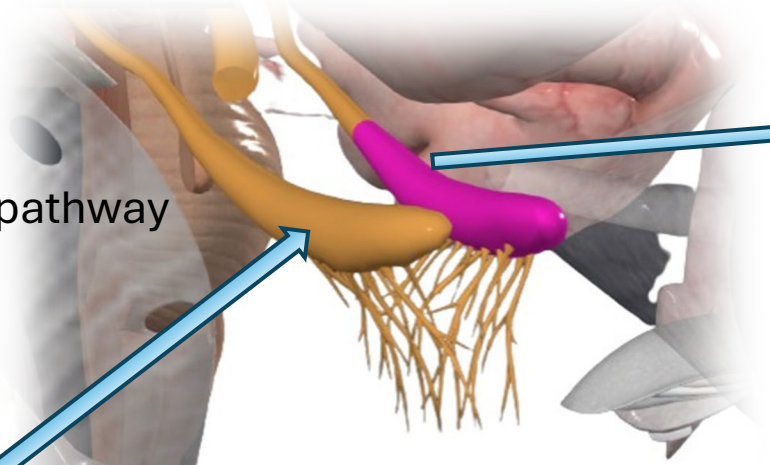


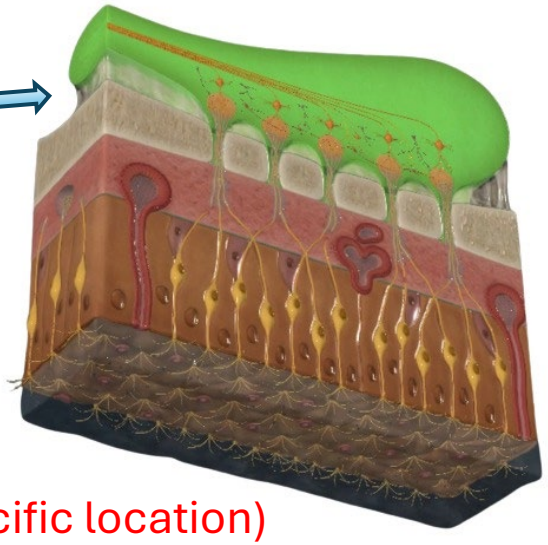
Brain Targeting Aspect

Pathways of CNS Transport

Olfactory pathway



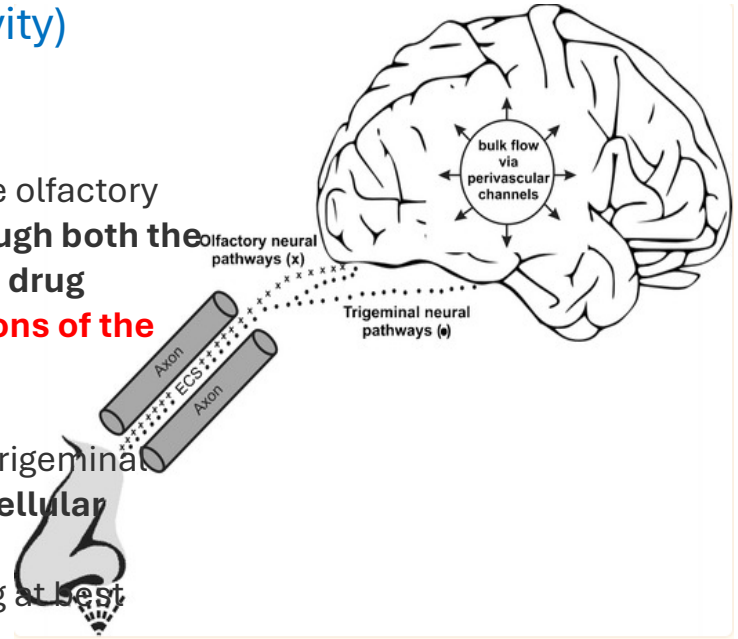




Routes of CNS transport

- Olfactory (fore focus due to specific location)
- Trigeminal (widespread in nasal cavity)
- Lymphatic Systemic

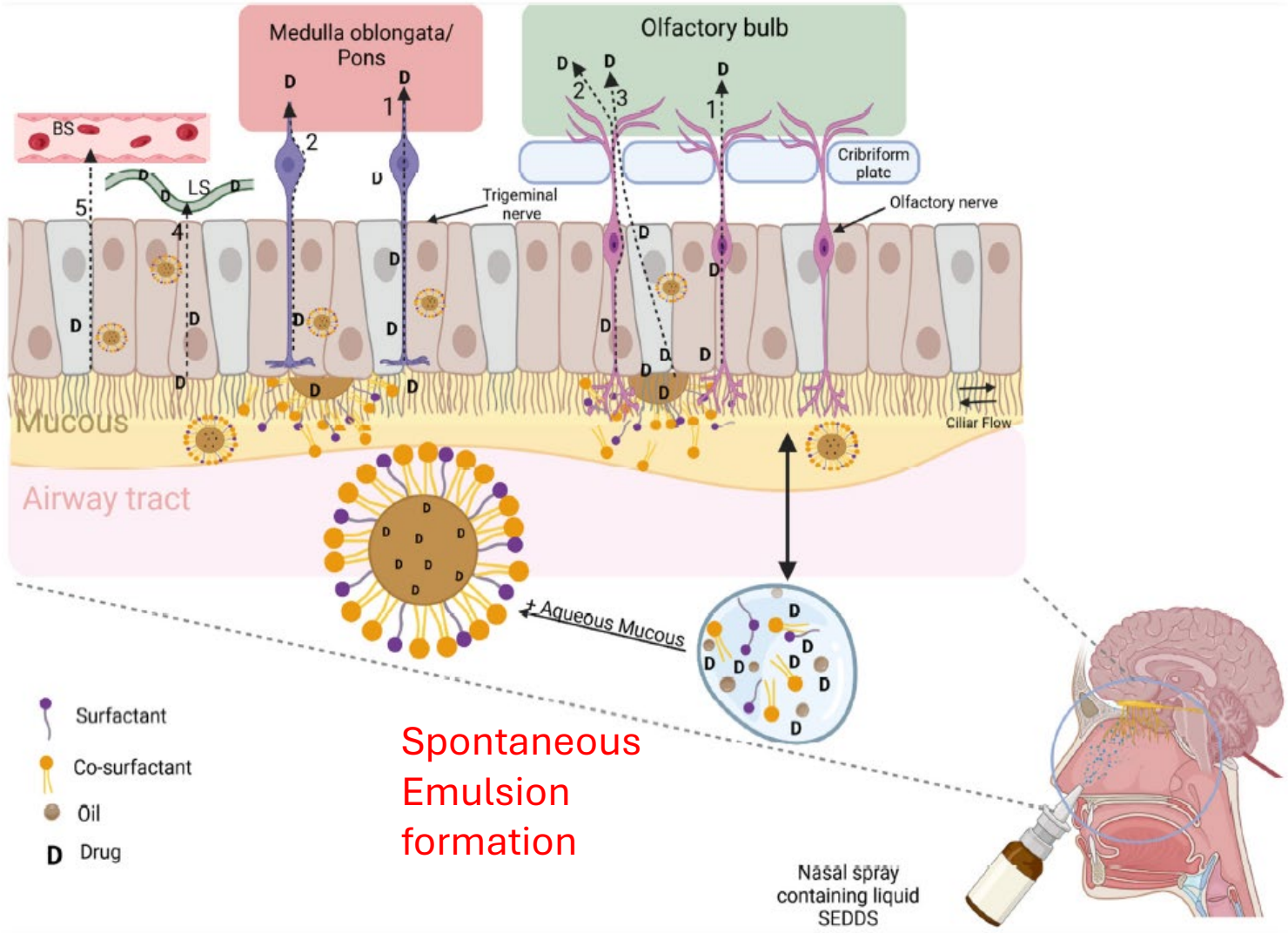
Unlike the olfactory nerve which terminates in the olfactory bulb, the **trigeminal nerve enters the brain through both the pons and the cribriform plate, which allows for drug delivery to both the anterior and posterior regions of the brain.**



Transport of substances along the olfactory and trigeminal nerve pathways by both **intracellular and extracellular mechanisms**.
Intracellular transport is a slow process, requiring at best several hours and at worst several days.
Extracellular transport, on the other hand, is rapid and likely accounts for much of the rapid delivery and onset of action
Source: doi: 10.1007/s11095-012-0915-1

