Gastro Retentive Drug Delivery System

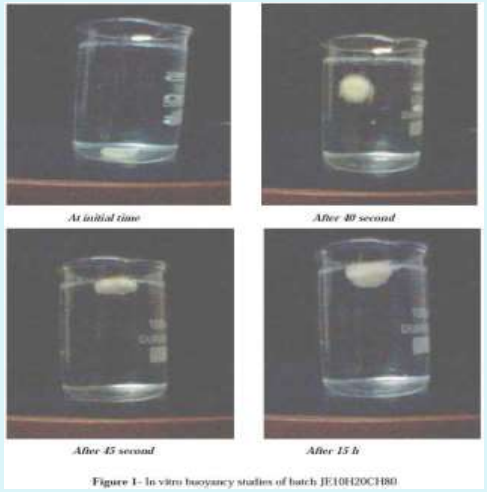

Figure 1- In vitro buoyancy studies of batch JE10H20CH80

By

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INTRODUCTION

- The oral route is considered as the most promising route of drug delivery. But it shows the maximum absorption window in GI tract. So to overcome this problem GRDDS has been developed.
- The control of gastrointestinal transit of orally administered dosage forms using gastroretentive drug delivery systems (GRDDS) can improve the bioavailability of drugs that exhibit site-specific absorption.

- Prolonged gastric retention can be achieved by using floating, swelling, bioadhesive or high-density systems.
- These are drug delivery system which possesses the ability of retaining drug in GIT particularly in the stomach for prolonged period of time and thereby, improve the bioavailability of drugs.

Potential drug candidates for gastroretentive drug delivery systems

- Locally active in the stomach (misoprostol, antacids, antibiotics against H.pylori).
- Have an absorption window in stomach or in the upper small intestine (L-dopa, P-aminobenzoic acid, furosemide).
- Are unstable in the intestine or colonic environment (captopril).
- Exhibit low solubility at high p^H values (diazepam, verapamil).
- Alter normal flora of the colon (antibiotics).

Drugs Those are Unsuitable for Gastroretentive Drug Delivery Systems

1) Drugs that have very limited acid solubility

   e.g. phenytoin etc.

2) Drugs that suffer instability in the gastric environment

   e.g. erythromycin etc.

3) Drugs intended for selective release in the colon

   e.g. 5- amino salicylic acid and corticosteroids etc.

Advantages

- Improved drug absorption, because of increased GRT
- Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
- Ease of administration and better patient compliance.

Limitations

- Require a sufficiently high level of fluids in the Stomach
- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluid
- Drugs that are irritant to gastric mucosa are not suitable for GRDDS

FACTORS CONTROLLING THE GASTRIC RETENTION TIME OF DOSAGE FORM

- Density of dosage form.
- Size of dosage form.
- Food intake and nature of food.
- Effects of Gender, Posture, And Age.

Density of dosage form

The density of dosage form also affects gastric emptying rate and determine the location of the system in the stomach.

- Low density – Float to the surface
- High density- Sink to bottom of the stomach

Shape and size of dosage form

- The larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pylorus into the intestine.
- Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

Food intake and its nature

- Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period.

Effect of Gender, Posture and Age

- Generally females have slower gastric emptying rates than male.
- The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright and supine state.
- In case of elderly persons, gastric emptying is slowed down.

APPROACHES

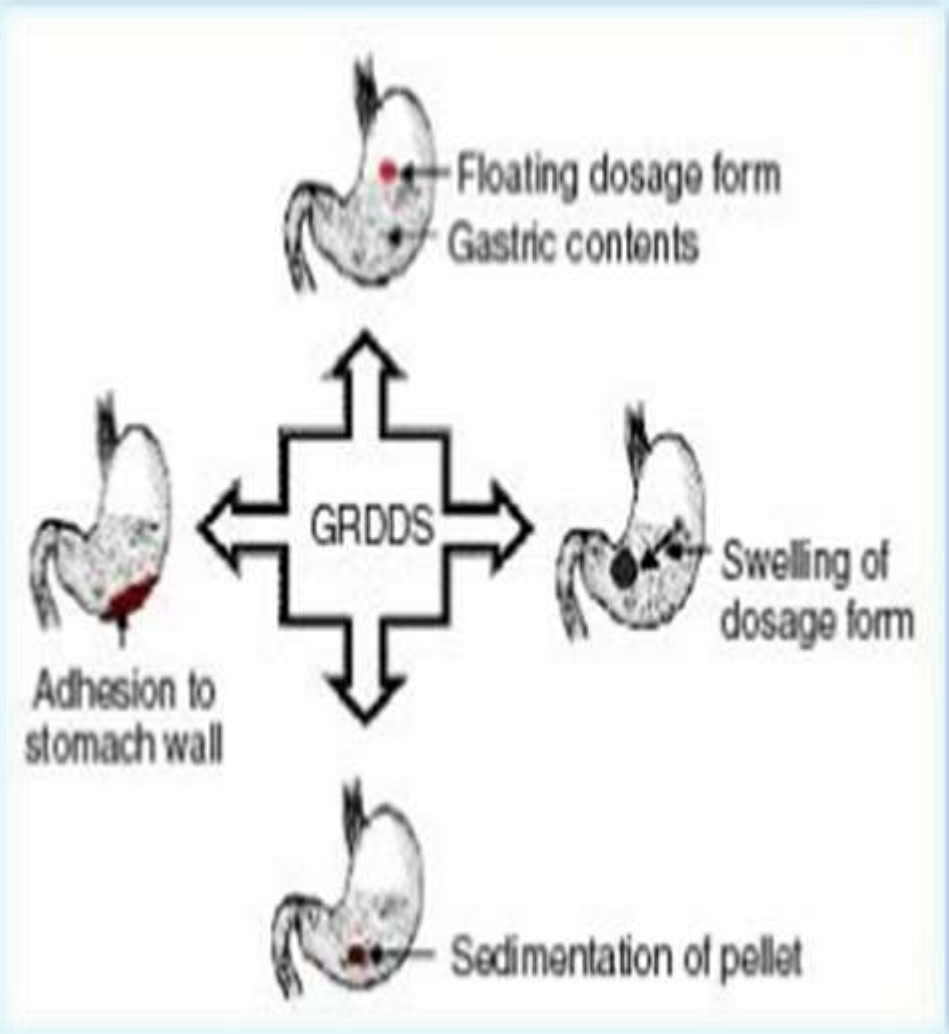
A. High density system

B. Floating systems

C. Expandable systems

D. Super porous hydrogels

E. Bioadhesive systems



A. High Density Systems

- Gastric contents have a density close to water (~1.004).
- A density close to 2.5g/cm^3 is necessary for significant prolongation of gastric residence time.
- The commonly used excipients in high density system includes barium sulphate, zinc oxide, iron powder, and titanium dioxide.
- The major drawback with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4-2.8g/cm^3.

B. Floating Systems

I] Single-unit floating dosage system

1. Noneffervescent systems
2. Effervescent (gas-generating) systems

II] Multiple-unit floating dosage system

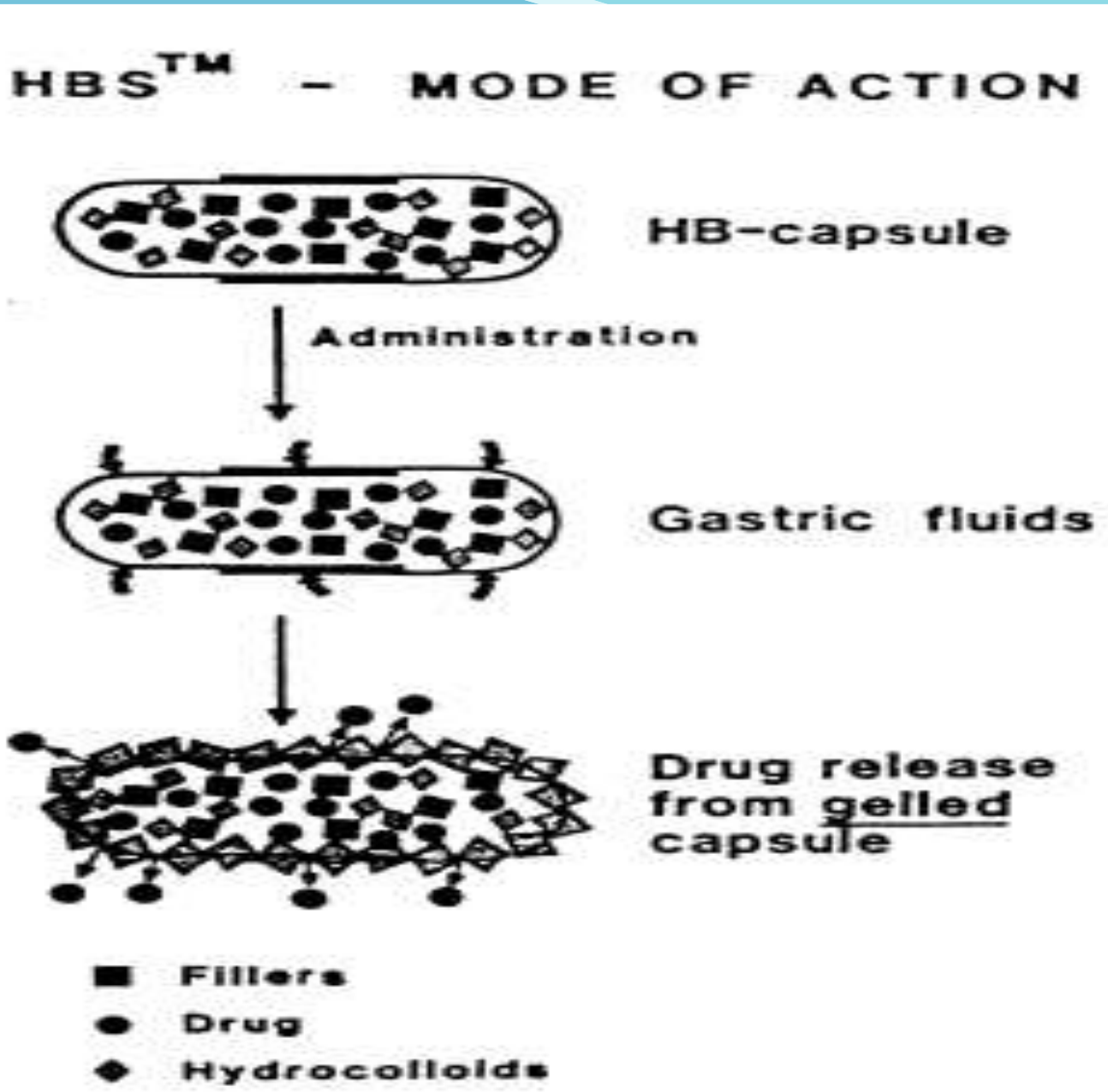
1. Hollow microspheres

I] Single-Unit Floating Dosage System

1. Noneffervescent Systems

- These systems contain one or more hydrocolloids and are made into a single unit along with drug and other additives.
- When coming in contact with water, the hydrocolloids at the surface of the system swell and facilitate floating.
- The coating forms a viscous barrier, and the inner polymer slowly gets hydrated as well, facilitating the controlled drug release. Such systems are called "*hydrodynamically balanced systems (HBS)*".

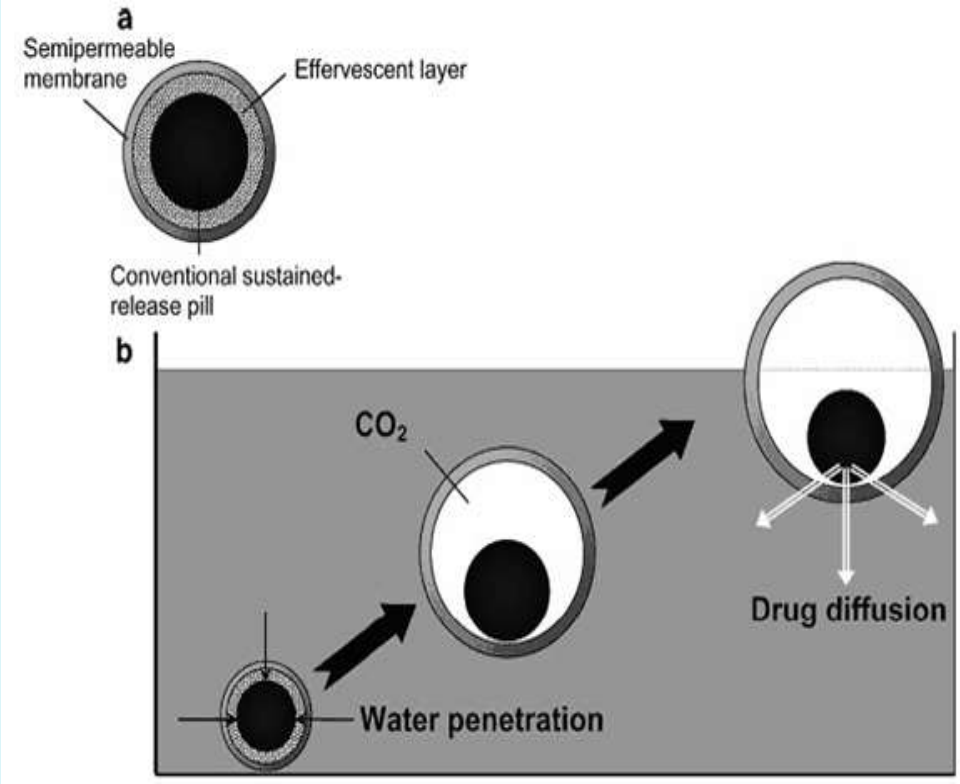
e.g. : HPMC, HEC, Sodium CMC, Agar, Alginic Acid



Hydrodynamically Balanced System (HBS)

2. Gas-Generating Systems

- **Carbonates or bicarbonates,** which react with gastric acid or any other acid **(e.g., citric or tartaric)** present in the formulation to produce CO_2, are usually incorporated in the dosage form, thus reducing the density of the system and making it float on the stomach content.
- The penetration of water into effervescent layer leads to a CO2 generation and makes the system to float.

