SYSTEMS FOR CONTROLLED DRUG DELIVERY AND DELIVERY MECHANISMS

15. WEEK

NASAL CONTROLLED RELEASE SYSTEMS

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents.

In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration.

- It is a useful delivery route for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides.
- One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism.
- The nasal route circumvents hepatic first pass elimination associated with the oral delivery:

  -it is easily accessible, and

  -suitable for self-medication.

BENEFITS OF NASAL DELIVERY

1) Drug degradation that is observed in the gastrointestinal tract is absent.

2) Hepatic first pass metabolism is avoided.

3) Rapid drug absorption and quick onset of action can be achieved.

4) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

5) The nasal bioavailability for smaller drug molecules is good.

6) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.

7) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.

8) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

9) Drugs possessing poor stability in gastrointestinal fluids are given by nasal route.

10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

LIMITATIONS OF NASAL DELIVERY

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.

2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.

3) Nasal cavity provides smaller absorption surface area when compared to gastrointestinal tract.

4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.

5) Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.

6) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

7) Nasal absorption can be affected by the physicochemical characteristics of the administered drug such as Mw, solubility, dissolution rate, partition coefficient, charge, pKa, particle size and polymorphism.

8) Generally, polar and low molecular weights drugs show low bioavailability of about 10 and 1 %, respectively. The most important factor limiting nasal absorption of polar and large molecular weight drugs is low membrane permeability and this can be overcome by incorporating absorption enhancers in the formulation.

MECHANISIM OF NASAL DRUG ABSORPTION

1. First Mechanism

It involves an aqueous route of transport, which is also known as the paracellular route but this is a slow and passive route. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

2. Second Mechanism

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

- The mechanism of nasal drug absorption is affected by several factors. For systemic drug delivery, the anatomically most important region in the nose is the respiratory region between the three distinct functional regions identified as vestibular, respiratory, and olfactory.
- Physicochemical properties of the drugs such as ionization, lipophilicity, surface charge and hydrophobicity of molecules are the other important factors besides the molecular weight.

- Briefly, properties desired for nasal bioadhesive formulations can be summarized as,

(a) good adherence to nasal mucous membrane, and ability to absorb mucus;

(b) form a viscous layer or show a slow clearance; and

(c) protect active agent/drug or release it slowly.

NASAL DRUG DELIVERY STRATEGIES

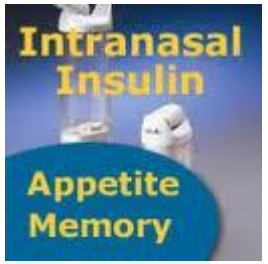
- Bioadhesive powders
- Micro- and nano- particulate systems
- Hydrogels
- Inserts

