AIMS OF THE LECTURE

✓ To give an overview of the uptake and translocation of particulate drug carriers at the main mucosal sites, and describe the absorption mechanisms;

✓ To describe the therapeutic applications of biodegradable microspheres and nanoparticles as drug and vaccine carriers, administered via the mucosal surfaces;

✓ To emphasize the role of the nasal and the pulmonary mucosal routes for the administration of drug-containing particulate carriers.
The **magic bullet** concept

The term used to describe a specific cure for syphilis, which would attack the syphilis spirochaete while having no effect whatsoever on human tissue.

Paul Ehrlich (1854-1915)

“**Magic bullets revisited:**
*from sweet dreams, via nightmares to clinical reality***
### Rationale for Site-Specific Drug Delivery

- Exclusive delivery to specific compartments (and/or diseases)
- Access to previously inaccessible sites (e.g. intracellular infections)
- Protection of drug and body from unwanted deposition, which could lead to unwanted reactions and metabolism, etc.
- Controlled rate and modality of delivery to pharmacological receptor
- Reduction in the amount of drug employed

↑ Drug safety  
↑ Drug efficacy  
↑ Patient compliance

---

**Target site**  
**Carrier**

**Other sites**  
**Drug**

---

*Adapted from Puisieux and Roblot-Treupel (1989) STP Pharma*
MAIN DRUG TARGETING SYSTEMS

- Soluble carriers (monoclonal antibodies, dextrans, soluble synthetic polymers)
- Particulate carriers (liposomes, microspheres, nanoparticles, micelles, etc.)
- Target-specific recognition moieties (monoclonal antibodies, carbohydrates)
- Antibody-directed enzyme/prodrug therapy
- Virus-directed enzyme/prodrug therapy

MAIN ROUTE OF ADMINISTRATION FOR DRUG TARGETING

Parenteral Administration

- Unpleasant drug administration route
- Low patient compliance
- Intravenous injections may only be given by qualified medical professionals
- Usually associated with short-term effects
- Need for final sterilisation or aseptic processing.

Need for alternative administration routes
MUCOSAL DRUG DELIVERY

Mucosal Delivery
- Ocular delivery
- Nasal
- Pulmonary
- Buccal
- Sublingual
- Gingival
- Rectal
- Vaginal

Oral Delivery
- GI absorption
- Portal circulation
- First-pass
- Liver
- Target Tissue
- Pharmacological Response

Systemic circulation

MUCOSAL DRUG DELIVERY

<table>
<thead>
<tr>
<th>Feature</th>
<th>Parenteral</th>
<th>Oral</th>
<th>Dermal</th>
<th>Buccal</th>
<th>Pulmonary</th>
<th>Nasal</th>
<th>Vaginal</th>
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<tr>
<td>Accessible</td>
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<tr>
<td>Patient acceptability</td>
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<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Rate of uptake</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Surface area</td>
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<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Blood supply</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Enzyme activity</td>
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<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>First-pass effects</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Permeability</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Reproducibility</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clearance mechanisms</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+/++/+++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

A.J. Almeida, 2007

Chien (1992) Novel Drug Delivery Systems

Hillery (2001) In: Drug Targeting and Delivery
**EVIDENCE OF MICRORGANISMS’ UPTAKE AT MUCOSAL SITES**

**Bacteria**
- *Campylobacter jejuni*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Mycobacterium bovis*
- *Neisseria meningitidis*
- *Shigella flexneri*
- *Salmonella typhi*
- *Vibrio cholerae*
- *Yersinia enterocolitica*

**Viruses**
- *Reovirus*
- *Poliovirus*
- *HIV-1*

**Protozoa**
- *Cryptosporidium*

---

**EARLIER EVIDENCE OF PARTICLE UPTAKE AT THE GI TRACT**

- **Herbst, 1844** - Penetration of particles through the wall of the gastrointestinal tract into the blood and lymph vessels.
- **Hirsch, 1906** - Observation that raw starch fed to rats was absorbed across the intestinal mucosa.
- **Payne et al, 1960** - Intestinal and subsequent hepatocellular uptake of 1-5 μm particles.
- **Volkheimer, 1960’s** - First quantitative studies on intestinal uptake of particles ≤120μm, as a regular process, even in human beings; process called **persorption**.
- **LeFèvre et al, 1970’s** - Demonstration that GALT was the route of entry of latex particles.
- **Jani et al, 1990’s** - Further demonstration and clarification of the uptake process.

