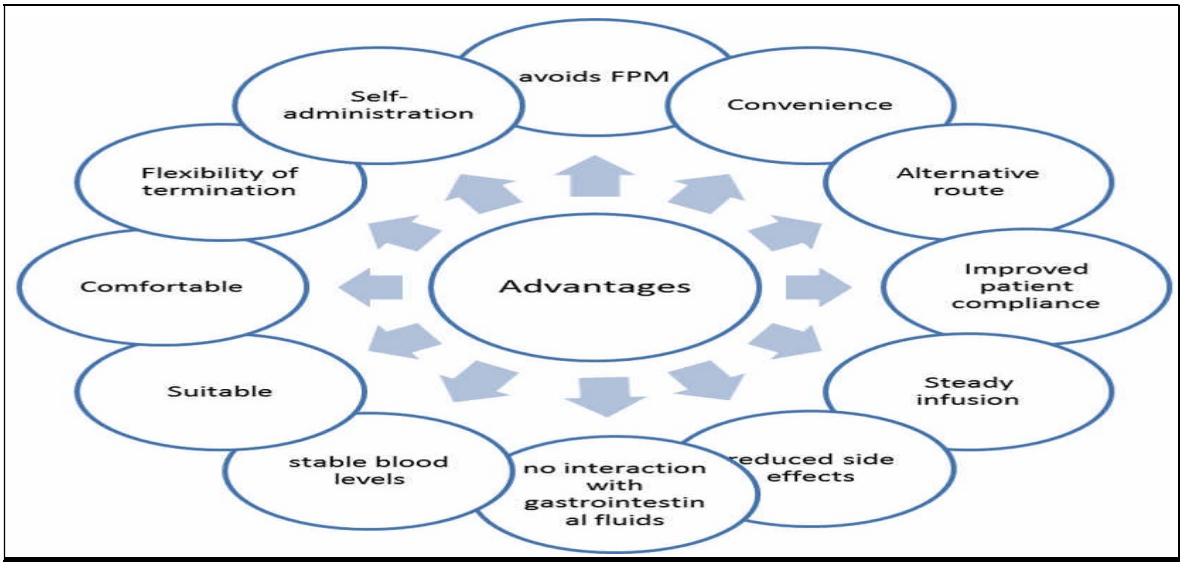
1. Transdermal Drug Delivery Systems:

Introduction:

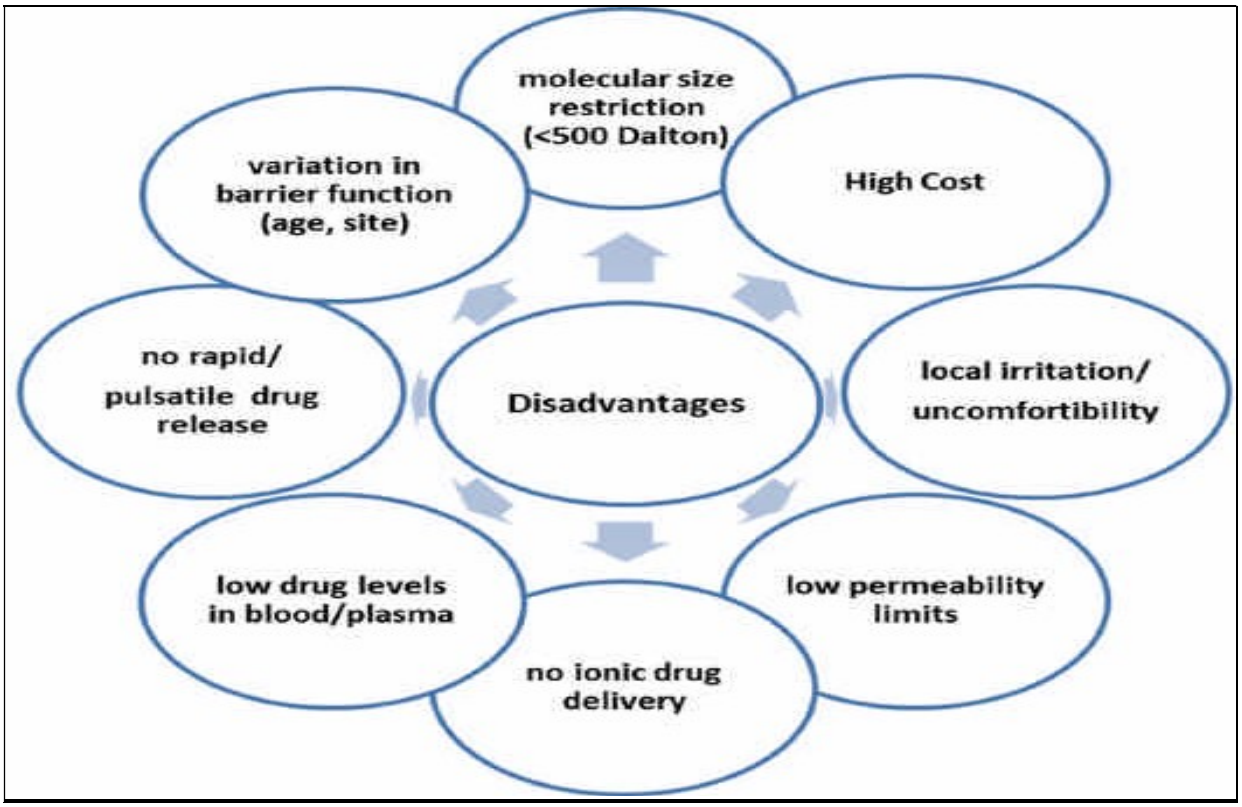
Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects.

Advantages of TDDS

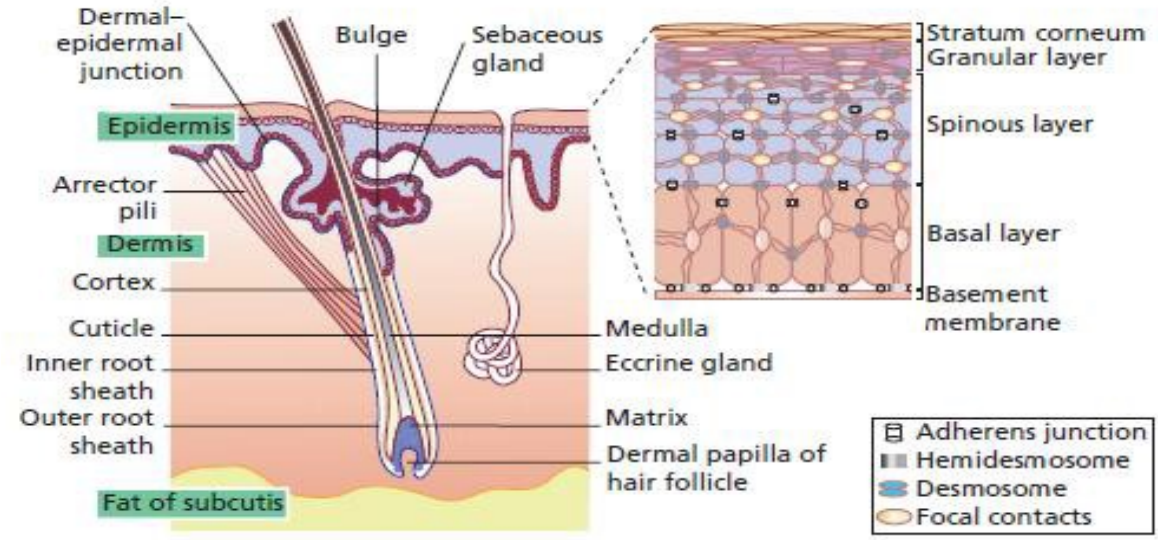


Disadvantages of TDDS:



Permeation through skin:

To improvise the current potential of TDDS it is necessary to understand the very basic of skin anatomy. Skin is multi-layered organ composed of many histological layers. The major divisions of the skin, from top to bottom, are the, epidermis, the dermis and the hypodermis.



