INTRA NASAL DRUG DELIVERY SYSTEM

Molecular Pharmaceutics

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INTRODUCTION

- Administration of drug through nasal route is referred as nasal drug delivery system.
- The nasal route is an attractive alternative to invasive administrations and provides a direct access to the systemic circulation.
- The systemic bioavailability by nasal delivery of some peptide and protein drugs with low nasal absorption has been improved by coadministering them with absorption promotors, enzyme inhibitors

ADVANTAGES

- Rapid drug absorption, higher bioavailability therefore lower dose.
- Fast onset of action.
- Easily administered to unconscious patients.
- Lower dose reduced side effects.
- Self-administration.
- Avoidance of liver first pass effect.
- Avoidance of gut wall metabolism.
- Avoidance of destruction drug in the GIT
- Patient convenience and compliance is improved

- Better nasal bioavailability for smaller drug molecules.
- The bioavailability of larger drug molecules improved by means of absorption enhancer.
- Direct transport into systemic circulation and CNS is possible.

LIMITATION

- Very specific amount i.e. 25-200µl can be delivered through intra nasal route. Once the drug administered cannot be removed.
- Irritation of nasal mucosa by drug eg: Budesonide, Azilactine
- Local side effects and irreversible damage of the cilia of nasal mucosa.

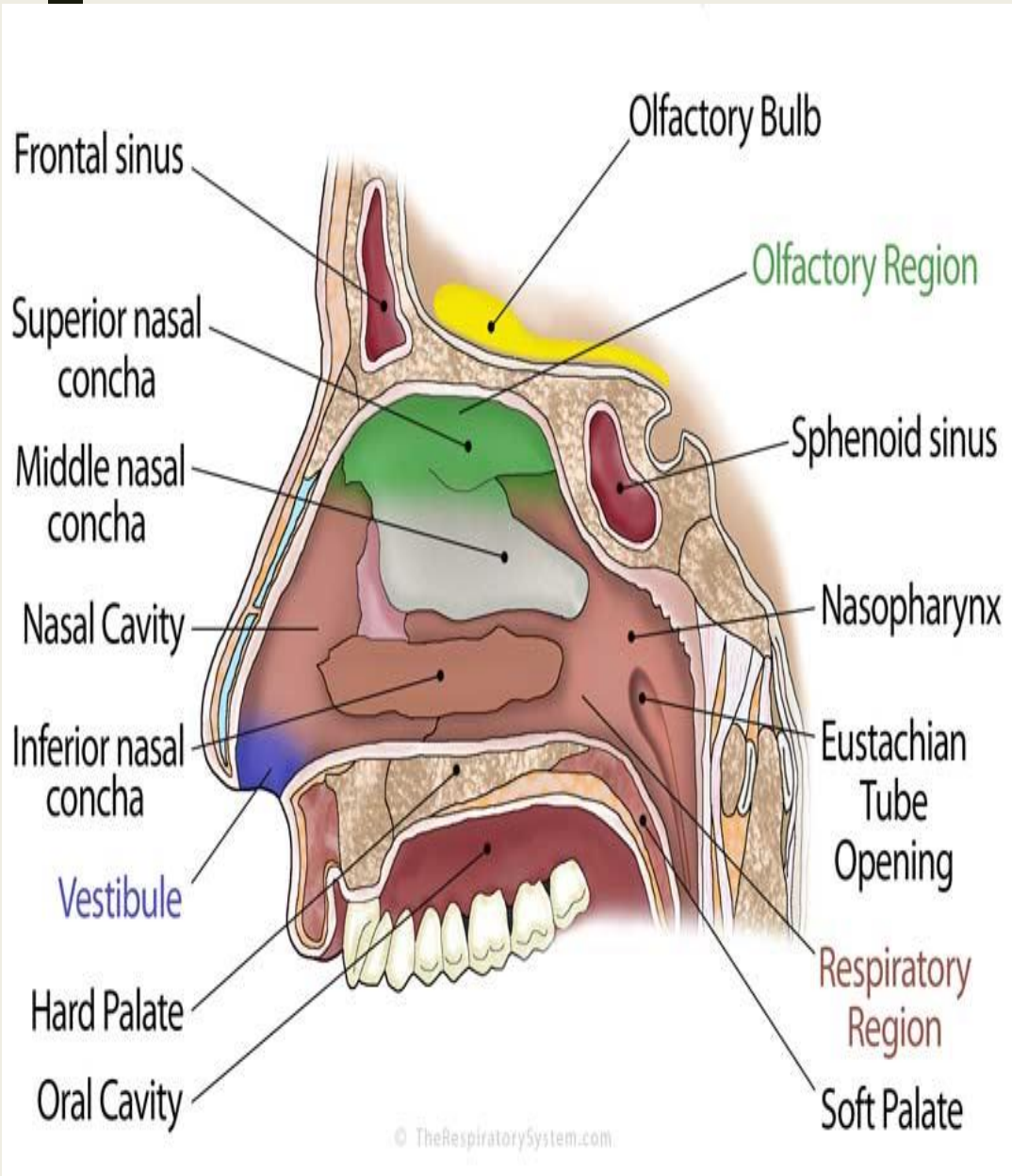
- Mechanical loss of the dosage form into the other parts of the respiratory tract.
- Absorption surface area is less when compared to GIT.
- Difficult to administered drug in pathological condition such as nasal congestion due to cold or allergic reaction.
- Enzymatic barrier to permeability of drug

NASAL ANATOMY AND PHYSIOLOGY

- The nasal passage - nasal vestibule to the nasopharynx, **depth** approximately **12-14 cm^2**.
- The human nasal cavity has a **total volume** about - **16-19ml.**
- **Total surface area** - about **180 cm^2.**
- Nasal cavity is covered with mucous membrane which contains - **goblet cells, basal cell & non ciliated & ciliated columnar cell.**
- Nasal **pH** : **5.5-6.5** (Adults)

  5.0-6.7 (Infants)

Nasal Enzymes - Cytochrome P-450, Carboxyl esterase and Glutathione S- tranferase, lactate dehydrogenase, oxido reductase, phosphates , hydrolases.



