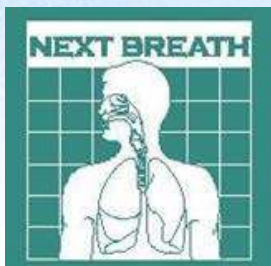


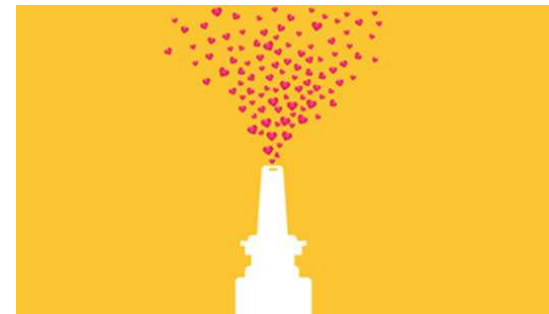
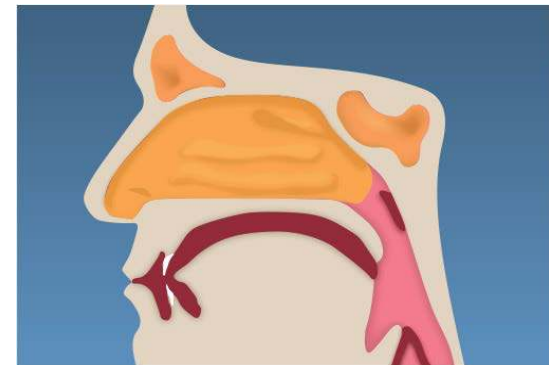
■ ■ Leveraging Old Drugs: A Critical Review of Delivery Systems and Life Cycle Management

■ ■ Julie D. Suman, PhD
Respiratory Drug Delivery Europe
May 7, 2015



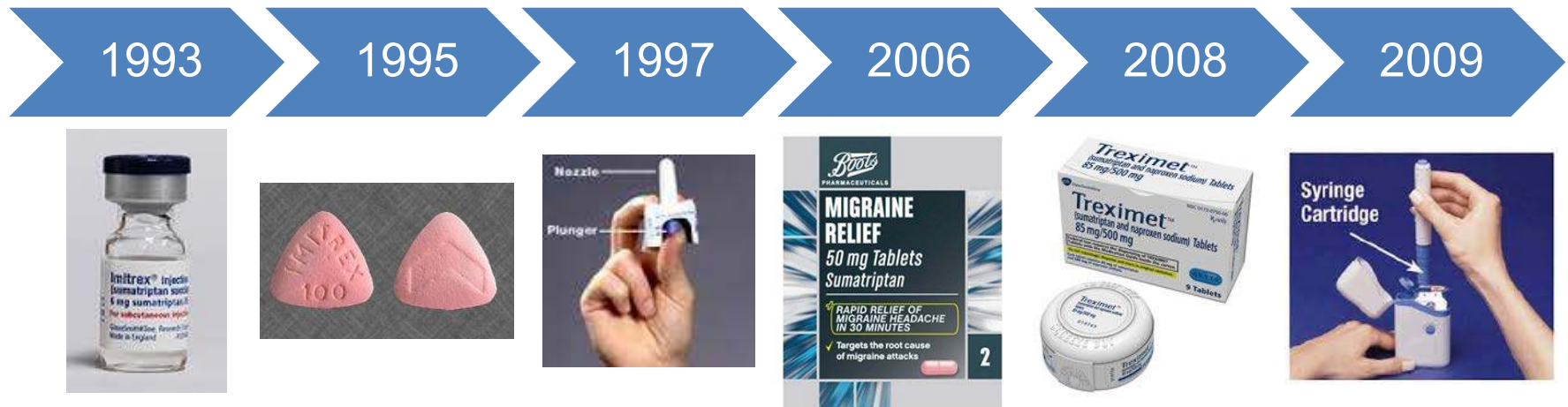
Presentation Outline

- ▣▣ Life Cycle Management (LCM)
- ▣▣ Benefits of Nasal Drug Delivery
- ▣▣ Challenges
 - ▣ Site of deposition
 - ▣ Retention
 - ▣ Absorption
- ▣▣ Overcoming Challenges
- ▣▣ Regulatory Considerations



LCM: Leveraging Old Drugs

- Reformulation, new route of administration, new indication
- OTC switch
- Regulatory pathway → US FDA 505(b)(2)
- Example: Sumatriptan

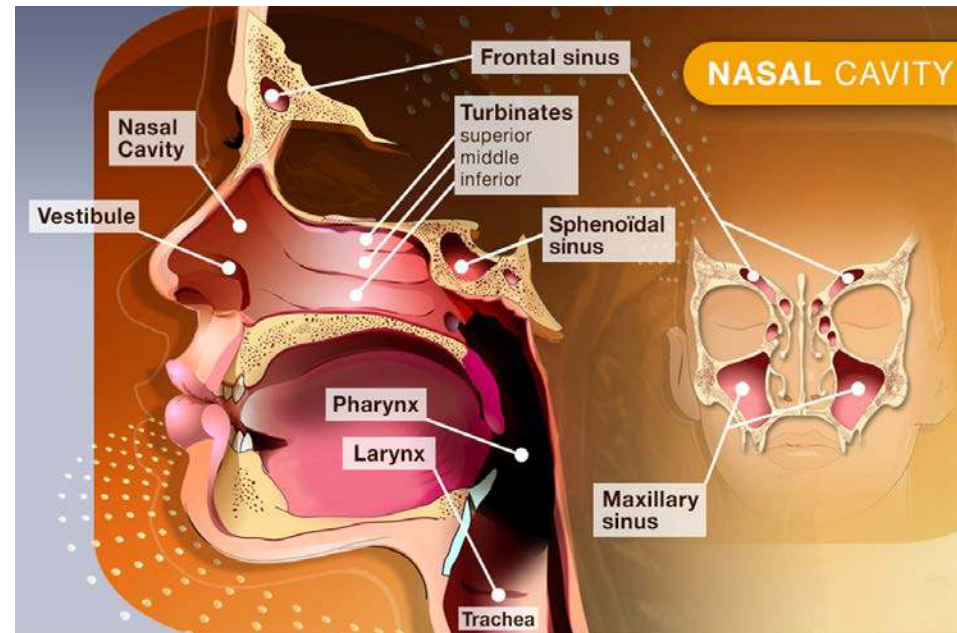


OTC (UK)

