NASAL INNOVATION FORUM

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Strategic Product Design for Liquid Nasal Formulations: A Target Profile Perspective

18 September 2025

Lucas Silva

Delivering solutions, shaping the future.

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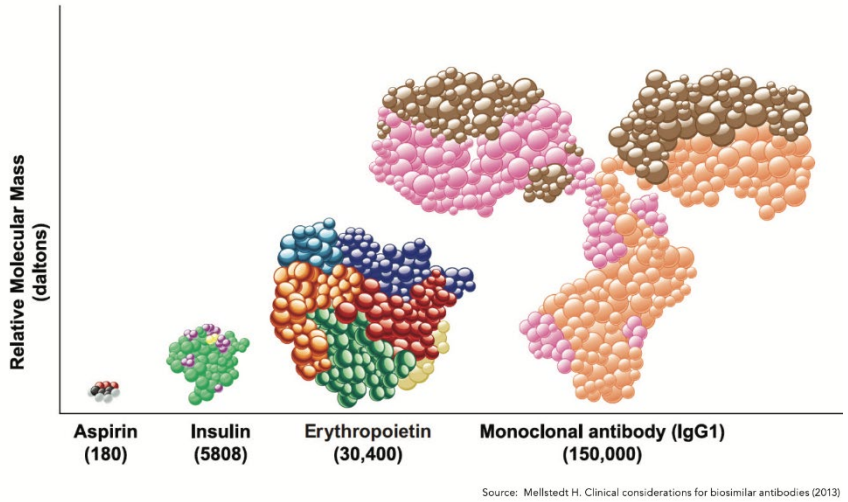
Agenda

1. Formulation Strategies and General Considerations
2. Structure, Stability and Targeted Delivery for Nasal
3. General Requirements of Nasal Formulations and their Impact on Delivery
4. Rheology, Mucoadhesion and Permeation
5. Development of Nasal Sprays and Case Studies
6. Conjugation and Encapsulation Examples
7. Conclusions

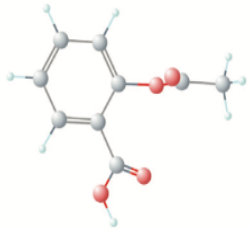
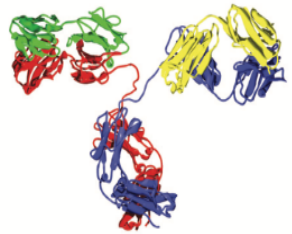
Small Molecules vs Biologics



Source: Mellstedt H. Clinical considerations for biosimilar antibodies (2013)

- Small-molecule drugs (<900 daltons) such as chemotherapeutics, antibiotics and steroids have been identified, developed and used as pharmaceuticals since the late 1800s.

- Biologics include peptides, antibodies, recombinant proteins, or oligonucleotides.

	Small-Molecule Medicines (chemical-based)	Biological Medicines (protein-based)
Example	 Acetylsalicylic acid (anti-inflammatory & pain relief) [5]	 Monoclonal antibody (treats cancer & autoimmune diseases)
Molecular Weight	180 daltons [9]	~144,000 daltons [10]
Size	Small [11]	Large [11]
Structure	Simple and well defined [11]	Complex [12]
Manufacturing	Predictable chemical process; Identical copies can be made.[12]	Each manufactured in a unique living cell line; similar-but-not-identical copies can be made.[12]
Characterisation	Easy to fully characterise [12]	Difficult to fully characterise [12]
Stability	Usually stable [12]	More sensitive than small-molecule medicines to handling and storage conditions [12]
Immunogenicity	Usually unexpected [11]	Higher potential; always need to be tested during development [11]

Source: Carton JM & Strohl WR. Protein therapeutics)

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Formulation Strategies & Considerations

Fundamental Suitability for Nasal Delivery

Physico-chemical Properties of Molecule

Mucoadhesives and absorption & Penetration Enhancers

Nanoparticulate Carrier Systems & Targeted Delivery

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Structure Matters

After synthesis…

After formulating/mixing….

After spraying….

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Stability Matters

Aggregation

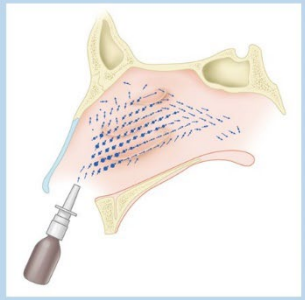
Intact Molecule

Precipitation

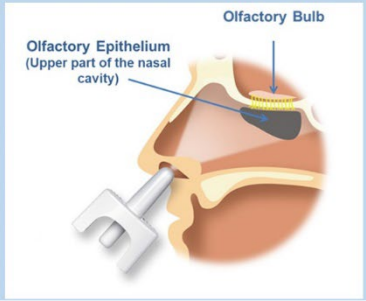
Control this through formulation design:

- pH
- Osmolality
- Viscosity
- Stabilising agents
- Formulation modifiers
- Formulation enhancers