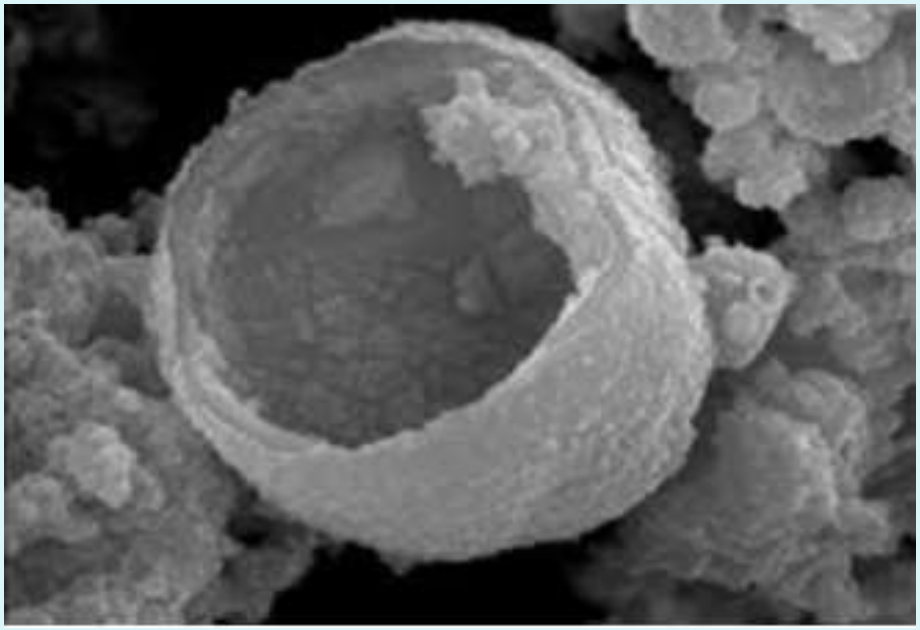


II] Multiple-Unit Floating Dosage Systems

2. Hollow Microspheres

- Hollow microspheres possess the unique advantages of multiple-unit systems and better floating properties as a result of the central hollow space inside the microsphere.
- The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation.

- The drug release and better floating properties mainly depend on the type of polymer, plasticizer, and solvent employed for the preparation.
- Polymers such as polycarbonate and cellulose acetate are generally used in the preparation of hollow microspheres.



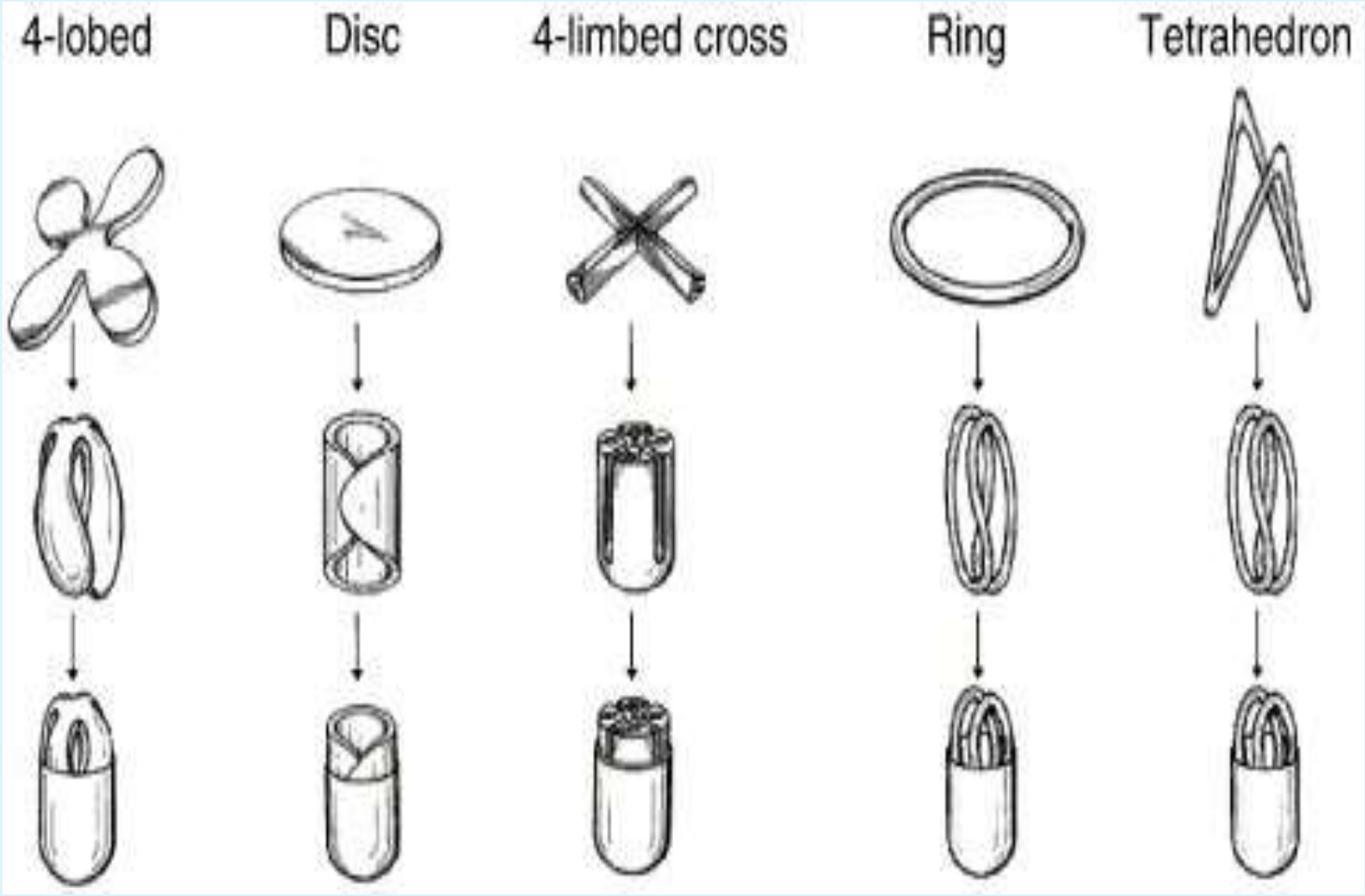
C. Expandable systems

These systems include **Unfoldable and Swellable systems**

I] Unfoldable:

- Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends in the stomach.
- Caldwell et al. proposed different geometric forms (tetrahedron, ring or planar membrane [4-lobed, disc or 4-limbed cross form]) of bioerodible polymer compressed within a capsule.

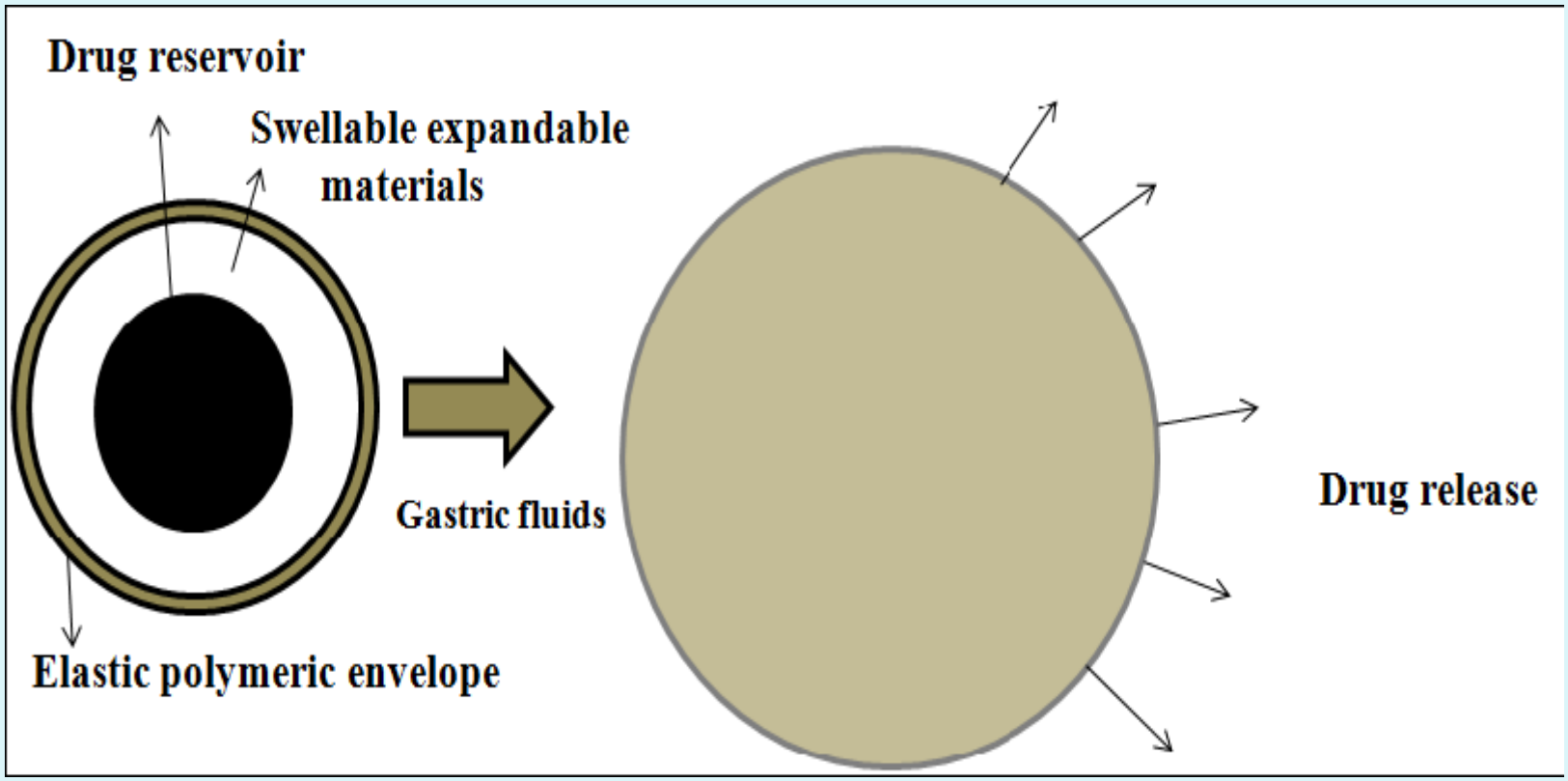
Different geometric forms of unfoldable systems



II] Swellable system:

- Swellable systems are retained because of their mechanical properties. The swelling is usually results from absorption of water.
- The dosage form is small enough to be swallowed, and swells in gastric liquids. The bulk enables gastric retention and maintain the stomach in fed state, suppressing housekeeper waves.
- The whole system is coated by an elastic outer polymeric membrane which was permeable to both drug and body fluids and could control the drug release.
- The device gradually decreases in volume and rigidity as a result depletion of drug and expanding agent or bioreosion of polymer layer, enabling its elimination.