“It must be currently regarded that colloidal particles are not able to traverse the epithelium of the gastrointestinal tract intact or in a manner significant for drug use, except under exceptional and unusual circumstances”.

Paracellular event occurring in the gut.

Several particulate materials were regularly demonstrable in blood and urine after peroral administration including:

- Corn starch (3-25 \( \mu \text{m} \))
- Rice starch (3-10 \( \mu \text{m} \))
- PVC particles (5-100 \( \mu \text{m} \))

Speculation that uptake resulted from the muscular activity in the mucosa, resulting in the ‘kneading’ of the particles between the cells at the desquamation zones of the intestinal villi.

**EPITHELIAL STRUCTURES**

- Simple epithelia
- Stratified epithelia
THE COMMON MUCOSAL IMMUNE SYSTEM

DETERMINANTS OF PARTICLE UPTAKE
**ROUTES AND MECHANISMS OF DRUG TRANSPORT ACROSS EPITHELIA**

**PARACELLULAR ROUTE**
- Paracellular diffusion

**TRANSCELLULAR ROUTE**
- Passive diffusion
- Carrier-mediated transport
- Endocytic process

\[
\frac{dm}{dt} = D_k \frac{A \cdot \Delta C}{h} = P \cdot A \cdot \Delta C
\]

**INTERACTION OF PARTICULATE CARRIERS WITH MUCOSAL SITES**

Interaction with mucus

- surface tension
- wettability
- ionisable surfaces (\(\xi\)-potential)
- particle size

\[
P = \frac{kT}{6 \pi \eta r h}
\]

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Hillery (2001) In: Drug Targeting and Delivery

PARTICLE UPTAKE AT THE GI TRACT

500 nm fluorescent latex nanoparticles adhering to lymphoid tissue

500 nm fluorescent latex nanoparticles adhering to non-lymphoid tissue


Review
The Oral Absorption of Micro- and Nanoparticulates: Neither Exceptional Nor Unusual

Alexander T. Florence1,2

Received December 5, 1996; accepted January 2, 1997

This mini-review reviews some of the historical and recent arguments over the experimental evidence on the uptake by and translocation from the intestinal mucosa of nanoparticles after oral administration. It is concluded that there is now no dispute over the fact that this is a normal occurrence. Particulate uptake does take place, not only via the M-cells in the Peyer’s pouches and the isolated follicles of the gut-associated lymphoid tissue but also via the normal intestinal enterocytes. Factors affecting uptake include particle size, surface charge and hydrophobicity and the presence or absence of surface ligands. The critical attraction of enteric or inflamed macrophages to the surface of certain particles leads to greater systemic uptake. Whether or not this can be achieved for the passive administration of therapeutic agents which are not normally absorbed from the gut or not very easily. Many studies show that 2-5% of the ingested dose of substances particles can be absorbed. The increasing absence of enteric systems, especially in the case of non-absorbable substances, leads to be exploited fully. More also must be known about the size and non-specific variability of lymphoid tissue so that appropriate selectivity can be achieved through the design of specific carriers.