Anatomy of Skin

Epidermis:

Stratified, squamous, keratinizing epithelium. Keratinocytes comprise the major cellular component (> 90%) and are responsible for the evolution of barrier function. Keratinocytes change their shape, size and physical properties when migrating to the skin surface. Microscopically, the epidermis further divided into five anatomical layers with approximately 100-150 micrometres thick, Stratum corneum (SC) forming the outer most layer of the epidermis, exposing to the external environment. This is the most important layer to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. SC is large, flat, polyhedral, plate-like envelopes filled with keratin that is made up of dead cells that have migrated up from the stratum granulosum. The SC consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 μm in the dry state to 40 μm when they are hydrated.

Dermis:

Dermis consists of extensive microvasculature network structures like sweat glands, hair follicles, and the smaller blood vessels. Therefore, in order to have drug delivery via the skin, the drug must pass through the epidermis into the dermis where it can be absorbed by capillaries into the circulatory system. Inner and larger (90%) skin layer comprises primarily of connective tissue and provides supports to the epidermis layer of the skin. The boundary between dermis and epidermis layer is called Dermal- Epidermal junction which provides a physical barrier for the large molecules of drug and cells. It incorporates blood and lymphatic vesicles and nerve endings. Dermis can be divided into two anatomical region; papillary dermis and reticular dermis. Papillary is the thinner outermost portion of the dermis. Collagen and elastin fibres are mostly vertically oriented in the papillary region and connected with the dermal-epidermal junction.

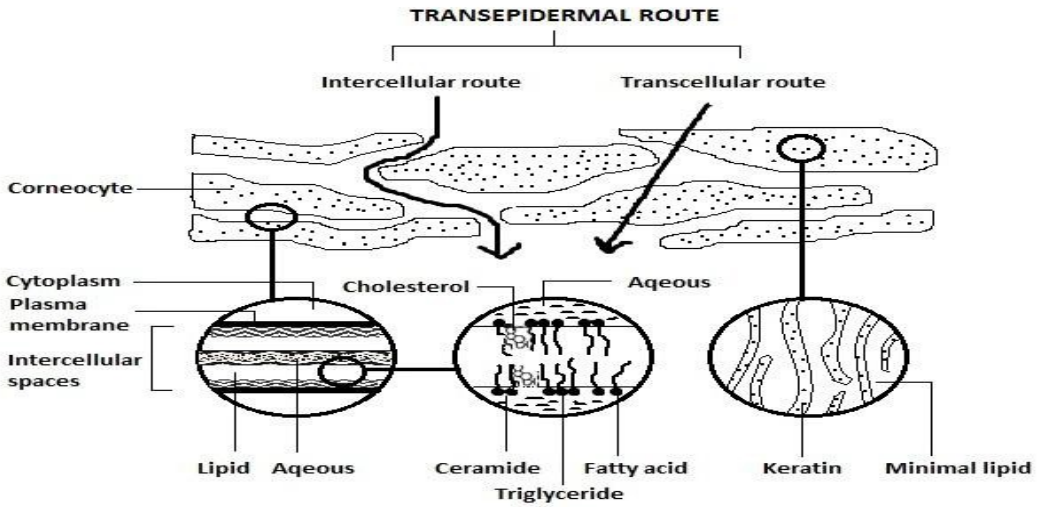
Hypodermis

Subcutaneous, or hypodermis in histology, is the third layer beneath the dermis. Subcutaneous is an elastic layer and includes a large amount of fat cells that work as a shock absorber for blood vessels and nerve endings. The thickness of this layer is 4 to 9 mm on average. However, the actual thickness differs from person to person and it depends on the body region.

When a molecule reaches intact skin, it contacts with the cellular debris, normal flora of microorganisms, sebum and other materials.

Routes of skin penetration

The main route of transport for water-soluble molecules is transcellular. It involves the passage through the cytoplasm of corneocytes and lipid arrangement of the stratum corneum9. The pathway of transport for lipid soluble molecules is intercellular; it implicates the passage apparently through the endogenous lipid within the stratum corneum. The transcellular and intercellular route is collectively known as trans-epidermal route as shown below.



Solute molecules may penetrate the skin through the hair follicles, sweat duct or through the sebaceous glands. These passages are collectively known as shunt or appendageal route.

It is generally accepted that the skin appendages comprises of approximately 0.1% of fractional area for drug permeation. Thus, the main focus is to develop permeation strategies through the stratum corneum rather than through the appendages.

The main barriers to absorption are the dead cells of the SC, restricting the inward and outward movement of drug substances and having high electrical resistance. The SC is a heterogeneous tissue, composed of flattened keratinized cells.

The outer layers of these cells are less densely packed than those adjacent to the underlying granular layer. Therefore, the epidermal barrier becomes more impermeable in the

lower part and this fact has led to suggestion that a separate barrier exists at this level, the so-called SC.

Thus as molecules move from the environment into the skin, the rate limiting barrier i.e. the tissue that presents the greatest resistance to the movement of molecules, is the SC.

Once the dosage form is applied topically, the percutaneous absorption or transdermal permeation can be visualized as a composite of a series of steps.

a. Adsorption of a penetrant molecule onto the surface layers of SC.

b. Diffusion through SC and through viable epidermis.

Percutaneous Absorption

It is a step-wise process of penetration of substances into various layers of skin and permeation across the skin into systemic circulations and can be divided into three parts:

a. Penetration: the entry of a substance into a particular layer.

b. Permeation: the penetration from one layer into another, and is different both functionally and structurally from the first layer.

c. Absorption: the uptake of a substance into systemic circulation.

Factors affecting Permeation

The principle transport mechanism across mammalian skin is by passive diffusion through primarily the trans-epidermal route at steady state or through trans-appendageal route at initially, non-steady state.

The factors that affect the permeability of the skin are classified into following three categories:

A. Physicochemical properties of the permeate molecule

i. Partition co-efficient:

Drug possessing both water and lipid solubility are favorably absorbed through the skin. Transdermal permeability co-efficient shows a linear dependence on partition co-efficient. Varying the vehicle may also alter a lipid/water partition co-efficient of a drug molecule. The partition co-efficient of a drug molecule may be altered by chemical modification without affecting the pharmacological activity of the drug.

ii. Molecular size: There is an inverse relationship existed between transdermal flux and molecular weight of the molecule. The drug molecule selected as candidates for transdermal delivery tend to lie within narrow range of molecular weight (100-500 Dalton).

iii. Solubility / Melting point: Lipophilicity is a desired property of transdermal candidates as lipophilic molecules tend to permeate through the skin faster than more hydrophilic molecules. Drugs with high melting points have relatively low aqueous solubility at normal temperature and pressure.

iv. PH condition:

The pH mainly affects the rates of absorption of acidic and basic drugs whereas unchanged form of drug has better penetrating capacity. Transport of ionizable species

from aqueous solutions shows strong pH dependence. According to pH partition hypothesis, only the unionized form of the drugs can permeate through the lipid barrier in significant amounts.

