Program	B. Pharmacy
Name of Unit	Transdermal drug delivery systems, gastroretentive drug delivery systems and nasopulmonary drug delivery system
Subject /Course name	Novel Drug Delivery System
Subject/Course ID	BP 704T
Class/Semester	7th Semester
Module	III
Course coordinator	Punam Gaba

Learning Outcome of Module 03

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will learnt about permeation enhancers of TDDS	BP704.2
LO2	Students will learnt about approaches for GRDDS and their applications	BP704.2
LO3	Students will learnt about Nasopulmonary drug delivery system nasal sprays, nebulizers.	BP704.3

Content Table

Topic
• **Transdermal Drug Delivery Systems:** Introduction, Permeation through skin, factors affecting permeation, permeation enhancers, basic components of TDDS, formulation approaches • **Gastroretentive drug delivery systems:** Introduction, advantages, disadvantages, approaches for GRDDS – Floating, high-density systems, inflatable and gastroadhesive systems and their applications • **Nasopulmonary drug delivery system:** Introduction to Nasal and Pulmonary routes of drug delivery, Formulation of Inhalers (dry powder and metered dose), nasal sprays, nebulizers.

Transdermal Drug Delivery Systems

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. Transdermal Drug Delivery System (TDDS) are defined as self contained, discrete dosage forms which are also known as "patches" when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application. That will improves bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal delivery not only provides controlled, constant administration of drugs, 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. Several important advantages of transdermal drug delivery are limitations of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady plasma level of drug. The developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy. The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and

its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.

Advantages of transdermal drug delivery:

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.
- Avoidance of first pass metabolism.
- The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
- As a substitute for oral route.
- The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
- Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
- Avoidance of gastro intestinal incompatibility.
- Convenience especially notable in patches that require only once weekly application, such a simple dosing regimen can aid in patient adherence to drug therapy.
- Minimizing undesirable side effects.
- Provide utilization of drug with short biological half lives, narrow therapeutic window.
- Avoiding in drug fluctuation drug levels.
- Inter and intra patient variation.
- Termination of therapy is easy at any point of time.
- Provide suitability for self administration.
- They are non invasive, avoiding the inconvenience of parentral therapy.
- The activity of drugs having a short half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- It is of great advantages in patients who are nauseated or unconscious.
- Transdermal patches are better way to deliver substances that are broken down by the stomach aids, not well absorbed from the gut, or extensively degraded by the liver.
- Transdermal patches are cost effective.

Disadvantages of transdermal drug delivery:

- Transdermal drug delivery system cannot deliver ionic drugs.
- It cannot achieve high drug levels in blood.

- It cannot develop for drugs of large molecular size.
- It cannot deliver drugs in a pulsatile fashion.
- It cannot develop if drug or formulation causes irritation to skin.
- Possibility of local irritation at site of application.
- May cause allergic reaction.
- Sufficient aqueous and lipid solubility, a log P (octanol/ water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
- Long time adherence is difficult.

Transdermal route and drug delivery prospects Skin: The largest organ: The skin is the largest organ of the human body which covers a surface area of approximately 2 sq.m. and receives about one third of the blood circulation through the body. It serves as a permeability barrier against the transdermal absorption of various chemical and biological agents. It is one of the most readily available organs of the body with a thickness of few millimeters **(**2.97 0.28 mm**)** which,

- Separates the underlying blood circulation network from the outside environment.
- Serves as a barrier against physical, chemical and microbiological attacks.
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.
- Skin is a major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. The diffusional resistance of the skin is greatly dependent on its anatomy and ultrastructure.

Anatomy of Skin: The structure of human skin (figure.1) can be categorized into four main layers:

1. The epidermis
2. The overlying dermis
3. The innermost subcutaneous fat layer **(**Hypodermis)

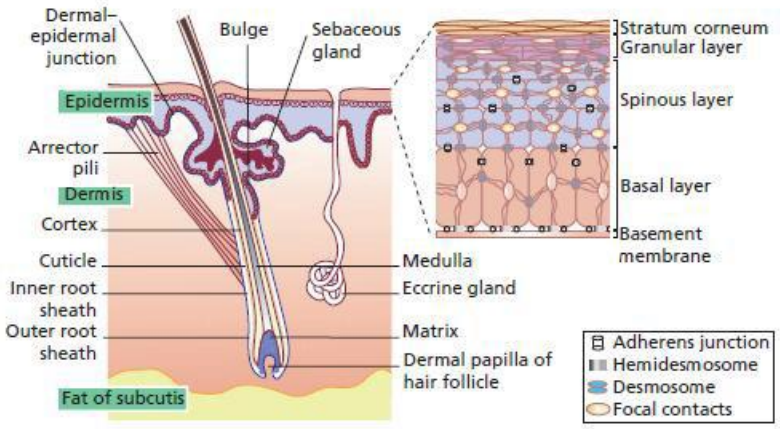


Figure 1 : Anatomy of Skin

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.