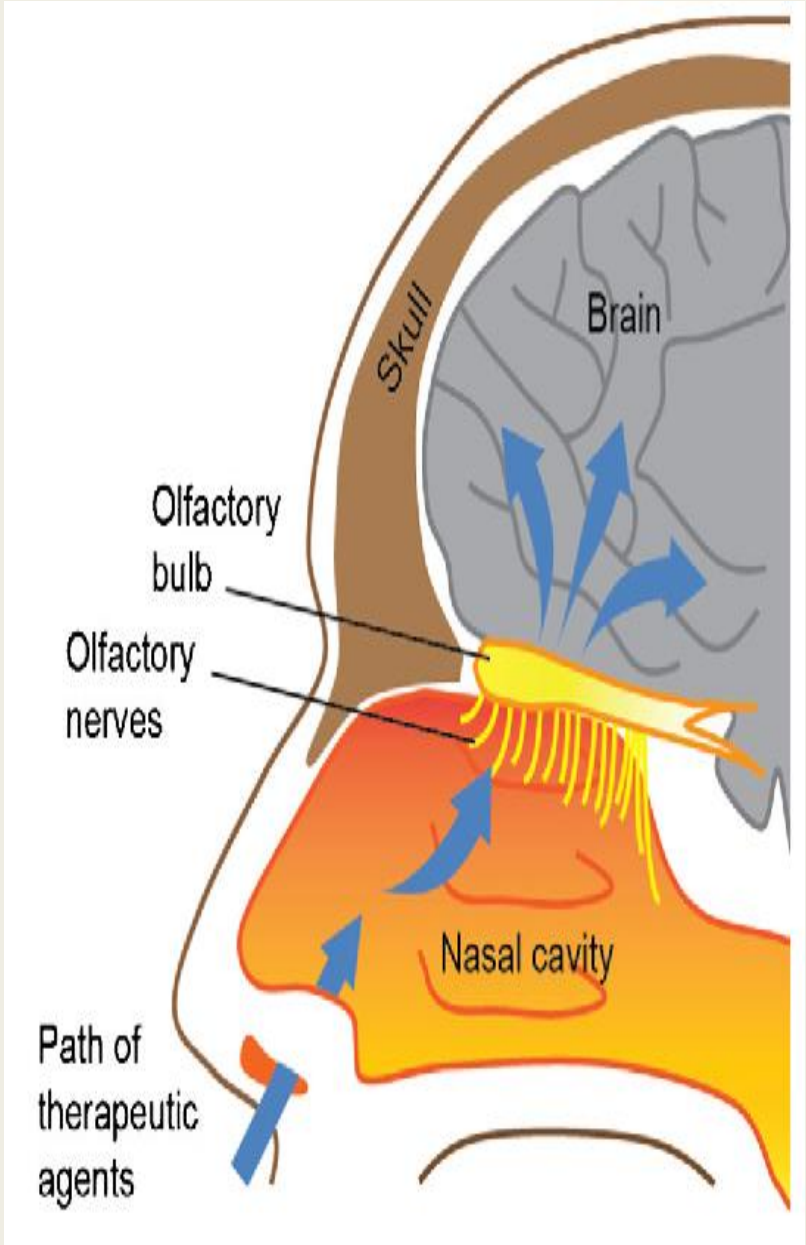


Fig1: Nasal Cavity

- It contains 3 region:

a) Vestibule region

b) Respiratory region

c) Olfactory region

1)Vestibular Region:

- Located at the opening of nasal passage.
- Responsible for filtering out the air borne particles.

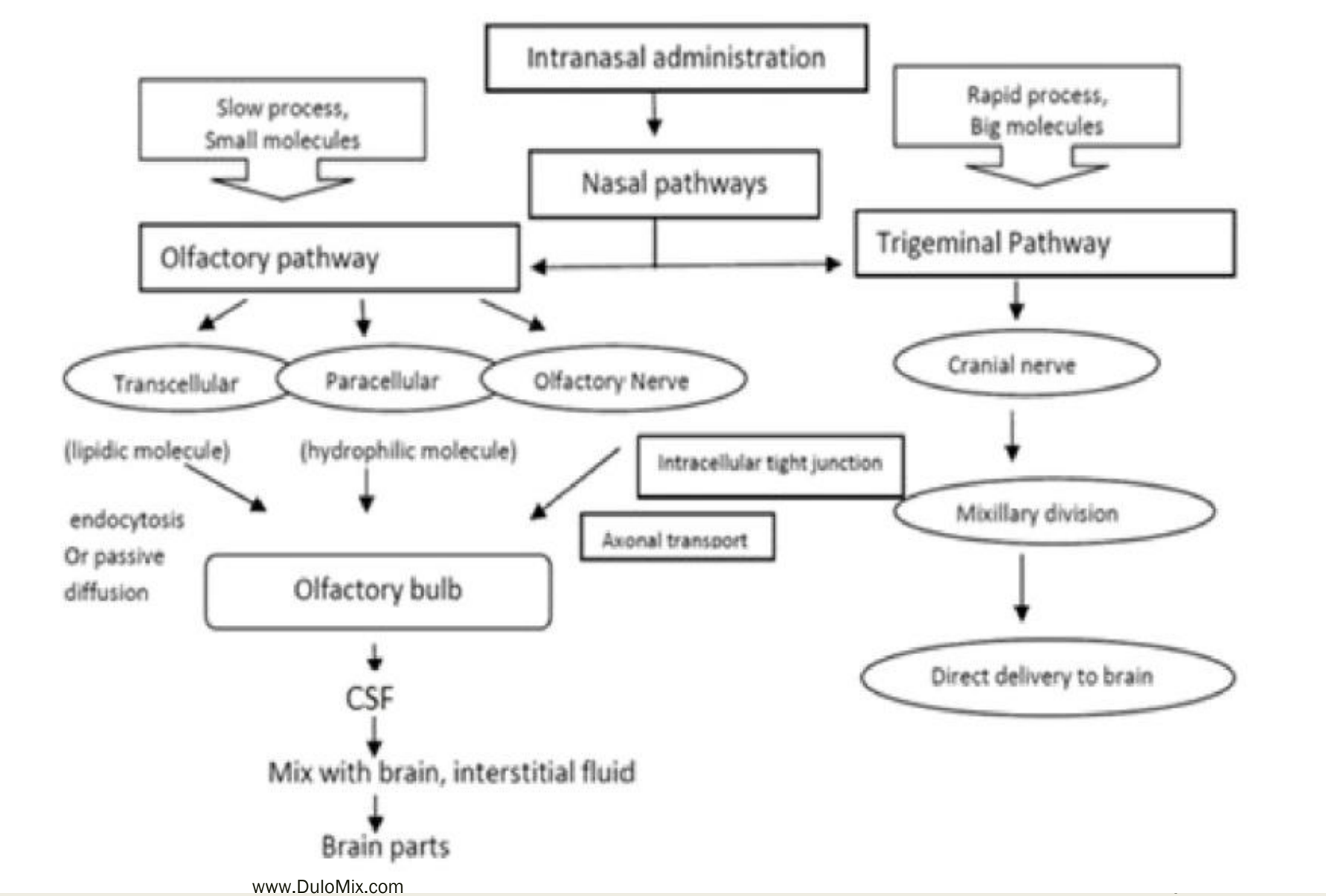
2)Respiratory Region:

- It having the highest degree of vascularity.
- Mainly responsible for systemic drug absorption.