B. Physicochemical properties of the drug delivery system

i. The affinity of the vehicle for the drug molecules:
It can influence the release of the drug molecule from the carrier. Solubility in the carrier determines the release rate of the drug. The mechanism of drug release depends on whether the drug is dissolved or suspended in the delivery/carrier system and on the interfacial partition co-efficient of the drug from the delivery system to skin tissue.

ii. Composition of drug delivery system:
Composition of drug delivery system may affect not only the rate of drug release but also the permeability of the SC by means of hydration.

iii. Enhancement of transdermal permeation:
Due to the dead nature of the SC the release of the drug from the dosage form is less. Penetration enhancers thus can cause the physicochemical or physiological changes in SC and increase the penetration of the drug through the skin. Various chemical substances are found to possess such drug penetration enhancing property.

C. Physiological and pathological condition of the skin:

a. Skin age:
Foetal and infant skin appears to be more permeable than mature adult skin and therefore percutaneous absorption of topical steroids occurs more rapidly in children than in adults whereas, water permeation has shown to be same in adults and in children.

b. Lipid film:
The thin lipid film on skin surface is formed by the excretion of sebaceous glands and cell lipids like sebum and epidermal cell which contain emulsifying agent may provide a protective film to prevent the removal of natural moisturising factor from the skin and help in maintaining the barrier function of the SC.

c. Skin hydration:
Hydration of SC can enhance transdermal permeability. The rate of penetration study of salicylic acid through skin with dry and hydrated corneum showed that when the tissues were hydrated, the rate of penetration of the most water-soluble esters increased more than that of the other esters.

d. Skin temperature:
Raising skin temperature results in an increase in the rate of skin permeation. Rise in skin temperature may also increase vasodilation of blood vessels, which are in contact with skin leading to an increase in percutaneous absorption.

e. Cutaneous drug metabolism:

After crossing the SC barrier, some of the drug reaches the general circulation in active form and some of this in inactive form or metabolic form, because of the presence of metabolic enzymes present in the skin layers. It was reported that more than 95% of testosterone absorbed was metabolized as it present through the skin.

f. Species differences:

Mammalian skin from different species display wide differences in anatomy in such characteristics as the thickness of SC, number of sweat glands and hair follicles per unit surface area.

g. Pathological injury to the skin:

Injuries to the skin can cause the disturbance in the continuity of SC and leads to increase in skin permeability.

Permeation Enhancers:

These are compounds that promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allows the drug to penetrate to the viable tissues and enter the systemic circulation.

The flux J of drug across the skin can be written as

$$J = D [dc/dx]$$

J = The Flux, D = diffusion coefficient, C = Concentration of the diffusing species, X = Spatial coordinate.

The methods employed for modifying the barrier properties of the SC to enhance the drug penetration (and absorption) through the skin can be categorized as chemical and physical methods of enhancement.

1. Chemical Enhancers

Chemical permeation enhancers can work by one or more of the following three principle mechanisms:

- Relaxation of the extremely ordered lipid structure of the stratum corneum.
- Interacting with aqueous domain of bilayer of lipid.
- Enhanced partition of the drug, by addition of co-enhancer or solvent into the stratum corneum.
- Promoting penetration and establishing drugs reservoir in the stratum corneum.

Chemical permeation enhancers exert their effect through above modifications in the skin structure. Various Chemical permeation enhancers interact with the polar head groups through hydrogen bonding and ionic interactions. The resultant disruption of the lipid hydration spheres and change in head group properties cause the relaxation at the head portion. This relaxation can decrease the resistances of this lipid-enriched domain for polar molecules. Another aspect can be an increase in the volume of the water layer resulting in more water flow to the tissue, a process

known as solvent swelling, leading to increased cross sectional area for diffusion of polar molecules. A portion of free water becomes available, besides the water in structure, at the lipid interface. This process can also occur due to simple hydration. Some of the most widely studied permeation enhancers are di-methylsulfoxide (DMSO), di-methylacetamide (DMA), and diethyl-toluamide (DEET), propylene glycol (PG).

The penetration enhancers, such as DMSO, urea and surfactants, can also interact with the keratin filaments present in corneocytes which leads to disruption within the cell thereby increasing diffusion coefficient and permeability.

2. Physical Enhancers:

Electroporation

The use of electro-permeabilization as a method of enhancing diffusion across biological barriers dates back as far as 100 years. Electroporation involves the application of highvoltage pulses to induce skin perturbation. High voltages (≥100 V) 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).

Iontophoresis

This method involves enhancing the permeation of a topically applied therapeutic agent by the application of a low-level electric current, either directly to the skin or indirectly via the dosage form. Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes), and electro-perturbation (for both charged and uncharged) mechanisms.

Ultrasound

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or through pretreatment, and is frequently referred to as sonophoresis. The proposed mechanism behind the increase in skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound, resulting in disruption of the stratum corneum.

Magnetophoresis

This method involves the application of a magnetic field that acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability.

Thermophoresis

The skin surface temperature is usually maintained at 32°C in humans by a range of homeostatic controls.

Microneedle-based devices

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs is based on this method. These micro-needles of length 50 to 110 mm will penetrate the stratum corneum and epidermis to deliver the drug from the reservoir.

Needleless injection

Needleless injection is reported to involve a pain-free method of administering drugs to the skin. This method therefore avoids the issues of safety, pain, and fear associated with the use of hypodermic needles.

Ideal properties of penetration enhancer

The ideal properties of penetration enhancers are:

- It should be pharmacologically inert.
- It is should be nontoxic, nonirritating, and non-allergenic to the skin.
- It should produce rapid onset of action; predictable and suitable duration of action for the drug used
- Following removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property.
- The barrier function of the skin should decrease in one direction only i.e., they should permit therapeutic agents into the body and efflux of endogenous materials should not occur.
- It should be chemically and physically compatible with the delivery system.
- It should be non-damaging to viable cells.
- They should be Inexpensive and cosmetically acceptable.
- The Penetration enhancer used should be economical.

Basic Components of TDDS:

Transdermal drug delivery system consists of the following components.

1. **Polymer Matrix:**

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, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b. Synthetic Elastomers: e.g., polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c. Synthetic Polymers: e.g., polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethy lmethacrylate, Epoxy etc.

2. **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:

- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have low melting point.
- Along with these properties the drug should be potent, having short half life and be non-irritating.

3. Permeation Enhancers:

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. These includes water,pyrolidones,fatty acids and alcohols, zone and its derivatives, alcohol and glycols, essential oils,terpenes and derivatives,sulfoxides like DMSO and their derivatives, urea and surfactant.

4 Pressure sensitive adhesives (PSA):

The fastening of all transdermal devices to the skin can be done by using a PSA, positioned on the face of the device or in the back of the device and extending peripherally.

- The first approach involves the development of new polymers, which include hydrogel hydrophilic polymers, and polyurethanes.
- The second approach is to physically or chemically modify the chemistries of the PSAs in current use (such as silicones, and acrylates). Physical modification refers to the formulation of the base adhesives with some unique additives so that, in synergy with the drug and excipients in the system formulation, the result is enhanced drug delivery and improved skin-adhesion properties. Chemical modification involves chemically incorporating or grafting functional monomers to the conventional PSA polymers in order to improve drug delivery rates

5 Backings Laminates:

Backings laminates are selected for appearance, flexibility and need for occlusion. Examples of backings are polyester film, polyethylene film and polyolefin film, and aluminum vapor coated layer. Other assiduities are the backing additives leaching out and diffusion of drug or the compositions, through the backing. An over emphasis on the chemical resistance often may leads to stiffness and high occlusivity to moisture vapor and air. It causes the TDDS to lift and may possibly irritate the skin during long-term use.