Ideal Drug Properties for (Systemic) Nasal Administration

- Lipophilic
- Low MW (<1kDa)
- Low degree of ionization

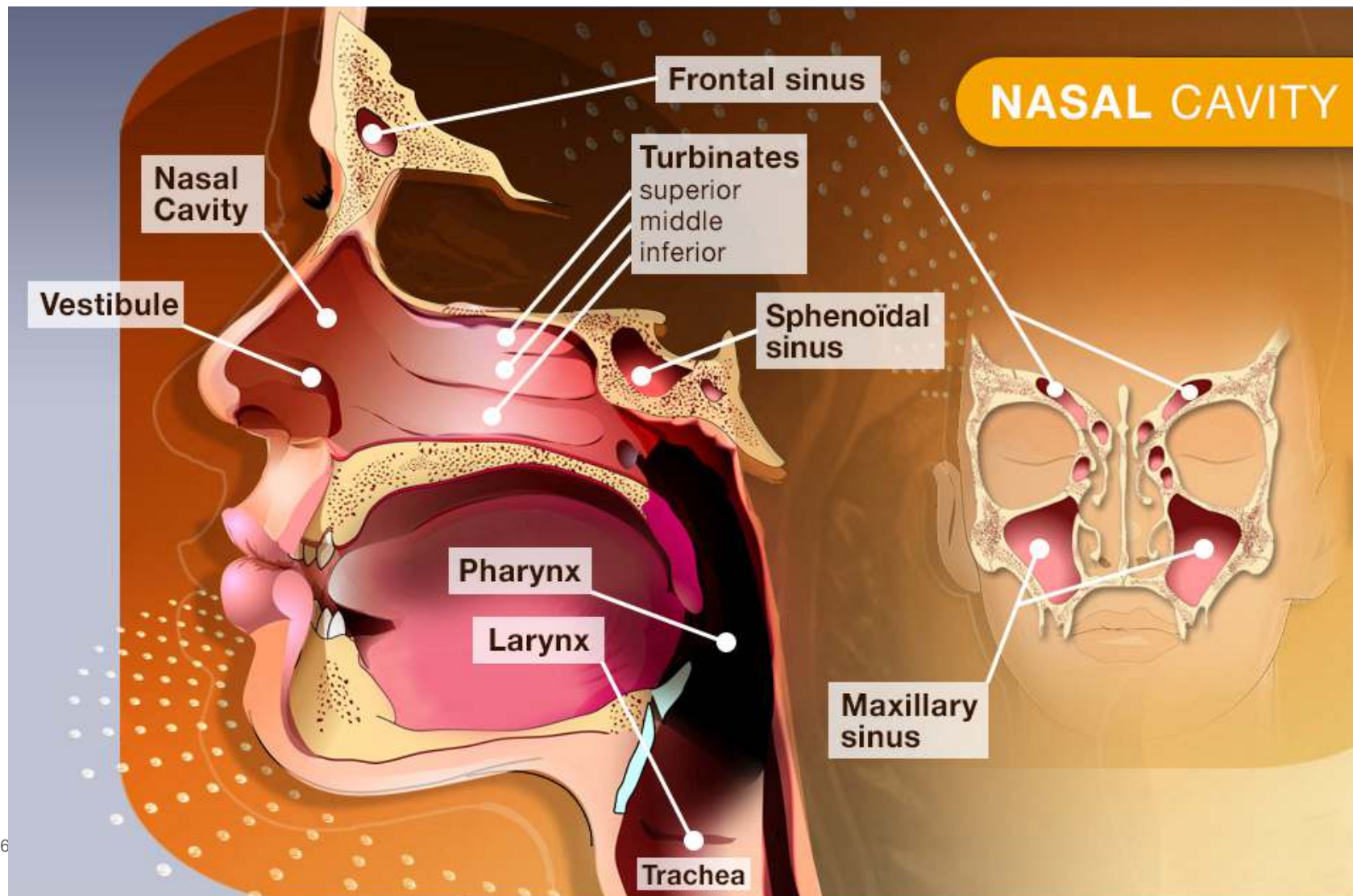
- Expected bioavailability
 - 20-90% for small molecules
 - 3-10% for large molecules



New Opportunities

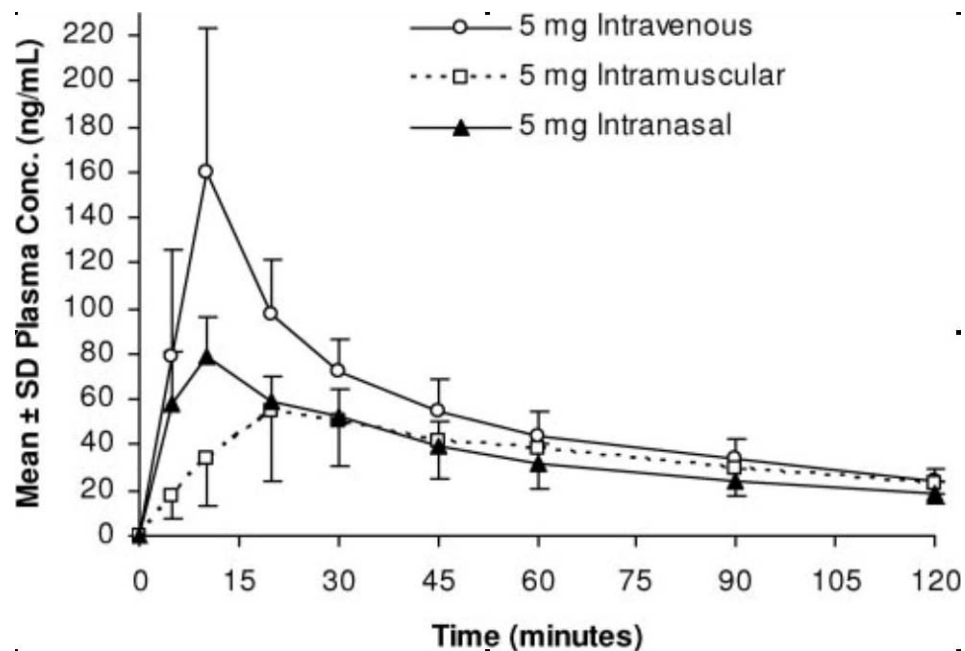
| Small Molecule | Large Molecule | OTC Switch |
|----------------------|--------------------|-----------------|
| Alzheimer's | Anticoagulation | Analgesia |
| Antimicrobial | Acromegaly | Diabetes rescue |
| Antiemetic | Cancer* | Pain |
| Anxiety | Endometriosis* | Sleep |
| Cardiovascular | Multiple Sclerosis | |
| Pain* | Neuroprotection | |
| Parkinson's | Obesity | |
| Seizures | Osteoporosis | |
| Sleep ^{*,b} | Vaccines | |

