The problem !!!
NEEDLE STICKS

- Nasal drug delivery is attractive not because it is **BETTER** than injectable therapy……

BUT

- …Because it is **SAFER!**

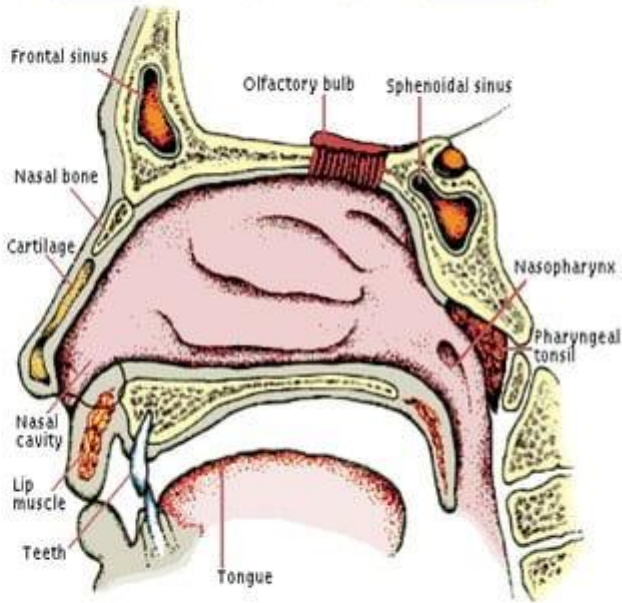
  …No needle

  …NO needle stick risk!

NASAL DRUG DELIVERY SYSTEM

INTRODUCTION

- Anatomy of nose:-
- The nasal cavity consists of passage of a depth of approximately 12-14cm.
- The nasal passage runs from nasal vestibule to nasopharynx.



- The lining is ciliated, highly vascular and rich in mucus gland.
- Nasal secretions are secreted by goblet cells, nasal glands and transudate from plasma.
- It contains sodium, potassium, calcium, albumin, enzymes like leucine,$CYP_{450,}$Transaminase,etc.
- The pH of nasal secretion is 5.5-6.5 in adults and 5.0-6.7 in infants.

Advantages

- Large nasal mucosal surface area for dose absorption
- Rapid drug absorption via highly-vascularized mucosa
- Rapid onset of action
- Ease of administration, non-invasive

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- Avoidance of the gastrointestinal tract and first-pass metabolism
- Improved bioavailability
- Lower dose/reduced side effects
- Improved convenience and compliance
- Self-administration.

Disadvantages

- Nasal cavity provides smaller absorption surface when compared to GIT.
- Relatively inconvenient to patients when compared to oral delivery since there is possibility of nasal irritation.
- The histological toxicity of absorption enhancers used in the nasal drug delivery system is not yet clearly established.

Factors affecting nasal absorption

1. Molecular weight :-

- The nasal absorption of drugs decreases as the molecular weight increases.

- Martin reported a sharp decline in drug absorption having molecular weight greater than 1000 daltons.

2. Lipophilicity :-

- Absorption of drug through nasal route is dependent on the lipophilicity of drugs.

- E.g. Alprenolol and Propranolol which are lipophilic, has greater absorption than that of hydrophilic Metoprolol.

3. pH of solution :-

- pH should be optimum for maximum absorption.
- Nonionised lipophilic form crosses the nasal epithelial barriers via transcellular route and hydrophilic ionized form passes through the aqueous paracellular route.
- E.g. Decanoic acid shows maximum absorption at pH 4.5. Beyond this it decreases as solution becomes more acidic or basic.

4. Drug concentration :-

- The absorption of drug through nasal route is increased as concentration is increased.

- E.g. 1-tyrosine shows increased absorption at high concentration in rate.

Pathway

- In systemic absorption the drugs generally get diffused from epithelial cell into systemic circulation.

- It is reported that nasal cavity have alternative pathways of drugs absorption through olfactory epithelium to CNS and peripheral circulation.

Enhancement in absorption

- Following approaches used for absorption enhancement :-
  - Use of absorption enhancers
  - Increase in residence time.
  - Administration of drug in the form of microspheres.
  - Use of physiological modifying agents

Use of absorption enhancers:-

Absorption enhancers work by increasing the rate at which the drug pass through the nasal mucosa.