3)Olfactory Region:

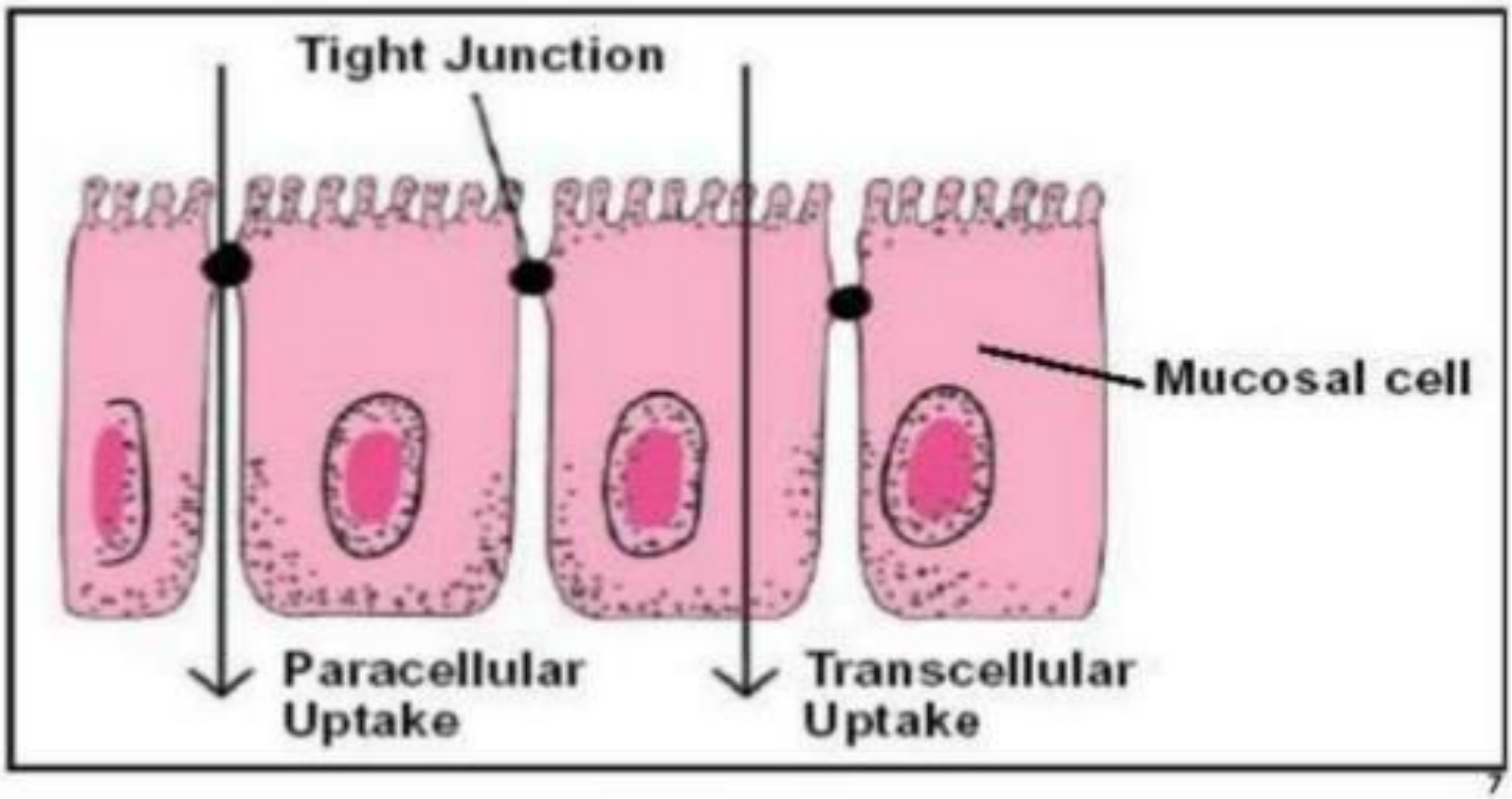
- Located roof of the nasal cavity .

MECHANISM OF NASAL ABSORPTION



By paracellular process

By transcellular process



Mechanism of drug absorption

FACTOR INFLUENCING THE NASAL DRUG ABSORPTION

Factors Related To Drug:

- Molecular weight and size
- Chemical form
- Polymorphism
- Lipophilicity, Partition coefficient and pKa.
- Solubility & dissolution.

Factor Related To Formulation

1.Physicochemical properties of formulation

- pH
- Viscosity
- Osmolarity

2.Dosage form used for developing the formulation

- Nasal drops
  - Most simple, convenient
  - Disadvantage :lack of dose precision
- Nasal sprays
  - Both solution and suspension – formulated in this form
  - Metered dose pumps – exact dose
  - Preferred over powder spray
- Nasal gels –precise dosing
- Nasal powders
  - This form may be developed due to lack of stability
  - Advantage :absence of preservatives, superior stability

STRATEGIES TO IMPROVE NASAL ABSORPTION

- Prodrugs:
  - Improve taste, odor, solubility eg. L-Dopa
- Nasal enzymatic inhibitors:
  - Minimize metabolism of drug
  - Minimizing activity of enzyme in cavity
  - **Eg:bestatine & comostate amylase** – amino peptidase inhibitors.
  - Protease and peptidase used as inhibitors for peptide and protein molecule

- Structural modification:
  - Eg, Calcitonin to Ecatonin
- Mucoadhesive polymer :
  - To improve the nasal residence and absorption
  - Eg: Chitosan, alginate, cellulose & its derivative,
- Novel formulation / particulate drug delivery
  - Eg: Microspheres, liposomes, nanoparticles
- Absorption or permeation enhancers

PERMEATION ENHANCER

Type of compound	Examples	Mechanisms of action
Bile salts(and derivatives)	Sodium deoxycholate Sodium glycocholate	Disrupt membrane, open tight junctions, enzyme inhibition, mucolytic activity
Surfactants	SLS, Saponin	Disrupt membranes
Chelating agents	EDTA, Salicylates	Open tight junction
Fatty acids	Sodium laurate Phospholipids	Disrupt membranes
Bioadhesive materials	Carbopol, Chitosan	Open tight junctions, reduce nasal clearance