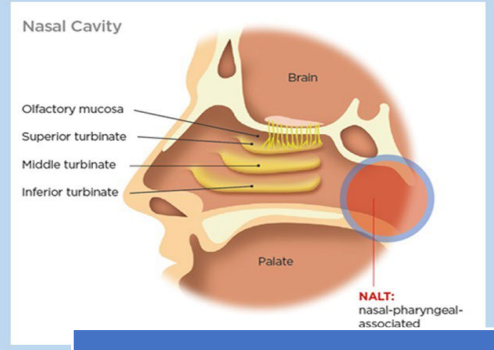
Deposition Targets



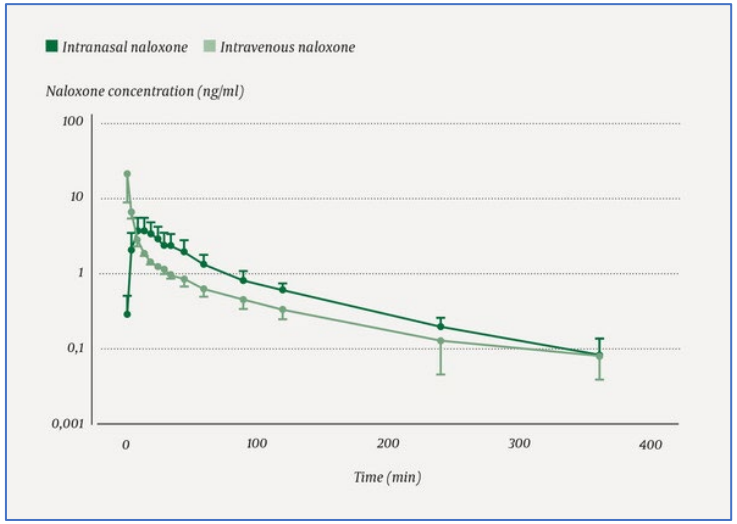
Topical/Systemic

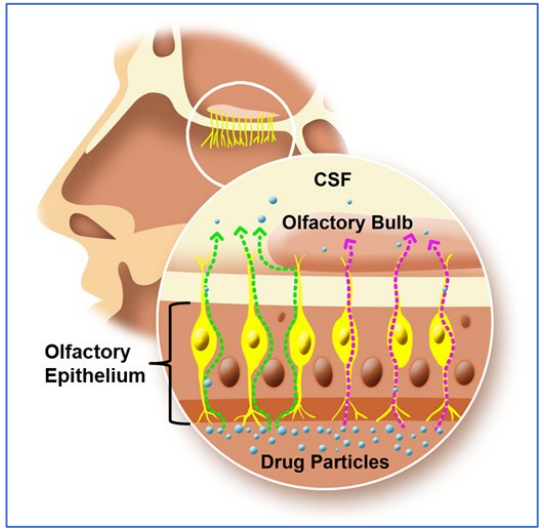


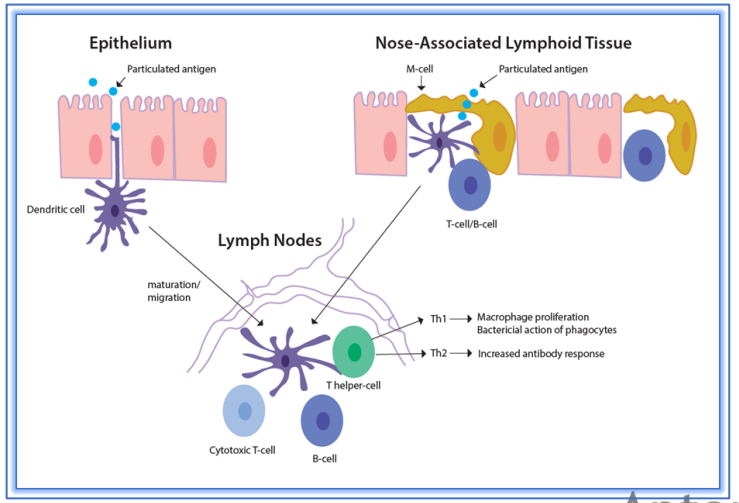
CNS



Vaccine







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General Requirements for Nasal Formulations

Deposition, retention & permeation, mucus interaction and penetration

Osmolality

pH

Physiological tolerability, drug solubility/stability

Rheology

Preservatives

Physical state

Particle / droplet size

Drug dissolution & permeation, device delivery

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Properties of API and Formulation Impact on Nasal Delivery

API PROPERTIES

- Molecular weight and size
- Charge
- Buffer/pH compatibility
- Solubility

- Ability to formulate into a concentrated system
- Stability of formulation and API in the formulation
- Compatibility with excipients (especially preservatives)

- Cell vs. Tight Junction permeability
- Interact with or penetrate mucus
- pH or tonicity of nasal environment
- Inherent impact on nose physiology