Drug release from swellable system



D. Superporous hydrogels

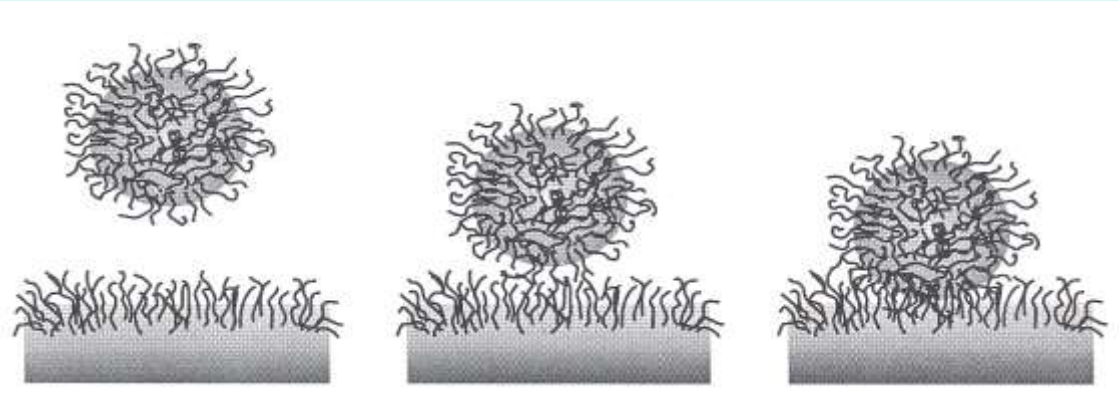
- Swellable agents with pore size ranging between 10nm - 10µm
- Swell to equilibrium size within a minute
- They swell to large size and are intended to have sufficient mechanical strength to withstand pressure by the gastric contraction.

E. Mucoadhesive or bioadhesive system

The technique involves coating of microcapsules with bioadhesive polymer, which enables them to adhere to intestinal mucosa and remain for longer time period in the GI while the active drug is released from the device matrix.

Polymer

Mucus membrane



EVALUATION OF GRDDS

- ***Buoyancy test (In vitro and In vivo test)***
- Dissolution profiles
- Content uniformity & Weight Uniformity
- Hardness & Friability

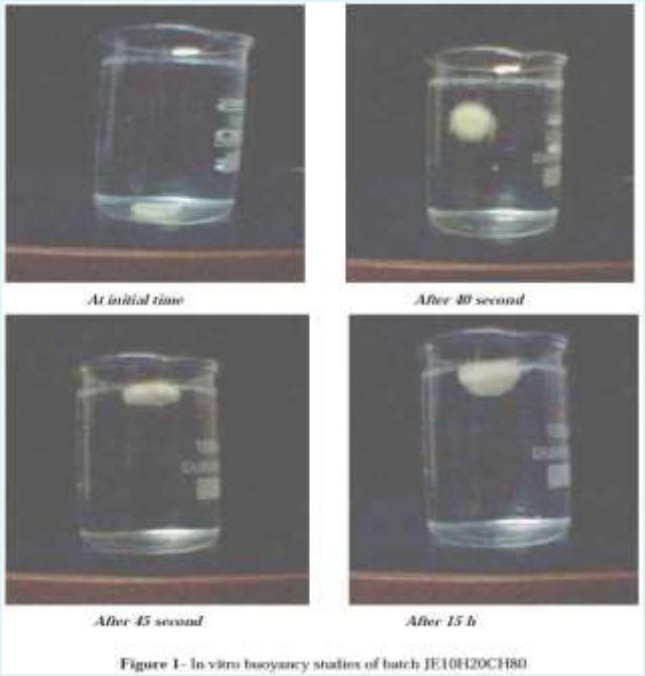


Figure 1- In vitro buoyancy studies of batch JE10H20CH80

Methods to asses Gastroretentivity

I] Magnetic Resonance Imaging:

- It is a noninvasive technique and allow observation of total anatomical structure in relatively high resolution.
- The visualization of GI tract by MRI has to be further improved by the administration of contrast media.
- For solid DFs, the incorporation of a super paramagnetic compound such as ferrous oxide enables their visualization by MRI.

II] Radiology (X-Ray):

- In this technique a radio-opaque material has to be incorporated in the DF, and its location is tracked by X-ray picture.

III] ɣ- Scintigraphy:

- Gamma scintigraphy relies on the administration of a DF containing a small amount of radioisotope, e.g..,^{152}Sm,which is a gamma ray emitter with a relatively short half life.

IV] Gastroscopy:

- Gastroscopy is commonly used for the diagnosis and monitoring of the GI tract.
- This technique utilizes a fiberoptic or video system and can be easily applied for monitoring and locating GRDFs in the stomach.

Buoyancy lag time & Duration of Buoyancy

- The buoyancy time & duration of buoyancy is performed in U.S.P dissolution apparatus 2 in simulated fluid & 0.1N HCL maintained at 37˚C environment.
- The time taken by the dosage form to float is termed as **floating lag time** and the time for which the dosage form floats is termed as the **floating or flotation time.**

THANK YOU

NASOPULMONARY DRUG DELIVERY SYSTEM

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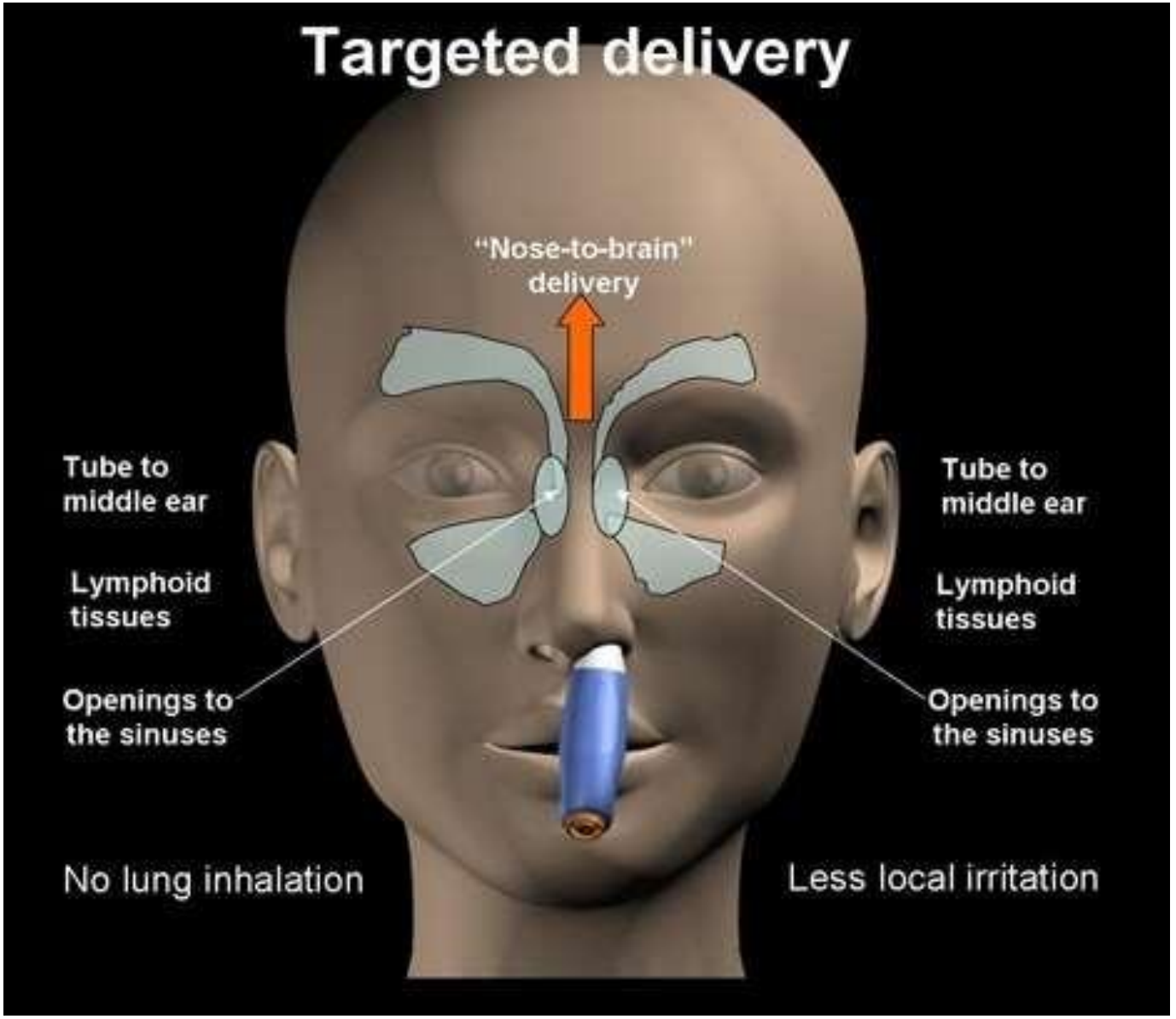
NASAL DRUG DELIVERY SYSTEM

CONTENTS

- INTRODUCTION
- ADVANTAGES AND DISADVANTAGES
- ANATOMY & PHYSIOLOGY OF NASAL CAVITY
- MECHANISM OF DRUG ABSORPTION
- FORMULATION APPROACHES
- EVALUATION TEST

NASAL DRUG DELIVERY SYSTEM



INTRODUCTION:

- In ancient times the Indian Ayurvedic system of medicines used nasal route for administration of drug and the process is called as **“Nasya”**
- Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Undoubtedly, the intranasal administration of medicines for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time.
- However, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery.

- In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides,proteins and polar drugs. The nasal delivery seems to be a favourable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds.