FORMULATION

- Drugs
- Viscosifying agents
- Solubilizers
- Surfactants
- Preservative
- Antioxidants
- Humectants
- Osmotic agent
- Bioadhesive polymers

1.Drug

- Appropriate nasal absorption properties.
- No nasal irritation from the drug .
- Rapid onset of action.
- Low dose generally 25 mg per dose.
- No toxic metabolites.
- No offensive odors associated with the drug.
- Suitable stability characteristics.
- Eg: anticholinergic(ipratropium bromide)

  Mast cell stabilizer(sodium cromogylate),

  corticosteroids(budesonide)

2.Viscosifying /Gelling agents:

- Increasing solution viscosity may provide prolong therapeutic effect of nasal preparations.
- Highly viscous formulations interfere with mucociliary clearance and alter the permeability of drug.Eg: Methyl cellulose, Hydroxy propyl cellulose, Carbopol.

3.pH of the formulation:

- It is important to avoid irritation of nasal mucosa.
- Use phosphate buffer pH 6.8 as a vehicle.

4.Solubilizers:

- Aqueous solubility of drug always a limitation for nasal drug delivery.
- Eg: Alcohol, Labrasol, Surfactants, Transcutol

5.Preservatives:

- These are used to prevent the growth of micro organisms.
- Mercury containing preservatives are not used.
- Eg: Paraben, Benzalkonium chloride, Phenyl ethyl alcohol, EDTA etc.

6.Antioxidants:

- These are used to prevent drug oxidation.
- Eg: Sodium Metabisulphite, Sodium Bisulfite, Butylated hydroxy toluene, Tocopherol etc.

7.Humectants :

- To prevent dehydration, adequate intranasal moisture is required to prevent nasal irritation.
- Eg: Glycerine, Sorbitol, Mannitol.

8.Osmotic agent :

- It affect the nasal absorption of the drug.
- The higher concentration of drug not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium.
- Eg: Sodium Chloride, Sodium Sulfite, Sodium Acid Phosphate.

9.Bioadhesive polymers:

- Compounds capable of interacting with biological material through interfacial forces and retained on such material for prolonged periods
- Eg: cellulose derivatives

  Polyacrylates, starch

NASAL DROPS

- Most simple and convenient systems developed for nasal delivery.
- These are solution emulsion suspensions intended for instillation into the nostrils with dropper.
- Nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.
- **Disadvantage:** Lack of the dose precision.
- Eg: Xylometazoline, Phenylephrine, Sodium chloride.

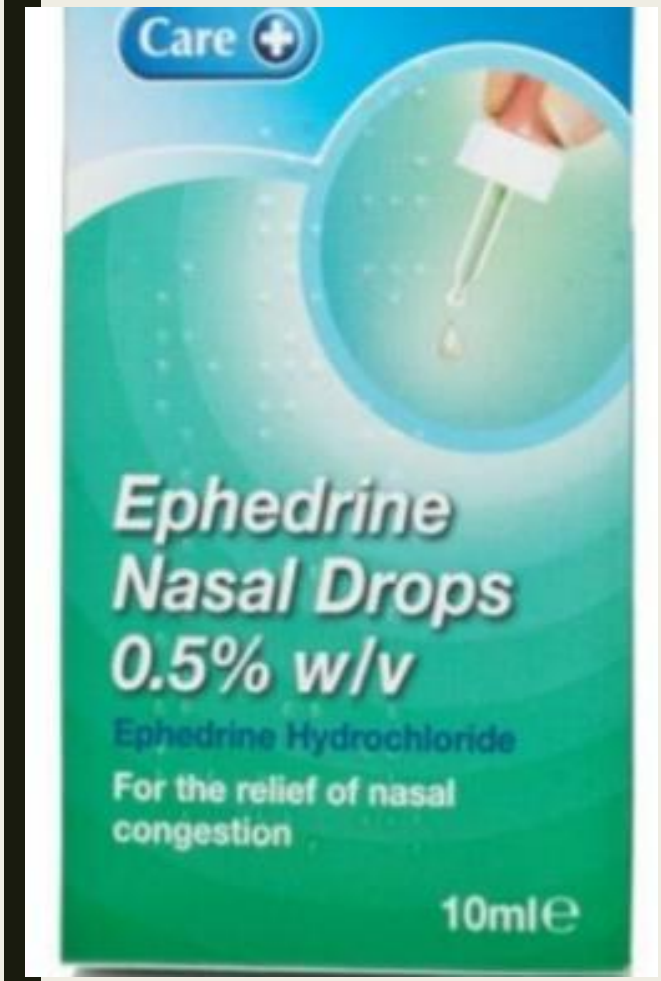


Fig 4 : Ephedrine Nasal Drops

NASAL SPRAY

- These are solution emulsion suspensions intended for spraying into the nostrils.
- Aim - To retain the nasal solution in the droplet form in the nasal cavity.
- Availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µg.
- Advantage : Simple & convenient system.
- Disadvantage: Lack of dose precision.

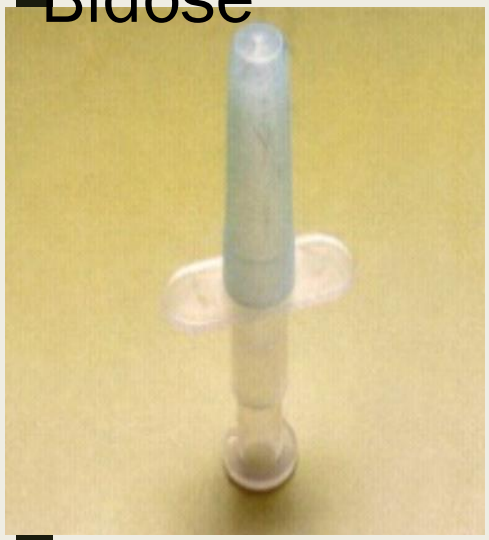
Eg: Xylometazolin, Beclomethasone, Normal

Fig 5 : Otrivine Nasal Spray (0.1 % w/v)

- Nasal spray products contain - therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g. preservatives, viscosity modifiers and buffering agents).
- Used for local therapy & systemic therapy.