Targeting the Nose



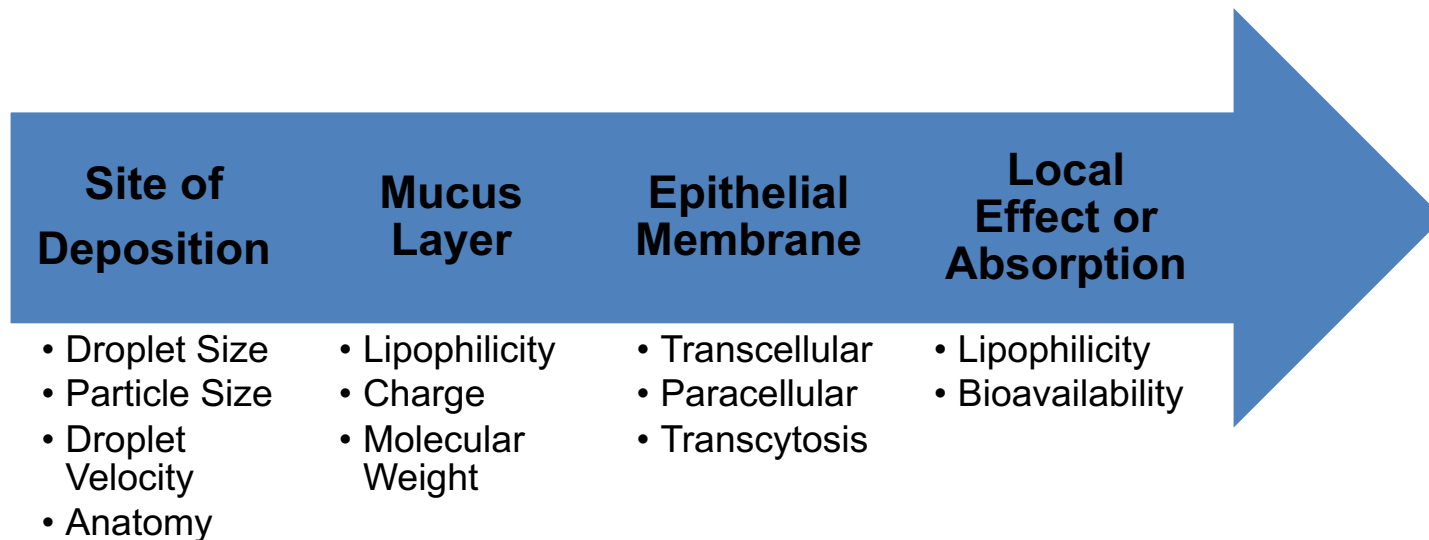
Rationale for Systemic Drug Delivery

- Large surface area
- Highly vascularized
- High permeability
- Limited local enzymatic distribution
- Avoids first pass hepatic metabolism
- Potentially rapid onset of action → achieve PK profile similar to injection



Wermeling, et. al., Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. *International Anesthesia Research Society* (2006)

Key Processes Affecting Nasal Drug Delivery

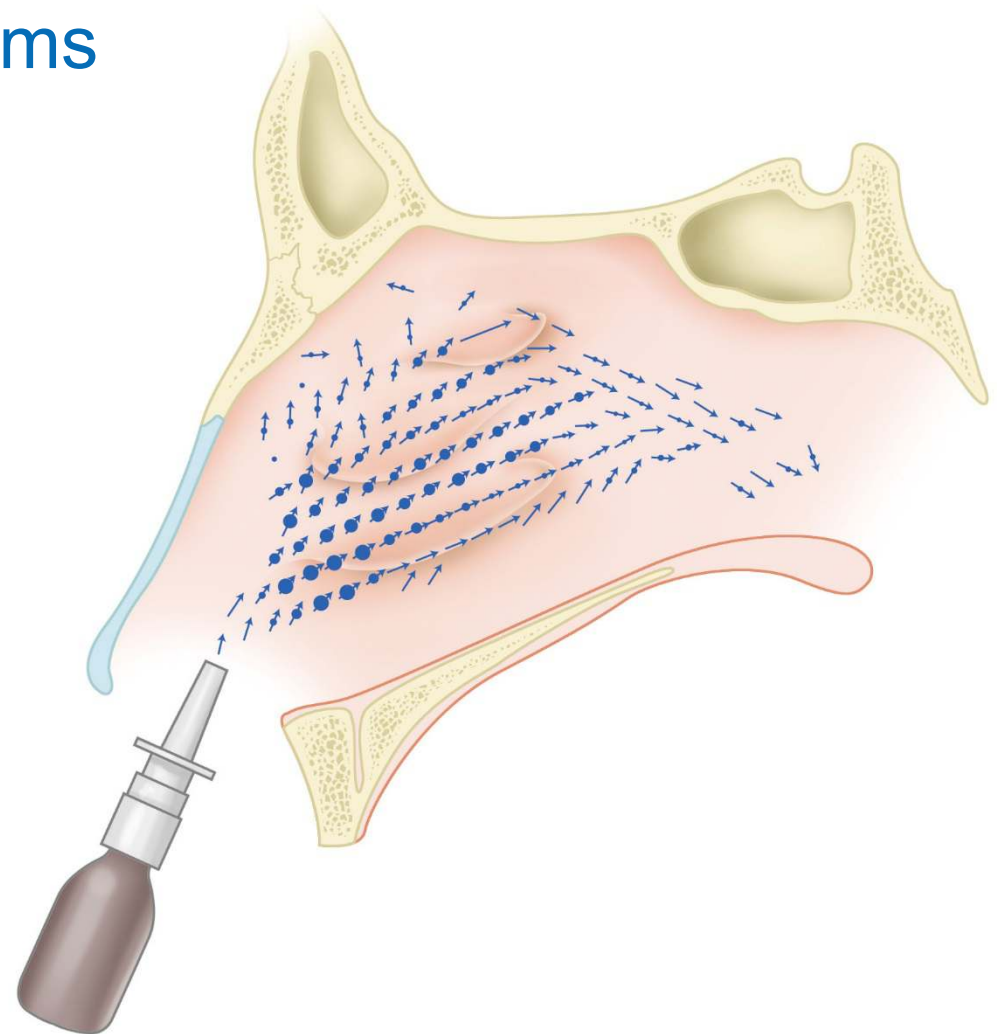


- First goal → Deposition in desired location
- Second goal → Retention within nasal cavity
- Third goal → Therapeutic effect