Drawn using "Complete Anatomy 2023" software. By 3D4Medical by Elsevier

Potential Nose to Brain (N2B) transport: Challenges

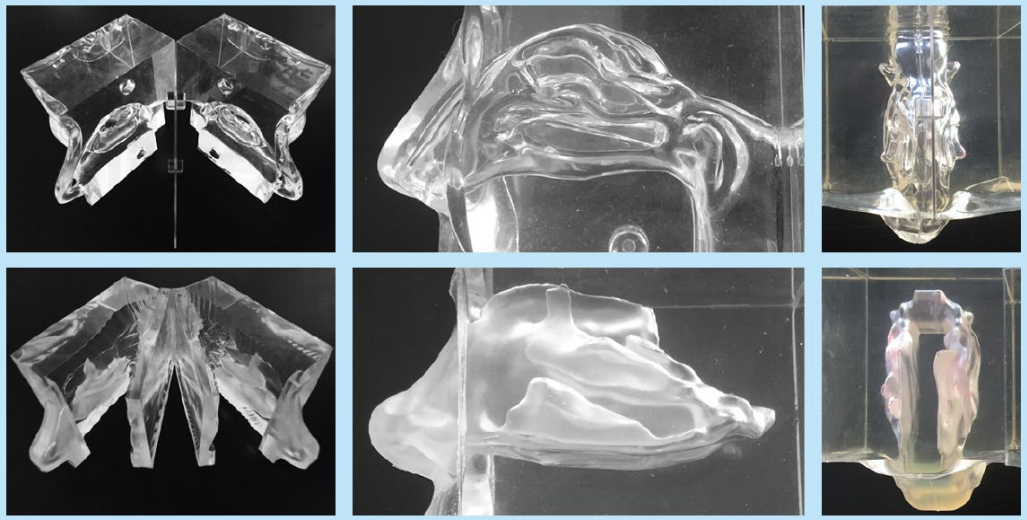


- Solubility & Permeability enhancement
- High Drug Loading required
- Oral Loading Ratio -
  - 1:30:30 :: Drug: Surfactant Blend: Water
- Nasal Loading Ratio -
  - 1:5:5 :: Drug: Surfactant Blend: Water (Not more than 200 µl in each nostril/per dose)
- 6 times more solubility required for Nasal vs. Oral SNEDDS
- Polymeric Mucus Penetrating Nano-Micelles from sol to gel to sol transformation by slow dissolution

Ref: https://pubmed.ncbi.nlm.nih.gov/35890385/

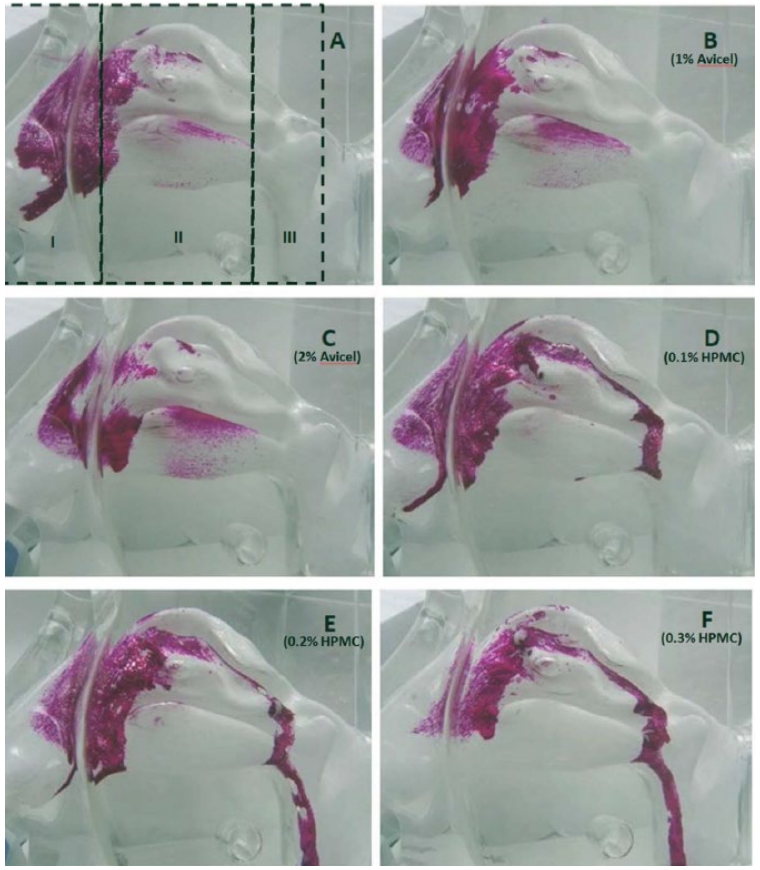
Utilization of Nasal Cast Model for Deposition Studies

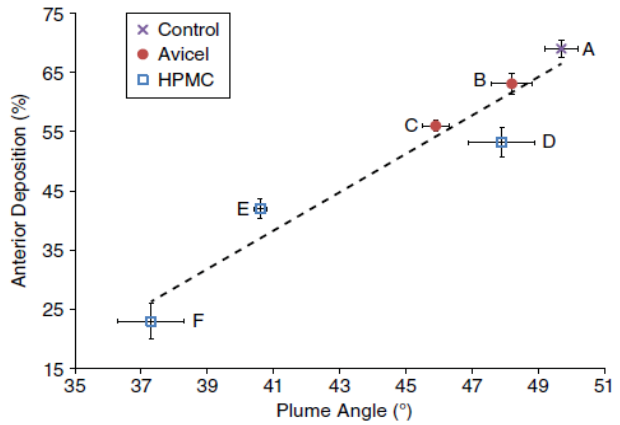
Commercially available nasal “Koken cast”, is based on a female cadaver considered as ‘anatomically correct’. The Optinose cast is derived from magnetic resonance imaging of a healthy male during velum closure.

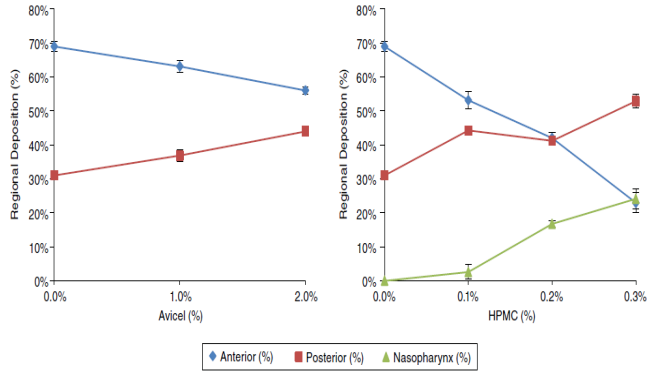


Casts. (Top) Koken cast. **(Bottom)** Optinose cast. Far left panels show the casts opened. The Koken cast is split in two silicone parts and a central, thin, flat, transparent, plastic septum separating the nasal cavities. Optinose cast is split in four parts: two lateral parts and two central parts constituting the boarded septum with the true geometry of the medial sides of the nasal septum. Middle panels show lateral view of the two silicone casts. Far right panels show superior view of the two casts.

Ref: https://www.future-science.com/doi/10.4155/tde-2020-0054
https://doi.org/10.1080/02786826.2014.931566
https://www.tandfonline.com/doi/full/10.1080/02786826.2014.931566







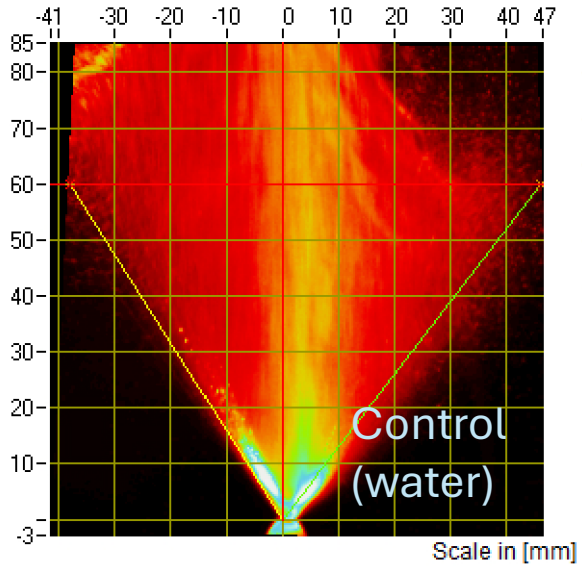
Relationship/Correlation:

Plume angel & site of deposition

Polymer type & overall deposition

Does “tighter” plume help in targeted deposition?

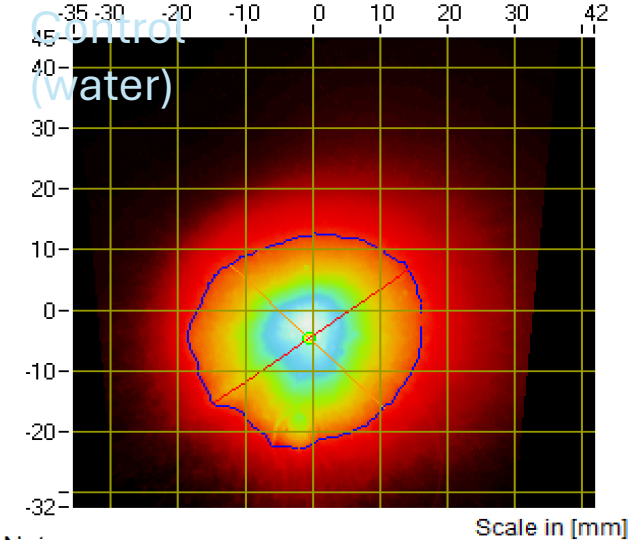
Spray characteristics actuated by a standardized device



Arm 1: 37.7 deg
Arm 2: 32.3 deg
Angle: 70.0 deg
Distance: 59.9 mm
Width: 84.1 mm
Time: 78.0 ms

Plume geometry (side view): Measurements of plume angle & width.