SPRAY PUMP DEVICES

Unidose
Bidose



Multidose

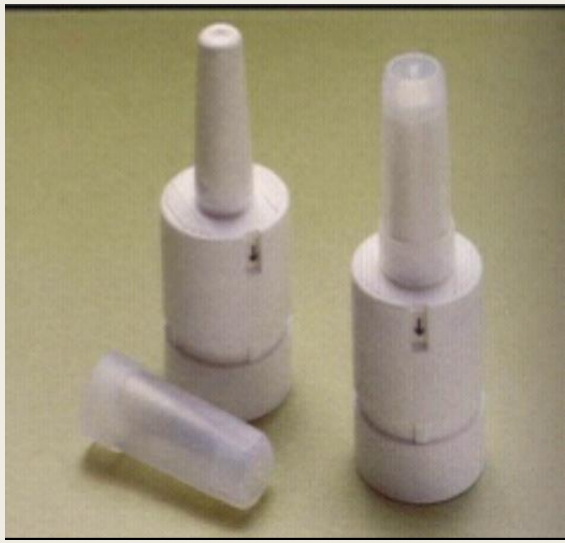


Fig 6 : Spray Pump Devices

NASAL POWDER

- This dosage form may be developed if solution and suspension dosage forms cannot be developed.
- These are powders intended for insufflation into the nostrils by means of suitable device.
- Nasal powder formulation depends on the solubility, particles size and nasal irritancy of the active drug and excipients.

Advantages :

- The absence of preservative.
- Superior stability of the formulation.

- Eg: Normal Saline , Sumatriptan.

NASAL GEL

- Nasal gels are high-viscose thickened solutions or suspensions.

Advantages :

- Reduction of post-nasal drip.
- Reduction of taste impact due to reduced swallowing.
- Reduction of anterior leakage of the formulation.
- Reduction of irritation by using emollient excipients.

- Eg: Oxytocin, Metoclopramide Hydrocloride

Fig 8 : Chlorpheniramine Nasal Gel

NASAL INSERTS

- Nasal inserts are bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route.
- Nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.
- Eg: Chlorpromazine, Albuterol .

Fig 9 : Nasal Inserts

LIPOSOMES

- Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included.

Advantages :

- Effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values

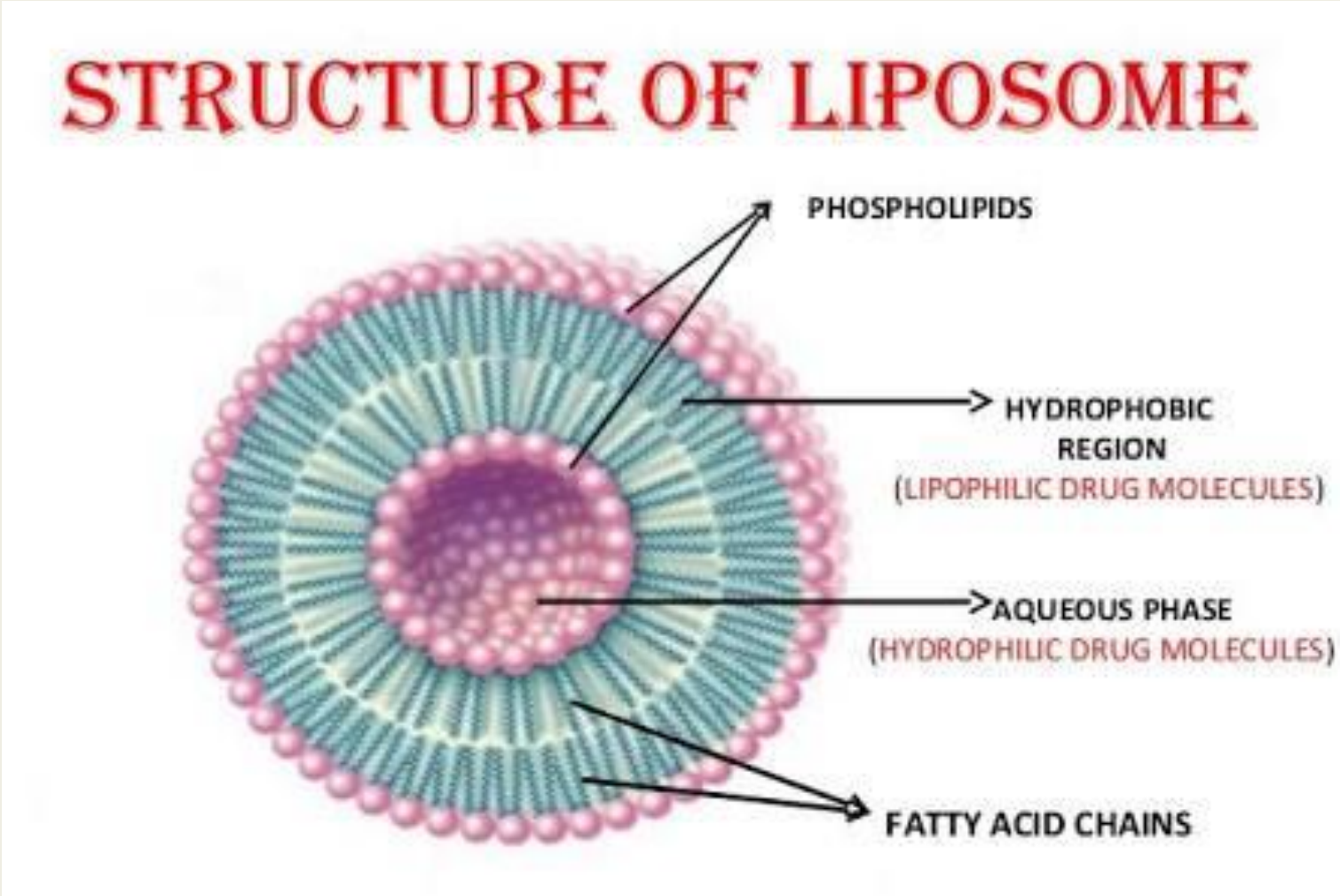


Fig 10 : Liposome

- Administered to the respiratory tract as an aerosol or solution for a nebulizer & micro fine powder for insufflations, alone or in combination with an inert carrier such as lactose.
- The particles of the formulation have diameters of less than 50 microns.
- Eg: Insulin, Calcitonin, Influenza vaccine, Levonorgestrol, Acyclovir, non-peptide drug (Nifedipine)

NANOPARTICLES

Nanoparticles are sub-nanosized colloidal structures composed of synthetic or semi-synthetic polymers.

The drug is dissolved, entrapped, encapsulated or attached to polymer matrix.

Size range : 10–1000 nm.