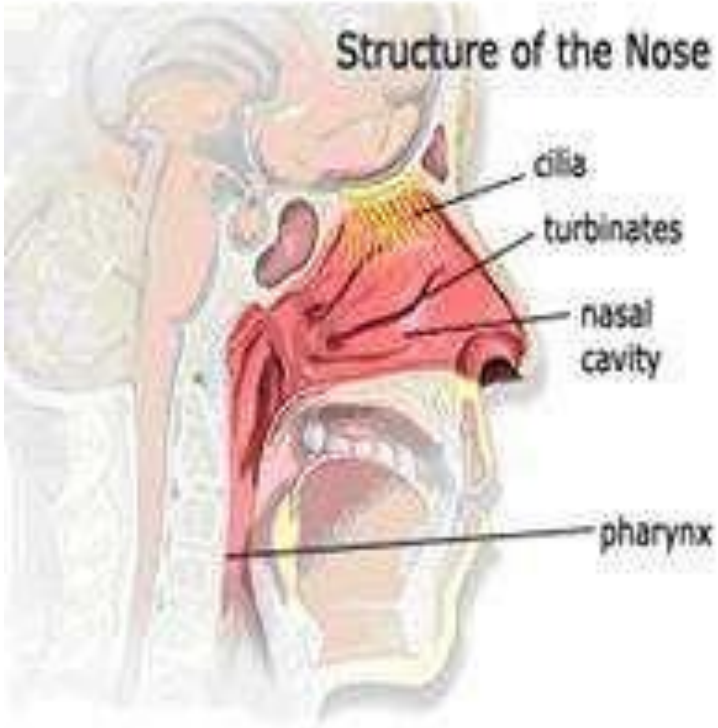
ADVANTAGES

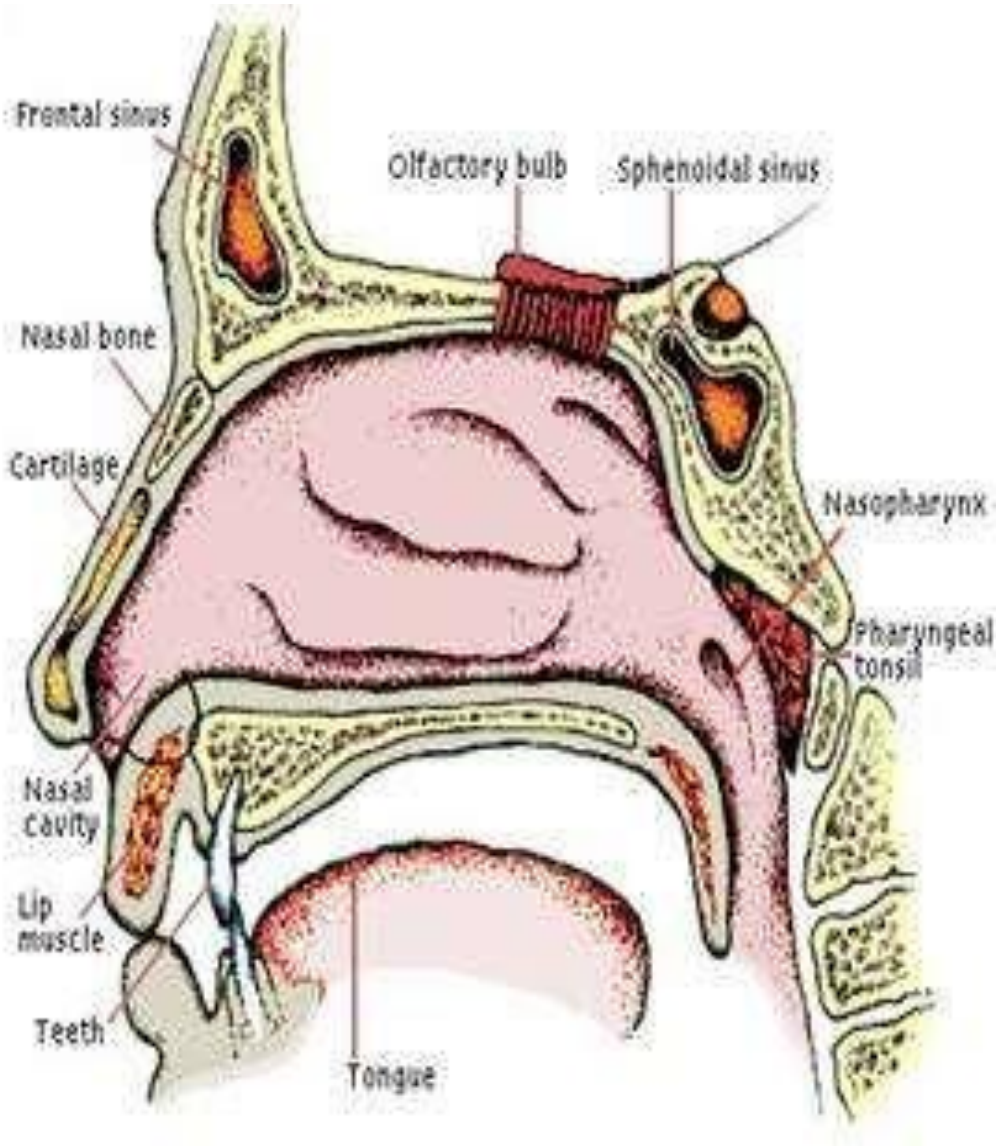
- Hepatic first pass metabolism avoided.
- Rapid drug absorption and quick onset of action.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer.
- BA for smaller drug molecules is good.
- Convenient for long term therapy, compared to parenteral medication.
- Drugs possessing poor stability G.I.T fluids given by nasal route.
- Easy and convenient.
- Easily administered to unconscious patients.

DISADVANTAGES

- Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailabilty.
- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.

ANATOMY & PHYSIOLOGY OF NASAL CAVITY





- The nasal cavity consists three main regions:

1) Nasal vestibule

2) Respiratory region

major drug absorption.

3) Olfactory region

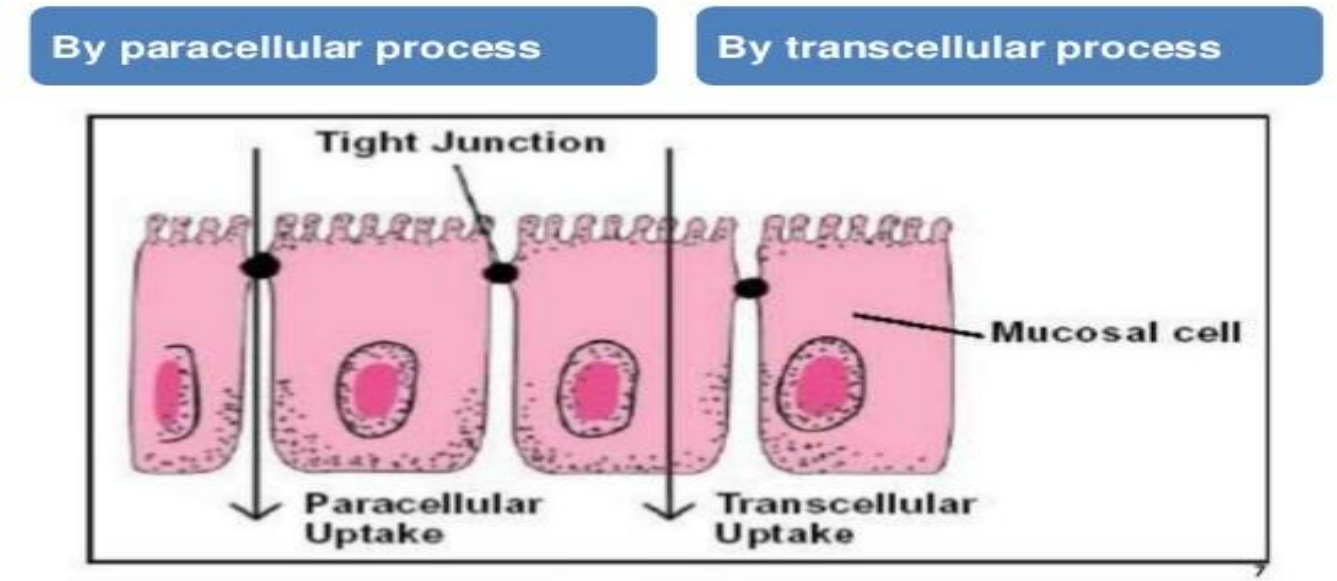
small area in the roof of the nasal cavity of about 10 cm2

- Normal pH of the nasal secretions in adult 5.5-6.5.
- Infants and young children 5.0- 6.7.
- Nasal cavity is covered with a mucous membrane.Mucus secretion is composed of 95%- water, 2%-mucin, 1%-salts, 1%-of other proteins such as albumin,lysozyme and lactoferrin and 1%-lipids.

MECHANISM OF DRUG ABSORPTION

- ***Paracellular (intercellular)*** Slow and passive absorption of peptides and proteins associated with intercellular spaces and tight junctions.

- ***Transcellular*** : Transport of lipophilic drugs passive diffusion/active transport.



FORMULATION APPROACHES

- Nasal gels
- Nasal Drops
- Nasal sprays
- Nasal Powder

Nasal Gels

- High-viscosity thickened solutions or suspensions
  Advantages:
  - reduction of post-nasal drip due to high viscosity
  - reduction of taste impact due to reduced swallowing
  - reduction of anterior leakage of the formulation
- Reduction of irritation by using emollient excipients.

Nasal Drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products.

Nasal sprays

- Both solution and suspension formulations can be formulated into nasal sprays.
- Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm.The particles size and morphology (for suspensions)of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

Nasal Powder

- This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability.
- The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the stability of the powder formulation is dependent on the solubility, particles size and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system.

STRATEGIES TO IMPROVE NASAL ABSORPTION

- **Permeation enhancers**

Type of compound	Examples	Mechanisms of action
Bile salts (and derivatives)	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Disrupt membrane, open tight junctions, enzyme inhibition, mucolytic activity
Surfactancts	SLS, saponin, polyoxyethylene-9-lauryl ether	Disrupt membranes
Chelating agents	Ethylenediaminetetraacetic acid(EDTA), salicylates	Open tight junction
Fatty acids	Sodium caprylate, sodium laurate, phospholipids	Disrupt membranes
Bioadhesive materials Powders	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions
Liquids	Chitosan, carbopol	Reduce nasal clearance, open tight junction

- **Prodrug approach**

- The absorption of peptides like angiotensin II, bradykinin, vasopressin and calcitonin are improved when prepared into enamine derivatives.

- **Structural modification**

- Chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability.

- **Particulate drug delivery**

- Microspheres, nanoparticles and liposomes

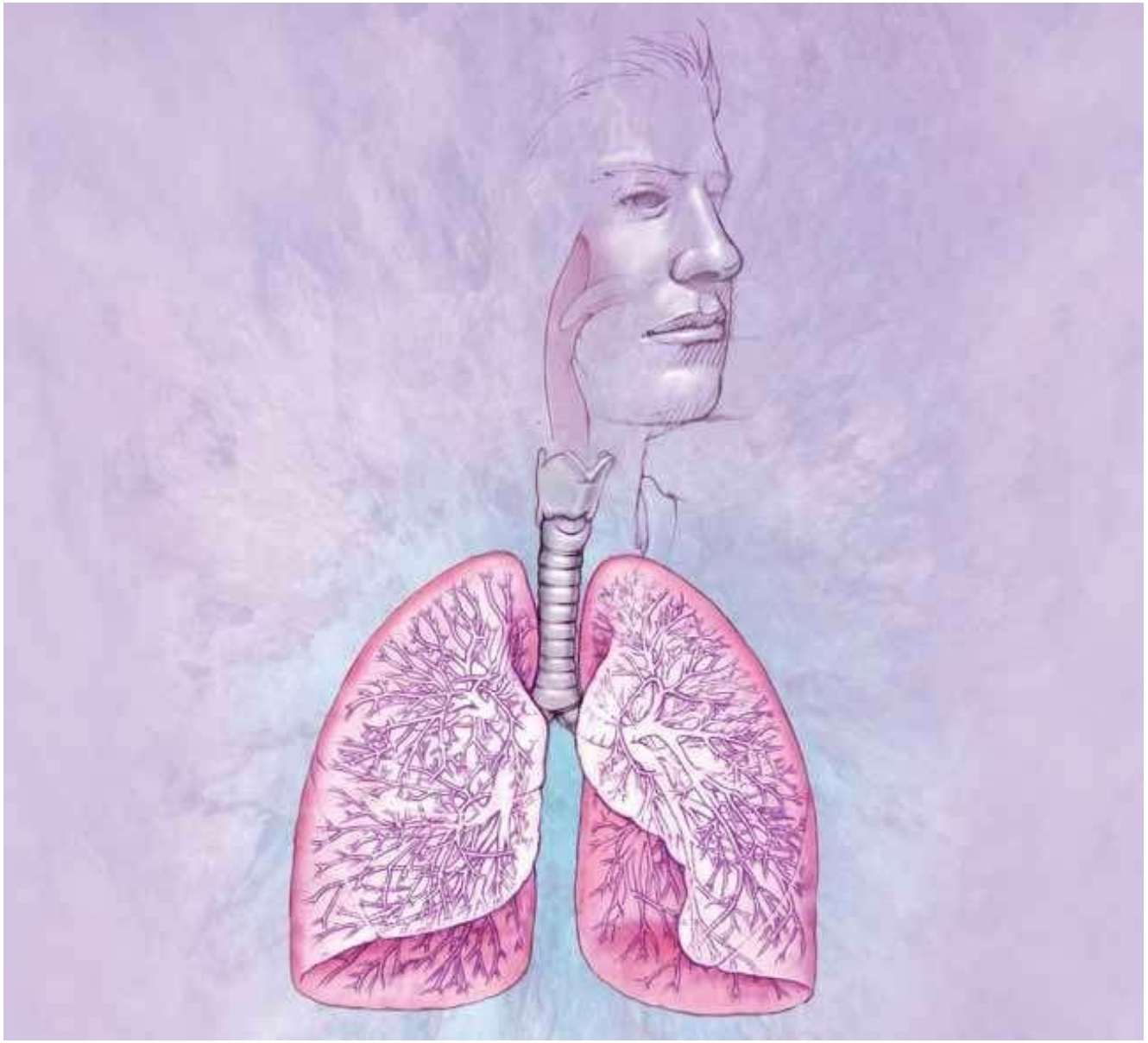
Evaluation tests

For Nasal Gels

- Mucoadhesive testing
- A 1x1 cm piece of goat nasal mucosa was tied to a glass slide using thread. Gel was spread on the tissue specimen and the prepared glass slide was hung on one of the groves of a USP tablet disintegration test apparatus.The tissue specimen was given regular up and down movements in the beaker of the disintegration apparatus containing phosphate buffer pH 6.4.
- Time required for complete washing of gels was noted.
- *In vitro* drug diffusion study
- The drug diffusion from different formulation was determined using treated cellophane membrane and Franz diffusion cell.
- Drug was placed on cellophane membrane in the donor compartment contained phosphate buffer (pH 6.4).
- Samples were analyzed spectrophotometrically.

- ## Measurement of Gelation Temperature (T1) and Gel Melting Temperature (T2):
- A 2ml aliquot of gel was taken in a test tube, immersed in a water bath.
- The temperature of water bath was increased slowly.
- The sample was then examined for gelation, i.e **GELATION temp T1**.
- Further heating of gel causes liquefaction of gel and form viscous liquid and it starts flowing, this temperature is noted as T2

PULMONARY DRUG DELIVERY SYSTEM



CONTENTS

- INTRODUCTION
- ADVANTAGES AND LIMITATIONS
- THE RESPIRATORY TRACT
- FORMULATIONS APPROACHES AND DEVICES

INTRODUCTION

- Pulmonary drug delivery is primarily used to treat conditions of the airways, delivering locally acting drugs directly to their site of action.

- The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease)

- The drugs which are administered by pulmonary route are not only for lungs delivery but it goes to systemic circulation and produce the effect where it is desired through out the body.