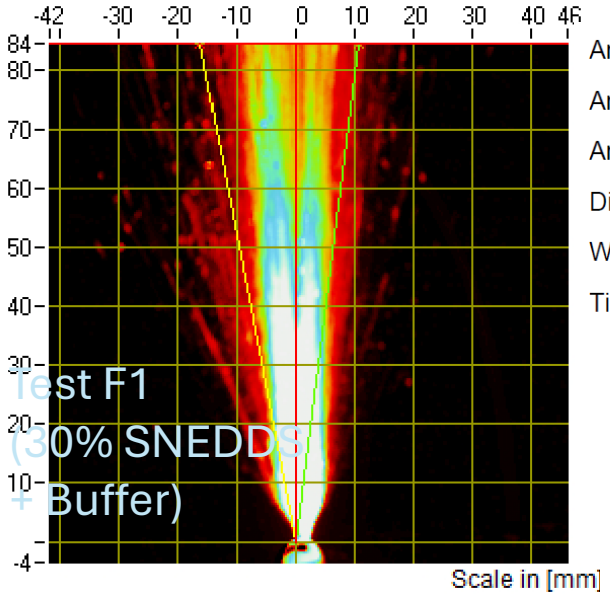
Maximum coverage in nasal turbinates (widespread)



Spray Pattern Height: 30.0

Major: 35.44 mm
Minor: 32.85 mm
Ellipticity: 1.079
Inclusion: 0.056
Inclination: 45.1 deg

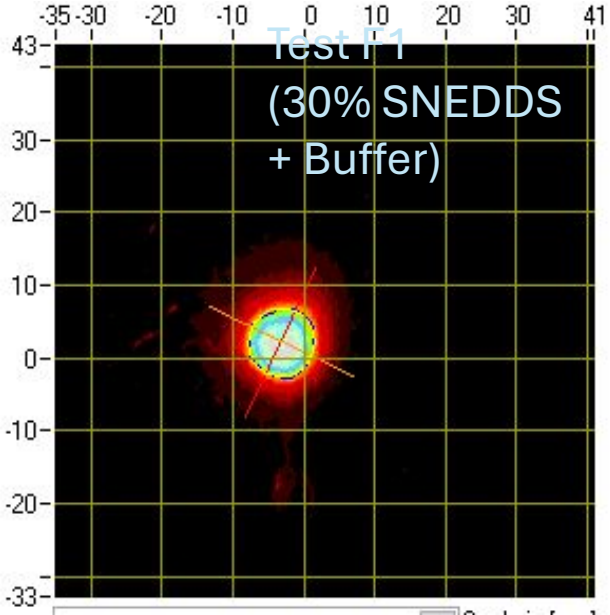
Dmin: 32.50 mm
Dmax: 36.88 mm
Ovality: 1.135
Perimeter: 111.70 mm
Area: 926.7 mm²
Area Percent: 15.0 %



Arm 1: 7.2 deg
Arm 2: 11.0 deg
Angle: 18.2 deg
Distance: 84.3 mm
Width: 27.1 mm
Time: 72.0 ms

Spray pattern (Top view): Measurements of major (Dmax) & minor (Dmin) diameters. Ovality = Dmax/Dmin

Targeted deposition in a specific nasal turbinate (narrow spread)



Major: 9.60 mm
Minor: 9.12 mm
Ellipticity: 1.053
Inclusion: 0.071
Inclination: 65.0 deg

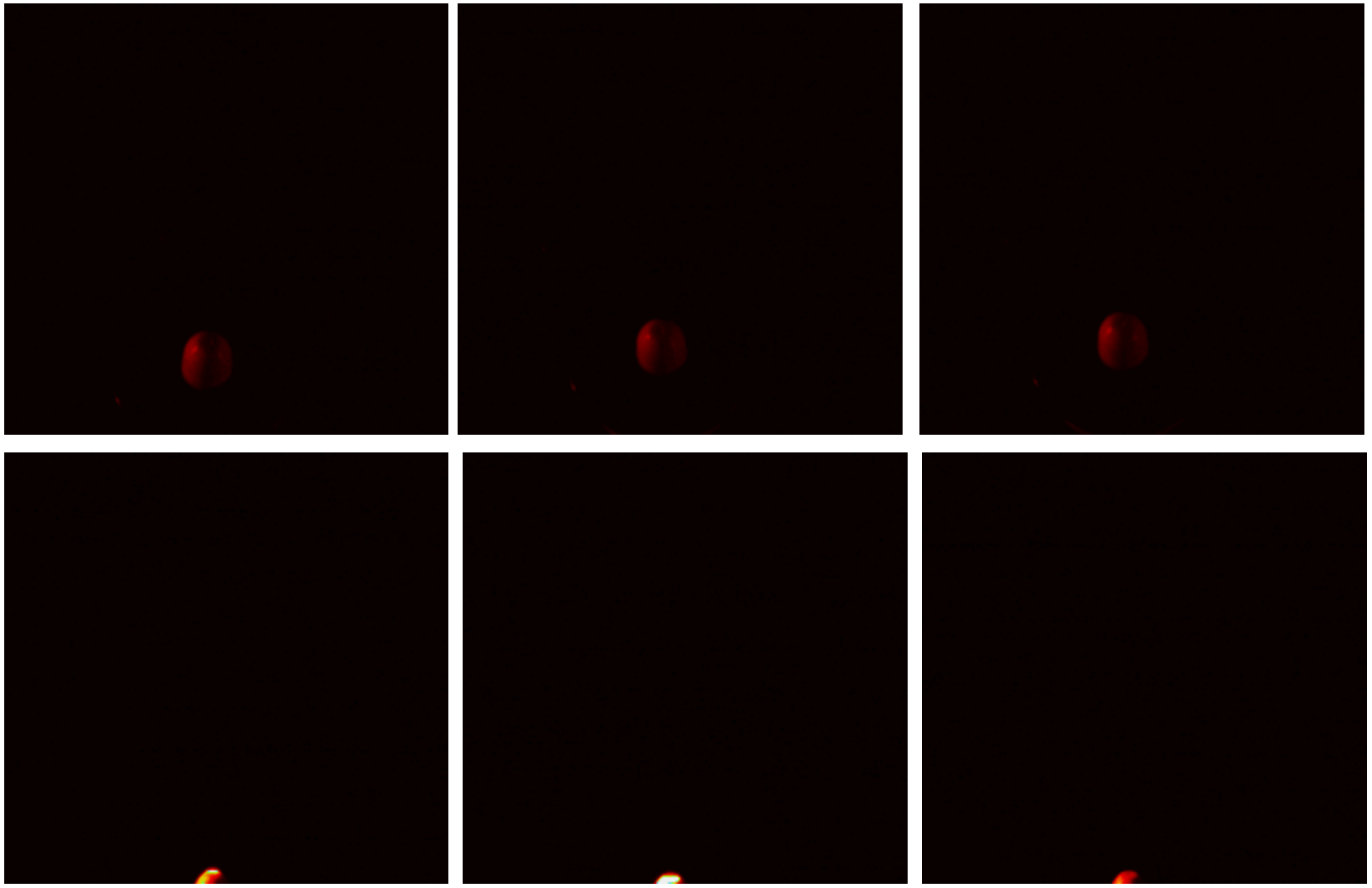
Dmin: 9.12 mm
Dmax: 10.23 mm
Ovality: 1.122
Perimeter: 30.82 mm
Area: 72.8 mm²
Area Percent: 1.2 %

Spray characteristics for olfactory region deposition modeling

Control (water)

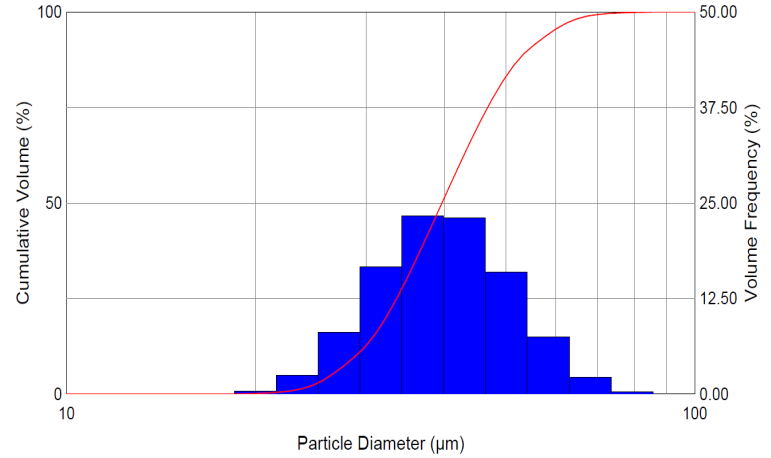
Test F1
(30% SNEDDS
+ Buffer)

Test F4
(50% SNEDDS
+ Buffer)



Standard Values:

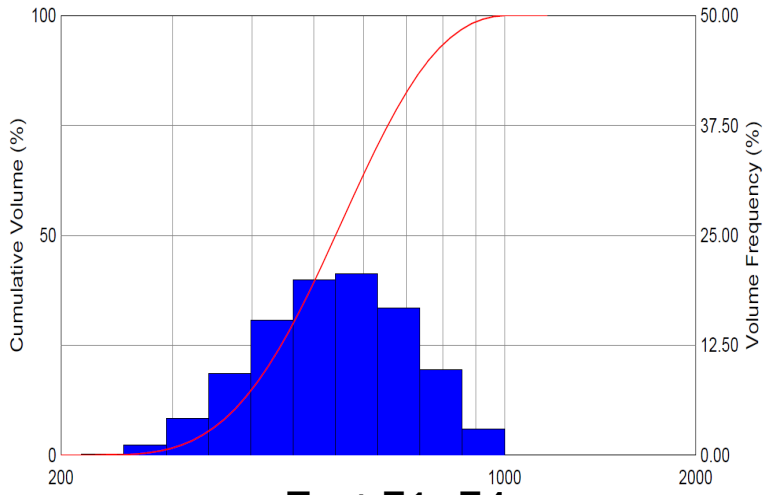
Trans = 85.9 (%)	Dv(10) = 28.84 (µm)	Span = 0.6413
Cv = 18.91 (PPM)	Dv(50) = 39.57 (µm)	D[3][2] = 38.41 (µm)
SSA = 0.1562 (m²/cc)	Dv(90) = 54.22 (µm)	D[4][3] = 40.78 (µm)



Control

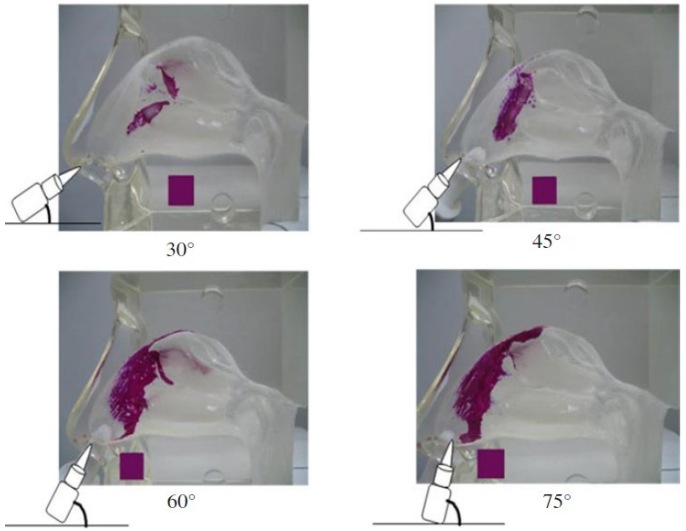
Standard Values:

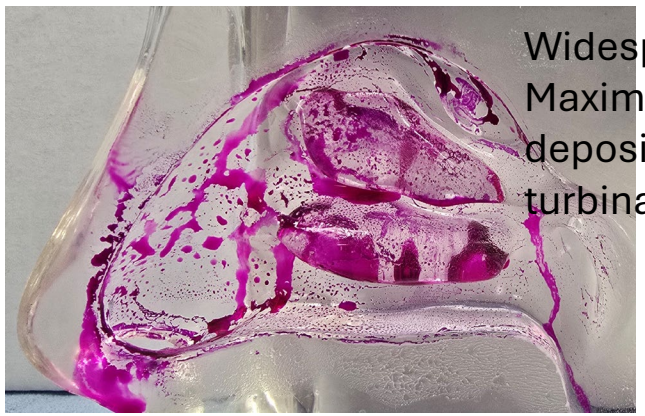
Trans = 98.9 (%)	Dv(10) = 372.8 (µm)	Span = 0.7158
Cv = 18.63 (PPM)	Dv(50) = 541.5 (µm)	D[3][2] = 516.3 (µm)
SSA = 0.0116 (m²/cc)	Dv(90) = 760.4 (µm)	D[4][3] = 555.9 (µm)