Nano drug delivery system used for treatment of CNS disorders.

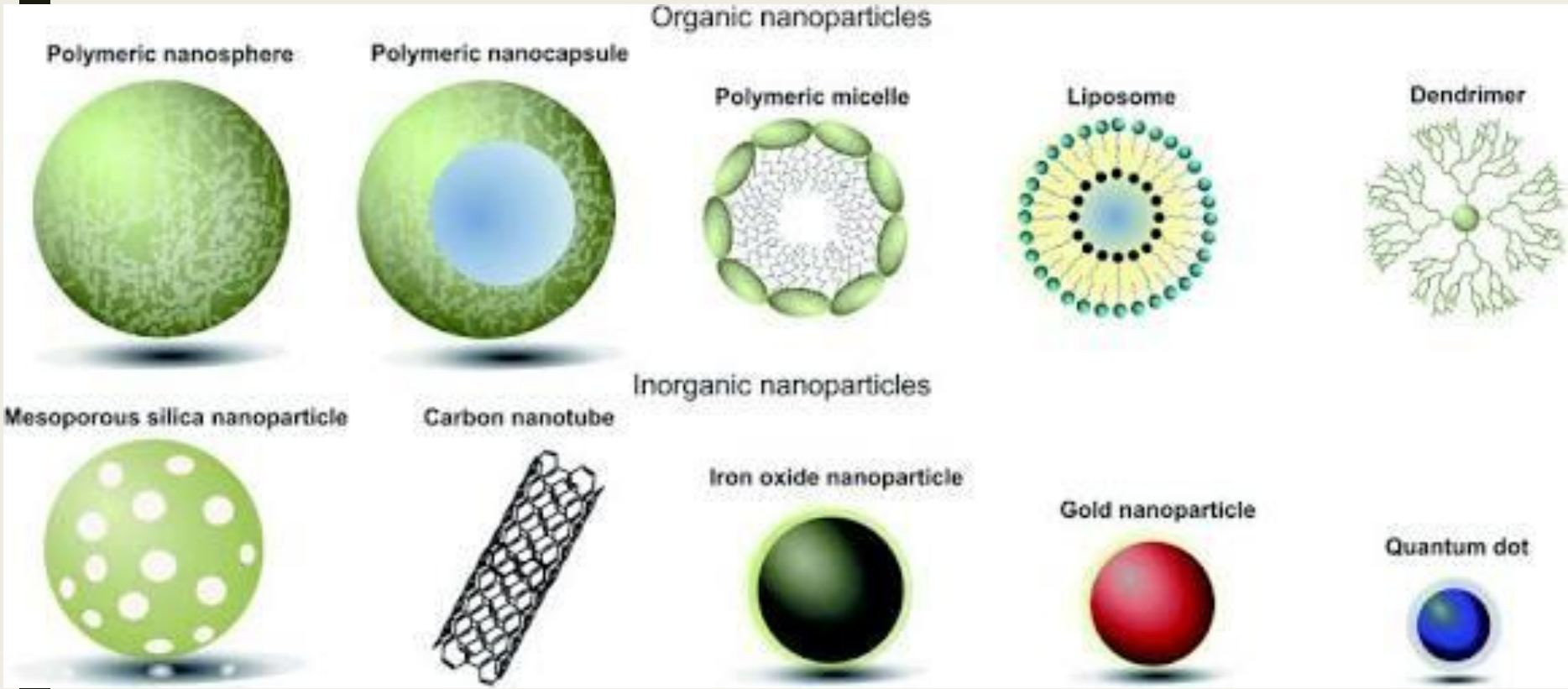
Types:

Nanospheres

Nanocapsules

- Solid Lipid Nanoparticles
- Polymeric Nanoparticles
- Ceramic Nanoparticles
- Hydrogel Nanoparticles
- Copolymerized Peptide Nanoparticles
- Nanocrystals and Nanosuspensions
- Nanotubes and Nanowires
- Functionalized Nanocarriers

- Eg: Vaccines



www.DuloMix.com Fig 11 : Nanoparticles

MICROSPHERES

- It provides prolonged contact with nasal mucosa.
- Microspheres swell in contact with nasal mucosa to form a gel and control the rate of clearance from the nasal cavity.
- The ideal microsphere particle size requirement for nasal delivery - range from 10 to 50 µm as smaller particles.
- The materials used in formulation : Starch, Dextran, Albumin and Hyaluronic acid, Mucoadhesive polymer (chitosan, alginate).
- Eg. Carbamazepine Chitosan Microspheres, Dextran Gentamicin, Insulin