Deposition Mechanisms

- Impaction
(primary factor)
- Sedimentation
- Diffusion (related to olfaction)

- *Droplet size and velocity of droplets are key factors*

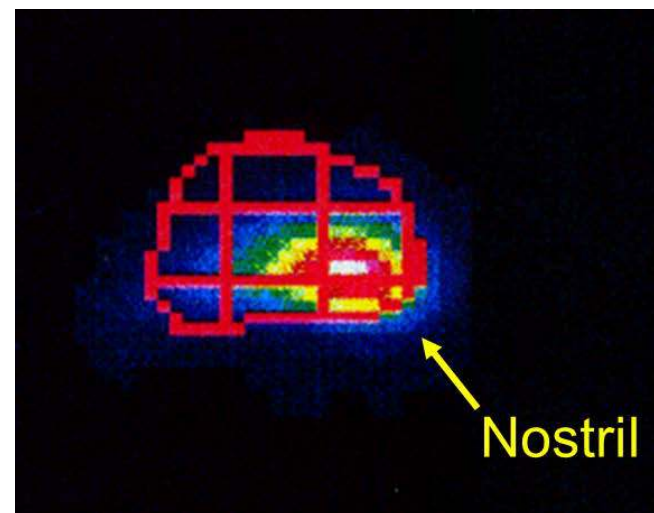
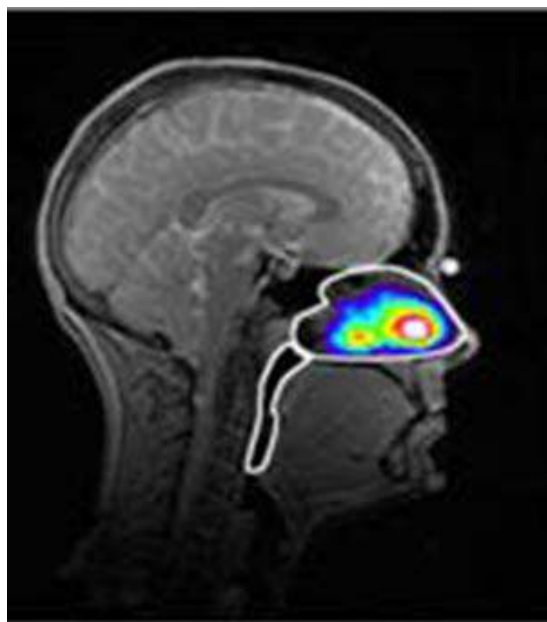


Velocity Vector Schematic



Aqueous Nasal Spray Typical Deposition Pattern

- Anterior deposition predominates

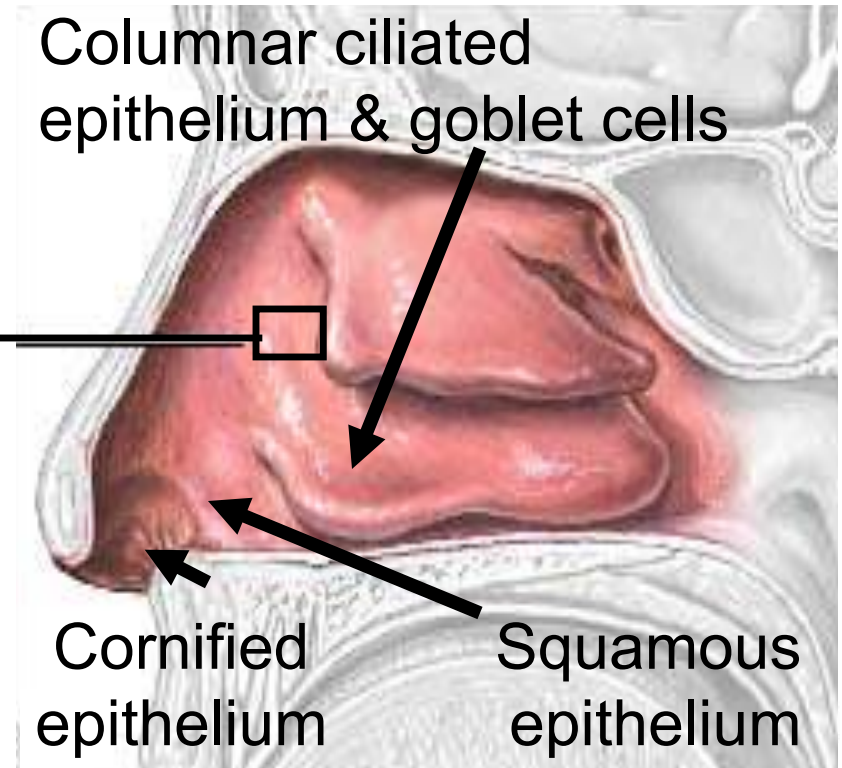
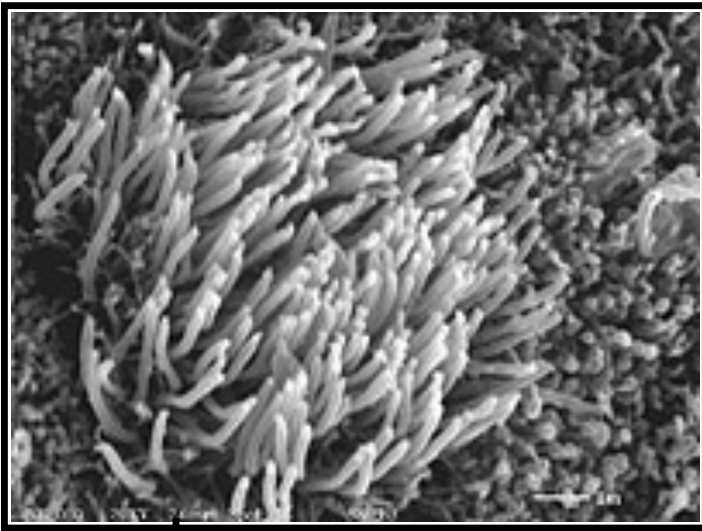


Shah, In Vivo Nasal Deposition from Different Delivery Devices and Formulations.