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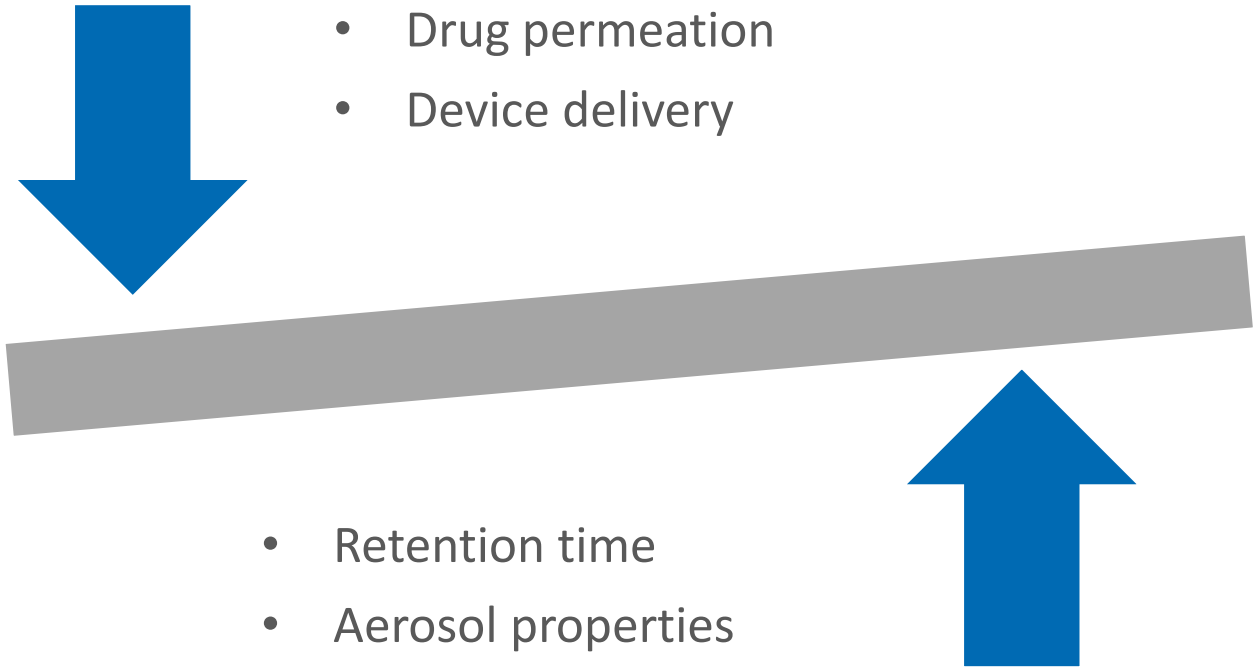
Influence of Rheological Profile

- Not one size fits all composition
- Thixotropic systems
- Inherent mucoadhesive or permeation enhancer properties
- Viscosity will have an impact on the spray performance:
  - Crucial for Generics
  - Assess DSD and SP



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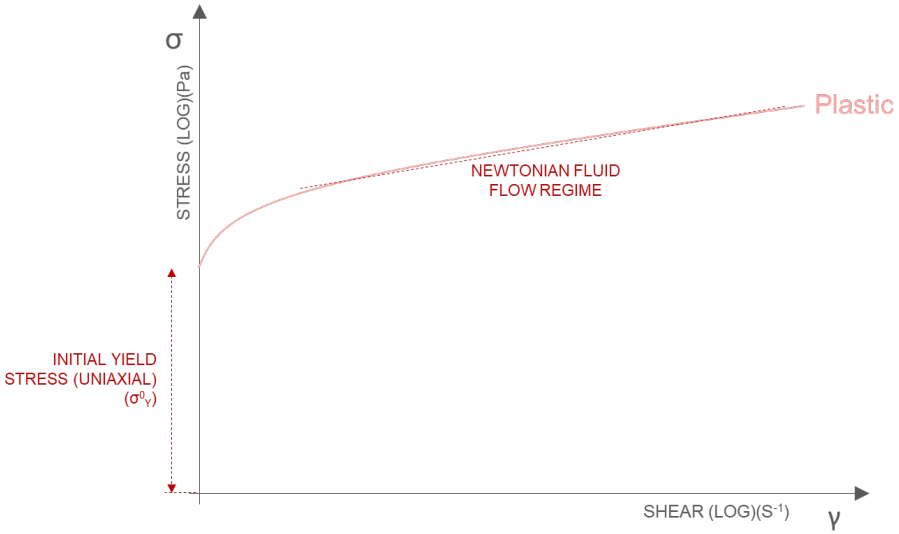
Influence of Rheological Profile

RHEOLOGY: LIMITED EXCIPIENTS

- Achieving the right rheology can be complex, because the amount of **approved excipients, or the acceptable / precedential levels** used, are very limited.
- It can mean that some formulations need 1 or more rheological modifiers in order to create the rheological characteristics desired / preferred.



Psudoplastic flow curve: *The idealised stress/strain curve for a nasal spray*

FDA IID Can Limit Options: *Many customers want to limit the risks to the development program by working within the excipients and limits used on the IID*

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Mucus - Adhesion vs Permeation

- "Binding to" and "passing through" mucus are not the same

- Mucoadhesive polymers
  - Chitosan
  - HPMC, CMC
  - Carbopol
  - PLA, PEG & PLGA

- Hydrophobic / cationic molecules
  - stick to mucus
  - pass through cells

Mucus is negatively charged

- Hydrophilic / polar molecules
  - permeate through TJ
  - Struggle to interact with mucus

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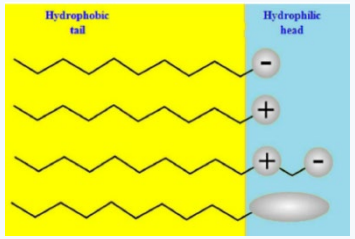
Permeation Enhancers