ADVANTAGES OF PULMONARY DRUG DELIVERY

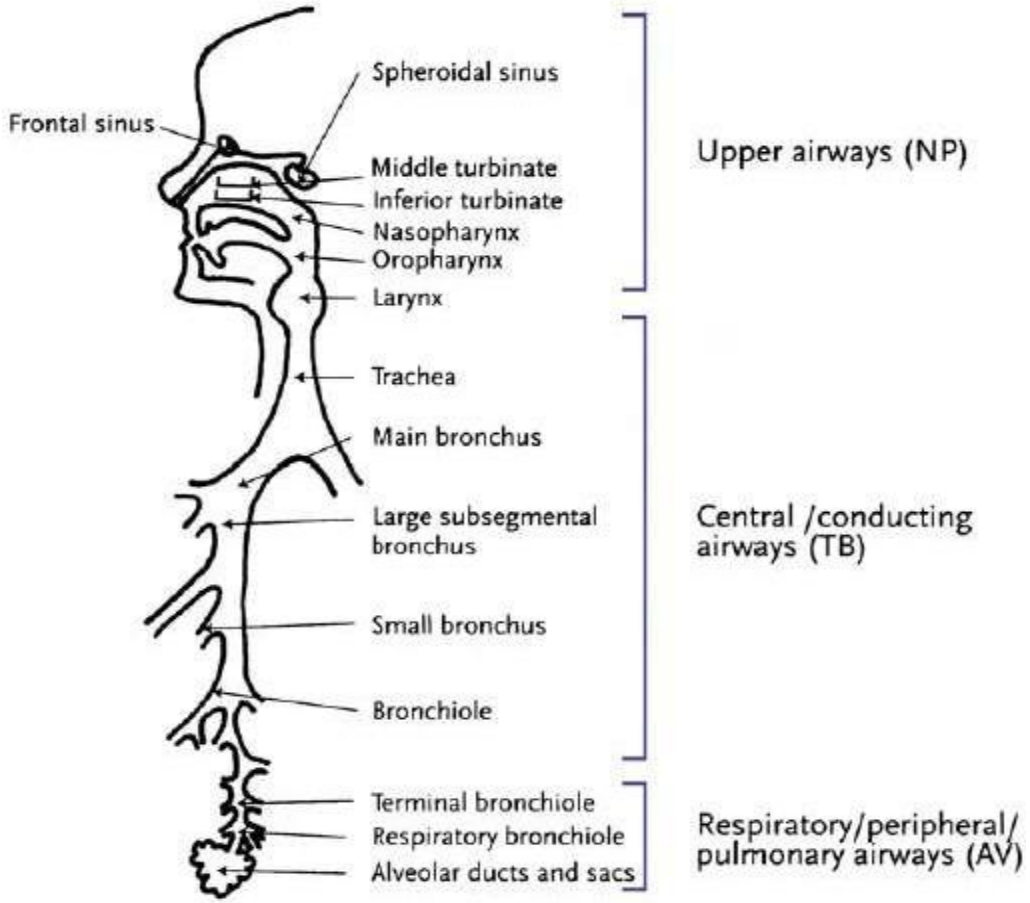
- It is needle free pulmonary delivery.
- It requires low and fraction of oral dose.
- Pulmonary drug delivery having very negligible side effects since rest
- of body is not exposed to drug.
- Onset of action is very quick with pulmonary drug delivery.
- Degradation of drug by liver is avoided in pulmonary drug delivery.

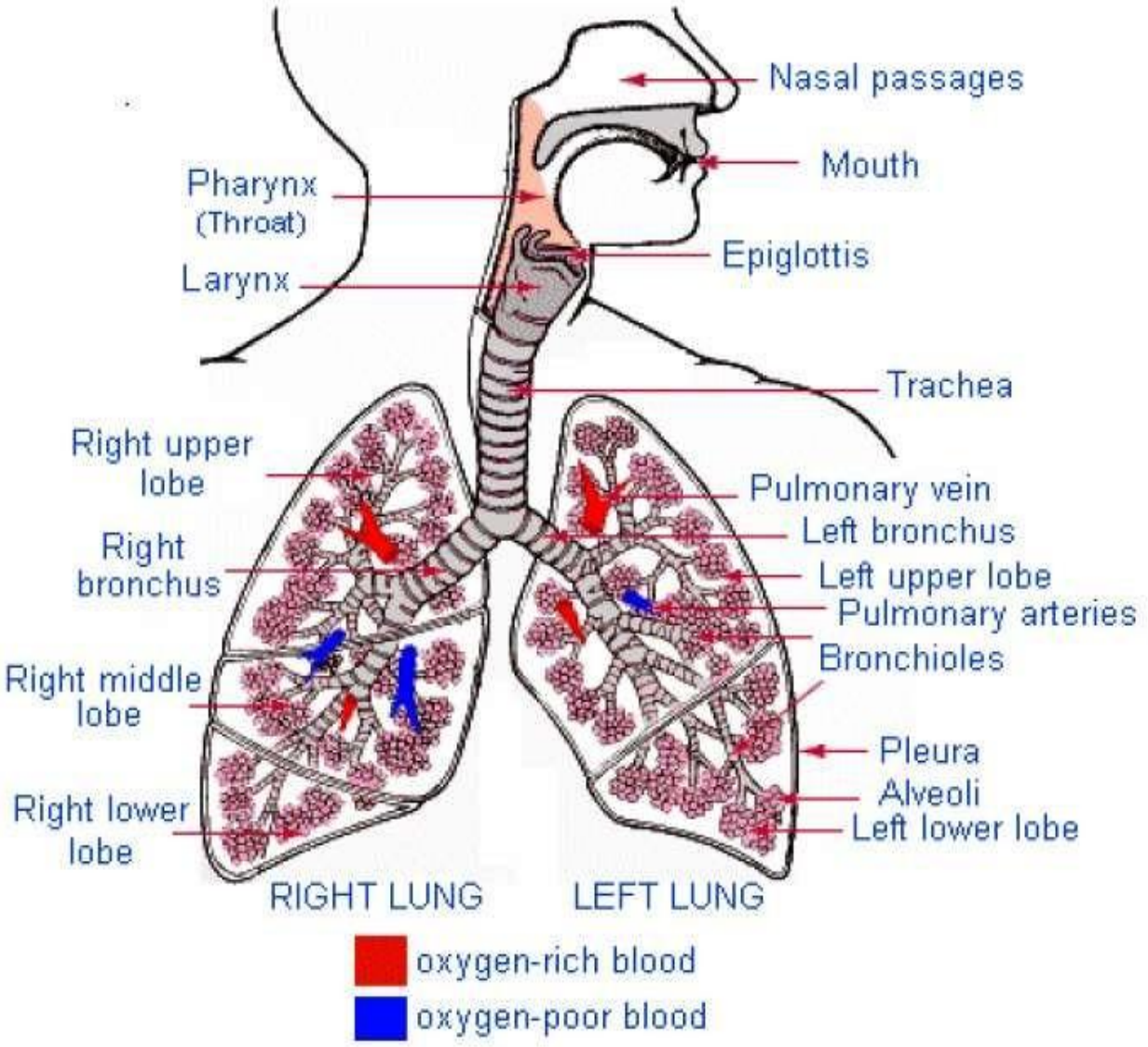
LIMITATIONS

- Drug irritation and toxicity.
- Drug stability problem
- Low efficiency of inhalation system
- Improper dosing

ANATOMY & PHYSIOLOGY OF RESPIRATORY TRACT

1. Lungs region
2. Nasopharyngeal region
3. Tracheo-bronchial region
4. Alveolar Region




Nasal passages
Mouth
Pharynx
(Throat)
Epiglottis
Larynx
Trachea
Right upper
lobe
Pulmonary vein
Left bronchus
Right
bronchus
Left upper lobe
Pulmonary arteries
Bronchioles
Right middle
lobe
Pleura
Alveoli
Right lower
lobe
Left lower lobe
RIGHT LUNG
LEFT LUNG
oxygen-rich blood
oxygen-poor blood

AEROSOLS

Aerosol is a pressurized dosage forms containing one or more therapeutic active ingredients which upon actuation emit a fine dispersion of liquid and/or solid materials in a gaseous medium.

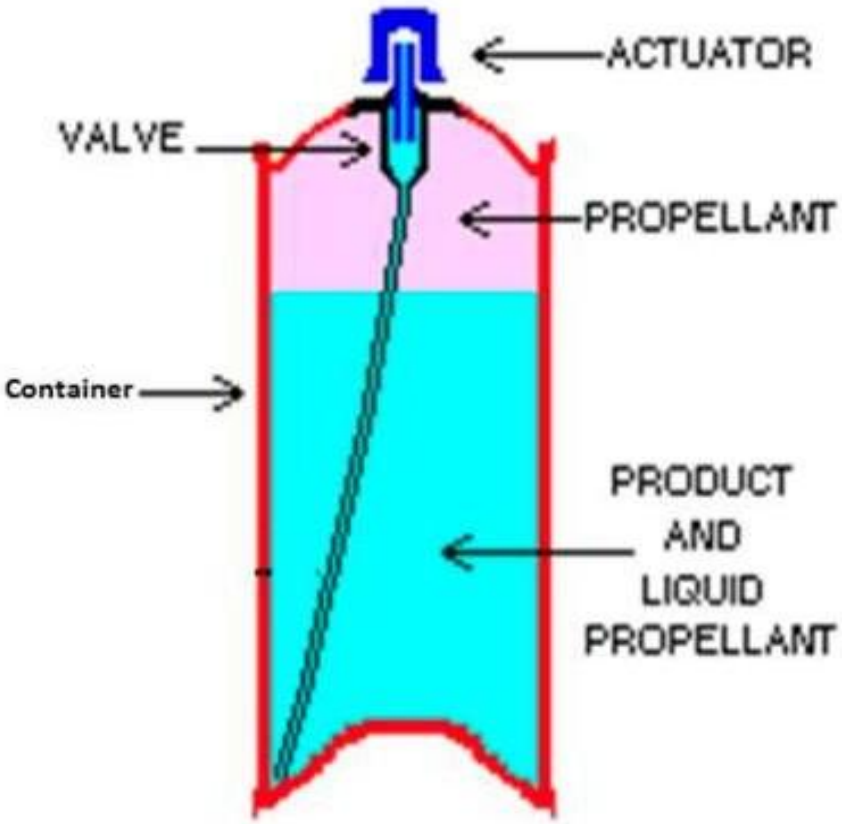
There are three commonly used clinical aerosols:-

1. Jet or ultrasonic nebulizers,
2. Metered–dose Inhaler (MDI)
3. dry-powder inhaler (DPI)

- The basic function of these three completely different devices is to generate a drug-containing aerosol cloud that contains the highest possible fraction of particles in the desired size range.

Components of Aerosols

1. Propellant
2. Container
3. Valve and actuator
4. Product concentrate



Propellants

- Responsible for developing proper pressure within the container.
- Provide driving force to expel the product from the container.

TYPES OF PROPELLANTS

(a) Liquefied gases Propellants

(a) Compressed gases Propellants

Types of Propellants

1. Liquefied Gas Propellants :-

1) For oral and inhalation

- Tri-chloro-mono-flouro methane (propellant 11)
- Di-chloro di-fluro methane (propellant 12)

2) Topical Pharmaceutical aerosols

- Propane
- Butane

2. Compressed Gas Propellants :-

- Nitrogen
- Carbon di-oxide

Liquefied Gas Propellants

- Exist as liquids underpressure.
- Because the aerosol is under pressure propellant exists mainly as a liquid, but it will also be in the head space as a gas.
- The product is used up as the valve is opened, some of the liquid propellant turns to gas and keeps the head space full of gas.
- In this way the pressure in the can remains essentially constant and the spray performance is maintained.

Chloro Fluoro Carbon

Advantages

- Chemical inertness
- Lack of toxicity
- Non flammability.
- Lack of explosiveness.

Disadvantages

- High cost
- It depletes the ozone layer

Hydrocarbon

Advantages

- Inexpensive
- Excellent solvents

Disadvantages

- Inflammable
- Unknown toxicity produced

Compressed Gas Propellants

- Compressed gas propellants occupy the head space above the liquid in the can.
- When the aerosol valve is opened the gas 'pushes' the liquid out of the can.
- The amount of gas in the headspace remains the same but it has more space, and as a result the pressure will drop.
- Spray performance is maintained however by careful choice of the aerosol valve and actuator.
- Examples:

  Carbon dioxide, Nitrous oxide and Nitrogen

Containers

They must be able to withstand pressures as high as 140 to 180 psig.

AEROSOL CONTAINERS

A. Metals
   i. Tinplated steel
   ii. Aluminum
   iii. Stainless steel

B. Glass
   I. Uncoated glass
   II. Plastic coated glass

Tin Plated Steel Containers

- It consist of a sheet of steel plate, this sheet is coated with tin material.
- The coated sheet is cut into three pieces (top , bottom and body)

Aluminium Containers

- Light in weight, less fragile.
- Greater resistance to corrosion .
- Pure water and pure ethanol cause corrosion to Al containers.