IPAC RS March 2011

10 Suman, RDDVIII 2002

Nasal Mucosa Histology



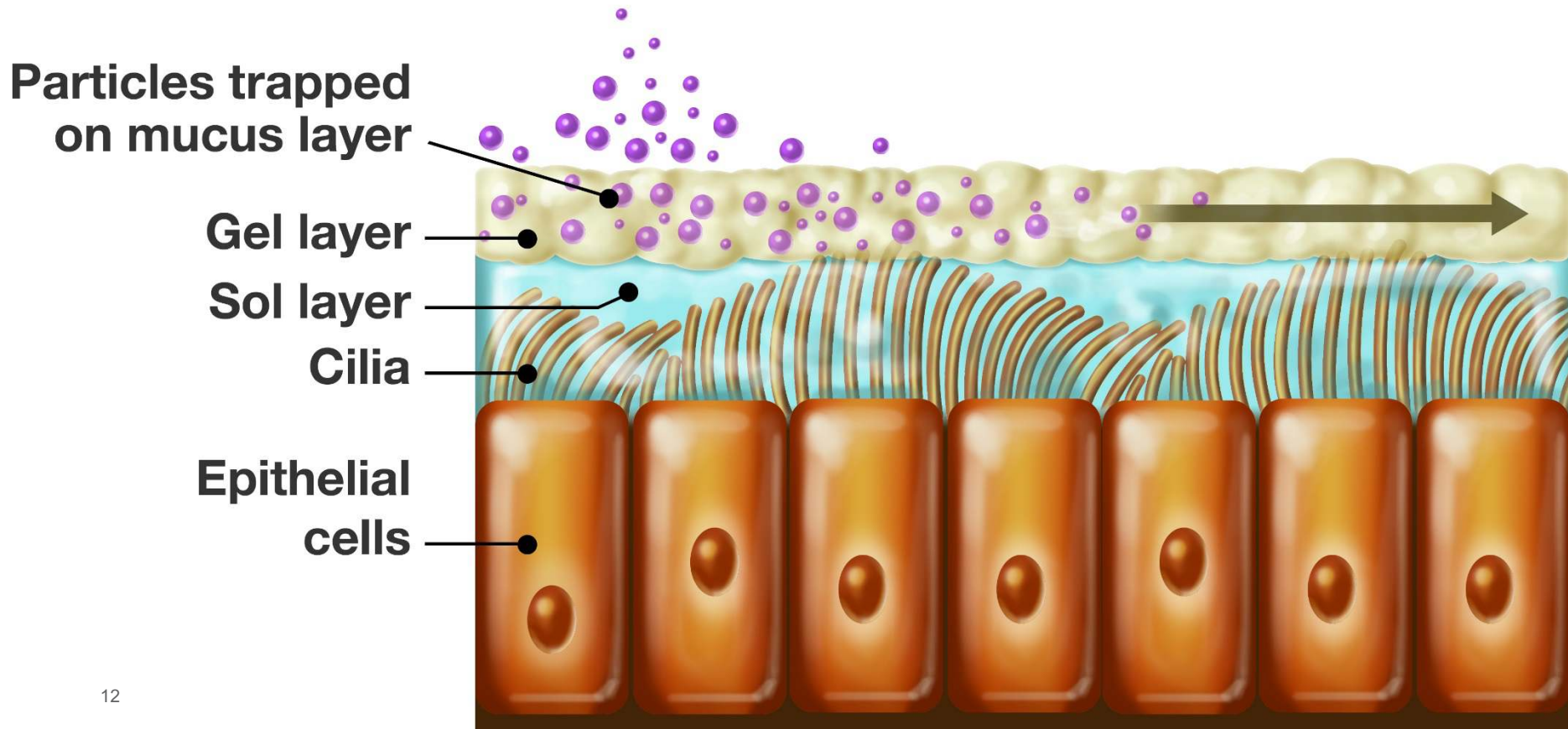
Columnar ciliated epithelium & goblet cells

Cornified epithelium

Squamous epithelium

Mucus Bilayer

- ❑ Mucociliary clearance rate 6mm/min
- ❑ Dissolution → mucus 95% aqueous

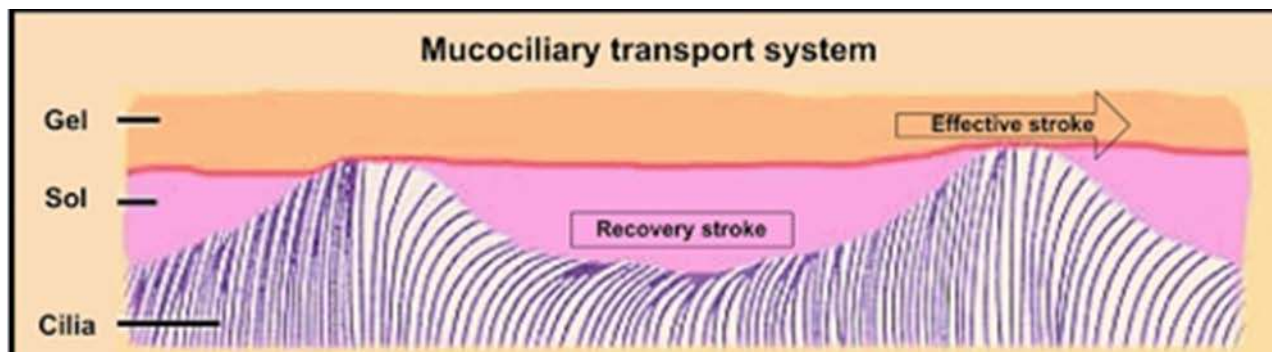


Lipophilicity

| Opioid | MW | logP | Bioavailability |
|-------------|-------|------|-----------------|
| Morphine | 284.3 | 0.8 | 10-22% |
| Butorphanol | 327.5 | 3.7 | 60-70% |
| Fentanyl | 336.5 | 4.1 | 89% |