6. Release Liner:

During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Since the liner is in intimate contact with the TDDS, the liner should be chemically inert. The release liner is composed of a base layer which may be non-occlusive (*e.g.* paper fabric) or occlusive (*e.g.* polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS liners include, polyester foil and metalized laminate that protects the patch during storage. The liner is removed prior to use.

7. **Other Excipients:**

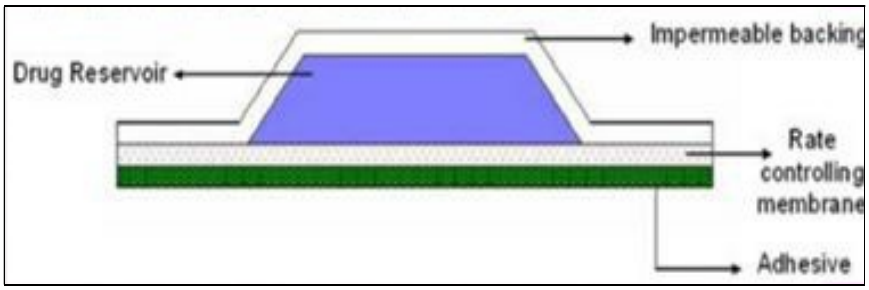
Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition, plasticizers such as di-butyl-phthalate, trietyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Formulation Approaches of TDDS:

The different formulation approaches for TDDS are discussed as follows.

1. Polymer membrane permeation controlled TDD system:

Drug reservoir sandwiched between drug impermeable backing laminate and rate controlling polymeric membrane. In drug reservoir compartment drug is dispersed homogeneously in a solid polymeric matrix(e.g. polyisobutylene), suspended in a un leachable viscous liquid medium(e.g. silicon fluid) to form a paste like suspension. Rate controlling membrane is either a micro-porous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer. Example of this type of patch are Estraderm(twice a week in treatment of postmenopausal syndrome) and Duragesic (management of chronic pain for 72 hrs)



Membrane permeation controlled system.

The intrinsic rate of drug release from this type of drug delivery system is defined by {dq/dt}=Cr/1/Pm+1/Pa. Where, Cr = Concentration of drug in the drug reservoir. Pa= Permeation Co-efficient of adhesive layer. Pm= Permeation Co-efficient of rate controlling membrane.

For any micro porous rate – controlling membrane, Pm approximately represents the sum of permeability co-efficient across the pores and polymeric material. **Pa** and **Pm** may be separately defined as **Pa**

Pa=**Ka/m.Da/ha**

Pm=**Km/r.Dm/hm**

Where,

Da= Diffusion Co-efficient of an derive layer

Dm=Diffusion Co-efficient of rate – controlling membrane

Ka/m= Partition Co-efficient for interfacial partitioning of drug from rate controlling membrane to adhesive layer

Km/r=Partition Co-efficient for interfacial partitioning of drug from reservoir to rate controlling membrane

hm= Thickness of rate = Controlling membrane.

Ha= Thickness of adhesive layer

2. Polymer matrix diffusion controlled TDD system:

   In this the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic (or) lipophilic polymer matrix. The resulting polymer matrix is then moulded into discs with defined surface area and controlled thickness. The medicated disc is then moulded onto an occlusive base plate in a compartment made up of a drug impermeable backing. Finally adhesive polymer is spread along the circumference of the film. **Examples:** Nitro-glycerine releasing transdermal therapeutic system at a daily dose of 0.5g/cm2 for angina pectoris.

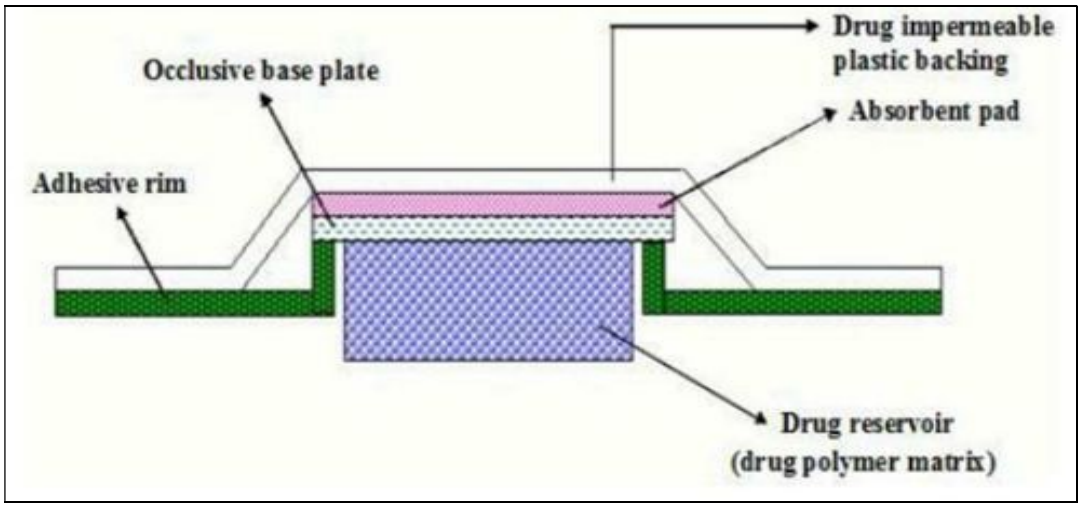
   Rate of drug release in this system is given by the equation **dq/dt** = $\{\mathbf{ACpDp/2t}\}^{1/2}$

Where,

A= Initial drug loading dose dispersed in polymer matrix

Cp = Solubility of drug in Polymer

Dp = Diffusivity of drug in Polymer since **Cp** is equal to **Cr.**



Matrix diffusion controlled Systems

3. **Adhesive Dispersion – Type Systems:**

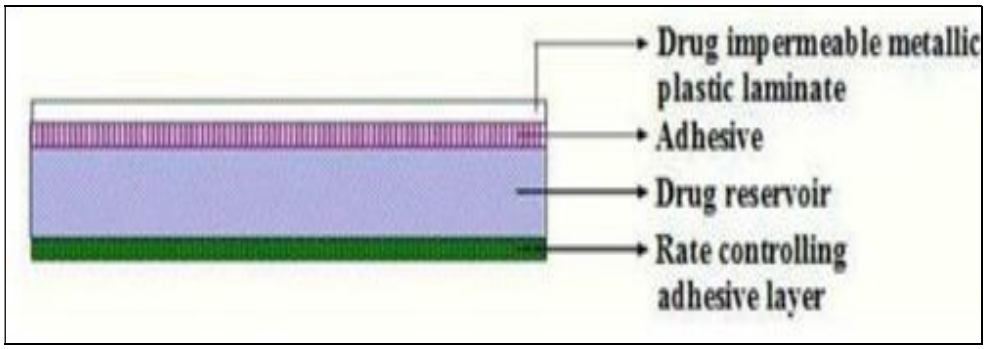
   This is a Simplified form of membrane Permeation–Controlled Systems . In this system, drug and other selected excipients are directly incorporated into the adhesive solution. They are then

mixed and casted as thin films and finally the solvent is evaporated by drying the film. The drug reservoir (film) is the then sandwiched between the banking laminate and rate – controlling adhesive polymer membrane.

The rate of drug release from this system is given by, **dq/dt = Cr.Ka/r .Da/ha**

Where **Ka/r** = Partition co-efficient for interfacial partitioning of drug from reservoir layer to adhesive layer.