- **Tight junctions permeability is driven by ion-selective pores -> polar/positively charged, hydrophilic molecules permeate**
- **Lipophilic / non-polar / macromolecules won't naturally permeate -> permeation enhancers and/or carriers**

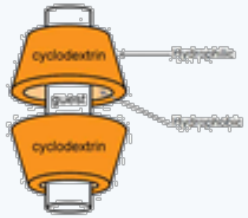
Surfactants

- Cationic e.g. benzalkonium chloride
- Non-ionic e.g. alkylsaccahrides (DDM), polysorbates
- Bile salts
- Anionic e.g. SLS



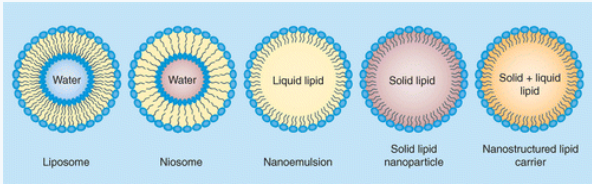
Polymers & Oligosaccharides

- Natural e.g. chitosan, hyaluronic acid, cyclodextrin
- Synthetic e.g. PEG, PCL
- Inclusion complexes or drug-polymer complexes



Drug Encapsulation & Augmentation

- Cell Penetrating Peptides
- PEGylation
- Lipid nanoparticles e.g. NLC, SLC
- Polymer nanoparticles e.g. PLGA
- Exosomes / liposomes / nanoemulsions



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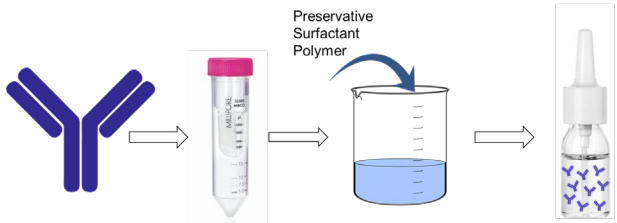
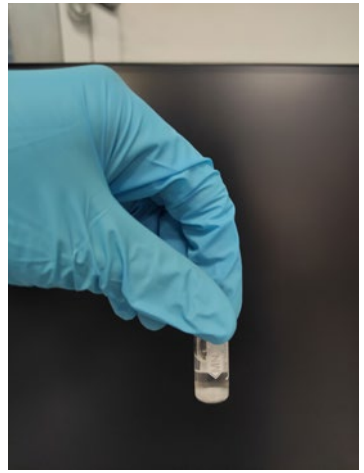
Excipients Compatibility Studies

- Buffer (type and pH) to avoid instability and precipitation
- Surfactants can be added to reduce aggregation (screening of surfactants and their concentration)
- Cryoprotectants (i.e. sugars and sugar alcohols)
- Mucoadhesive polymers (i.e. cellulose and its derivatives)
- Permeation/absorption enhancers (i.e. cyclodextrins, DPC)



- **Presevatives**

0.02% of Benzalkonium Chloride most common preservative for nasal sprays can precipitate proteins
[Meyler's Side Effects of Drugs (Sixteenth Edition), 2016; Contemporary Practice in Clinical Chemistry (Fourth Edition), 2020]



Screening Studies to Test Compatibility Under Stressful Conditions

Alternative Preservatives to BAC:
- Edetate Disodium typically 0.1%
- Potassium Sorbate typically 0.2%
- Benzyl alcohol typically 1%
- Phenylethyl alcohol: 0.25-1%

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Nasal Spray Development

Critical Considerations for a Liquid Nasal Spray

- Spray technology (shear stress) influence on biologic's structure/activity (CD, ELISA, *in vitro* cell culture models, *in vivo* etc.)
  - Load biologic into nanoparticles, micelles etc.
  - Buffer system
  - pH
  - Viscosity and Rheological Profile
  - Excipients compatibility
  - Device material compatibility (Extractables/Leachables)
  - Preservatives
  - Storage conditions/Cold chain & Freeze/Thaw cycles

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General qTPP for a Nasal Spray comprising a Liquid Formulation

	Definition	How to assess it	Target
Assay & Degradation Products	Assessment of intact biomolecule content in the formulation and agglomerates/fragments or degradation related substances	Size Exclusion Chromatography, Reverse Phase High Performance Liquid Chromatography, Mass Spectroscopy. Use of orthogonal techniques such as Dynamic Light Scattering to assess agglomeration/fragmentations.	100% of theoretical concentration. Area percentage of formulated biologic matching reference standard (i.e. IgG dimeric fraction same of reference standard)
pH	Measure of formulation acidity/basicity. Choice of the appropriate buffer	pH meter	4.5-6.5 (i.e. buffers: sodium acetate, citrate, phosphate etc.)
Osmolality	Measure of the number of osmotically active solute particles dissolved in a kilogram of solvent	Osmometer	290-550 mOsm/Kg
Viscosity	Measure of fluid resistance to deformation at a given rate. Deposition depends on viscosity.	Capillary and Rotational Viscometer and/or Rheometer (rheological profile)	Max 20-35 cP
Droplet Size	Size of the droplets generated by formulation + device combination	Laser Diffraction	Minimize Fraction <10um. However, deposition depends also on Spray Pattern and Plume Geometry
Dose Volume and Dose Content Uniformity	Determination of shot weight and uniformity of dose emitted	Automated actuator USP <601> apparatus A	Ideal dose volume: 100 µL (max 250-300 µL per nostril)
Drug in Small Droplets	Determine mass of “small droplets” (used to determine the % of droplets that could deposit in the lung)	U.S. Pharmacopeia (USP) <601> Apparatus 1 (flow rate of 28.3 L/min), Apparatus 6 (flow rate of 15 L/min)	Expect 2% or less to enter impactor
Activity Assay	Assessment of any change in the functionality of the biological molecule	Specific biological activity assay for each molecule (e.g. ELISA)	Activity of formulated and sprayed biologic comparable to reference standard