Various enhancers used are surfactants, bile salts, chelaters, fatty acid salts, phospholipids, cyclodextrins, glycols etc.

Various mechanisms involved in absorption enhancements are:-

- Increased drug solubility
- Decreased mucosal viscosity
- Decrease enzymatic degradation
- Increased paracellular transport
- Increased transcellular transport

- Increase in residence time:-
- By increasing the residence time the increase in the higher local drug concentration in the mucous lining of the nasal mucosa is obtained.

- Various mucoadhesive polymers like methylcellulose, carboxymethylcellulose or polyacrylic acid are used for increasing the residence time.

- Administration of drug in the form of microspheres:-
- Microspheres have good bioadhesive property and they swell when in contact with mucosa.

- Microspheres provide two advantages-
  a. Control the rate of clearance.
  b. Protect drug from enzymatic degradation.

The microspheres of various materials showed increased half-life of clearance. E.g. starch, albumin, gelatin and dextran.

- Use of physiological modifying agents:-

- These agents are vasoactive agents and exert their action by increasing the nasal blood flow.

- The example of such agents are histamine, leukotrienene D4, prostaglandin E1 and β-adrenergic agents like isoprenaline and terbutaline.

Nasal Delivery Systems

- They contain the drug in a liquid or powder formulation delivered by a pressurized or pump system.

- Various drug delivery systems are used for nasal drug delivery.

- Liquid formulation :-

- These are usually aqueous solutions of the drug. The simplest way to give a liquid is by nose drops.

- They are simple to develop and manufacture compared to solid dosage forms but have a lower microbiological and chemical stability, requiring the use of various preservatives.

- Squeezed bottles :-

- These are used for nasal decongestant and work by spraying a partially atomized jet of liquid into the nasal cavity.

- They give a better absorption of drug by directing the formulation into the anterior part of the cavity and covering a large part of nasal mucosa.

- Metered-dose pump system :-

- They can deliver solutions, suspensions or emulsions with a predetermined volume between 25 and 200 µL, thus offering deposition over a large area.

- Particle size and dose volume are two important factors for controlling delivery from metered-dose systems.

- The optimum particle size for deposition in the nasal cavity is 10μm.
- The volume of formulation that can be delivered is limited by the size of the nasal cavity.
- Better absorption is achieved by administering two doses, one in each nostril, rather than a single large dose.

Applications of nasal drug delivery

A. Nasal delivery of organic based pharmaceuticals :-

- Various organic based pharmaceuticals have been investigated for nasal delivery which includes drug with extensive presystemic metabolism.
- E.g. Progesterone, Estradiol, Nitroglycerin, Propranolol, etc.

B. Nasal delivery of peptide based drugs :-

- Nasal delivery of peptides and proteins is depend on –
  - The structure and size of the molecule.
  - Nasal residence time
  - Formulation variables (pH, viscosity)

- E.g. calcitonin, secretin, albumins, insulin, glucagon, etc.

Pulmonary Drug Delivery System

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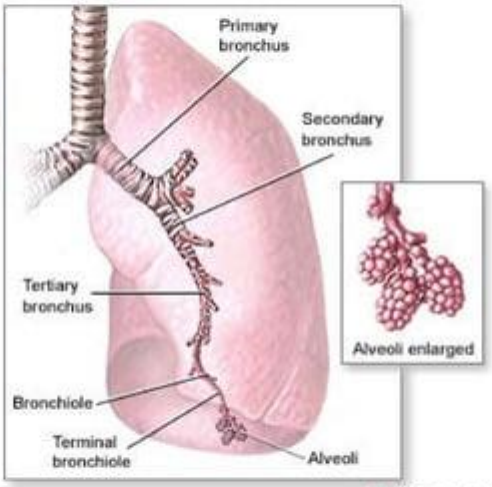
- Anatomy of pulmonary system
- Delivery systems
- Advantages of pulmonary drug delivery systems

Anatomy of pulmonary system



- The lung is the organ of external respiration, in which oxygen and carbon dioxide are exchanged between blood and inhaled air.

- The structure of the airways prevent the entry of and promotes the removal of airborne foreign particles including microorganisms.

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- The respiratory tract consists of conducting regions (trachea, bronchi, bronchioles, terminal and respiratory bronchioles) and respiratory regions (respiratory bronchioles and alveolar regions).