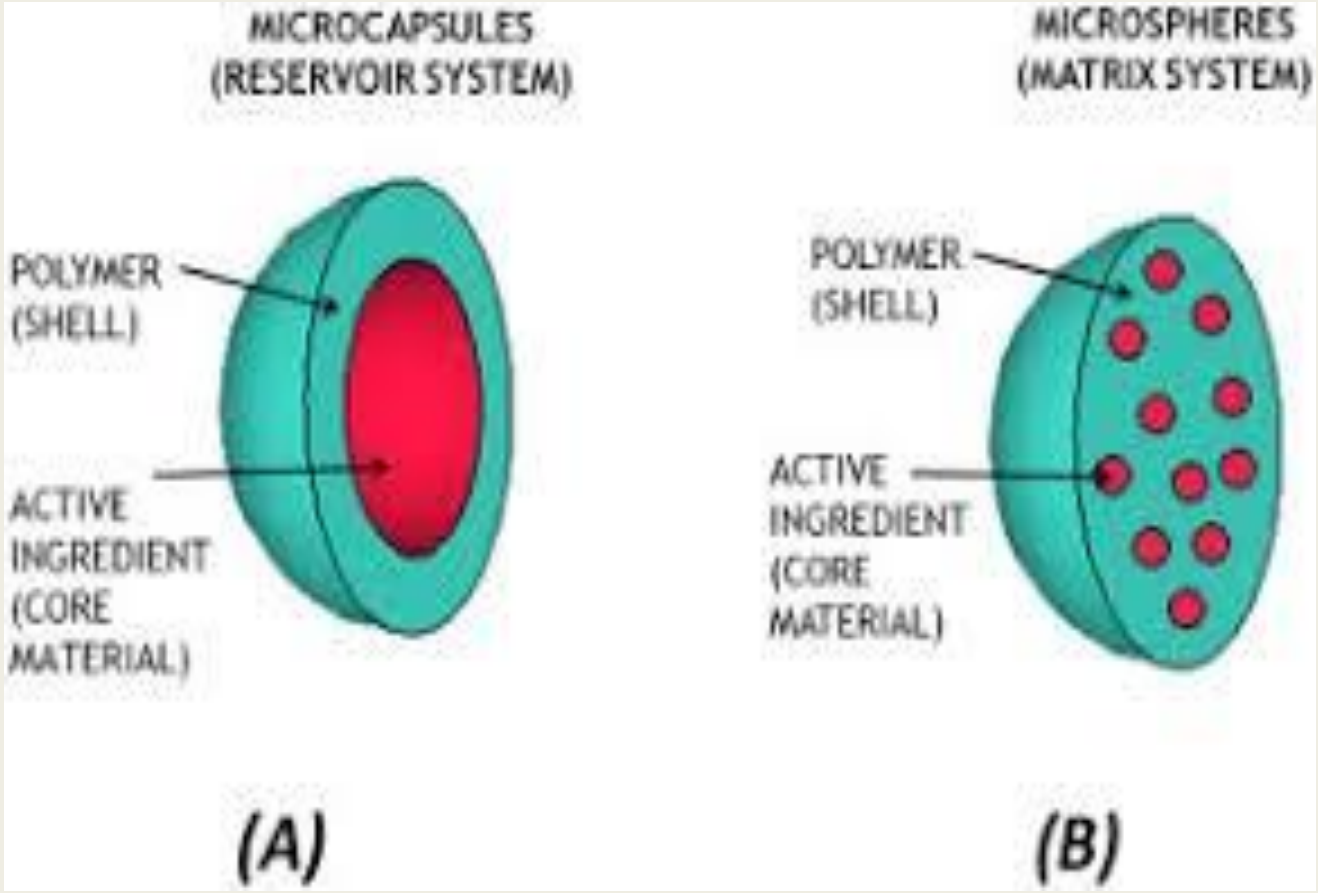


Fig 12 :Microcapsules & Microspheres

NASAL *IN-SITU* GEL

- *In-situ* gel formulations are drug delivery systems that are in solution form before administration in the nasal cavity, but after administration it undergoes gelation to form gel.
- This can be achieved by using different polymers such as Chitosan, PVA, Poloxamers, Carbopol.
- Eg: Midazolam, Insulin, Diltiazem.

MICROEMUSION & NANOEMULSION

- It composed of oil, surfactant & co-surfactant was developed for intranasal delivery.
- Oil phase : Lauroglycol 90.
- Surfactant : Labrasol.
- Co-surfactant : Plurol oleique or its mixture with PEG 400 (1:1).
- Eg: Fexofenadine, Resperidone.

NASAL DELIVERY DEVICES

Common devices

- Droppers
- Squeeze bottle
- Spray pump/Atomizers (MAD- Mucosal Atomization Device)
- Gel applicators
- Nasal nebulizers (Sinus Nebulizer Rhino Clear)
- Pressurized Meter Dose Nasal Inhaler

MUCOSAL ATOMIZATION DEVICE (MAD)

- Device designed to allow emergency personnel to delivery nasal medications as an atomized spray.
- Broad 30-micron spray ensure excellent mucosal coverage.
- It is disposable and single use only.
- Eg: Naloxone.

Fig 13 : Mucosal Atomization Device

METERED DOSE NEBULIZER

- Operates by mechanical actuation.
- Delivers a predetermined volume with precision.
- Atomization results in higher bioavailability than either spray or drops.
- Eg : Corticosteroids.

Fig 14 : Nasal Nebulizer

NASAL AEROSOLS INHALER

- Aerosol inhalations are solutions suspensions or emulsions of drug in a mixture of propellant held under pressure in aerosol container.
- Form droplet - 50 µm or less using metered valve.
- Eg:-Budesonide & Beclomethasone .

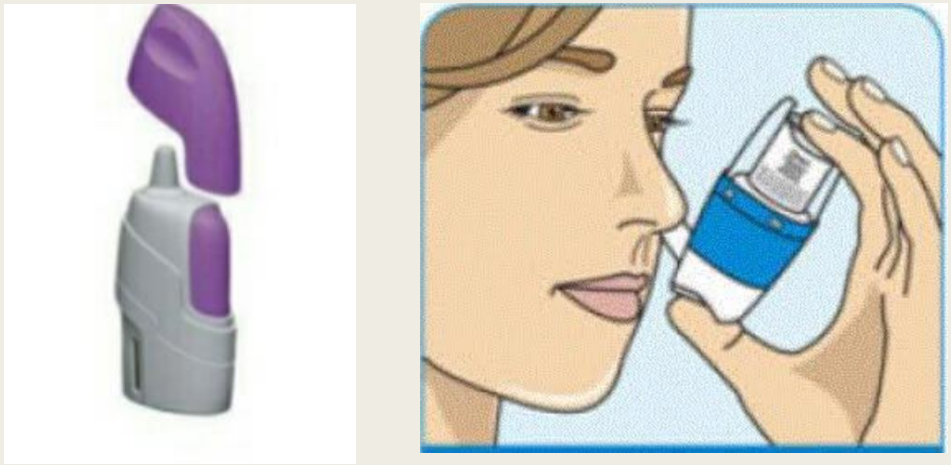


Fig 15: Nasal Aerosol Inhaler

EXAMPLES OF MARKETED PREODUCT

LOCAL DELIVERY

DRUG	BRAND	MAIN EXCIPIENTS	MAIN INDICATION
Beclomethasone	Beconase	Microcrystalline cellulose, Carboxy methyl cellulose sodium.	Management/ treatment of symptoms of seasonal and perennial rhinosinusitis
Budesonide	Rhinocort	Microcrystalline cellulose, Carboxy methyl cellulose .	

SYSTEMIC DELIVERY

DRUG	BRAND	MAIN EXCIPIENTS	MAIN INDICATION
Estradiol	Aerodiol	Methyl beta dextrin, Sodium chloride.	Hormone replacement therapy
Cyanocobalamin	Nascobal	Sodium citrate, Citric acid, Benzalkonium chloride	Vitamin B12 deficiency

EVALUATION OF NASAL DRUG FORMULATION

A.*IN VIVO* NASAL ABSORPTION STUDIES

1.RAT MODEL

- The rat is anaesthetized-intraperitoneal injection (sodium pentobarbital) .After incision is made in the neck, the trachea is cannulated with a polyethylene tube.
- Another tube is inserted through the esophagus towards the posterior region of the nasal cavity.
- The drug solution is delivered to the nasal cavity through the nostril or esophageal tubing.
- The blood samples are collected from the femoral vein.