Test F1~F4

Narrow spread: Targeted deposition





Widespread: Maximum deposition in all 3 turbinates

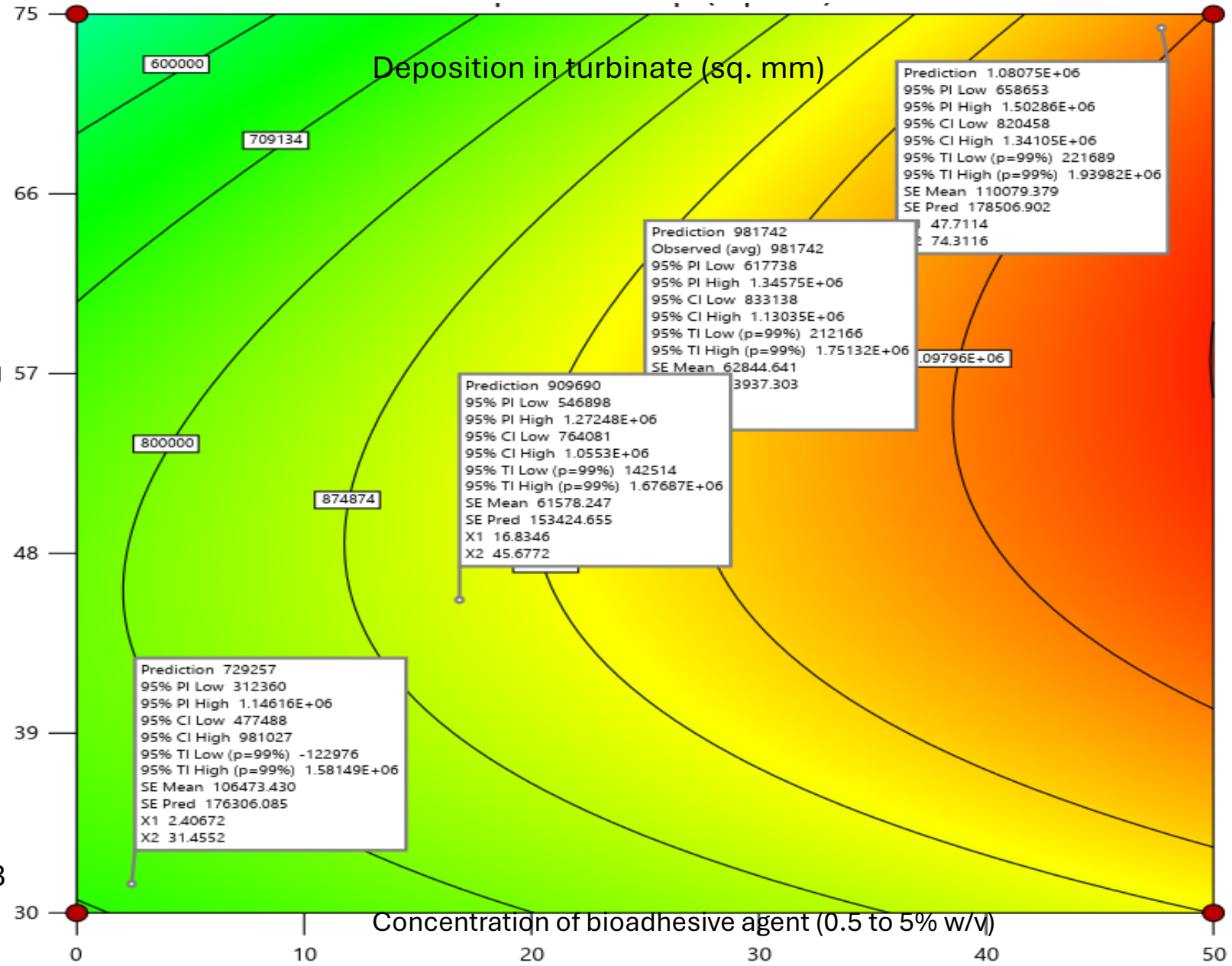


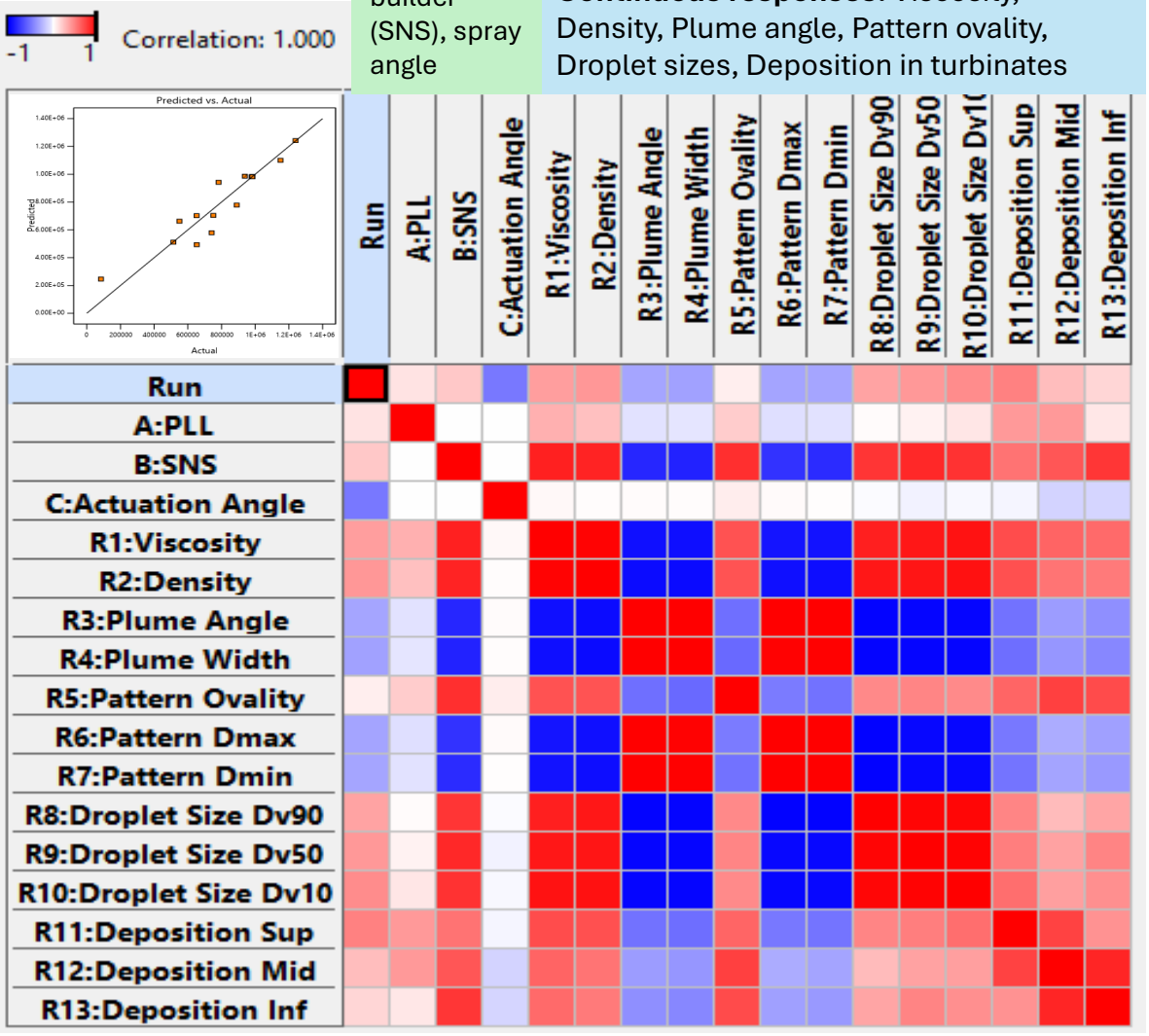
Fig 3. Contour plot of relationship between bioadhesive concentration, angle of actuation & deposition in nasal turbinates with focus on olfactory area

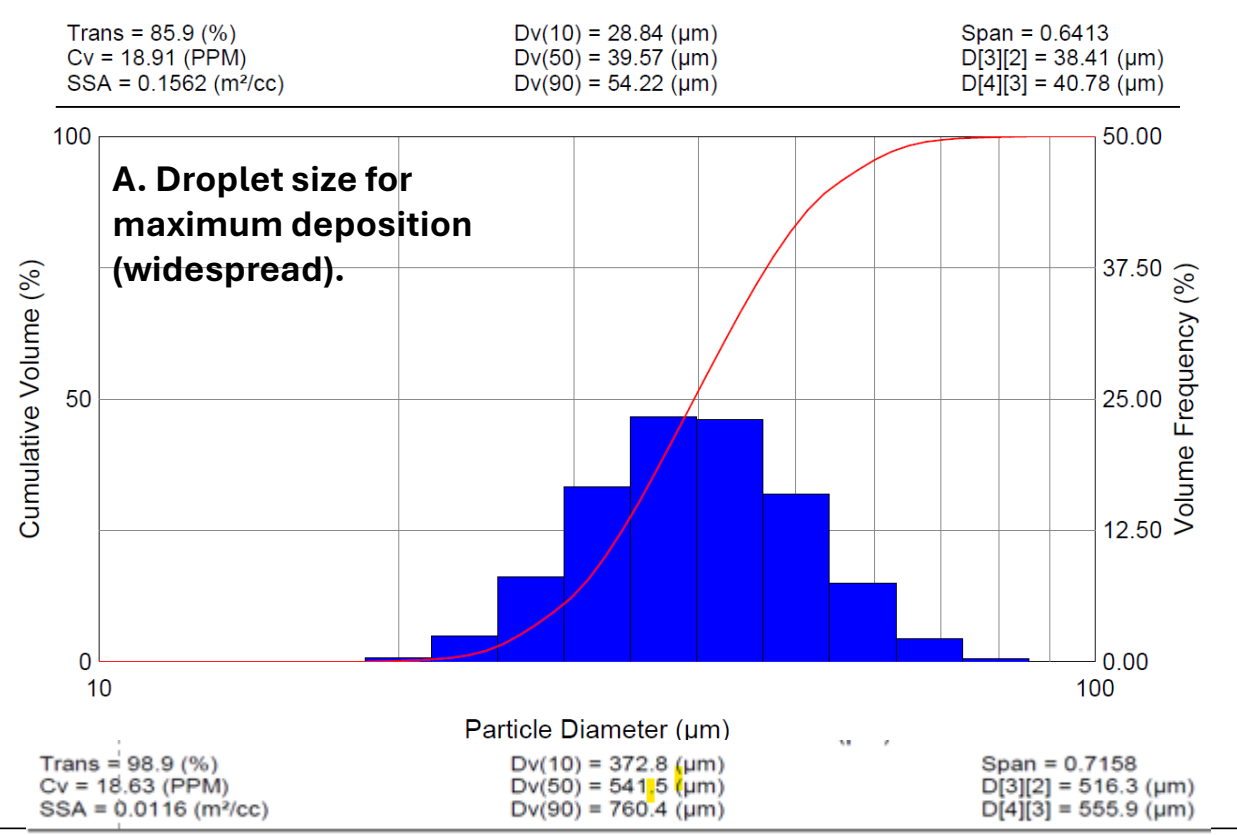
Comparison of factors influencing deposition; model correlation summary

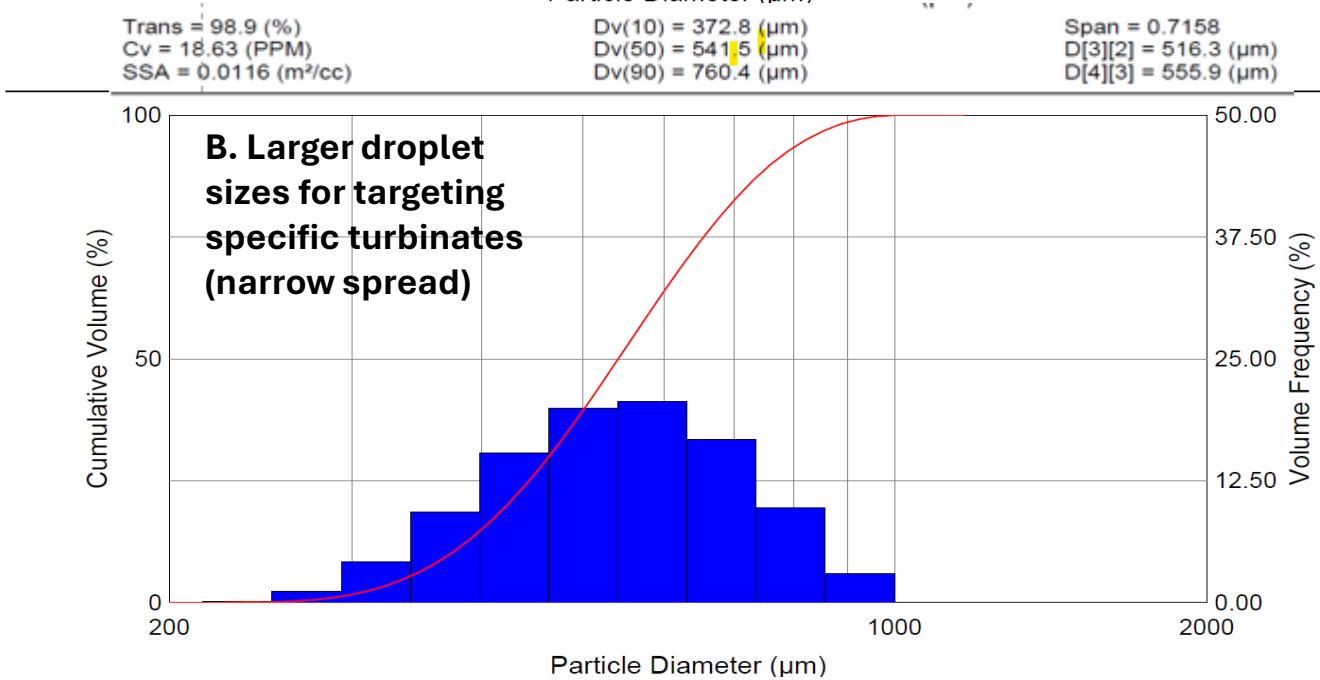
Model order: Quadratic;
Type: Polynomial

Factors: Concentration of mucoadhesive (PLL), viscosity builder (SNS), spray angle

Continuous responses: Viscosity, Density, Plume angle, Pattern ovality, Droplet sizes, Deposition in turbinates