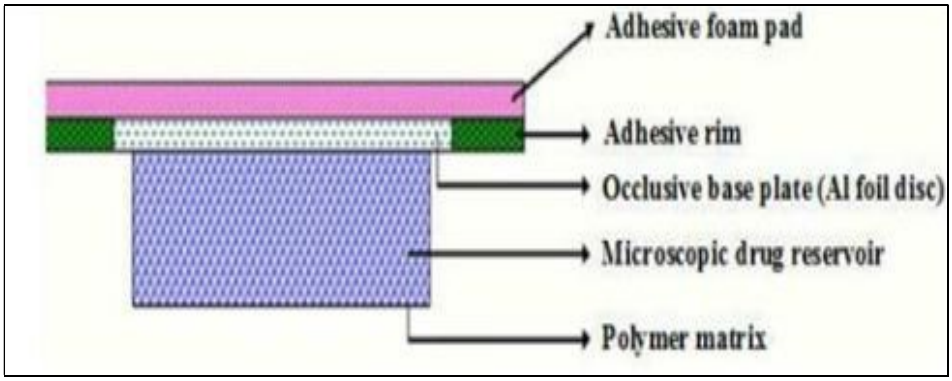
Examples: Iso sorbide dinitrate – releasing TDDS – 24 hr, Used in Angina Pectoris Verapamil – releasing TDDS – 24 hrs, used in Hypertension.



Adhesive Dispersion – Type Systems

4. Microreservoir dissolution controlled TDD system:

It is considered as the hybrid system of reservoir and matrix dispersion type drug delivery. In this system the drug reservoir is formed by first suspending the drug solids in aqueous solution of water-miscible drug solubilser e.g. polyethylene glycol and than homogeneously dispersing the drug suspension with controlled aqueous soluble lipophillic polymer by high shear mechanical force to form thousands of un-leachable microscopic drug reservoir.



Micro reservoir type Systems

2. Gastro-retentive drug delivery systems:

Introduction:

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.

Gastro-retentive drug delivery systems provide efficient means of enhancing the bioavailability and controlled delivery of many drugs. The concept involved in GRDDS is increasing the gastric retention time. Drugs which require increase in bioavailability and controlled delivery can be formulated by utilizing the novel concept GRDDS.

The popularity of this system increases day by day due to its easy of manufacture and cost effective. Wide range of drugs can be used in these system with improved bioavailability. The system can also be used for targeting of drugs to particular part of the body especially in gastric and duodenal part for the treatment of cancer and inflammation. GRDDS serves as a valuable tool for the patients who prefer oral route with less frequent dosing.

Need for gastro-retention:

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Treatment of peptic ulcers caused by H.Pylori infections.

Potential Drug Candidates for Gastro-retentive Drug Delivery Systems:

- Drugs those are locally active in the stomach.
- Drugs that have narrow absorption window in gastrointestinal tract (GIT).
- Drugs those are unstable in the intestinal or colonic environment.
- Drugs that disturb normal colonic microbes Drugs that exhibit low solubility at high pH values.

Advantages of GRDDS:

- This system offers improved bioavailability
- It reduces dose and dosing frequency.
- This system minimizes fluctuation of drug concentration in blood
- This system helps in targeting of drugs
- Local action can be achieved in GIT. Eg. Antacids
- This system reduces the side effect.
- Sustained release can be achieved.
- Safest route of administration
- It is economic and can be used for wide range of drugs.

Disadvantages of GRDDS:

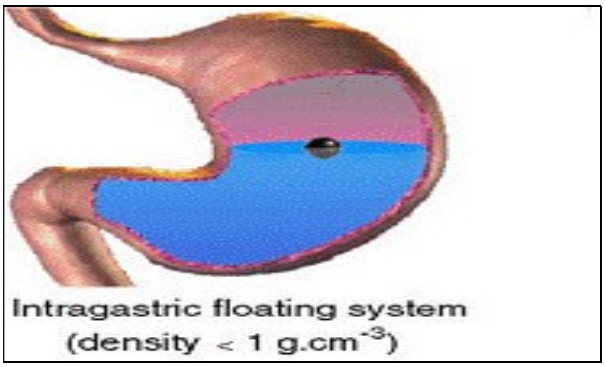
- This system should be administered with plenty of water.
- Drugs with solubility or stability problem in GIT can't be administered.
- Drugs, which undergoes first pass metabolism, are not suitable. e.g. Nifedipine.
- Drugs which are irritant to gastric mucosa are not suitable. E.g. Aspirin & NSAID.
- Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifidipine

Approaches for GRDDS:

Different approaches of gastro-retentive drug delivery systems are discussed as follows:

1. Floating system or Low density system:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly at a desired rate from the system, results in an increase in the gastric residence time and a better control of fluctuations in the plasma drug concentrations and after complete release of the drug, the residual system is emptied from the stomach.



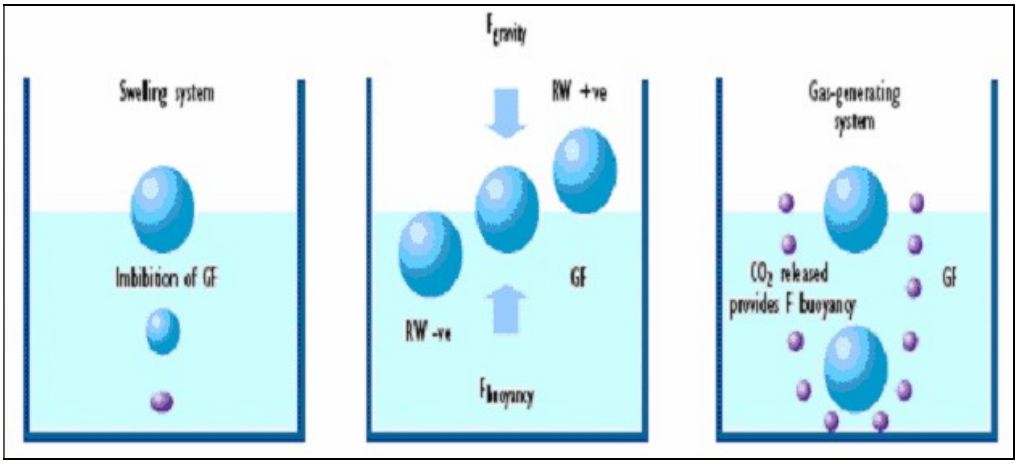
Low-density systems (Floating system)

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. The floating force kinetics is measured using a novel apparatus by determining the resultant weight (RW). The RW

apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object.
The object floats better if RW is on the higher positive side.

RW or F = F buoyancy - F gravity
= (Df - Ds) gV,

Where,
RW = total vertical force,
Df = fluid density,
Ds = object density,
V = volume and
g = acceleration due to gravity.



Mechanism of Floating Systems

Gf= gastric fluid

In case of gas generating systems, carbon dioxide is released causing the beads to float in the stomach. And in case of non-effervescent systems, the air trapped by the swollen polymer confers buoyancy to these dosage forms
Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems. These include:
a) Non- Effervescent system.
b) Effervescent system.

Non-Effervescent System

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio-adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent. FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums,

polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol).