KEY WORDS: nanoparticles, Peyer’s patch, CALT, particle absorption, oral delivery, lymphatics.
MAIN DETERMINANTS OF PARTICLE UPTAKE

- Factors prior to uptake
  - Physical and chemical stability of the particles and drug at the mucosal site
  - Residence times in regions of particle uptake
  - Interaction with mucosal contents
  - Transport through mucus
  - Adhesion to epithelial surfaces

- Particle diameter (<5 μm, preferably in the submicron range)
- Surface charge (mixed effect)
- Surface hydrophobicity (adsorbed hydrophilic materials influence uptake)
- Presence of specific ligand (lectins, invasins, CTB, Vitamin B12)
- Vehicle volume and tonicity
- Diet (oral route)
## Particle Size

<table>
<thead>
<tr>
<th>Particulate system</th>
<th>Species</th>
<th>Site</th>
<th>Diameter (μm)</th>
<th>Extent of Absorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene</td>
<td>rat</td>
<td>Intestine</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>PLGA</td>
<td>mouse</td>
<td>Intestine</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Polystyrene</td>
<td>rat</td>
<td>Intestine</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Polystyrene</td>
<td>rabbit</td>
<td>Nasal mucosa</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Polystyrene</td>
<td>mouse</td>
<td>Nasal mucosa</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

### Reference:
- Jani et al (1990) *J Pharm Pharmacol*
- Norris and Sinko (1997) *J Appl Poly Sci*

## Extent of Absorption

**Alpar et al (1989)**
- Polystyrene 1.1: 39% (Microscopy)

**Ebel (1990)**
- Polystyrene 2.65: 0.01% (FACS)

**Jani et al (1990)**
- Polystyrene 1: 5% (GPC)

**Hillery et al (1994)**
- Polystyrene 0.06: 10% (GPC)

**Florence et al (1995)**
- Plain Polystyrene 0.5: 4.28%
- Carboxylated Polystyrene 0.5: 0.1%
- Lectin-Polystyrene 0.5: 12.8%

**Desai et al (1996)**
- PLGA 0.1: 30–49% (PP: 28–35 NPP)
- PLGA 0.5: 0.11–0.12% (PP: 0.06–0.27 NPP)
- PLGA 1: 1.5–7.45% (PP: 0.01 NPP)

**Flourescence**
- PLGA 10: 0.8–1.33% (PP: 0.26–0.48 NPP)

**Damgé et al (1996)**
- PLGA 1–5: 12.7% (Flourescence)
SURFACE HYDROPHOBICITY OF DRUG CARRIERS

Determinant role on:

- Interaction with drugs;
- Interaction of carriers with cells in vitro;
- Interaction with phagocytes;
- MPS clearance of i.v. administered particulate carriers.

Mechanism of uptake at mucosal surfaces

In vivo distribution

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SURFACE HYDROPHOBICITY

Absorption of 1-10 μm microspheres

<table>
<thead>
<tr>
<th>Microsphere excipient</th>
<th>Absorption by the Peyer’s patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene</td>
<td>very good</td>
</tr>
<tr>
<td>Poly(methyl methacrylate)</td>
<td>very good</td>
</tr>
<tr>
<td>Poly(hydroxybutyrate)</td>
<td>very good</td>
</tr>
<tr>
<td>Poly(L-lactide)</td>
<td>good</td>
</tr>
<tr>
<td>Poly(DL-lactide)</td>
<td>good</td>
</tr>
<tr>
<td>Poly(DL-lactide-co-glycolide) 85:15</td>
<td>good</td>
</tr>
<tr>
<td>Poly(DL-lactide-co-glycolide) 50:50</td>
<td>good</td>
</tr>
<tr>
<td>Cellulose acetate hydrogen phthalate</td>
<td>none</td>
</tr>
<tr>
<td>Cellulose triacetate</td>
<td>none</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>none</td>
</tr>
</tbody>
</table>

Uptake of 60 nm polystyrene nanoparticles

SURFACE HYDROPHOBICITY (HIC)

Retention in column (%)

Stationary phase

- Polystyrene
- PLGA-AcEt
- PLGA-DCM

Stationary phase

- Polystyrene
- PLA-Tween 80
- PLA-PVA

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Azevedo and Almeida (1998) Proceed III Spanish-Portuguese Conf Cont Rel

INFLUENCE OF SURFACE CHARACTERISTICS

Uptake and tissue distribution of PLA nanospheres (137-156 nm) after nasal administration to rats