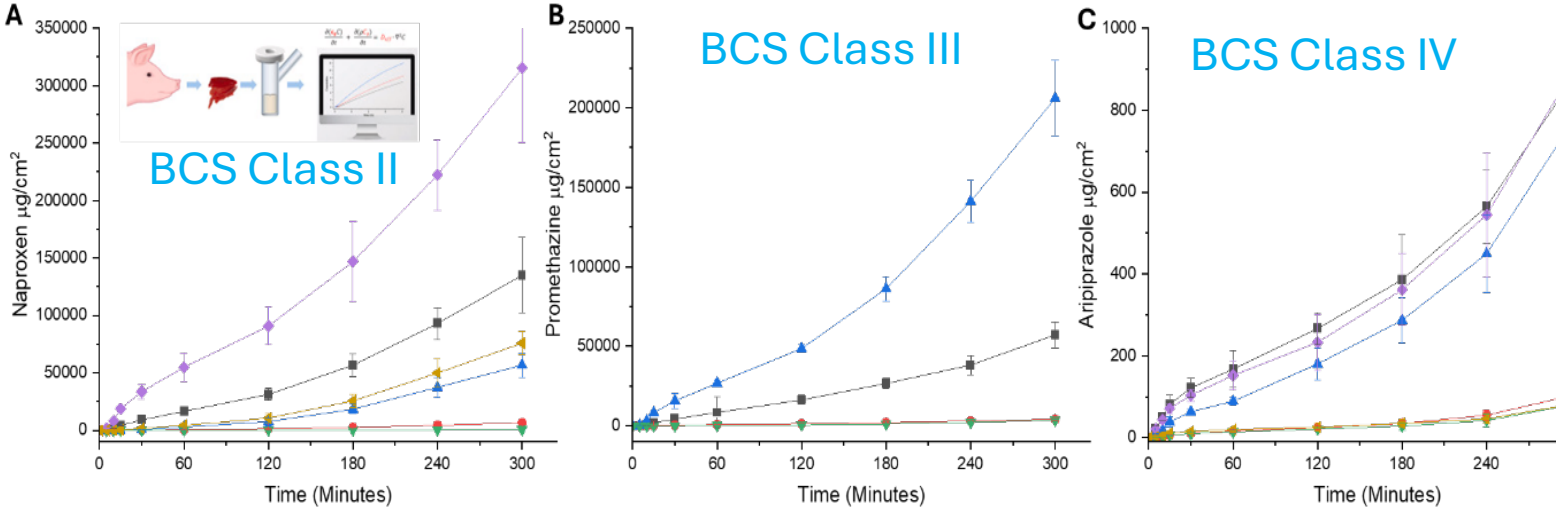


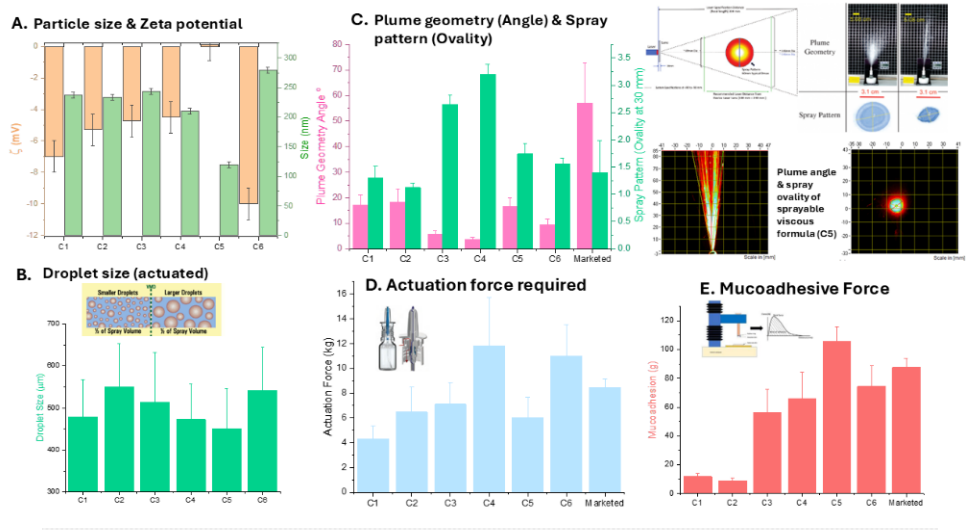


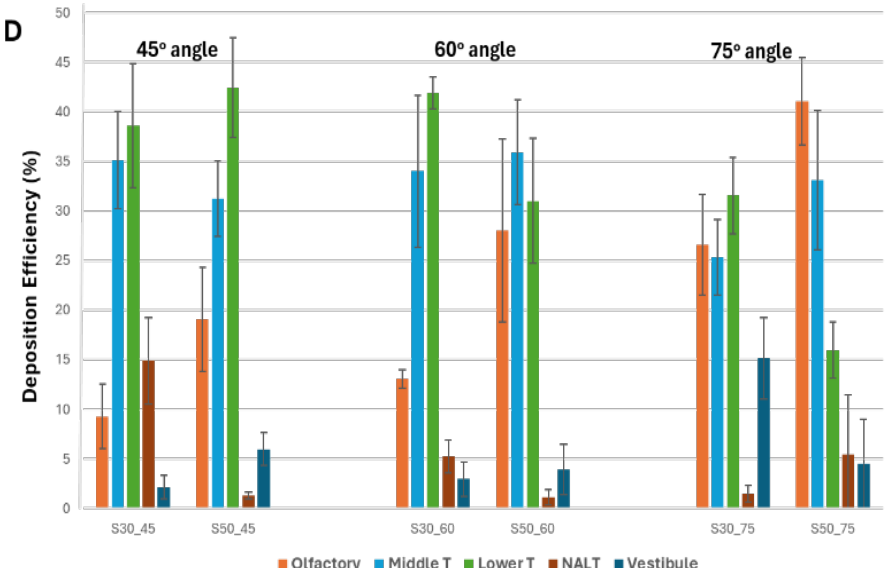


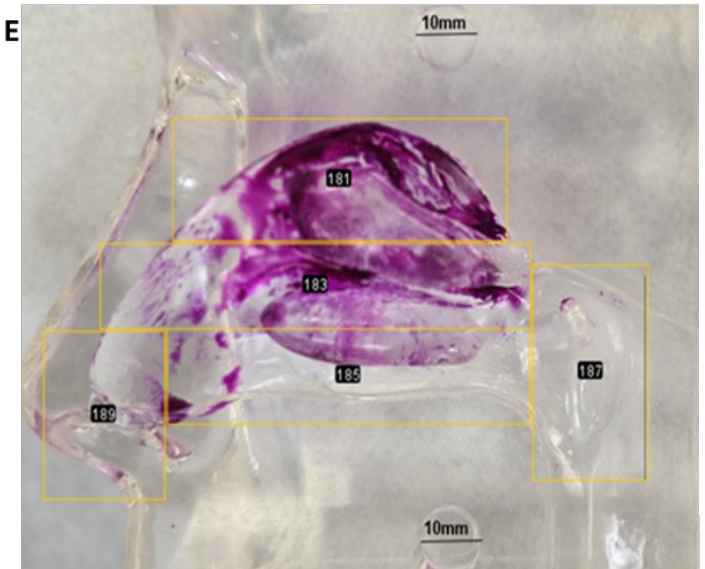
Targeted deposition & release in olfactory area

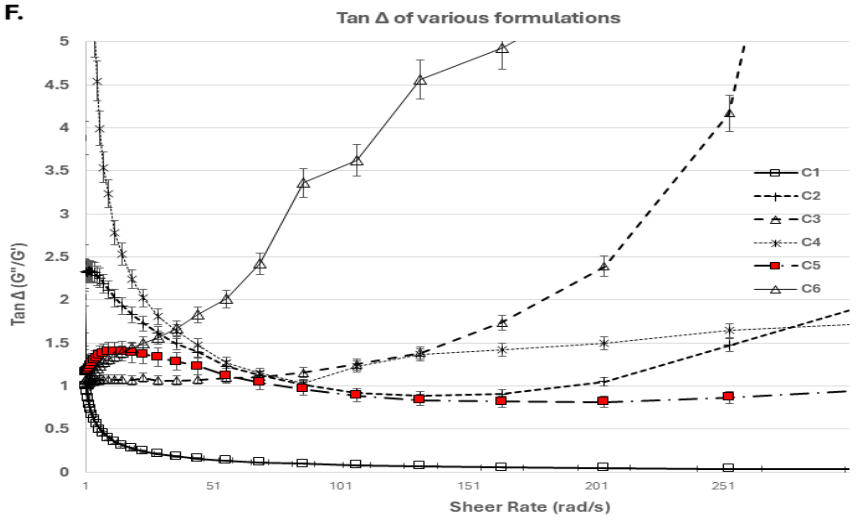
Optimization of factors: 1) Thixotropy 2) Tan Δ (G”/G’) @ 1-10 Hz (CBF 12-15 Hz) 3) PS & Zeta 4) Plume & Spray 5) Droplet size 6) Actuation force 7) Mucoadhesive force