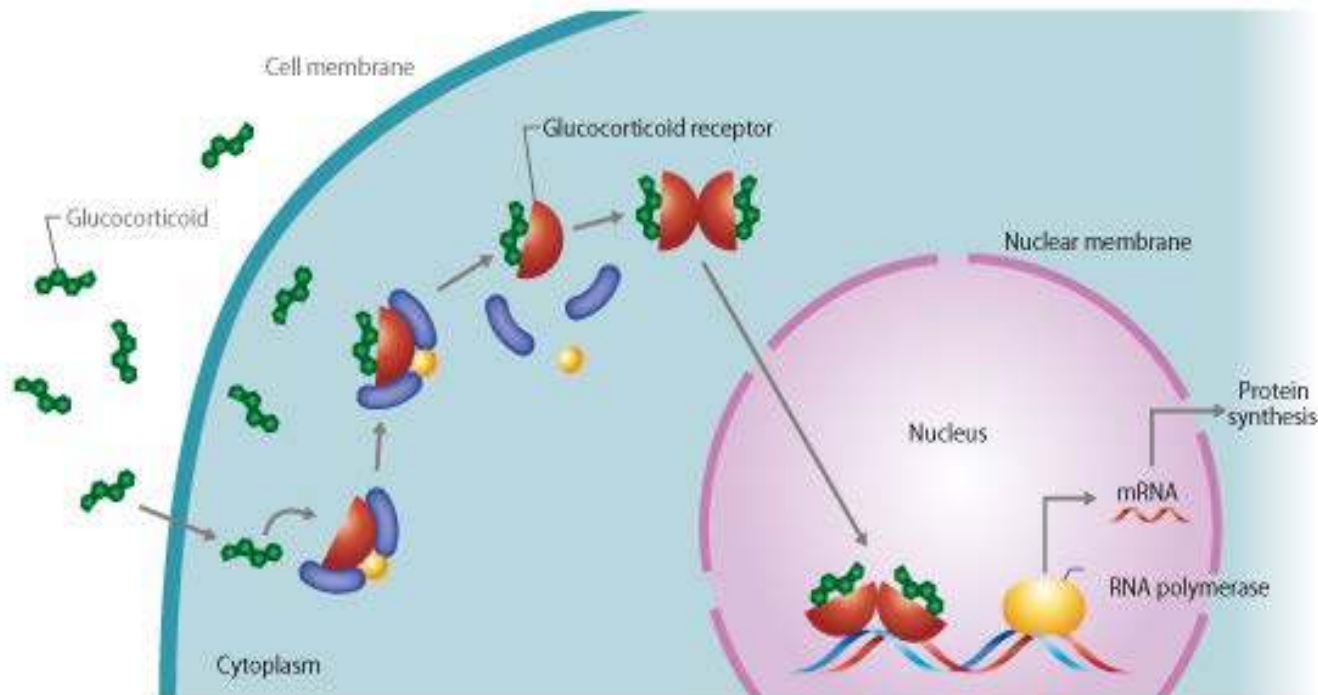
■ Morphine

- More hydrophilic
- Likely cleared faster as it resides in aqueous mucus layer



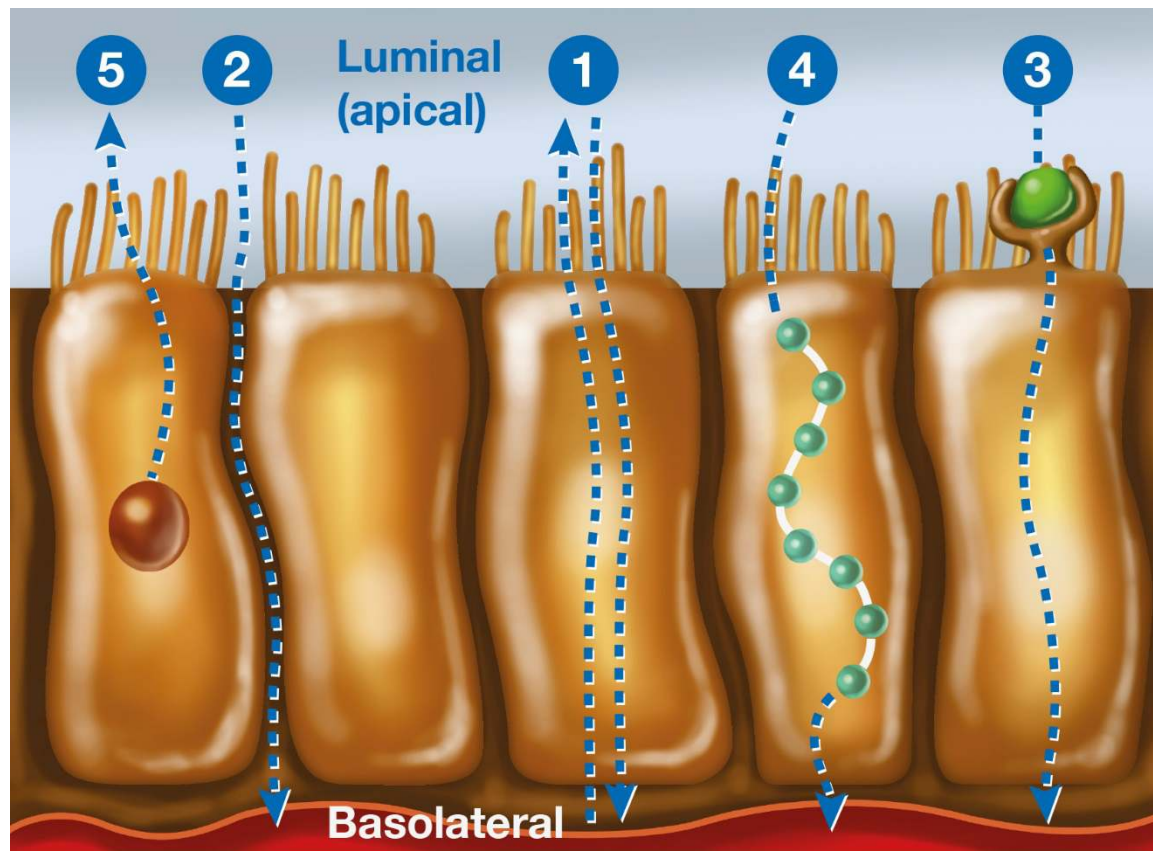
Epithelial Membrane

- Locally acting drugs
- Receptor interaction
 - e.g. glucocorticoid receptors



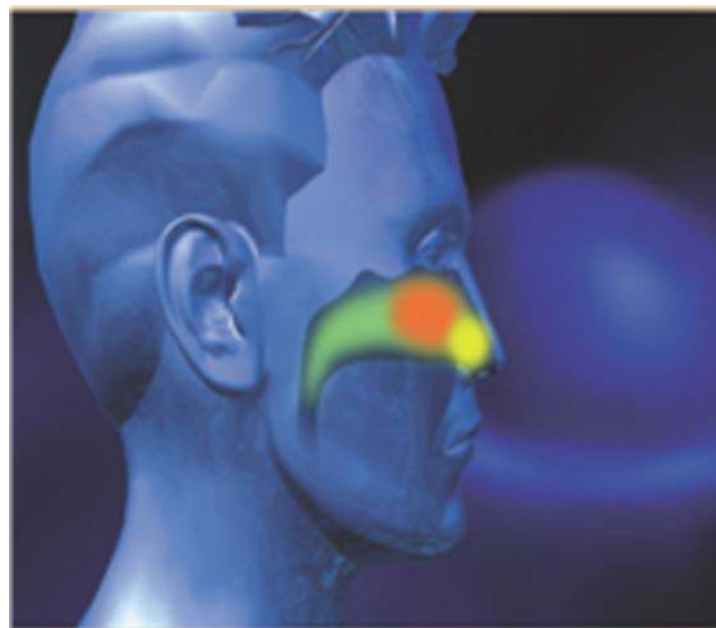
Transport Mechanisms

1. Transcellular diffusion
2. Paracellular
3. Active/carrier mediated
4. Transcytosis
5. Efflux
(p-glycoprotein does exist in nasal cavity)



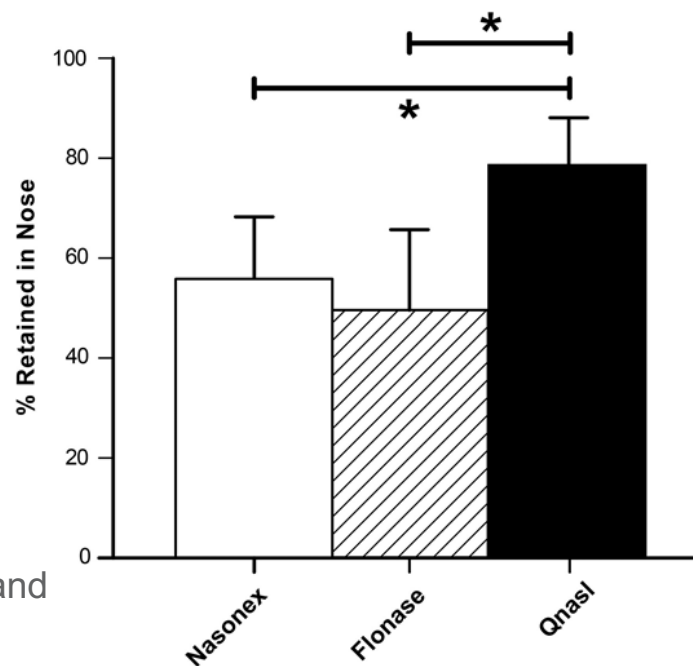
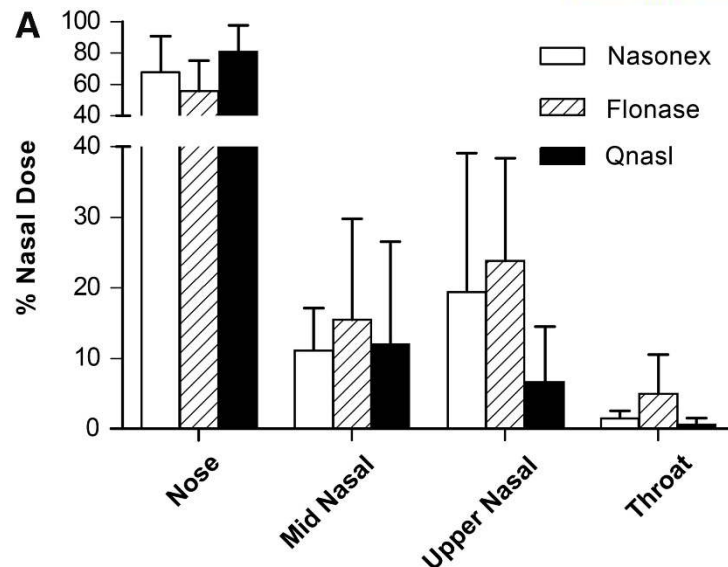
Overcoming Challenges

- Physical chemical properties of drug
- Device
- Formulation Strategy
 - Decrease enzymatic metabolism
 - Increase lipophilicity
 - Prolong retention
 - Improve transport
- Strategy may differ depend on local vs systemic indications



Changing Deposition Pattern

- Reduce droplet/particle size