% Original Dose/g Blood

Time (hour)

1 2 6 24 48

% Original Dose/g Tissue

Lymph nodes Liver Spleen Lung Small bowell

- PLA Nanospheres
- PLA-PEG Nanospheres
- Control (TT solution in PBS)

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SURFACE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Nanoparticles</th>
<th>Size (nm)</th>
<th>Uptake without mucus (Caco-2 cells)</th>
<th>Uptake with mucus (MTX-E12 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polystyrene</td>
<td>213 ± 8</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>PLA-PEG</td>
<td>196 ± 20</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chitosan</td>
<td>290 ± 7</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>


INFLUENCE OF SPECIFIC LIGANDS

Tomato lectin
(0.5 μm polystyrene particles)

Specific Ligands
- Lectins
- Bacterial invasins
- Vitamin B12
- Cholera toxin B-subunit (CTB)
- Monoclonal antibodies

**INFLUENCE OF VEHICLE**

Uptake and translocation of polystyrene particles (0.87 μm) from the GI tract

![Graph showing the influence of vehicle on uptake and speed of uptake](image)

**INFLUENCE OF AGE**

Bacterial colonisation (BC) and translocation (BT) of bacteria in rabbit GI tract

![Graph showing the influence of age on bacterial growth](image)
INFLUENCE OF DIET

Uptake and translocation of polystyrene particles (1.9 μm) from the GI tract

THE NASAL ROUTE
**Physiological Role of the Nose**

**Olfative Function**

**Respiratory Function**
- Filtering, warming, and humidifying the inhaled air.
- Inhaled droplets or particles become trapped by hair in the nasal vestibule or by the mucus layer in the main cavity.
- Metabolic capacity for converting materials into compounds that are more easily eliminated from the body.

**Protective Function**
- Filtering, warming, and humidifying the inhaled air.
- Inhaled droplets or particles become trapped by hair in the nasal vestibule or by the mucus layer in the main cavity.
- Metabolic capacity for converting materials into compounds that are more easily eliminated from the body.

**Main Features**
- The nasal cavity has a large surface area (200 cm²) readily accessible for drug absorption.
- Highly vascularized underlying epithelium.
- Drugs can reach widespread circulation within a few minutes after dosing.
- Plasma profiles and bioavailability are often comparable to those obtained from an intravenous injection.

**Historical and behavioural use**
- Mucosal diseases:
  - local effect to restore normal conditions
- Behavioural habit:
  - Tobacco, cocaine, etc.
ABSORPTION AT THE NASAL MUCOSA

Propanolol

PHYSIOLOGY OF THE NASAL CAVITY

http://www.distance.mun.ca/media/samples/cilia/
DEVELOPMENT CHALLENGES

- Small lipophilic molecules are easily absorbed.
- Limiting factors of nasal absorption are the polar nature and the larger size of drug molecules.
- Conventional polar drug molecules and hydrophilic biopharmaceuticals (peptides, proteins, carbohydrates, antisense agents, genes) present special drug delivery challenges.
- Most peptides and proteins have shown poor bioavailability of ≤1%.
- Drug molecules may be unstable due the presence of enzymes.
- The mucus layer represents an additional barrier to absorption.
- The mucociliary clearance mechanism leads to a short residence time at the site of absorption.

DEVELOPMENT CHALLENGES

Nasal delivery of peptides and proteins

- Nasal salmon calcitonin
- Nasal by Novartis
- Novel nasal formulations under development by other pharmaceutical companies
- Nasal desmopressin
- Marketed by Ferring and partners
- Nasal glucocorticoids
- Marketed by Aventis
- Nasal terbutaline
- Marketed by Serlet
- Nasal PTH, nasal leuprolide, nasal insulin, nasal interferon, etc.
- In clinical trials
FACTORS AFFECTING THE EFFICACY OF INTRANASAL DELIVERY

Physiological conditions of nasal vaculature
- Mucus layer barrier
- Mucociliary clearance / speed of mucus flow
- Enzymatic activity / degradation
- Effect of pathological condition (ex. infection)
- Atmospheric conditions