Glass Container

- These containers are preferred because of absence of incompatibilities.
- These containers are limited to the products having a lower pressure (33 psig)

Two types of glass aerosol containers

- Uncoated glass container:
- Less cost and high clarity and contents can be viewed at all times.
- Plastic coated glass containers:
- These are protected by plastic coating that prevents the glass from shattering in the event of breakage.

Valves

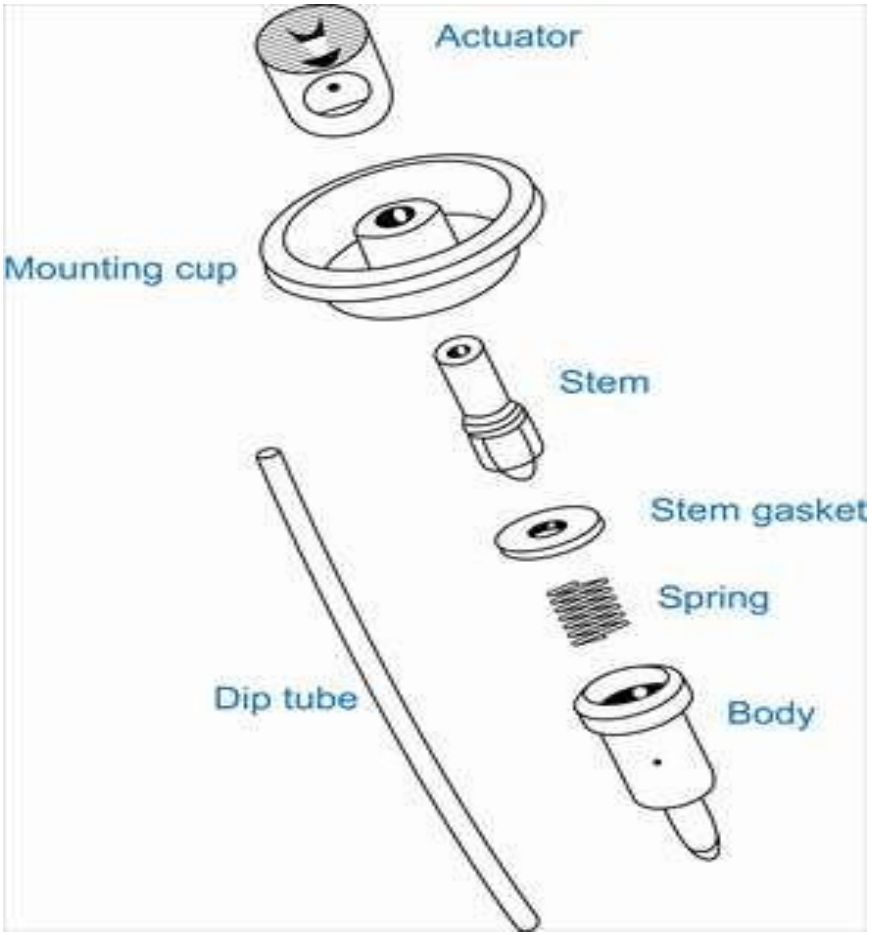
- To delivered the drug in desired form.
- To give proper amount of medication.

Types

- Continuous spray valve
- Metering valves

Valve Components

- Ferrule or mounting cup
- Valve body or housing
- Stem
- Gasket
- Spring
- Dip tube



Actuator

These are specially designed buttons which helps in delivering the drug in desired form i.e. spray, wet stream, foam or solid stream.

TYPES OF ACTUATORS:

- Spray actuators
- Foam actuators
- Solid steam actuators
- Special actuators

- SPRAY ACTUATORS : - It can be used for topical preparation, such as antiseptics, local anesthetics and spray on bandges etc.
- FOAM ACTUATORS : - These actuators are used for producing foam upon actuation.
- SOLID STREAM ACTUATORS : - These actuators are required for dispensing semi solid products such as ointments.
- SPECIAL ACTUATORS: These are used for specific purpose.

  It delivers the medicament to the appropriate site of action such as throat, nose, dental and eyes etc.

DEVICES

Nebulizers

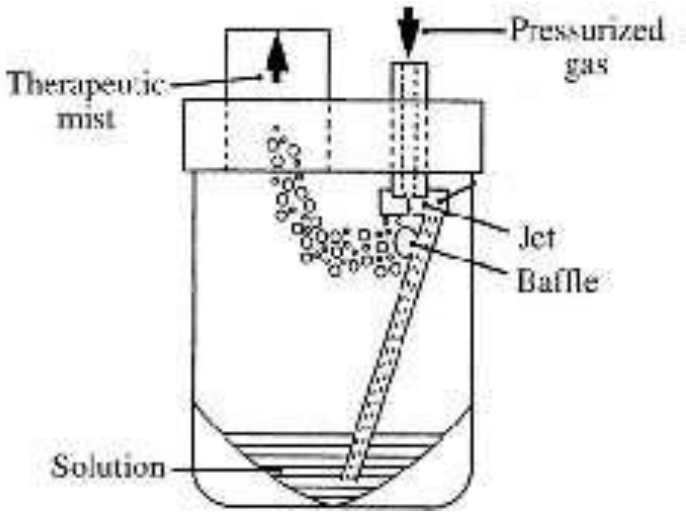
- Nebulizers are widely used as aerosolize drug solutions or suspensions for drug delivery to the respiratory tract and are particularly useful for the treatment of hospitalized patients.

- Delivered the drug in the form of mist.

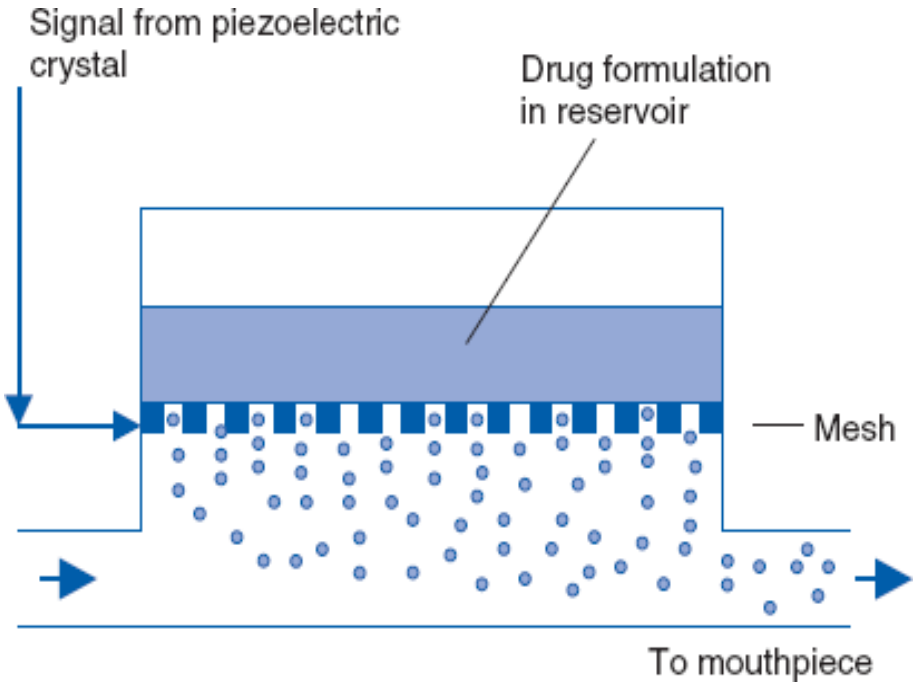
- There are two basic types:

1) Air jet
2) Ultrasonic nebulizer

Jet nebulizers



Ultrasonic nebulizers



Dry powder inhalers(DPI)

- DPIs contain solid drug in a dry powder mix (DPI) that is fluidized when the patient inhales.
- DPIs are typically formulated as one-phase, solid particle blends.The drug with particle sizes of less than 5µm is used
- Dry powder formulations either contain the active drug alone or have a carrier powder (e.g. lactose) mixed with the drug to increase flow properties of drug.
- DPIs are a widely accepted inhaled delivery dosage form, particularly in Europe, where they are currently used by approximately 40% of asthma patients.

Advantages

- ✓ Propellant-free.
- ✓ Less need for patient co-ordination.
- ✓ Less formulation problems.
- ✓ Dry powders are at a lower energy state, which reduces the rate of chemical degradation.

Disadvantages

- ✓ Dependency on patient's inspiratory flow rate and profile.
- ✓ Device resistance and other design issues.
- ✓ Greater potential problems in dose uniformity.
- ✓ More expensive than pressurized metered dose inhalers.

Unit-Dose Devices

- Single dose powder inhalers are devices in which a powder containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled.

Multidose Devices

- This device is truly a metered-dose powder delivery system. The drug is contained within a storage reservoir and can be dispensed into the dosing chamber by a simple back and forth twisting action on the base of the unit.

Dry Powder inhalers

Metered Dose Inhalers (MDI)

- Used for treatment of respiratory diseases such as asthma and COPD.
- They can be given in the form of suspension or solution.
- Particle size of less than 5 microns.
- Used to minimize the number of administrations errors.
- It can deliver accurate amount of medicament.

Advantages of MDI

- It delivers specified amount of dose.
- Small size and convenience.
- Usually inexpensive as compare to dry powder inhalers and nebulizers.
- Quick to use.
- Multi dose capability more than 100 doses available.

Disadvantages of MDI

- Difficult to deliver high doses.
- There is no information about the number of doses left in the MDI.

Push down on the canister and breathe in slowly

A.D.A.M.

Thank You….

Transdermal Drug Delivery System

By

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- At present, the most common form of delivery of drugs is the oral route. it has the notable advantage of easy administration.

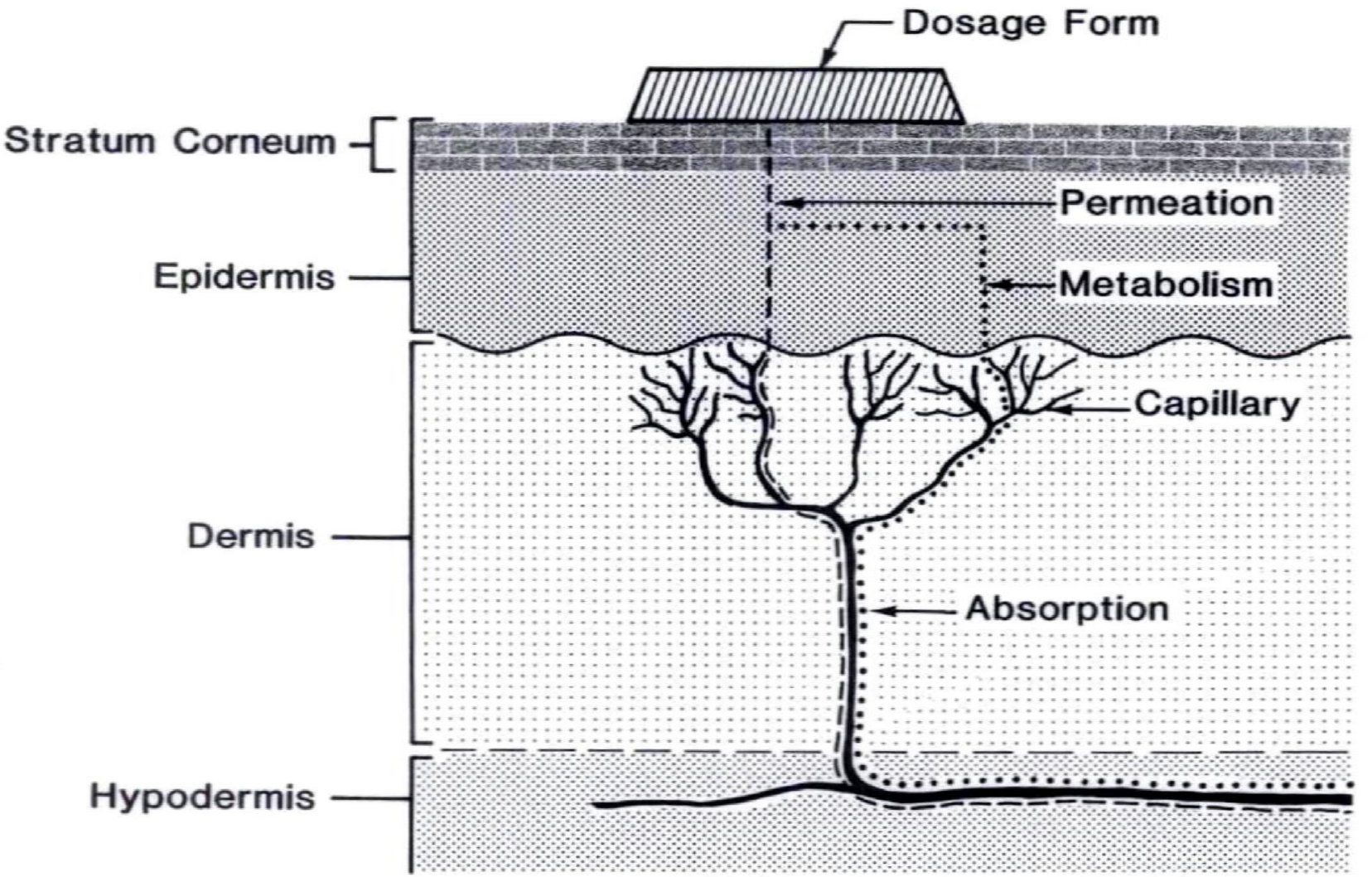
- Oral route also has significant drawbacks -- namely poor bioavailability due to poor solubility of drugs in G.I.T, due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both non-economic and inconvenient.