- Reduce velocity
- Notes of caution:
 - Droplets/particles $<10\mu\text{m}$ can bypass nose and deposit in the lung
 - Increasing posterior deposition may increase rate of clearance



Leach, et. al., Nasal Deposition of HFA-Beclomethasone, Aqueous Fluticasone Propionate and Aqueous Mometasone Furoate in Allergic Rhinitis Patients. *JAMPD 2015*

Changing Deposition Pattern?

Alternative device technology

- Nasal powders
- Impel
- Kurve
- OptiNose



Aptar Pharma
BDS



Impel POD
Technology



OptiNose Powder
Delivery Device



OptiNose Liquid
Delivery Device



ViaNase

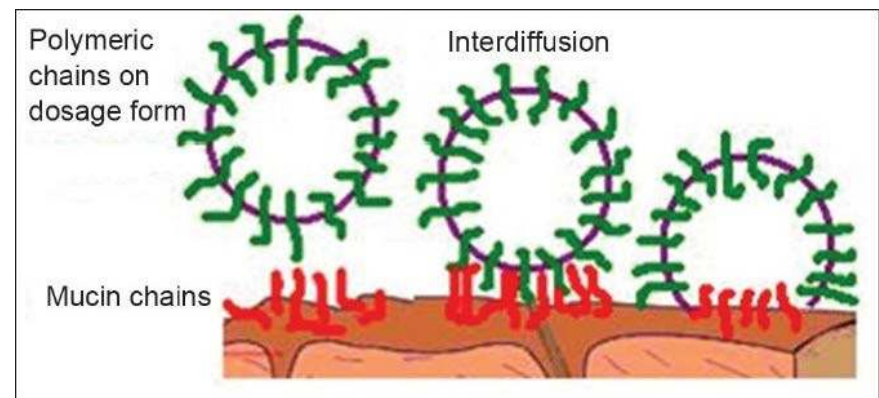
Promoting Retention and Absorption

❑ Permeation Enhancers

- Reversible modifications on the epithelial barrier structure
- Increase the membrane fluidity
- Create transient hydrophilic pores
- Decrease the viscosity of mucus layer
- Open the tight junctions