Dosage form factors
- Molecular weight
- Drug concentration, dose and dose volume
- Physicochemical properties of drug (ex. permeability)
- Density of dosage form
- Viscosity of dosage form
- pH
- Buffer capacity
- Osmolarity of dosage form (liquid preparations)
- Excipients

Techniques/devices for administration
- Size of droplets or solid particles
- Site of deposition
- Rate of clearance

FACTORS AFFECTING DRUG ABSORPTION

Molecular Weight vs. % of Absorption

pH (4.5-6.5) vs. Absorption

A.J. Almeida, 2007
Washington et al. (2001) Physiological Pharmaceutics
FACTORS AFFECTING DRUG ABSORPTION

pH / Effect of buffers

![Graphs showing pH effect on drug absorption]

Figure 9.9: Effect of buffers on nasal pH. Anterior pH black line and posterior pH grey line.

FORMULATIONS FOR NASAL ADMINISTRATION

MAIN REQUIREMENTS

- Stable.
- Non-irritant, non-toxic.
- Non-odorous.
- Achieve optimum delivery as solutions, suspensions or dry powders when applied in the form of the following nasal delivery systems: drops, sprays, gels, powders.

A.J. Almeida, 2007

Washington et al. (2001) Physiological Pharmaceutics
FORMULATIONS FOR NASAL ADMINISTRATION

OVERCOMING BARRIERS

- Structural modification of drugs
- Salt or ester formation
- Formulation design
  - Gelling / viscosity enhancers or gel-forming carriers
  - Bioadhesive systems
  - Solubilizers (glycols, ethanol, Transcutol®, Cyds)
  - Preservatives (toxicidade do Hg)
  - Antioxidants
  - Humectants (sorbitol, glycerol)
  - Absorption enhancers (Cyds, PEG, surfactants, chitosan)

Inhibit enzyme activity
Reduce mucus viscosity or elasticity
Decrease mucociliary clearance
Open tight junctions
Solubilize or stabilize the drug

Gelling / viscosity enhancers or gel-forming carriers

OVERCOMING BARRIERS

Viscosity Enhancers

CHITOSAN

✓ Cationic a low toxicity bioadhesive biopolymer.
✓ Derived from shellfish chitin.
✓ Chitosan is produced by a well defined process, under GMP conditions
✓ Chemically is a linear polysaccharide formed from monomers of glucosamine and N-acetyl glucosamine.
✓ DMF for chitosan has been submitted to the FDA.
✓ Chitosan has been submitted for inclusion in the Ph.Eur.

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CHITOSAN

ChiSys®

A.J. Almeida, 2007
NASAL DELIVERY SYSTEMS

Liquid nasal formulations

- Instillation and rhinyle catheter
- Drops
- Unit-dose containers
- Squeezed bottle
- Metered-dose pump sprays
- Airless and preservative-free sprays
- Compressed air nebulizers

Powder dosage forms

- Insufflators
- Mono-dose powder inhaler
- Multi-dose dry powder systems

Pressurized MDIs

Nasal gels

Liquid versus Powder Formulations

Fig. 1. Flubaseo<sup>TM</sup> (Salmeterol xinafoxime/CMC). Powder: 50 mcg/1 day vs. Drops: 105 mcg/1 day. Allergic rhinitis, seasonal versus chronic (uniliated).

Fig. 3. Plasma concentration of eTD after nasal administration of MCC powder preparation or spray formulation to healthy.

A.J. Almeida, 2007

Images from Pharmaceutical Profiles
NASAL DELIVERY SYSTEMS

Liquid nasal formulations
- Instillation and rhinyle catheter
- Drops
- Unit-dose containers
- Squeezed bottle
- Metered-dose pump sprays
- Airless and preservative-free sprays
- Compressed air nebulizers

Powder dosage forms
- Insufflaters
- Mono-dose powder inhaler
- Multi-dose dry powder systems
Particle Size

- Particle sizes >10 µm are deposited in the nasal cavity
- Particles that are 2 to 10 µm can be retained in the lungs and particles <1 µm are exhaled

Earlier evidence of particle uptake at the nasal cavity

- **Bull and McKee, 1929** - Intranasal vaccination of rabbits with a suspension of killed pneumococci resulted in protection against experimental infection.