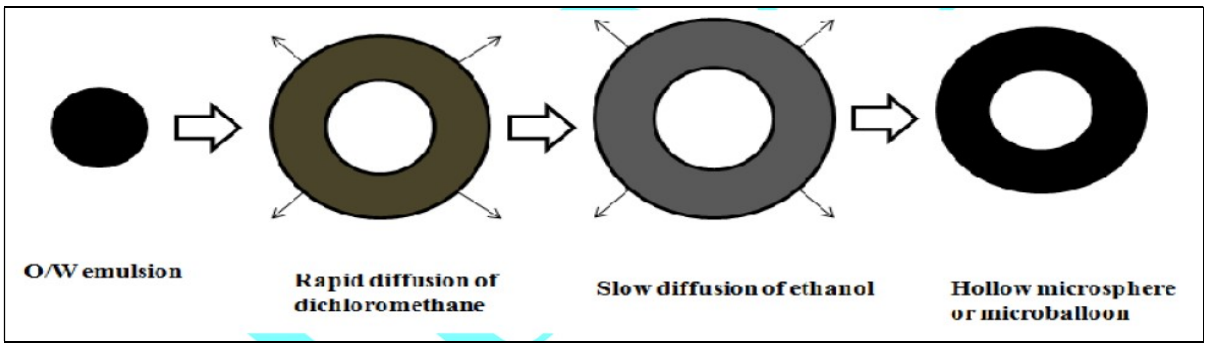
This system can be further divided in to the su-types:

a. Hydrodynamically balanced systems.

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low density formulations reducing the erosion. Madopar LPR, based on the system was marketed during the 1980's. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems.

b. Microballoons / Hollow microspheres:

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The micro-balloons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.



Microballoons

Effervescent System

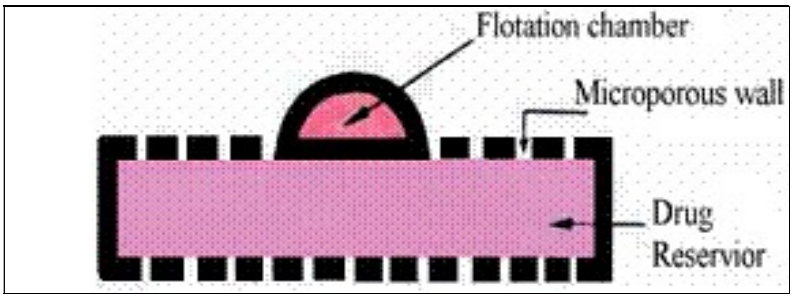
A drug delivery system can be made to float in the stomach by incorporating afloating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts . These effervescent systems further classified into two types:

1) Volatile liquid or vacuum containing systems.
2) Gas generating systems.

Volatile liquid or vacuum containing systems

(a) Intragastric floating gastrointestinal drug delivery system

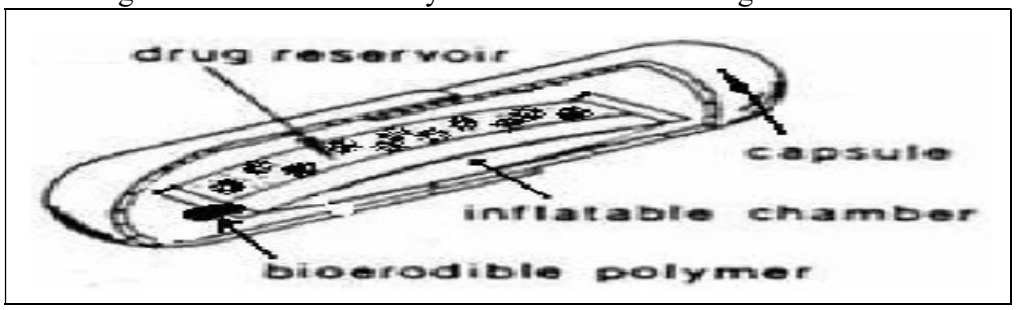
This system floats in the stomach because of floatation chamber, which is vacuum or filled with a harmless gas or air, while the drug reservoir is encapsulated by a microporous compartment



Intragastric floating gastrointestinal drug delivery device

(b) Inflatable gastrointestinal delivery systems

These systems are incorporated with an inflatable chamber, which contains liquid ether that gasifies at body temperature to inflate the chamber in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid.



Inflation chamber

Bioadhesive Systems

Bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS) in the stomach by increasing the intimacy and duration of contact of drug with the

biological membrane. A bio/muco-adhesive substance is a natural or synthetic polymer capable of producing an adhesive interaction based on hydration–mediated, bonding mediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosa. The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories-

1. Hydration-mediated adhesion
2. Bonding-mediated adhesion
3. Receptor-mediated adhesion

1. Hydration-mediated adhesion

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

2. Bonding-mediated adhesion

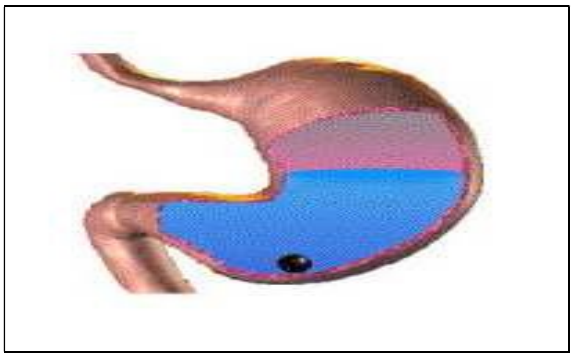
The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

3. Receptor-mediated adhesion

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus.

High Density Systems

These systems with a density of about 3 g/cm3 are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.5 g/cm3. This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time. But, effectiveness of this system in human beings was not observed and no system has been marketed.



High-density systems

Raft forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.

Application of GRDDS:

Gastro-retentive drug delivery system offer several applications as follows:

1. Bioavailability: The bioavailability of controlled release GRDDS is significantly enhanced in comparison to the administration of non-GRDDS controlled release polymeric formulations . There are several different processes, related to absorptions and transit of the drugs in the gastrointestinal tract, that act concomitantly to influence the magnitude of drugs absorption.
2. Site Specific Drug Delivery Systems: These systems are particularly advantageous for drugs those are specifically absorbed form intestine e.g. Furosemide. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drugs. It reduces the side effects which are caused by the drugs in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.
3. Sustained Drug Delivery: In this system, dose large and passing from pyloric opening is prohibited. New sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. Plasma concentration time curves shows a longer duration for administration (16 hours) in the sustained release floating capsules as compared

with conventional capsules (8 hours). Hydrodynamically balance system (HBS) can remain in stomach for prolong periods and hence release the drug in sustained manner for prolong period of time.

4. Enhancement of Absorption: Drugs which are having poor bioavailability because of site-specific absorption from the upper parts of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. By virtue of its floating ability these dosage forms can be retained in the gastric region for prolong period of that drug can be targeted with maximum absorption rate.
5. Minimize adverse activity at the colon: Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undersirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine and whose presence in the colon leads to the development of microorganism's resistance.

3. **Naso-pulmonary drug delivery system:**

Introduction to Nasal routes of drug delivery:

Nasal route of drug delivery 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.

It is a useful delivery method 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 muco-ciliary clearance mechanism.

For many years, drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions. Prominent therapeutic classes of drugs delivered are decongestants for cold nasal symptoms and antihistamines and corticosteroids for allergic rhinitis

The intranasal administration of drugs is an effective way for the systemic availability of drugs as compared to oral and intravascular routes of administration. It provided fast and extended drug absorption than oral and parenteral administration. Therapeutic classes of drugs delivered include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone, and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir).

Advantages of nasal drug 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 g.i.t. fluids are given by nasal route.
10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery

Limitations

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 GIT.
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.

Mechanism of Nasal Absorption

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.) So many absorption mechanisms were established earlier but only two mechanisms have been predominantly used, such as:

a) First mechanism- It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between

intranasal absorption and the molecular weight of water-soluble com-pounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.
b) 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 lipo-philicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions for examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.

Factors Influencing Nasal Drug Absorption

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can be affecting to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are described as follows.