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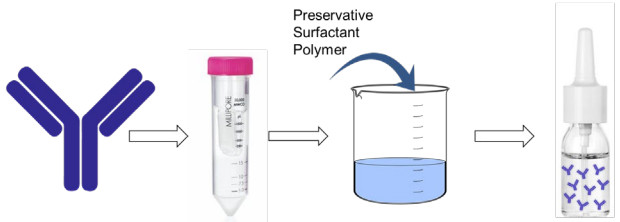
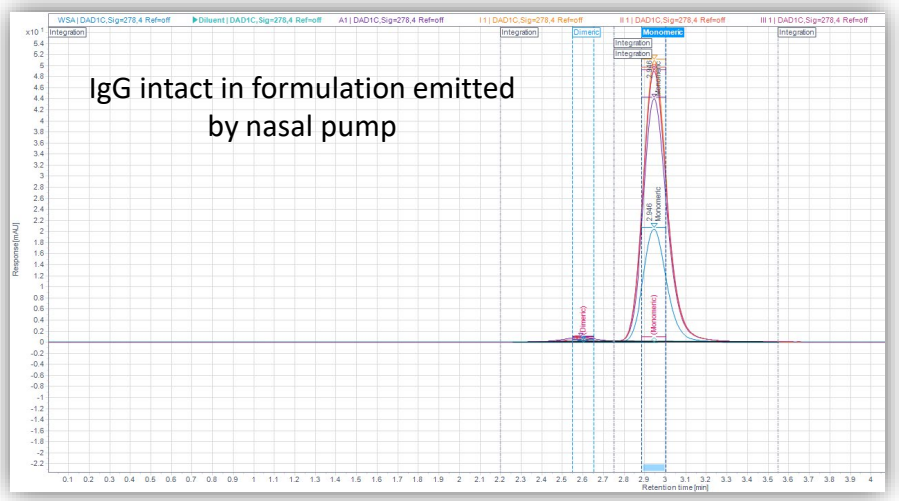
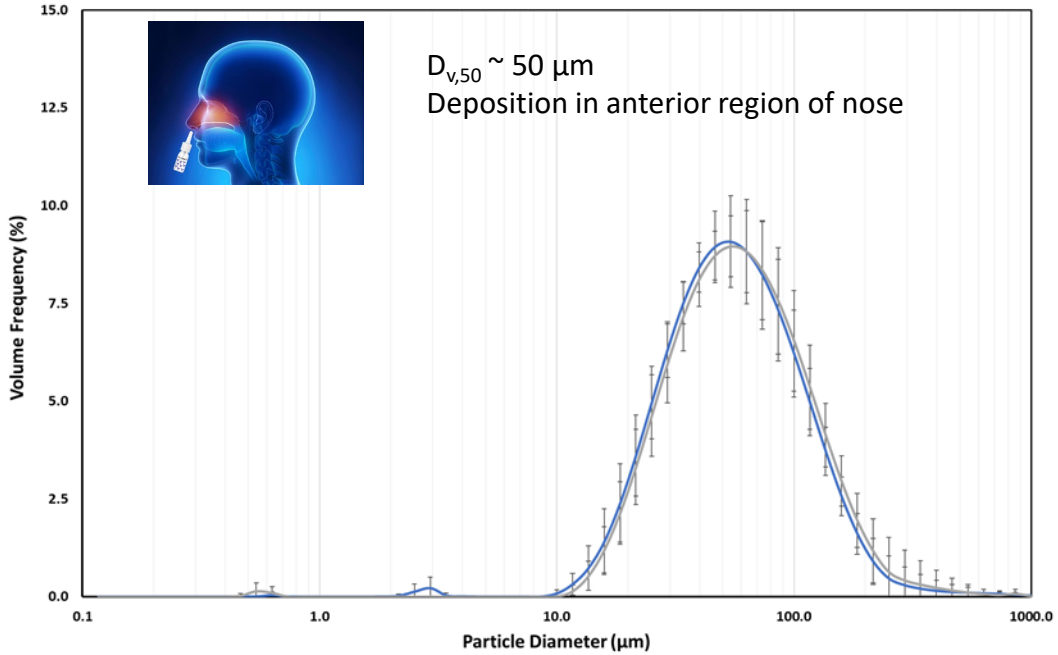
Case Study I - Development of a Nasal Spray Comprising IgG against SARS-CoV-2