- To overcome these difficulties there is a need for the development of new drug delivery system which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses.

- One of the methods most often utilized has been transdermal delivery - meaning transport of therapeutic substances through the skin for systemic effect.

Transdermal drug delivery system are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate.

Schematic of Skin Absorption



- There are two important layers in skin: **the dermis and the epidermis**. The outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the **stratum corneum.**

- **stratum corneum** is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out.

- Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body.

- If the drug is able to penetrate the stratum corneum, it can enter the blood stream thus stratum corneum is rate limiting step for permeation of trans dermal preparation.

Potential Benefits of Transdermal Systems

- Bypasses the first pass metabolism, avoids inactivation of drugs by pH effects and enzymes present in GI tract, which otherwise happens on oral administration.
- Provide for multiple daily doses with a single application.
- Provide a means to quickly terminate dosing.
- Provide improved systemic bioavailability of active ingredients.
- Permits self-administration
- Non-invasive (no injections)

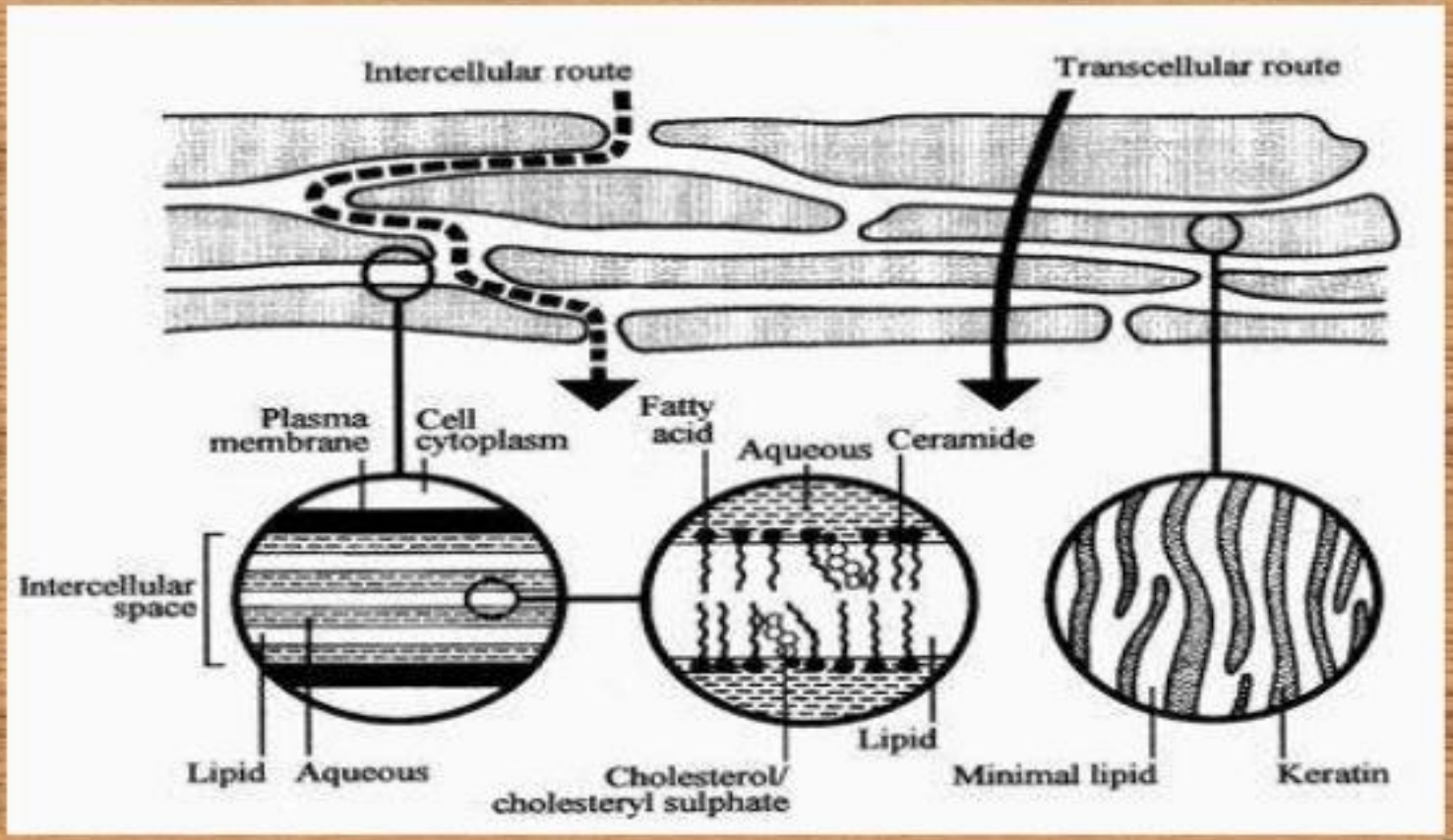
However Transdermal system has its **own limitations** in which

- The drug that require high blood levels cannot be administered

- The adhesives may not adhere well to all types of skin and may be uncomfortable to wear.

- Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

Routes of drug absorption through skin



Formulation components of TDDS

- Polymer
- Drug
- Permeation enhancers
- Other excipients

Polymer

The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are:

a) Natural Polymers:

e.g. Cellulose derivatives, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch, etc.

b) Synthetic Polymers:

e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene,

Polypropylene, Polyacrylate, Polyamide, Polyurea, etc

Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 Daltons.

.

2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.

3. The drug should have low melting point.

Along with these properties the drug should be ***potent, having short half life and be non irritating.***

Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by fluidizing lipids. Examples include

- water
- alcohols – methanol and ethanol;

- **Alkyl Methyl Sulfoxides** – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide ;

- **Pyrrolidones** – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone),

- **Miscellaneous Solvents** – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

b) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.

Bile Salts: e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Binary system*:* Two chemical in combine used as penetration enhancer.

e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

c) Miscellaneous chemicals

These include

- urea, a hydrating and keratolytic agent;
- N,N-dimethyl-m-toluamide

Other Excipients:

(a) Adhesive

- Should not cause imbalance in normal skin flora
- Should adhere skin aggressively during dosing interval
- Should be easily removed
- Should not leave any residue
- Should not affect permeation of drug

Example

- Poly isobutene
- Acrylics
- Silicones

(b) Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top.

Examples:

- Metallic plastic laminate,
- Plastic backing with absorbent pad and occlusive base plate (aluminum foil),

Evaluation of TDDS

The physical parameters such as

- Thickness
- Folding endurance
- Tensile strength
- Adhesion property

Patch thickness

- Patch thickness was measured using digital micrometer screw gauge at three different places and the mean value was calculated.

Folding endurance

- Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm x 2cm) at the same place till it broke.

- The number of times, the film could be folded at the same place without breaking gave the value of folding endurance.

The tensile strength

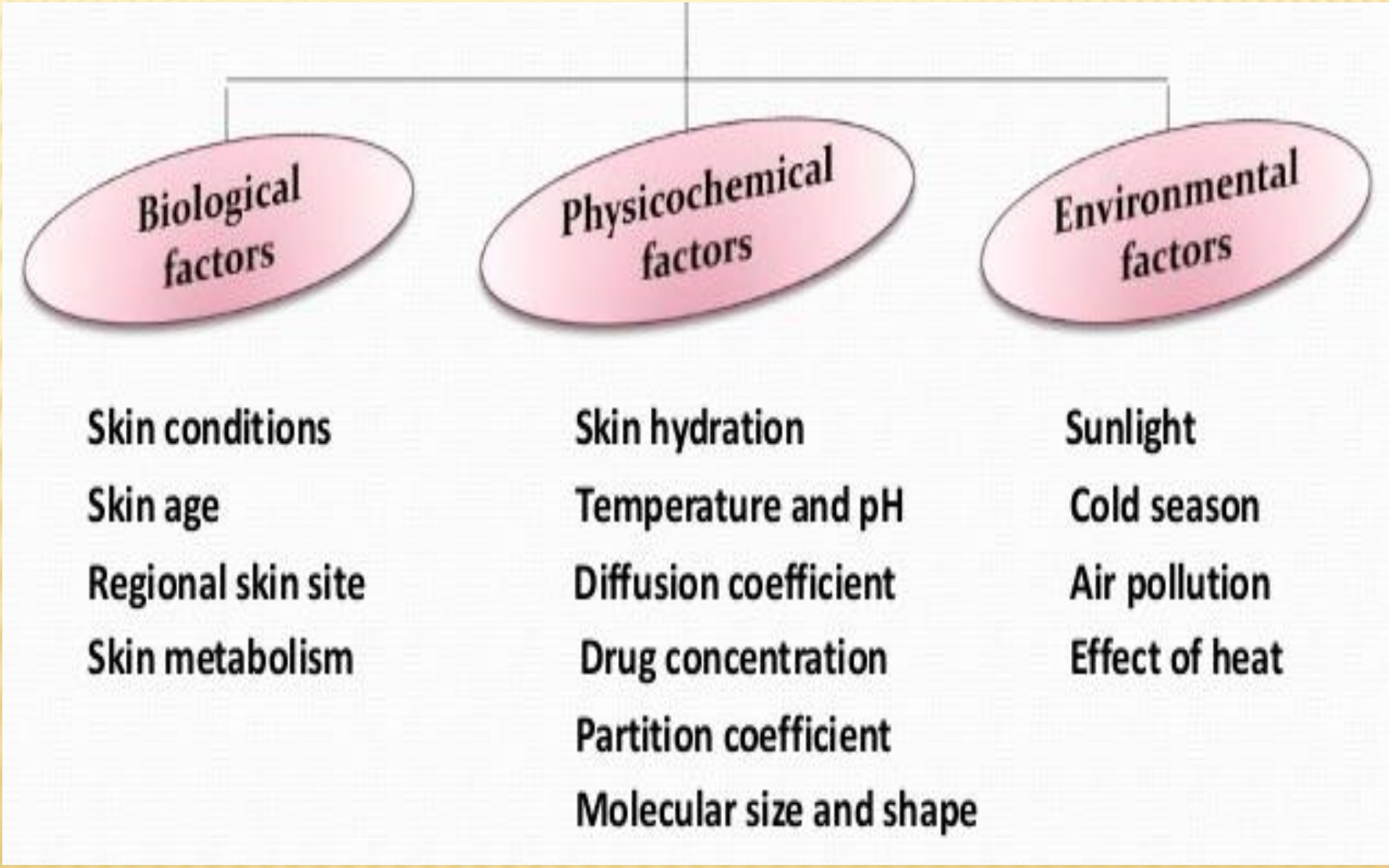
- The tensile strength was determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke.

Evaluation of adhesive

Peel adhesion properties:

- Force required to removed adhesive coating
- Affected by molecular weight, composition of adhesive Polymer type & amount of additives
- adhesive failure –indicate better adhesion property of patch.

FACTORS AFFECTING TRANSDERMAL PERMEATION



BIOLOGICAL FACTORS

- **Skin conditions:-** The intact skin itself acts as barrier.

- **Skin age:-** It is seen that the skin of adults and young ones are more permeable than the older ones, while the children shows toxic effects.

- **Regional skin site:-** Thickness of skin, nature of stratum corneum and density of appendages vary site to site.

PHYSICOCHEMICAL FACTORS

- **Skin hydration:-** In contact with water the permeability of skin increases significantly.

- **Temperature & pH :-** The permeation of drug increases with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH.

- **Diffussion coefficient:-** At a constant temperature the diffusion coefficient of drug depends on properties of drug.

- **Skin metabolism:-** Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

- **Partition coefficient:-** Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

- **Molecular size & shape: -** Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

ENVIRONMENTAL FACTORS

- **Sunlight:-** Due to Sunlight the walls of blood vessels become thinner leading to bruising with only minor trauma in sun-exposed areas.
- **Cold season:-** Often result in itchy, dry skin.
- **Air pollution:-** Dust can clog pores and increase bacteria on the face and surface of skin, both of which lead to acne or spots. This affects drug delivery through the skin.
- **Effect of heat on patch:-** In this case the patch should be removed immediately. Transdermal drug patches are stored in their original packing and keep in a cool, dry place until they are ready to used.