1. **Physiochemical properties of drug.**
   - Molecular size.
   - Lipophilic-hydrophilic balance.
   - Enzymatic degradation in nasal cavity.
   - Stability
   - Solubility
   - Physical state of drug
   - Chemical state of drug
2. **Nasal Effect**
   - Membrane permeability.
   - Environmental pH
   - Muco-ciliary clearance
   - Cold, rhinitis.
   - Blood flow
3. **Effect of drug formulation**
   - Formulation (Concentration, pH, osmolarity)
   - Delivery effects
   - Drugs distribution and deposition.
   - Viscosity
   - Pharmaceutical excipients

Nasal Sprays

Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate

cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants Metered- dose pump sprays include the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the sur-face tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

Excipients Used in Nasal Spray Formulations

There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are as follows

a. Buffers: Nasal secretions may alter the pH of the administrated dose, which can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ. Examples of buffer used in nasal spray sodium phosphate, Sodium citrate and citric acid.

b. Solubilizers: Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C8-C10 glyceride) can be used to enhance the solubility of drugs. Other compounds can be used like, the use of surfactants or cyclodextrins such as HP–s-Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In these cases, their impact on nasal irritancy should be considered.

c. Preservatives: Most nasal formulations are aqueous based so needs preservatives to prevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

d. Antioxidants: A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation.

e. Humectants; Because of allergic and chronic diseases there can be crusts and drying of mucous membrane. Certain preservatives/ antioxidants are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and do not affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

f. Surfactants: Surfactant incorporation into nasal dosage forms can modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug. It also increase stability of suspension. Common examples include Polysorbet.

g. Bioadhesive polymers: Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods is called as bioadhesive polymer. They are also called as mucoadhesive if biological material is mucus membrane. The bioadhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state). From a safety (nasal irritancy) point of view use of a combination of carriers is often recommended.

h. Penetration enhancer: Chemical penetration enhancers are widely used in the nasal drug delivery.

Characterization of Nasal Spray:

- pH
- Osmolality
- Viscosity
- Impurities and Degradation Products
- Preservatives and Stabilizing Excipients Assay
- Pump Delivery
- Spray Content Uniformity (SCU)
- Spray Pattern and Plume Geometry
- Droplet Size Distribution
- Particle Size Distribution

Pulmonary Routes of Drug Delivery:

Introduction:

Pulmonary drug delivery (PDD) systems were recently introduced into the pharmaceutical field to treat both the local and the systemic type of lung diseases. PDD systems are known to be able to simply deliver the drug to the required site in the body directly or to other distant sites through the bloodstream. The lungs provide a huge surface area of alveoli with rich capillary network, which acts as an excellent absorbing surface for administration of drugs.

Throughout the past several years, rapid onset of action and higher efficiency has been responsible for the success of pulmonary delivery system for symptomatic relief in treatment of asthma and chronic obstructive pulmonary disease (COPD). The efficacy of a treatment mostly depends on the techniques by which the drug is delivered and optimum concentration of the drug, above or below this range can be toxic or produce no therapeutic benefit at all. The slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a

multidisciplinary approach to the delivery of therapeutic agents to targets in tissues. The efficacy of the drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmaco-dynamics, immuneginecity, and bio-recognition. These new strategies based on interdisciplinary approaches such as polymer science, pharmaceutical technology, bio-conjugate chemistry, and molecular biology, are often called novel/advanced drug delivery systems. Different drug delivery/drug targeting systems already exist and currently under development can be efficiently used to minimize the drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. For over 20 years, the potential benefit of nanotechnology is appreciated by most of the researchers and it is providing vast improvements in drug delivery and drug targeting. New advancements in the drug delivery strategies are minimizing the unwanted toxicities and improving the efficacy of the treatments.

Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid. In this respect, growing attention has been given to the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and large absorptive surface area of lungs, (approximately 70-140 m^2 in adult humans having extremely thin absorptive mucosal membrane) and good blood supply.

Advantages:

1. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
2. Onset of action is very quick with pulmonary drug delivery.
3. Degradation of drug by liver is avoided in pulmonary drug delivery.
4. The ability to nebulize viscous drug formulations for pulmonary delivery, thereby overcoming drug solubility issues with the ability to use lipid, water or lipid/water emulsions as drug carriers.
5. Increased drug delivery efficacy due to size-stable aerosol droplets with reduced hygroscopic growth and evaporative shrinkage.
6. Liposomal drug formulations remain stable, when nebulized.
7. Ability to nebulizer protein-containing solutions.
8. Inhaled drug delivery puts drug where it is needed.

Limitations:

1. The oropharyngeal settlement may give local adverse effects.
2. Patients may have trouble using the delivery devices correctly.
3. Various aspects affect the reproducibility of drug delivery to the lungs, including physiological (respiratory scheme) and pharmaceutical (tool, formulation) variables. For the systemic delivery of drugs with a small therapeutic index, such deviations may be undesirable.

4. Drug absorption may be limited due to the barrier action of the mucus and the drug–mucus interactions.
5. Mucociliary clearance diminishes the retention time of drugs within the lungs that may affect the pharmacological efficacy of the slowly absorbed drugs.
6. The lungs are not an easily reachable surface for drug delivery, and complex delivery devices are required for targeted drug delivery.

Mechanisms of Respiratory Deposition:

The respiratory tract deposition of inhaled aerosol particles is due to three principal mechanisms: inertia impaction, Brownian diffusion and gravitational settling. A theory is developed to predict the particle deposition and its distribution in human respiratory tract for any breathing condition.

- Once the particle enters the respiratory tract *via* either the nose or mouth, it may be deposited in different regions of the respiratory tract. During breathing, the airflow undergoes several direction changes in the nasal/mouth, pharynx, larynx regions, and airway bifurcations.
- Larger particles (>0.5 μm) may deposit by **impaction** in these regions because they could not follow the air streamline. In fact, deposition by impaction in the oro-pharyngeal region remains a major portion of the emitted dose for pMDI and DPI devices.
- In the small airways and alveolar region, deposition by **sedimentation** is the major deposition mechanism of inhaled particles.
- Small particles (<0.2 μm) may be deposited by **diffusion** in all regions of the respiratory tract. Diffusion deposition is important for nano-particles <100 nm.
- **Interception** deposition is important for elongated particles such as fibrous aerosols when the long particle dimension is comparable with the pulmonary airway dimension.

Formulation of Inhalers:

1. Dry power inhalers:

The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs. Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus.

The dry powder platform comprises devices that generate an aerosol directly from 1 to 5 μm size drug powder, or mixtures with excipients. Excipients used in DPI are used as carrier for

Active Pharmaceutical Ingredient (API). Most commonly used carrier is Lactose Monohydrate.

Formulation of DPI mainly includes following three steps;

a. API Production

The important requirement of API in case of DPI is particle size. Particle size of drug should be less than 5 µm. It should be in the range of 2-5 µm. There are various sort of mills used for size reduction of drugs but few of them are appropriate for DPI to reduce the size in the range of 2-5 µm such as fluid-energy mills, such as the jet mill; high-peripheral-speed mills, such as the pin-mill; and the ball mill.

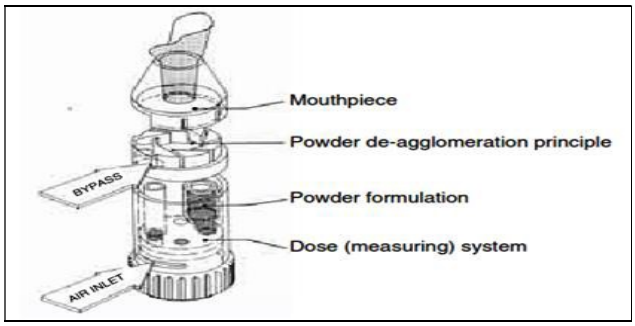
b. Formulation of API with or without carriers.