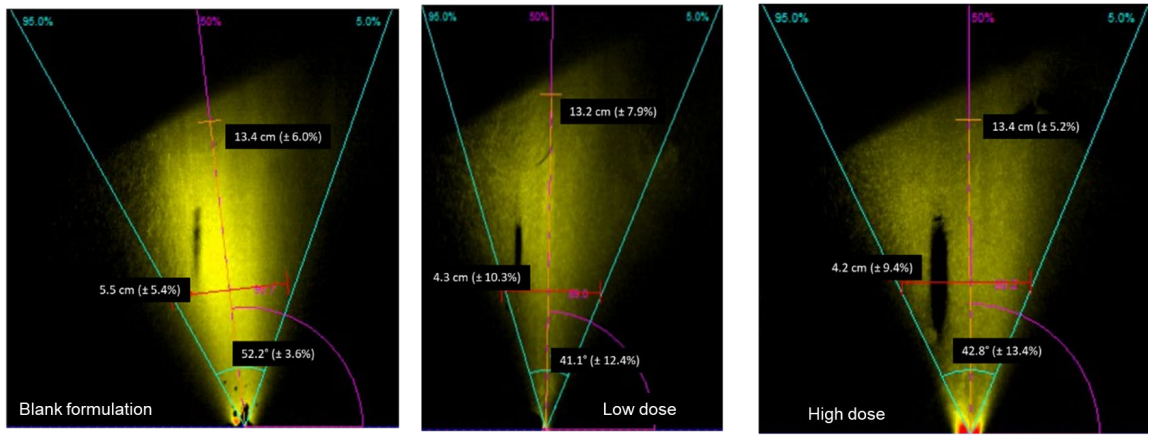


Formulation	IgG Concentration (mg/mL)
Low dose	2
High dose	20





Influence of viscosity and formulation composition on Spray Pattern and Plume Geometry



Zapata del Baño A et al. DDL 2021

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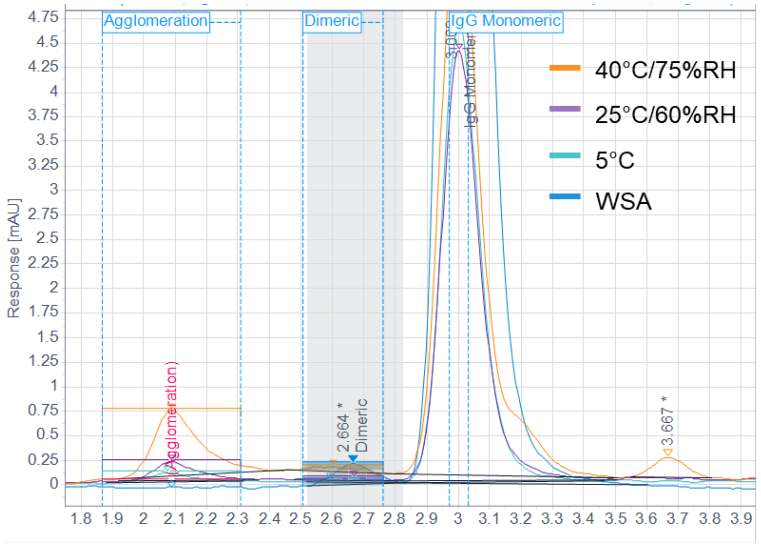
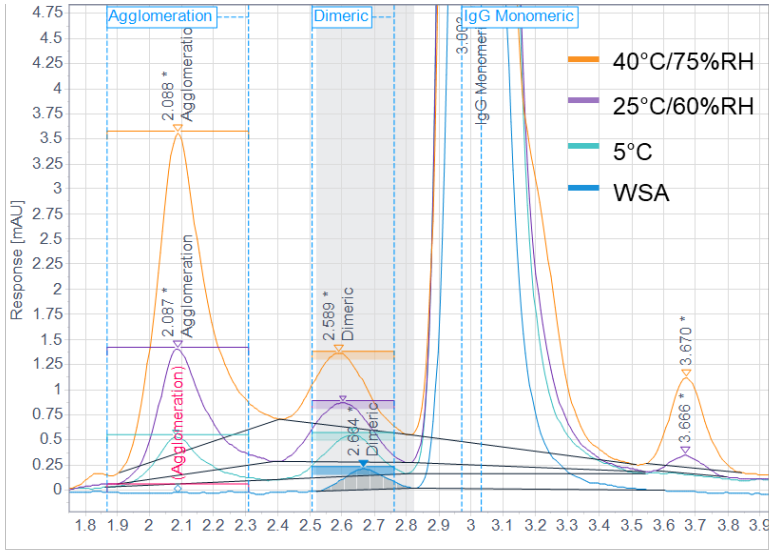
Development of a Nasal Spray Comprising IgG against SARS-CoV-2