- **Peters and Allison, 1929** - Nasal administration of antigens for immunisation against scarlet fever.

- **Perkins et al, 1969** - Immunisation of male volunteers against an inactivated strain of rhinovirus resulted in protection of the individuals.

- **Chen et al, 1989** - Uptake of carbon particles by the respiratory mucosa associated lymphoid tissue in sheep.

- **Alpar et al, 1994** - Polystyrene particles found in blood circulation after nasal administration to rats.
For its convenience, the nasal cavity has been considered as a route of administration for many decades, often for topical therapies such as decongestants.

The nasal mucosae presents a good blood supply that allows systemic absorption.

Immune responses elicited by intranasal vaccination are generally substantially stronger than those induced by the same antigens delivered orally.

Systemic immune responses, in addition to local immune responses, are generally easier to achieve by intranasal delivery than by oral delivery.

Mucosal response

SlgA

NALT

PCL

NALT

MLN

PARTICLE UPTAKE AT THE NALT AND ANTIGEN PROCESSING

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IMMUNE RESPONSE AFTER NASAL DELIVERY OF TETANUS TOXOID

Uptake of 0.51 µm polystyrene particles after nasal administration to rats

PARTICLE UPTAKE AT THE NASAL CAVITY
PARTICLE UPTAKE AT THE NASAL CAVITY

Uptake of 0.83 μm polystyrene particles after nasal administration to rats

Detected in blood circulation

Amount in blood circulation

Tissue distribution

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THE NALT STRUCTURE IN HUMANS

The Waldeyer’s Ronsillar Ring

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PHYSIOLOGY OF THE NASAL CAVITY

OLFACTORY REGION

Table 6: Studies of neuronal translocation of UFPs from respiratory tract

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodian and Howe 1941</td>
<td>Olfactory nasal transport of polio virus (i.e., after intranasal instillation in chinchillas, transport velocity, 2.4 cm/hr)</td>
</tr>
<tr>
<td>de Lellis 1970</td>
<td>Olfactory nasal transport of 50 nm gold-coated gold after intranasal instillation in Syrian hamster, transport velocity, 2.5 cm/hr</td>
</tr>
<tr>
<td>Hunter and Bray 1988</td>
<td>Kohler grade of bipolar neurons from nasal epithelium with microelectrodes</td>
</tr>
<tr>
<td>Hunter and Udin 1989</td>
<td>Rhodamine-labeled microphores (20–200 nm) translocation via sensory nerves of olfactory region to proplax nucleus in hamster after intranasal instillation</td>
</tr>
<tr>
<td>Oberdörster et al. 2004</td>
<td>99mTc particles (21–100 nm) in olfactory bulb after whole-body inhalation exposure in rats</td>
</tr>
<tr>
<td>TB, trachotomized</td>
<td></td>
</tr>
</tbody>
</table>

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ADVANTAGES OF THE NASAL ROUTE OF ADMINISTRATION

- Fast rate of absorption with rapid onset of action, critical to some disease states, such as pain.
- Avoidance of drug degradation in the gastrointestinal tract and of first-pass hepatic metabolism.
- Can provide a suitable, painless, non-invasive alternative to injection.
- Avoidance or compensation for problems associated with swallowing.
- Ability to deliver a wide range of therapeutics (either small or large molecules).
- Potential for direct delivery to the brain.
- Immune responses (local or systemic) elicited by intranasal vaccination are generally substantially stronger than those induced by the same antigens delivered orally.

THE PULMONARY ROUTE
PULMONARY DELIVERY USING PARTICULATE CARRIERS

- The lungs present unique features that can facilitate systemic drug delivery:
  - Large surface area (≈75 m²).
  - Good vascularisation.
  - Large capacity for solute exchange.
  - Ultra-thin alveolar epithelium.
  - First-pass metabolism is avoided.