❑ Mucoadhesives

- Prolong retention in mucus layer
- Gelling polymers
- Electrostatic interactions
- Thixotropic viscous suspensions



Permeation Enhancers and Mucoadhesives

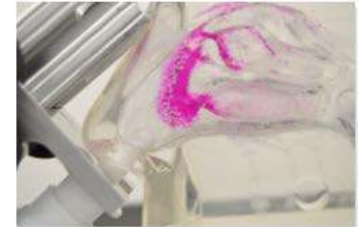
| Example | Function | Trade Name | Company | Applications |
|----------------------------------|-------------------|-----------------|--------------------------|------------------------|
| Cyclopenta Decalactone | Enhancer | CPE-215 | CPEX | Insulin |
| Alkylsaccharides | Enhancer | Intravail | Aegis | EPO, PTH, IFN- β |
| Chitosan | Enhancer Promoter | ChiSys | Archimedes | Vaccine, leuprolide |
| Pectin | Enhancer Promoter | PecSys; GelSite | Archimedes; ? | Fentanyl*; vaccines |
| Hydroxy fatty acid esters of PEG | Enhancer | CriticalSorb | Critical Pharamceuticals | hGH, PTH, insulin |

*Commercially available, Lazanda/PecFent

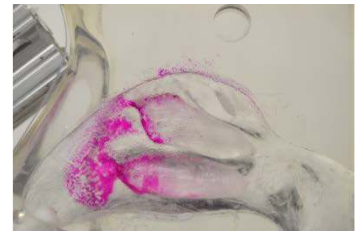
Excipients for Tuned Mucosal Delivery and Retention

- METHOCEL™ cellulose ethers (MC) are sprayable at room temperature and a gelled formulation at body temperature
- MC grades allow for tailored deposition patterns and viscosity properties tuned by polymer concentration and molecular weight
- MC polymer gelation can aid in retention on mucosal surfaces
- Gelation temperature can be tuned with formulation additives, polymer design, concentration and molecular weight

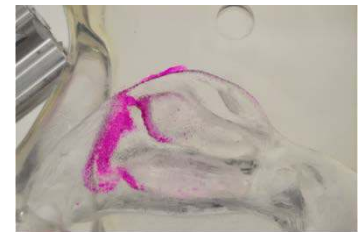
Mid-Range MC 1.25%



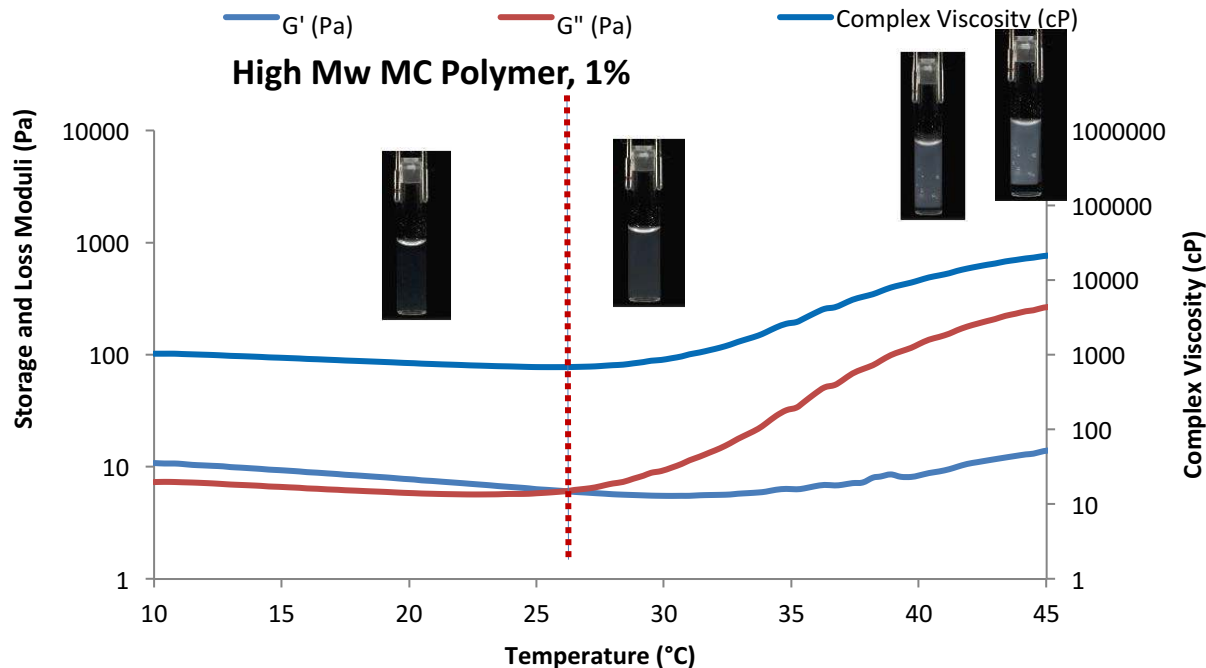
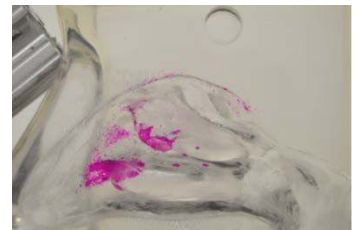
High MC 0.5%



High MC 1.0%



High MC 1.5%



*Data courtesy of The Dow Chemical Company

Regulatory Considerations

- ■ Novel excipients
 - Safety and toxicology
 - Long term effects
 - Reversibility

- ■ New device platforms
 - Deposition
 - Rate of mucociliary clearance
 - Lung deposition?



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



Summary

- ❑ Opportunities for local and systemic indications exist
- ❑ LCM strategies may involve increased risk
 - New device platform
 - Novel excipient
- ❑ Candidate selection
 - Understand key properties that drive absorption
 - Overcome challenges through optimizing physical chemistry properties of drug and formulation



Thank you for your attention!

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