Stability Storage

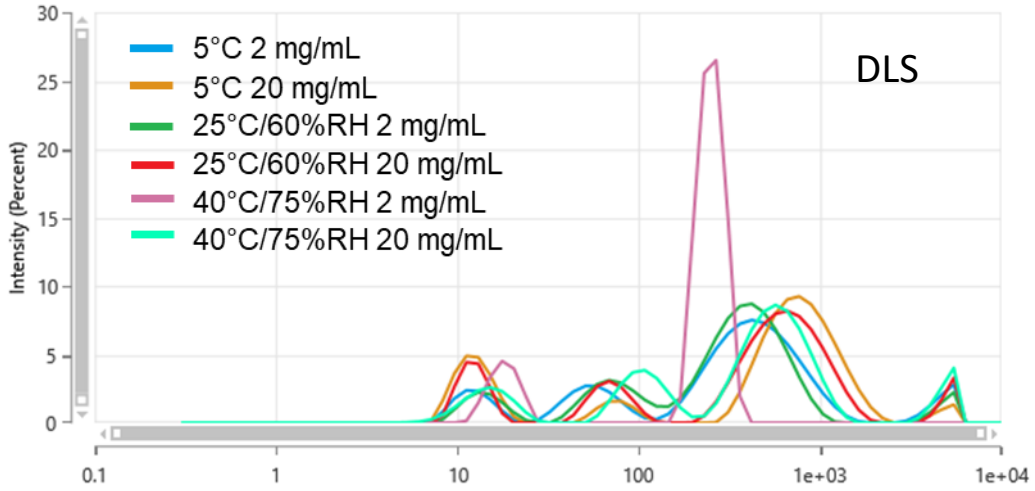
- For both formulations, degree of agglomeration was proportional to storage condition (5°C < 25/60 < 40/75)



SEC spectrum 2 mg/mL



SEC spectrum 20 mg/mL



Relative Potency and Binding Affinity by confirmed by ELISA

Zapata del Baño A et al. RDD 2022

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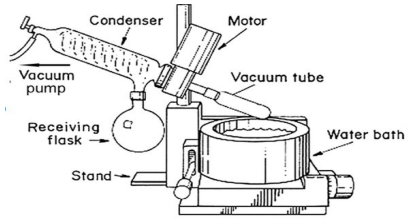
Case Study II - Encapsulation of nucleic acids and peptides

Liposomes IN Formulation Manufacture

12 mg of Lecithin + 3 mg of Cholesterol were dissolved in chloroform/ethanol 88/12% v/v

Rotary Evaporation
6 hours at 60°C



600 nm

DNA loaded liposomes

Rehydrated with 1 mg of model nucleic acid in 5 mL distilled water

Empty liposomes

Rehydrated with 5 mL distilled water

400 nm

Nasal Formulation Matrix
0.5% w/v TMC
3.0% w/v Sorbitol
2.0% w/v Mannitol
0.1M Phosphate Buffer

Rey-Blanes C et al. DDL 2022

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Case Study III - Encapsulation of peptides for N2B

- A buffered excipient solution was prepared consisting of 5.0% w/v of hydroxypropyl beta cyclodextrin, and 2.0% w/v polysorbate 80 in 0.01 M citrate buffer, pH 4.5.

- Formulation A (PLGA): 21.73 ± 0.09 mg/mL Octreotide Acetate (Q-Sphera™ Microspheres containing mannitol [0.17% w/w], carboxymethylcellulose [0.03% w/w] and Kolliphor 188 [0.01% w/w]) and buffered excipient solution.

- Formulation B: 19.60 ± 0.29 mg/mL Octreotide Acetate, 2.5% w/v mannitol with buffered excipient solution.

Table 1 - Average values of spray performance: DSD at 6 cm and SP (n=3, standard deviation in brackets).

Formulation	DSD				SP			
	D_v10 (µm)	D_v50 (µm)	D_v90 (µm)	Span	Dmin (cm)	Dmax (cm)	Area (cm^2)	Ovality Ratio
Formulation A - Microspheres	52.07 (2.34)	134.28 (4.22)	264.41 (14.39)	1.58 (0.07)	1.4 (0.1)	3.5 (0.2)	4.1 (0.3)	2.4 (0.3)
Formulation B – Octreotide solution	29.14 (0.83)	66.30 (1.84)	169.83 (5.10)	2.12 (0.06)	2.3 (0.2)	4.2 (0.2)	6.5 (0.6)	1.9 (0.3)

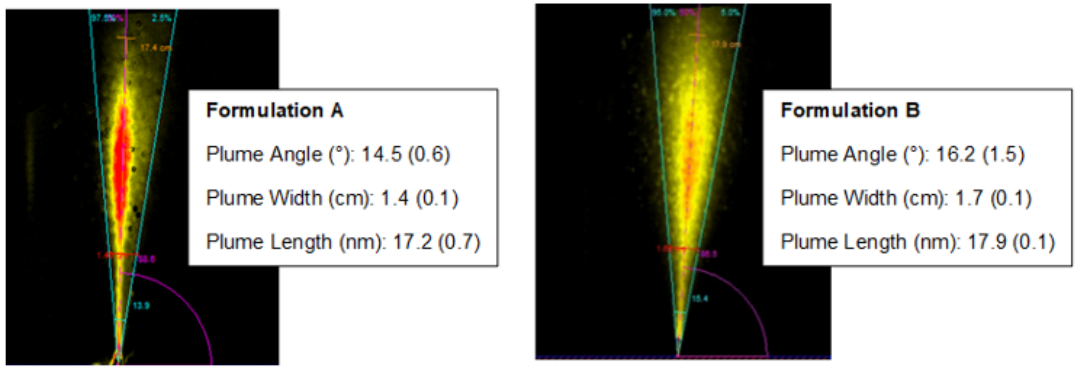
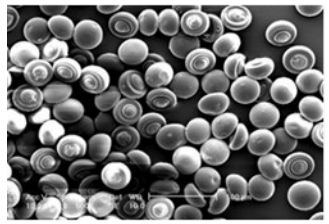
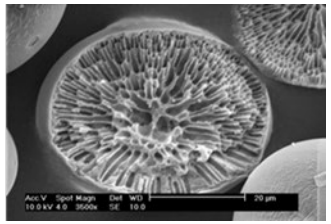
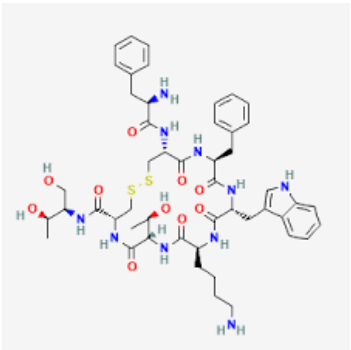