- The upper respiratory tract comprises the nose, throat, pharynx and larynx; the lower tract comprises the trachea, bronchi, bronchioles and the alveolar regions.

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- Trachea branches into two main bronchi- the right bronchus is wider and leaves the trachea at the smaller angle than the left.

- The conducting airways are lined with ciliated epithelial cells.

Delivery systems

- Aerosols are used for the delivery of the drug by this route of administration.

- The aerosols are defined as pressurized dosage from containing one or more active ingredients which upon actuation emit a fine dispersion of liquid or solid materials in gaseous medium.

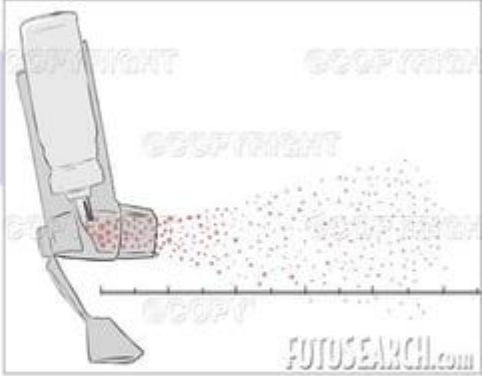
- There are three main types of aerosols generating devices:-

i. Pressurized metered dose inhalers.

ii. Dry powder inhalers.

iii. Nebulizers.

i. Pressurized metered dose inhalers:-



- In pMDI's, drug is either dissolved or suspended in liquid propellants together with other excipients and presented in pressurized cantainer fitted with metering valve.
- The predetermined dose is released as a spray on actuation of the metering valve.

- Containers:- Aerosol container must withstand pressure as high as 140-180 psig at 130°F.
- Pharmaceutical aerosols are packaged in tin-plated steel, plastic coated glass or aluminium containers.
- Aluminium is relatively inert and used uncoated where there is no chemical instability between containers and contents.
- Alternatively aluminium containers with an internal coating of chemically resistant organic material such as epoxy-resin or polytetrafluorine can be used

- Propellants:-

These are liquified gases like chlorofluorocarbons and hydrofluoroalkanes.

These develop proper pressure within the container & it expels the product when valve is opened.

At room temperature and pressure, these are gases but they are readily liquified by decreasing the temperature or increasing pressure.

The vapour pressure of the mixture of propellants is given by Raoult's law,

i.e. vapour pressure of the mixed system is equal to the sum of the mole fraction of each component multiplied by it's vapour pressure.

$$p = p_a + p_b$$

where p = total vapour pressure of the system, p_a & p_b = partial vapour pressures of the components a & b.

- Metering valves:-

It permits the reproducible delivery of small volumes of product.

Depression of the valve stem allows the contents of the metering chamber to be discharged through the orifice in the valve stem and made available to the patient.

After actuation the metering chamber refills with liquid from the bulk and is ready to dispense the next dose.

ii. Dry powder inhalers:-

In this system drug is inhaled as a cloud of fine particles.

DPI formulations are propellant free and do not contain any excipients.

They are breath activated avoiding the problems of inhalation/actuation coordination encountered with pMDI's.

iii. Nebulizers:-

It delivers relatively large volume of drug solutions and suspensions.

They are used for drugs that cannot be formulated into pMDI's or DPI's.

There are three categories :-

a. Jet nebulizers
b. Ultrasonic nebulizers
c. Vibrating-mesh nebulizers

a. Jet nebulizers:-

They are also called as air-jet or air-blast nebulizers using compressed gas.

The jet of high velocity gas is passed tangentially or coaxially through a narrow venturi nozzle typically 0.3 to 0.7 mm in diameter.

e.g. Pari LC nebulizer.

b. Ultrasonic nebulizers:-

In this the energy necessary to atomize liquids come from the piezoelectric crystal vibrating at high frequency.

c. Vibrating-mesh nebulizers:-

In this device aerosols are generated by passing liquids through a vibrating mesh or plate with multiple apertures.

Advantages

- Smaller doses can be administered locally.
- Reduce the potential incidence of adverse systemic effect.
- It used when a drug is poorly absorbed orally, e.g. Na cromoglicate.
- It is used when drug is rapidly metabolized orally, e.g. isoprenaline