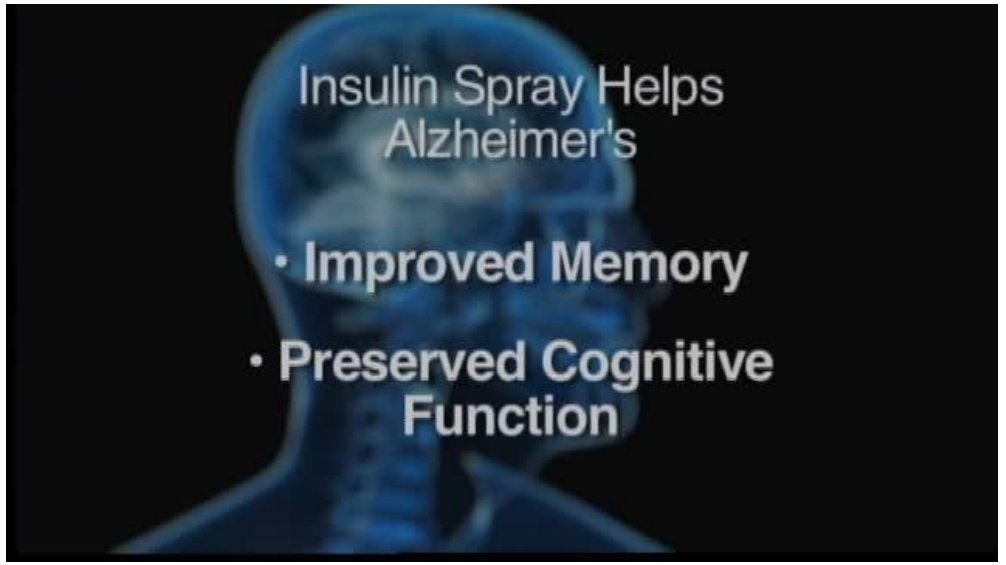
❖ Bioadhesive Powders

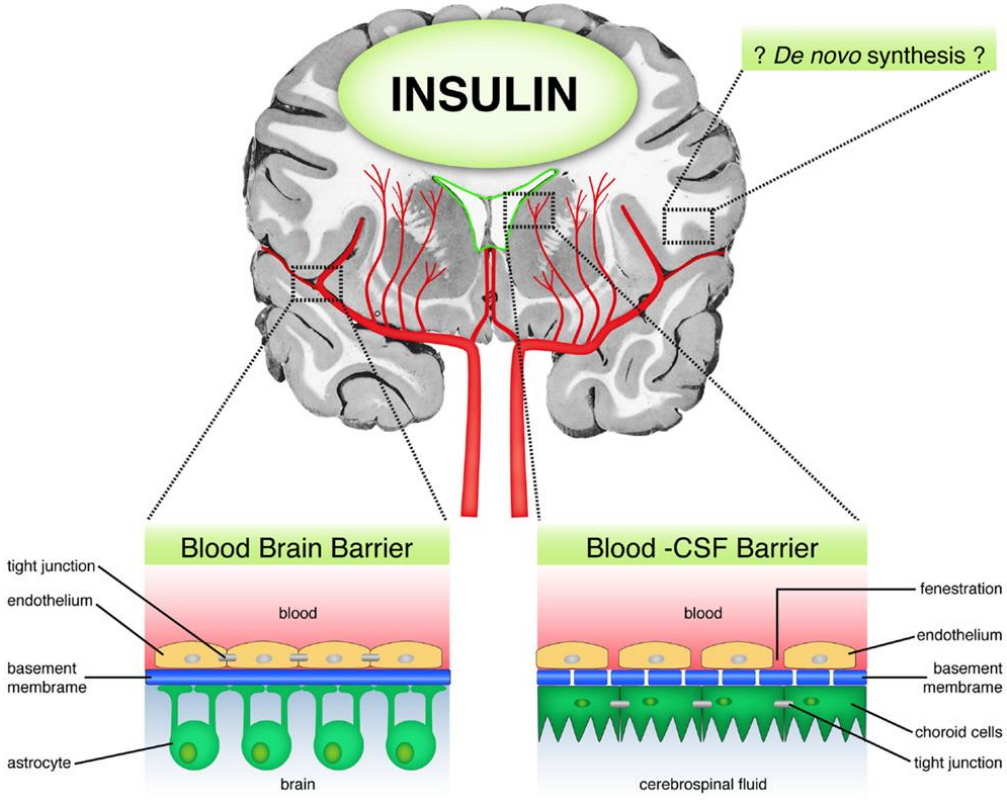
First patented system is **Rhinocort®** which contains Beklometasone Dipropionate

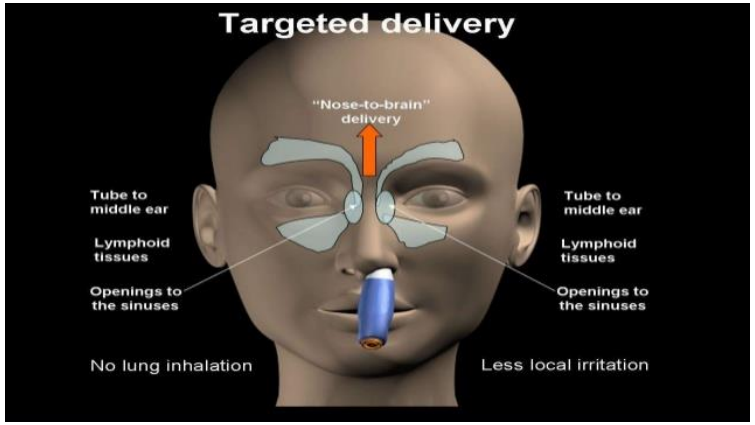
SYSTEMIC EFFECT NASAL PREPARATIONS (NASAL SPRAY)

SALMON CALCITONIN	MIACALCIC	OSTEOPOROSIS
TRIAMCINOLONE ACETONIDE	NASOCORT SPRAY	ALLERGIC RHINITIS
ZOLMITRAPINE	ZOMIG	MIGRAINE
CYANOBALAMIN	NASCOBAL JEL	VITAMIN B12 DEFICIENCY
ESTRADIOL	AERODIAL ESTRADIOL	OSTEOPOROSIS
INSULIN		TYPE 2 DIABETES


Intranasal
Insulin
Appetite
Memory


Insulin Spray Helps
Alzheimer's
• Improved Memory
• Preserved Cognitive
Function


INSULIN
? De novo synthesis ?
Blood Brain Barrier
Blood -CSF Barrier
tight junction
endothelium
basement
membrame
astrocyte
blood
brain
blood
fenestration
endothelium
basement
membrame
choroid cells
tight junction
cerebrospinal fluid


Targeted delivery
"Nose-to-brain"
delivery
Tube to
middle ear
Lymphoid
tissues
Openings to
the sinuses
Tube to
middle ear
Lymphoid
tissues
Openings to
the sinuses
No lung inhalation
Less local irritation

- **Chronic Sinusitis,**
- **Rhinitis,**
- **Migraine,**
- **Diabetes,**