- An alternative non-invasive means for both local and systemic drug delivery using particulate carriers.

- Allows high concentrations of drug in the lungs thus minimizing side toxic effects.

- A potential route for both drug therapy and immunisation.

PARTICLE DEPOSITION IN THE LUNGS

Deposition of inhaled particles in the upper and lower human respiratory tract.
### IN VIVO RETENTION OF PARTICLES IN LUNG LAVAGES AND ALVEOLAR MACROPHAGES

<table>
<thead>
<tr>
<th>Particle size</th>
<th>Initial</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15-20 μm</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>15-20 μm</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>2-3 μm</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 3 μm</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Possible Mechanisms
- Dissolution
- Macrophage phagocytosis
- Direct passage
- Uptake by vascular system
- Movement into the lymphatic system
- Axonal translocation to CNS

Elimination
- Mucociliary escalator
- Exhaled air

### PARTICLE UPTAKE AT THE LUNGS

![Diagram of particle uptake at the lungs]

- **Lymphatics**
- **Blood circulation**
- **LN**
- **Interstitium**
- **Pleura**
- **Alveolus**
PULMONARY ADMINISTRATION OF LIPID NANOPARTICLES

Lipid Nanoparticles

- Lipophilic efficient and non-toxic colloidal delivery system.
- Administration have been studied by parenteral and non-parenteral routes.

- To investigate LN as a potential drug carrier to the lungs and, through alveolar airways, to the lymphatic system, thus optimising concentration at the tumour site or at distant metastasis sites.
- To evaluate LN in vivo fate after pulmonary absorption upon nebulisation and delivery to laboratory animals.

CHARACTERISATION OF $^{99m}$Tc-HMPAO-LN

Average values

d.m. = 200 nm  
I.P. Range = 0.250  
Zeta potential = -15.4 mV
**BIODISTRIBUTION**

![99mTc-HMPAO](image1)

![99mTc-HMPAO-LN](image2)

A.J. Almeida, 2007

Videira et al. (2002) J Drug Targeting

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**LYMPHATIC DISTRIBUTION OF 99mTc-HMPAO-LN**

![Images of lymphatic distribution](image3)

A.J. Almeida, 2007

Videira et al. (2002) J Drug Targeting
BIODISTRIBUTION IN RATS 4h AFTER INHALATION

ALVEOLAR CLEARANCE

Uptake of 1.1 \( \mu \text{m} \) fluorescent polystyrene particles administered i.n. to mice
Eyles et al (2001) Vaccine

15 min

24 h

Alveolar clearance of 400 nm fluorescent polystyrene particles administered i.n. to mice
### CONCLUSIONS (I)

- Mucosal delivery is the most convenient way for drug administration. Therefore, the future of mucosal particulate delivery will highly depend on whether a sufficient level of absorption can be achieved.
- Pathways of particulate absorption and absorption efficiencies are not entirely consistent due to the different experimental adopted by different groups.
- Particle uptake and translocation are dependent on a complex series of interactions between particle physicochemical properties and the physiological attributes of the mucosal site.
- Direct comparison among different systems are clearly needed before a more comprehensive understanding of the absorption process can be obtained.
- An adequate selection of the biomaterials and specialised design of the nanosystems are required in order to optimise the capacity of particulate carriers to transport drugs across mucosal surfaces.

### CONCLUSIONS (II)

- Since vaccines typically require smaller quantities to be effective, mucosal particulate vaccines are more promising. Many of the particulate systems can also provide adjuvanticity to the antigens incorporated, which may compensate for the low amounts of antigens absorbed.
- Feasibility of mucosal particulate drug delivery, will largely depend on whether substantially improved particle absorption can be achieved in the future.
- The advances now being made in nanoparticle technology may provide the impetus needed for the development of new presentations of biologically active molecules using alternative administration routes.
Thank you for your attention!