Penetration Enhancers:-

Two types of principles have been employed to increase drug permeation (and drug absorption) through skin: chemical and physical.

Chemical enhancers-

Substance exist which temporarily diminish the impermeability of the skin, known also as accelerants or sorption promoters.

Examples-Sulphoxides and similar chemicals, Azone, Pyrrolidones, Fatty acids, Essential oils, terpenes, terpenoids, Oxazolidodienes and Urea.

Physical enhancers-

Physical enhancement technologies have taken off where the limitations of chemical enhancement have been reached.

Methodologies involved in the physical transdermal delivery including:

•Electrically-based techniques: iontophoresis, electroporation, ultrasound,

Product name	Drug	Manufacturer	Indication
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceutical	Angina pectoris
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Transdermal Scop	Scopolamine	Alza/Norvatis	Motion sickness

Formulation approaches

1. Iontophoresis
2. Electroporation
3. Sonophoresis
4. Needle less Injection
5. Physical Avoidance of Stratum corneum
6. Microfabricated microneedles

(1) Iontophoresis

- Means uses of **low voltage electrical current** to drive charged drugs through the skin.

- Iontophoresis method involves the application of a low level electric current to enhance permeation of a topically applied therapeutic agent.

- Current intensity should be selected below pain threshold level of patient.

- The current intensity must be within comfortable toleration of patient with a current intensity less than 0.5 amp/cm^2.

➢ Iontophoresis overcomes many limitation associated with conventional Transdermal system and could be feasible for ionic, hydrophilic and higher molecular weight drugs.

➢ Iontophoresis uses an electrical supply with an anode (negative Electrode) and a cathode (positive electrode).

Procedure for drug delivery via Iontophoresis.

▪ The charged drug is dissolve in a suitable vehicle and is placed in contact with electrode of same polarity.

- When current flow, the drug is repelled from the electrode of same polarity And is attracted towards the oppositely charged electrode.

➢ Two primary mechanism exist for increases drug delivery during Iontophoresis **Electro repulsion and Electro osmosis.**

❖ **Electro repulsion** for flux of charged drug molecules

❖ **Electro osmosis** for flux of neutral drug molecules.

✓ In Iontophoresis as electrical current is applied, endogenous ions within skin attract to oppositely charged electrode.

e.g. sodium ion (Na+) migrate to the Cathode (negatively charged)

Dis-advantage of Iontophoresis

- Electric shock
- Skin irritations
- Burns
- Cost of treatment.

(2) Electroporation:

- This method involves the application of high voltage current in form of pulses to the skin which has been suggested to induce the formation of transient pores.

- High voltages and short treatment durations (milliseconds) are most frequently employed.

- The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. **small molecules, proteins, peptides and oligonucleotides) .**

- Electroporation creates **aqueous pores in the barrier** and hence promote drug Flux.

- Electroporesis use **for delivering larger molecules** to the

- Smaller molecules also been delivered by electroporation.

- Electroporation gives **Higher permeation than Iontophoresis.** e.g. tetracycline delivery was increased by elecroporation (55 µg/cm2/h) as compared to Iontophoresis (17 µg/cm2/h)

(3) Sonophoresis

➢ When **Ultrasound** is used to improve drug delivery through skin is commonly known as Sonophoresis or phonophoresis.

➢ Ultrasound can be defines as that sound with a frequency above **20 kH_z** which subdivided as

- Power ultrasound (Low frequency, from 20 to 100 kHz)
- Therapeutic ultrasound (mid frequency, from 1 to 3 MHz)
- Diagnostic ultrasound (High frequency, above 3 MHz).

- **Low - frequency (power) ultrasound is effective for small organic molecules and macromolecules such as insulin, gamma interferon and erythropoietin .**

(4) Needle less Injection

Advantage

- Pain free administration as particles fires in to skin are too small to trigger pain Receptor within tissue, though some sensation may be felt.
- The fear of needle is avoided.
- Specific skin area can be targeted it is beneficial for e.g. vaccination when delivery to viable epidermal cell is desired.

However, there are still some problems when delivery via this technology

- Careful use of the device may be needed to avoid particles ‘bouncing off’ the skin surface, moreover if device not held vertically the dose may escape or could penetrate the skin to differing degrees.

- The thickness of stratum corneum and other skin layer s varies between individuals and so penetration depth of particles could vary.

- The external environment could affect delivery; for example, delivery through hydrated skin could differ to that through less hydrated skin.

Needle less injection may given in form of powder or liquid.

Powder

- When powder given by Needle less injection it is known as powderjet system.

- Powderjet system basically contain two chamber. One chamber contain drug Particles and other chamber contain compressed helium.

- on actuating the gas ,the helium push the chamber which contain drug particles, the powder is thus Fired down nozzle at around 500 meters per second in to and across stratum corneum.

- The component of device (Nozzle shape, gas pressure etc) can be modified to Optimized delivery to the skin and to specific skin area or across the skin for systemic delivery.

- Depth of particles penetration also depends on many particulate factors such as density, shape and size.

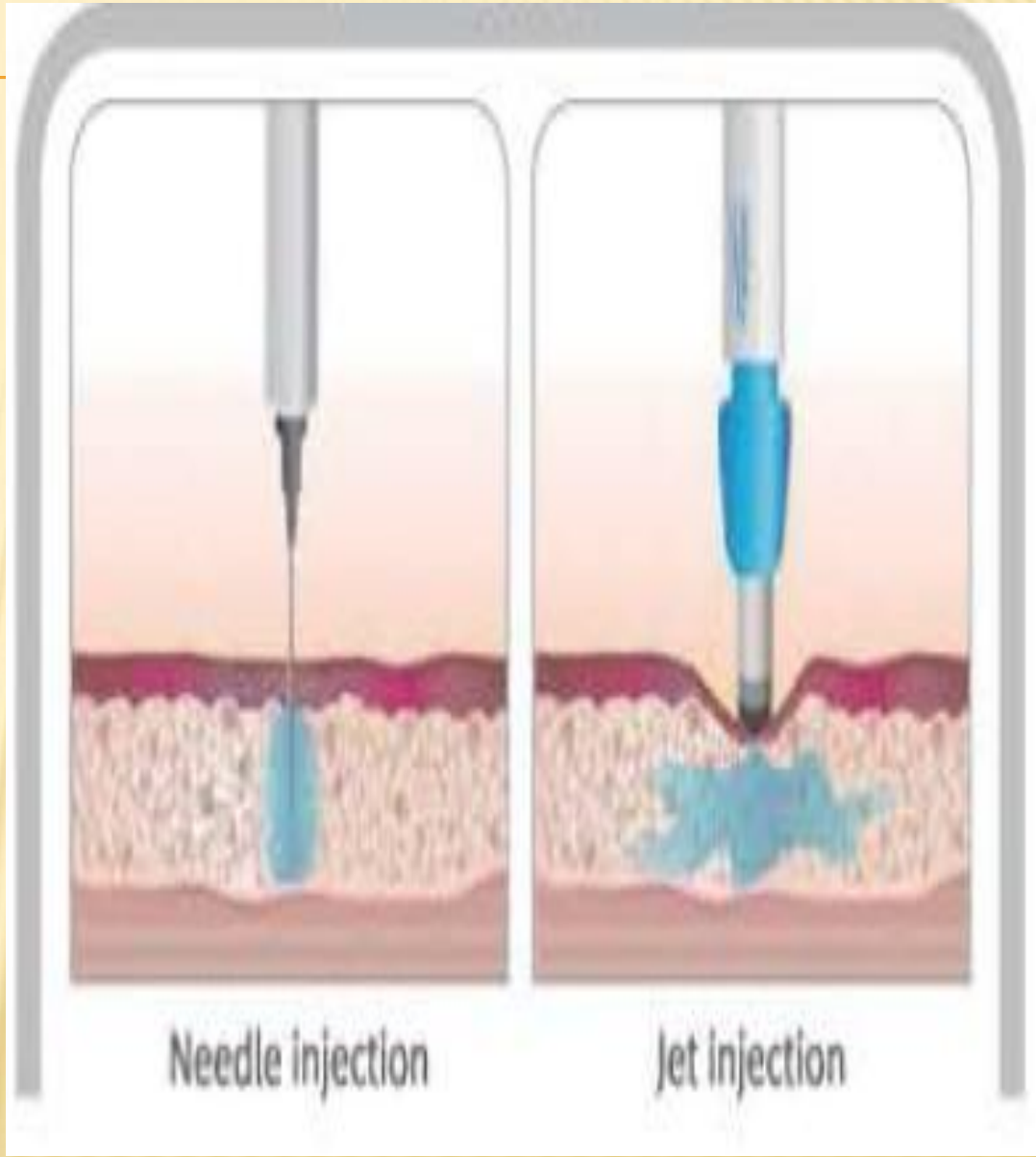
Liquids

- Single and multiple use needle free devices are being developed for liquid formulation.

- When liquid is given through needle less injection it is known as Intrajet.

- In Intrajet hammer-like plunger used while in powderjet compress gas (Helium) Used for pushing drug.


End Cap
Activation Lever
Gas Cartridge
Safety
Sterility Cap
Plunger
Piston
Orifice
Luer cap


Needle injection
Jet injection

(5) Physical Avoidance of Stratum corneum

- Major barrier to transdermal and topical drug delivery of most agents is stratum corneum , efforts for avoidance of this barrier.

- The use of micro needles and ablation of Stratum corneum by laser or other method used for Avoidance of Stratum corneum.

LASER ABLATION

- Removal of Stratum corneum known to increases flux of drug through skin and many method have been used to remove this outer layer from the underlying tissue such as tape stripping or the use of cynoacrylate adhesives.

- A more controlled method To remove the Stratum corneum is via the use of laser.

- Each laser ablates approximately 1μm of Stratum corneum, and that the efficiency of the process is depended upon the laser pulse energy used.

- Ablation of stratum corneum was shown to effective for delivery of both lipophilic and Hydrophilic drugs but it shows greater enhancement for hydrophilic molecules than lipophilic molecules.

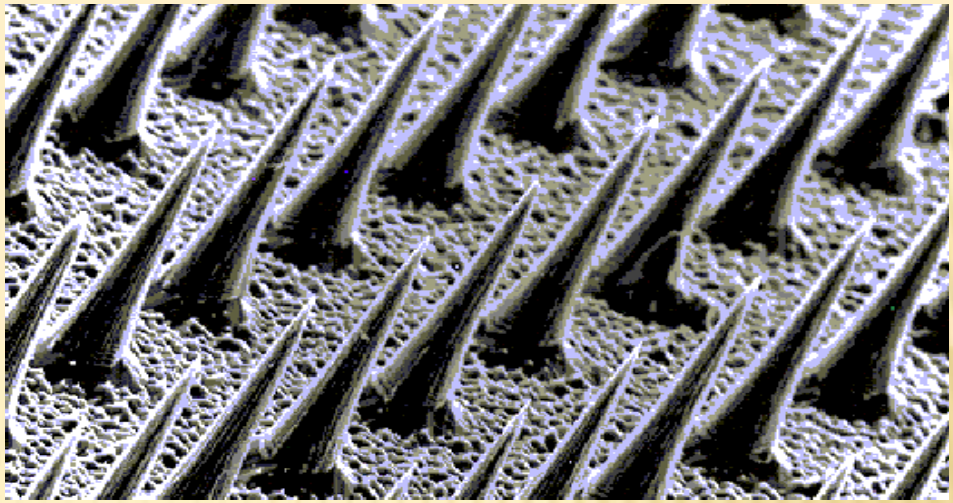
Other ablation method

- Chemical peel can remove layer varying from superfacial stratum corneum to the Epidermis or even dermal tissue.

- Aluminium oxide crystals can be fires at localized areas of the skin to remove tissue.

- All laser and other ablation method flux of both hydrophilic and lipophilic molecules.

Micro needles



- An alternative approaches to bypass the stratum corneum barrier is use a needles.

But disadvantages are

- ❖ Needle pain and phobia
- ❖ Repetitive injection collapsing veins and possibility of cross contamination.

- The needle can be applied to the skin and the removed to form pores within the Stratum corneum before drug formulation is applied to the region.

- Alternatively the drug can be loaded onto the micro needle tips for immediate delivery or micro needles can be made hollow , whereby a formulation could be delivered through needles passively.

- Microneedles used for delivery of larger molecular weight macromolecules such as Insulin.

Disadvantages:-

Skin damage (e.g. erythema, oedema) or microbial contamination.

Thank You