2.RABBIT MODEL

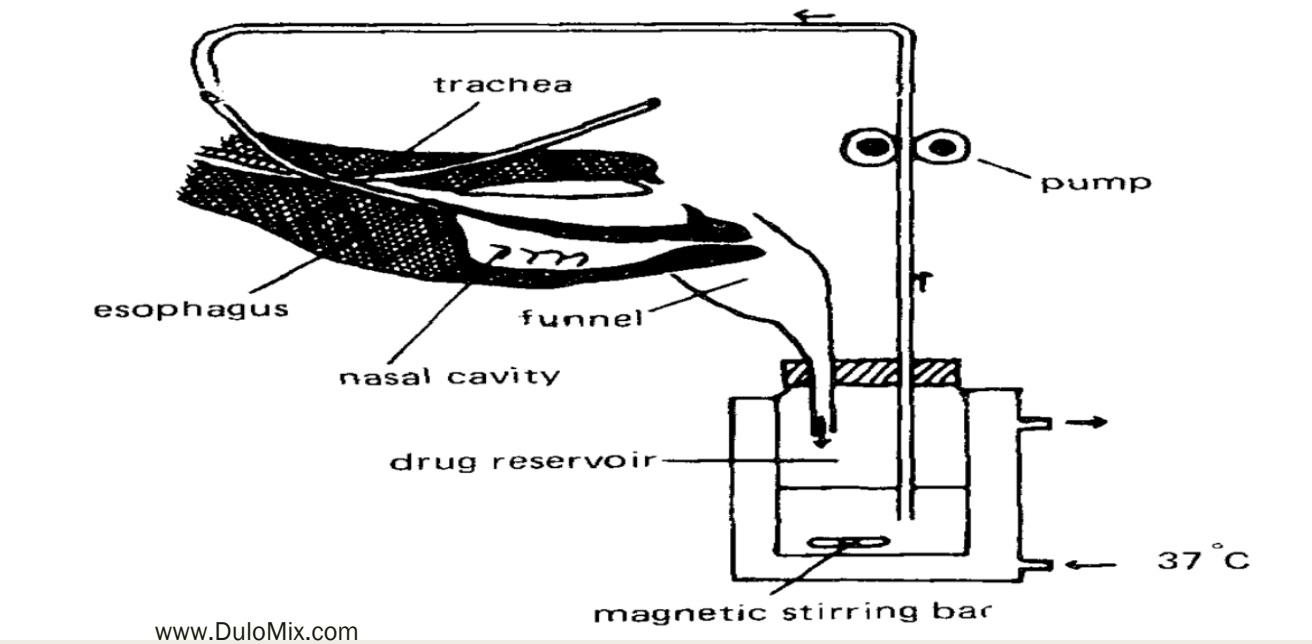
- The rabbit weighing approximately-3kg is anaesthetized by an intramuscular injection(combination of ketamine and xylazine)
- The rabbit head is held in an upright position.
- The drug solution is administered by nasal spray into each nostrils.
- During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad.
- The blood samples are collected by an catheter in the marginal ear vein or artery.

3.DOG MODEL

- Anaesthetized by intravenous injection of Sodium Thiopental and maintained in an anaesthetized state with Sodium Phenobarbital.
- A positive pressure pump provides ventilation through a cuffed endotracheal tube.
- Using heating pad keeps the body temperature at 37°C.
- Blood samples are collected from the jugular vein.

B.*EX VIVO* NASAL PERFUSION MODEL

- During perfusion studies, to minimize the loss of drug solution a funnel is placed between the nose and reservoir(drug).
- Maintained at 37°C and circulated through the nasal cavity of the rat by means of a peristaltic pump.



- The perfusion solution passes out from the nostril and through the funnel and flows in to the drug reservoir solution again.
- Drug solutions of 3–20 ml are continuously circulated through the nasal cavity of anaesthesized rats.
- The reservoir is stirred constantly.
- The amount of drug absorbed is determined by measuring the drug concentration remaining in the solution after a period of perfusion.

3.*IN VITRO* DRUG DIFFUSION STUDY

- Nasal diffusion cell is fabricated in glass.
- The water jacketed recipient chamber having total capacity-60ml.
- Three openings-sampling,thermometer and donor tube chamber.
- Nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water.
- The donor chamber tube is placed just touches the diffusion medium in recipient chamber.
- Sample (0.5ml) from recipient chamber are withdraw-transferred to amber coloured ampoules.
- Estimated by analytical techniques.

IN-VITRO STUDIES

In the case of nasal powders:

- Uniformity of content, Uniformity of weight, Particle size, Melting point, Angle of Repose, Carr's index etc.

In the case of nasal *in-situ* gelling system:

- Viscosity of solution, PH, Gelling Temperature & Gelling time, Spreadability, *in vitro* drug release, Mucoadhesive strength etc.

In the case of nasal drops:

- Uniformity of content, Uniformity of weight, Clarity test, Sterility test, Closure system etc.

In the case of nasal sprays:

- Clarity of liquid, sterilization, net content, pump delivery, spray content uniformity, spray pattern, particle size distribution(suspension), droplet size distribution etc.

APPLICATION

1.Delivery of vaccines through nasal route:

- Nasal mucosa is the first site of contacts with inhaled pathogens.
- Nasal passages are rich in lymphoid tissue
- Creation of both mucosal and systemic immune response
- Low cost ,non injectable
- Eg: For measeles, pertussis, meningitis

2.Delivery of drugs to Brain:

- For Treatment of Parkinson's disease, Alzheimer disease.
- For Delivery of Melanocyte Stimulating Hormone, ACTH, Insulin to brain.

3.Delivery of non-peptide pharmaceuticals:

- Eg. Propranolol, Nitroglycerin, vitamin B, sex hormone

4.Delivery of peptide based pharmaceuticals:

- Peptides – low BA because of physicochemical instability and susceptibility to hepato gastrointestinal first pass elimination
- Eg. Insulin, Calcitonin, Pituitary hormones etc.

5.Delivery of Diagnostic Drugs:

- Secretory function of gastric acid – Pentagastrin
- Secretin - For diagnosis of pancreatic disorders in diabetic patient

Drug substance	Indication	Dosage form
1.Proteins & peptides: Desmopressin	Antidiuretic hormone	Solution (spray)
Oxytocin	Lactation induction	Solution (spray)
2.Non-peptide: Zolmitriptan	Migraine	Solution (spray)
3.Vaccine Human influenza vaccine		spray

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THANK YOU

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