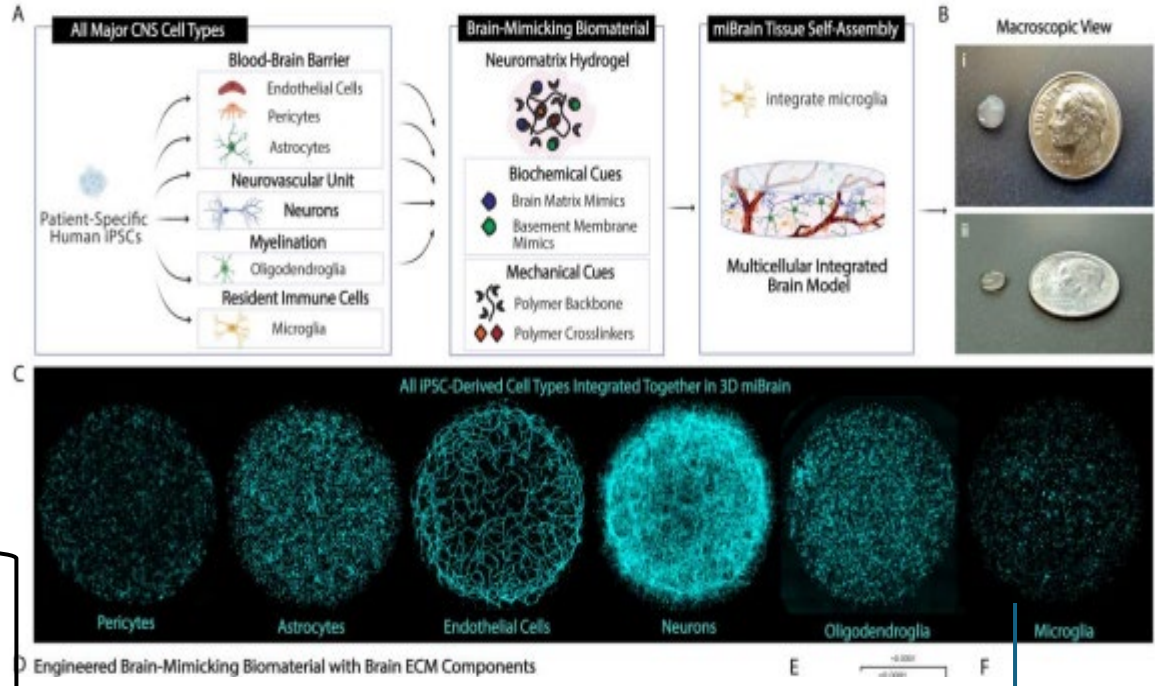




Surfactant-mediated olfactory neuronal uptake (in progress)

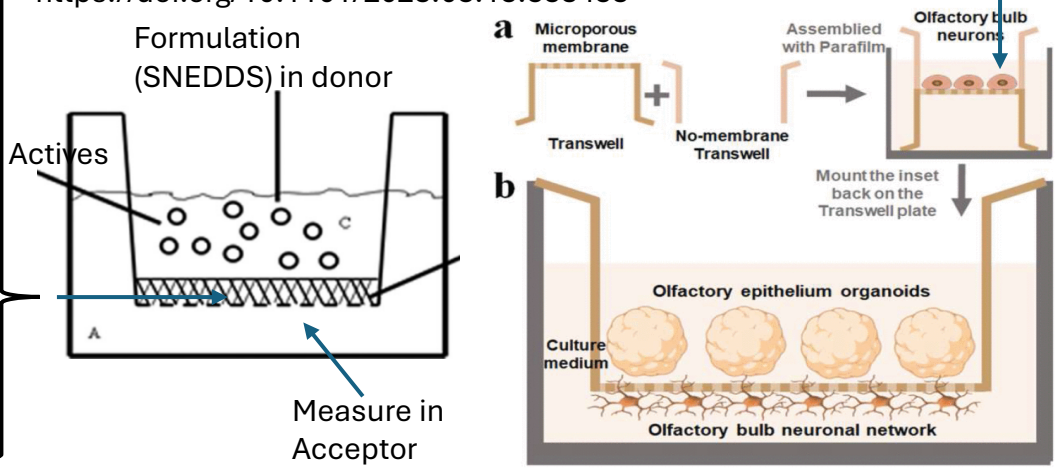
- Creating a specialized media mimicking chemical interior milieu of olfactory nerve Specific compositions of olfactory neuron
- Use modified PAMPA or Trans Well co-culture model

Component	General Neuron (%)	Olfactory Neuron (%)	Key Differences
Water	70-80%	70-75%	Slightly lower due to the presence of a more robust plasma membrane and sensory receptors.
Lipids	10-20%	**12-22%**	Higher due to **more membrane surface area** (cilia and receptor-rich dendrites).
Proteins	10-15%	**12-18%**	Increased due to a **higher density of odorant receptors** (GPCRs).
Nucleic Acids	1-2%	**2-3%**	Higher due to rapid turnover and neurogenesis in the olfactory epithelium.
Neurotransmitters & Vesicles	1%	1-2%	More synaptic vesicles due to continuous signal transmission.
Inorganic Ions (Na^+, K^+, Ca^{2+}, Cl^-)	1%	1-2%	**Higher Ca^{2+} and Cl^- concentration** for odor-induced depolarization.
Energy Molecules (ATP, Glucose)	2-3%	**3-5%**	**Increased energy demand** due to continuous odor transduction.
Enzymes & Regulatory Proteins	1%	**1.5-2%**	Higher cytochrome P450 enzymes for odorant metabolism.



"MiBrain" model: Engineered Brain Mimicking Biomaterial with ECM

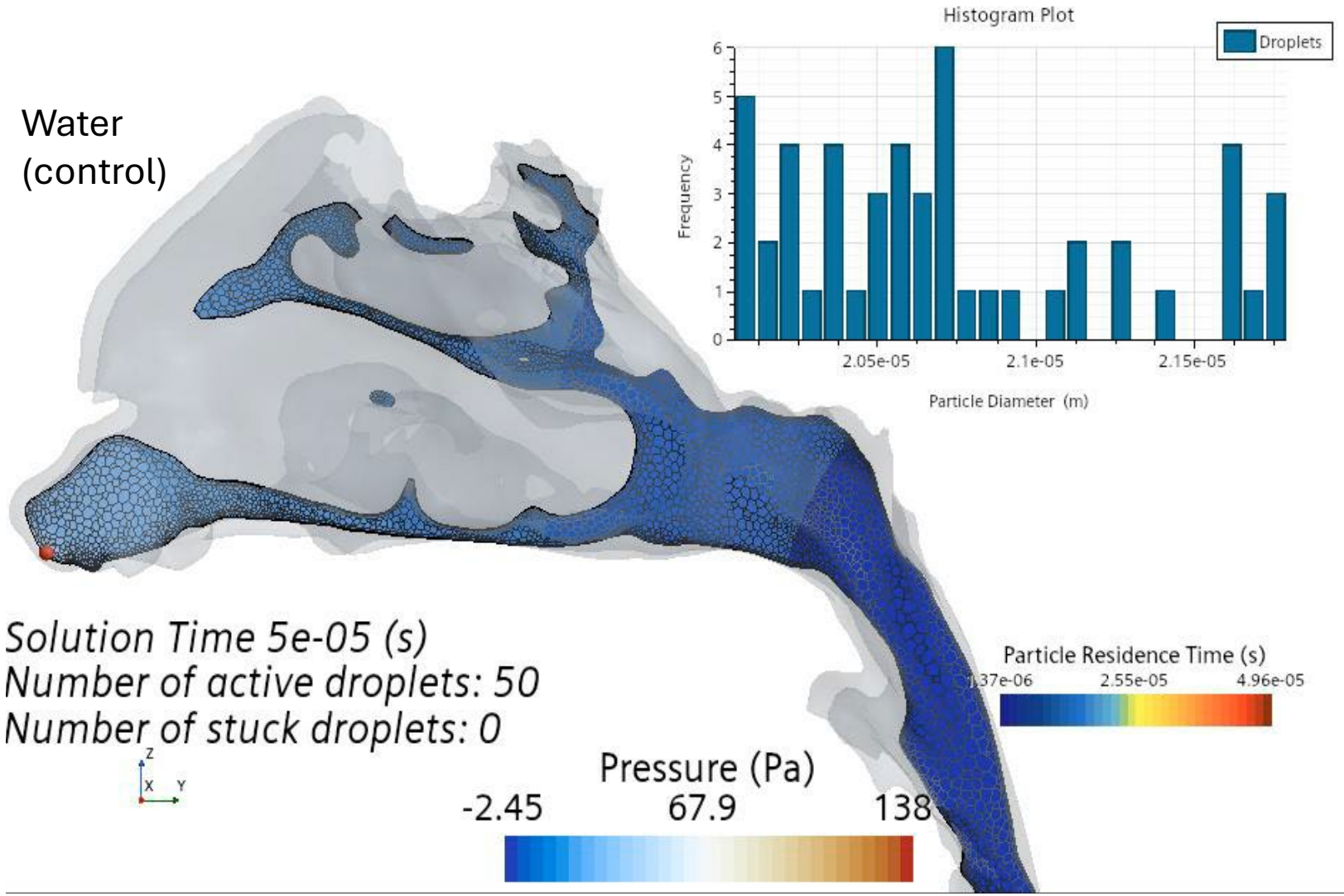
https://doi.org/10.1101/2023.08.15.553453