Figure 3 – PG results: images depict one repeat, values reported are n=3, standard deviation in brackets.

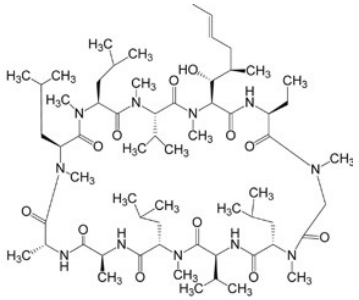






Beaird et al. DDL 2023

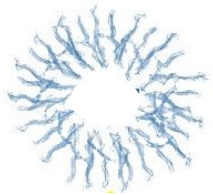
Case Study IV – Micellular formulation



Cyclosporin A

Encapsulated

TPGS micelles

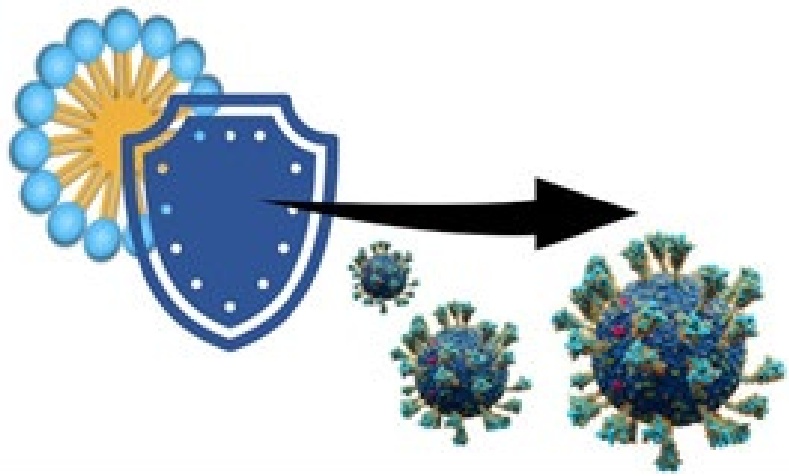


~10 nm

Formulation loaded

BiVax device (Aptar)

- Cyclosporin → prevent or treat viral pathogens.
- Liquid formulation loaded into the BiVax device.
- Mucoadhesive property and permeation study assessed.
- Micelles antiviral activity was measured against SARS-CoV-2 was tested on the Omicron BA.1 variant using Vero E6 cells.



Guareschi F et al. European Journal of Pharmaceutical Sciences

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Take-Away Messages

1. **Liquid Nasal Product Development** needs to follow an integrated approach which takes into consideration first of all the characteristics and stability/residual activity of the Molecule, the desired site of deposition/pharmacological effect and the combined performance of device + formulation.

2. Nasal Products can be formulated both as **Powder or Liquid**. Choice of form needs to be based on the molecule characteristics, dose, regimen, stability etc.

3. **Liquid Formulations** are the dominant proportion of marketed products. **Selection of excipients** to obtain **sustained release/permeation** and their **compatibility** with the molecule (i.e. preservatives) need to be carefully taken into consideration.

4. **Case Studies** demonstrate that Nasal devices are able to deliver Liquid formulations with a wide range of molecules for topical, systemic, CNS and anti-infective purposes.

5. **Encapsulation, Conjugation and Complexation** can be used to protect, stabilise and enhance the pharmacological effect of a Biomolecule.

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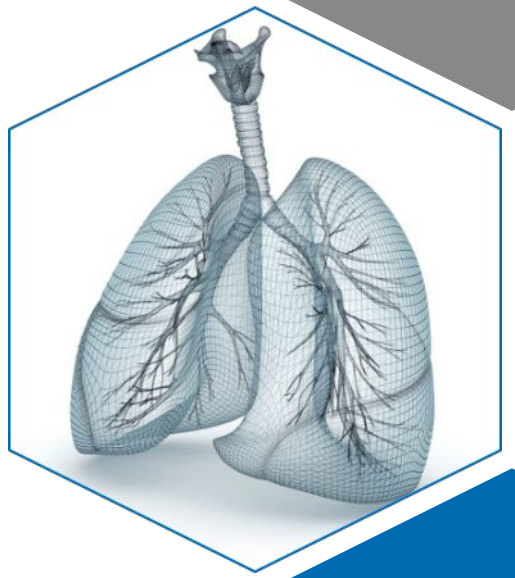
Thank you



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