The part of carrier in DPI is enhancing the flow property of powder and also aerosol performance of the cohesive drugs and fine lactose. After drug and carrier (s) have separately been brought to their desired forms, they are combined in the blending process.

c. Integration of the formulation into device

After the formulation has been blended, it is filled into capsules, multi-dose blisters, or reservoirs for use with the inhaler device. The filling process is automated and depends on the nature of the metering system.

The primary inhaler parts are same for all type of devices on the market and many in development. Dry Powder Inhaler device consists of; powder formulation, dose measuring system, powder de-agglomeration principle and mouthpiece.



Dry powder inhalers

Currently there are two types:

- **Unit dose devices:** In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual gelatin capsules, which are then embedded into the device for a single dose.
- **Multi dose Devices:** The multi-unit dose device utilizes factory metered and sealed doses packaged in a way that the device can hold multiple doses without having to reload. Commonly, the packaging comprises of replaceable disks or cartridges, or strips of foil-polymer blister packaging that may or may not be reloadable.

2. Formulation of Pressurized Metered Dose Inhalers:

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD.

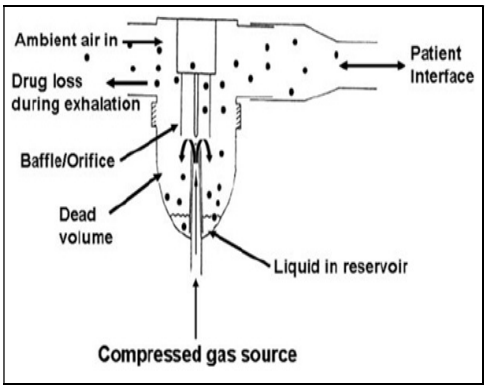
- Pressurized metered aerosols may be formulated as either solutions or suspensions of drug in the liquefied propellant. MDIs can be formulated with the drug completely dissolved in the formulation, rendering a solution formulation, or with the drug practically insoluble in the formulation, rendering a suspension formulation. Compared with suspension formulations, solution MDIs offer the benefits of homogenous formulation (i.e., patients do not need to shake the vial immediately prior to use and there is no concern related to sampling homogeneity), a finer residual aerosol.
- When formulating solution MDIs, the total amount of fine particle drug delivered cannot simply be increased by increasing the drug concentration in a formulation. Many drugs are not readily soluble in HFA propellants, which frequently limits the amount of drug that can be dosed using MDIs. Previously, surfactants or complexation aids were used in MDIs to increase drug solubility in CFC systems .However, many of the conventional excipients used in CFC formulations and approved for human use, are insoluble in HFA system.
- The method for preparing drug particles for MDI formulations needs to be selected based on the chemical stability of the drug. Proteins, for instance, require additional care when micronizing, due to being heat-labile and need to preserve any three-dimensional conformation. Frequently, spray-drying with another agent (i.e., sodium carboxymethylcellulose, polyvinyl alcohol, and/or polyvinylpyrrolidone (PVP)) is utilized for protein drugs due to the need to preserve the three-dimensional conformation and biological activity of the protein.
- The basic requirements for formulation of MDIs are containers, propellants, and metering valve.
- Filling Metered Dose inhaler canister: canister is filled by liquefying the propellant at reduced temperature or elevated pressure. In cold filling , active compound , excipients and propellant are chilled and filling at about-60^{o}c. additional propellant is then added at the same temperature and the canister sealed with the valve. In pressure filling, a drug/propellant concentrate is produced and filled at effectively room temperature and pressure (in fact, usually slightly chilled to below 20^{o}c). The value is crimped on to the canister and additional propellant is filled at elevated pressure through the valve, in

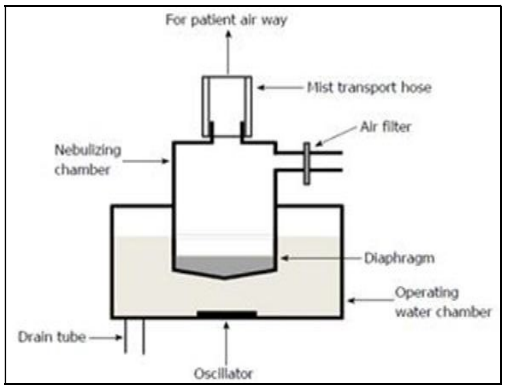
a process known as gassing. Pressure filling is most frequently employed for inhalation aerosols.

3. Nebulizers:

A device converts liquids into aerosols that can be inhaled into the lower respiratory tract. Nebulizers are used in aerosol drug delivery produce a poly-disperse aerosol where the drug delivered in the particles size range 1–5 µm in diameter. Most Nebulizers use compressed air for atomization, but some use ultrasonic energy. Nebulizers are generally used for the treatment of cystic fibrosis, asthma, COPD and other respiratory diseases or disorders. There are following three main types of nebulizers commercially available.

- **Jet Nebulizer:** This uses compressed gas to make an aerosol (tiny particles of medication in the air). Jet nebulizers are applicable for acute and domiciliary treatment of various respiratory diseases, pediatric and adult medical practices. These types of nebulizers required 2-10 L\min withdraw medication a capillary tube from the reservoir of the nebulizer. It may cause generate a wider range of particles which blasted into one or more baffles (to convert larger particles to smaller particles) out of suspension and return them to nebulizer.





Jet Nebulizer Ultrasonic Nebulizer

- **Ultrasonic Nebulizer.** This makes an aerosol through high-frequency vibrations. The particles are larger than with a jet nebulizer. Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) to produce an aerosol. Ultrasonic nebulizers work on the principle that converts electrical energy to high-frequency vibrations using a transducer. This nebulizer generates vibrations, which are transferred to solution surface that would create waves, and those waves produce aerosol; we can say that these types of nebulizers are large volume nebulizers to deliver hypertonic saline for sputum inductions.

- **Mesh Nebulizer.** Mesh nebulizers contain apertures or aperture plate; when we applied force, it will generate aerosol. They force liquid medications through multiple apertures in a mesh or aperture plate to generate aerosol. Comparisons of mesh and ultrasonic nebulizers demonstrated similar drug delivery in simulated ventilator-dependent patients. Mesh nebulizers are more efficient than jet nebulizers and can provide higher drug doses to patients. The efficiency of mesh nebulizers is affected by various factors like size of the pore, aerosol chamber, and reservoir.

Mesh Nebulizer

Formulating Nebulizer Fluids:

Nebulizer fluids are formulated in water, occasionally with the addition of co-solvents such as Ethanol or propylene glycol and with the addition of surfactants for suspension formulations. Because hypo-osmotic and hyper-osmotic solutions may cause bronchoconstriction, as may high hydrogen ion concentrations, iso-osmotic solutions of P^H greater than 5 are usually employed. Stabilizers such as antioxidants and preservatives may also be included, although these may also cause bronchospasm and for this reason sulfites in particular are generally avoided as antioxidant in such formulations.

Whilst most nebulizer formulations are solutions, suspensions of micronized drug are also available for delivery from nebulizers. In general, suspensions are poorly delivered from ultrasonic nebulizers, whereas with jet nebulizer the efficiency of drug delivery increases as the size of suspended drug is decreased, with little or no release of particles when they exceed the droplet size of the nebulizer aerosol.

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