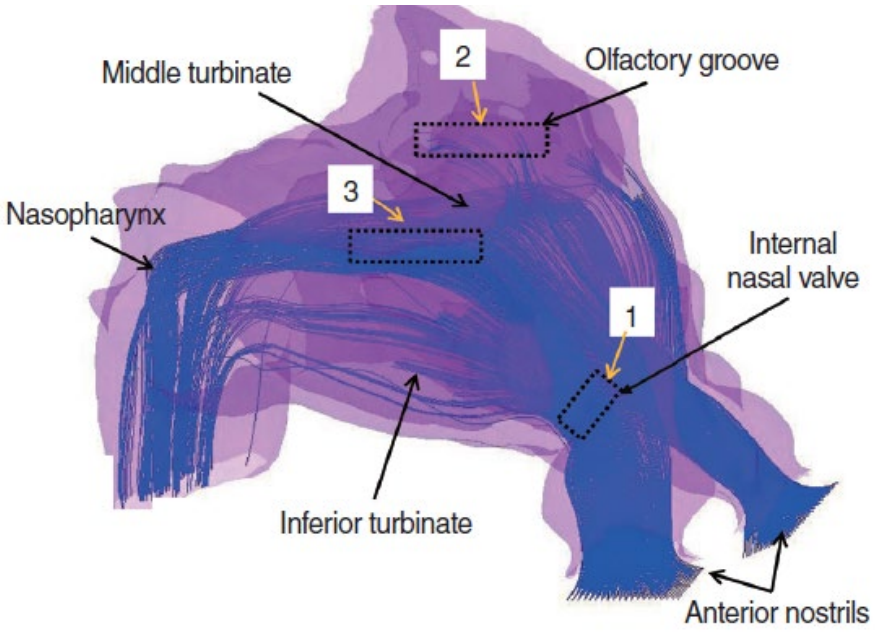


Trans well setup. Ref: Simulating Olfactory System in vitro based on a Transwell Co-culture Model Doi: 10.1109/ISOEN61239.2024.10556109

Development of CFD for Deposition Studies

Water
(control)





Data points	Velocity (m/second)		Pressure (Pa)		Wall shear stress (Pa)	
	Normal	Obstruct-ed	Normal	Obstruct-ed	Normal	Obstruct-ed
1	0.89	0.42	-16.68	-3.13	0.2	0.06
2	0.34	1.96	-12.08	-14.23	0.04	0.17
3	2.23	0.8	-13.56	-21.33	0.22	0.05

Three-dimensional (3D) model of inspiratory air streamlines (blue), with air velocity, pressure and wall shear stress measurements, at three points in both normal (healthy) and CFD simulation is 34.8 L/minute.
http://dx.doi.org/10.3342/ceo.2012.5.4.181

CFD by Dr. M. Tereziev, Dr. A. Lalatsa (Univ. of Strathclyde)

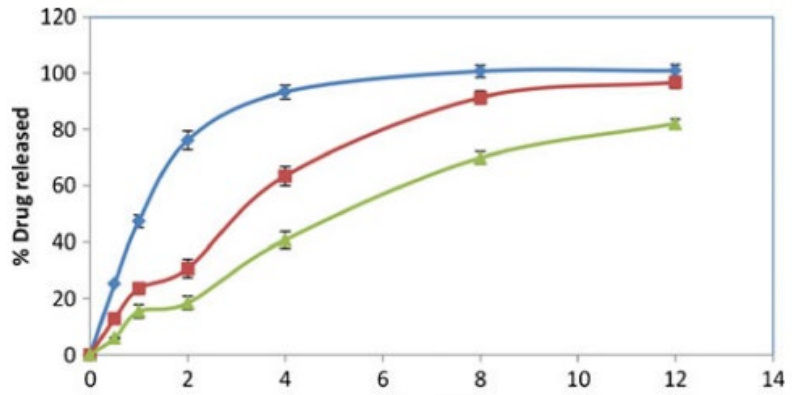
Summary

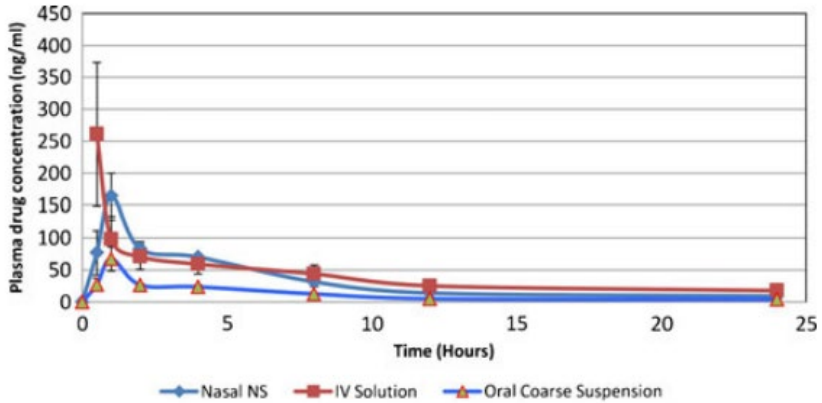
Current scenario: Nasal Modified Release formulations as in situ nasal gels

Review by Meirinho S, et al, 2022. https://pubmed.ncbi.nlm.nih.gov/35890385/

In situ gel formula: Tween 80, Span 40, PVP K-30, poloxamer 407 and poloxamer 188 (20-40%), stearic acid, oleic acid, pullulan, gellan gum.

Drug release study was performed by the USP paddle method (in vitro), animal model (in vivo).

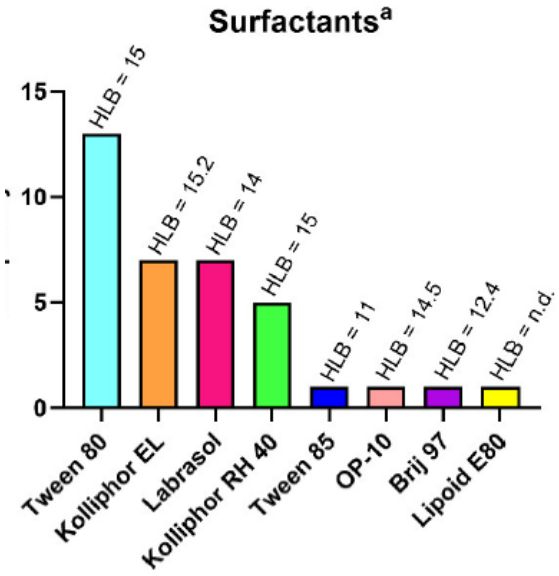


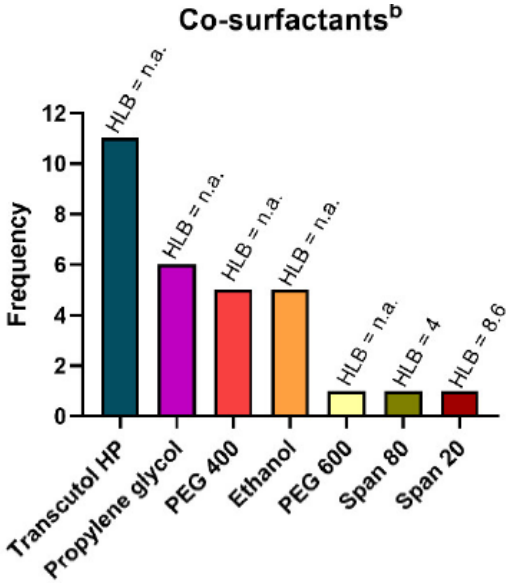


Cmax, AUC, Tmax:
IV>Nasal>Oral

Bioadhesive Nasal SNEDDS: Acconon MC8-2, Tween 80, Span 80, Caprol 3PGO, Span 85, PVP, PEG 800. Size range: 10-40 nm.

Needs more than surfactants, cosurfactants, oils & solvents to form bioadhesive nano-micelles for sustained release





Summary of this study

- Optimized final formulation:
  - SNEDDS only from 30% to 50% + 25mM PO4 buffer at pH 6 + (optional) pullulan at 0.5%
  - Sprayable from regular devices (gel & spray);
  - 100 µL intranasal dose per nostril
  - No other excipients necessary

- Meets CQAs/Objectives:
  - High drug loading from 30 to 50%
  - Enhances solubilities of all BCS Classes by 1000x and permeation flux by 50x in average.
  - Prevents drip-away, drug loss and & nasal clearance (Thixotropic & high elastic moduli)
  - SNEDDS interacts with water to form gel matrix for modified release for 24 hours (in vitro)
  - Targeting to olfactory area possible (up to 40%) by adjusting angle of delivery (75°) & formulation type

- Simple binary mix of drug-loaded SNEDDS + water can achieve all objectives, including potential brain targeting using standard spray devices

Modified nasal delivery: Versatile Advantages

Viable routes: *(N=Nose; Bl = Blood; Br = Brain)*
N2N (local) or N2Bl (systemic) &
N2Br or N2Bl2Br (Nose to brain)

N2N & N2Bl - Systemic & Local Delivery (Developed)

- Nasal Delivery is a versatile, non-invasive & patient-centric platform for drug delivery
- Local, systemic, immunization target
- PK/Animal modeling is available for local & systemic deliveries
- Accumulation kinetics known/Fast onset
- Devices available

N2Bl &/or N2Bl2Br - Nose to Brain delivery (Work in progress)

- Addressing unmet brain disorders
- N2B dose delivery variability
- Exclusive drugs (!); Depends on potency
- Often specialized device necessary
- Advanced Imaging, CFD required
- No widely used in vitro model currently available for N2B delivery (+ animal testing restriction)

Thank you & let’s work together!

Email : debanjan.das@bayer.com

Acknowledgements: Prof. A. Lalatsa, M. Tereziev (University of Strathclyde), E. Kaffash (Virginia Commonwealth University) Shabbir Lobo (Bayer)

Q & A