Percutaneous absorption:

Before a topically applied drug can act either locally or systemically, it must penetrate through *stratum corneum*. Percutaneous absorption is defined as penetration of substances into various layers of skin and permeation across the skin into systemic circulation. Percutaneous absorption of drug molecules is of particular importance in transdermal drug delivery system because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general once drug molecule cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process (figure 2) which involves:

- Dissolution within and release from the formulation into the skin's outermost layer, the *stratum corneum* (SC)
- Diffusion through the SC, principally via a lipidic intercellular pathway.
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, uptake into the papillary dermis (capillary system) and into the microcirculation.

Routes of drug penetration through skin:

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands as shown in figure 6**.** In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact *Stratum corneum* becomes the primary pathway for transdermal permeation. For any molecules applied to the skin, two main routes of skin permeation can be defined:

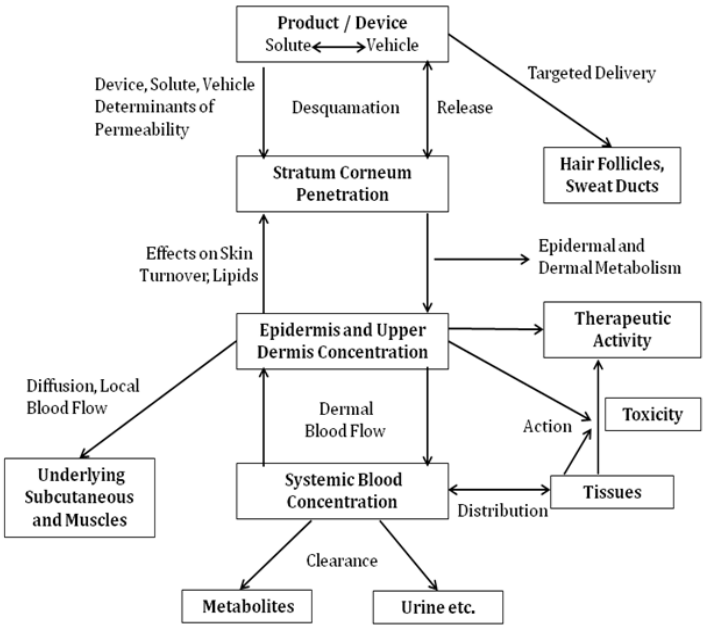


Figure 2: schematic representation of percutaneous permeation

1. Transepidermal route
2. Transfollicular route

Transepidermal route:

In transepidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway as shown in Figure. 3,

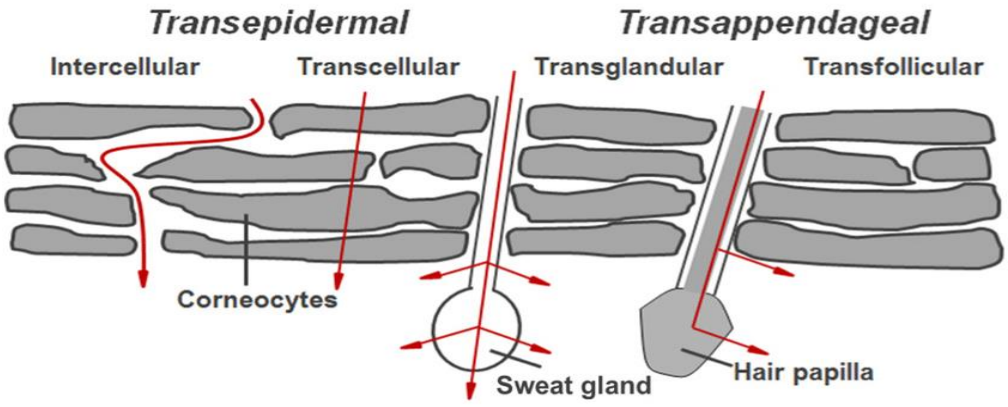


Figure 3: schematic representation of transepidermal route

Both polar and non-polar substances diffuse via transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated *stratum corneum* whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the *stratum corneum*. Thus the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophillic permeants (octanol/water log K > 2) traverse the *stratum corneum* via the intercellular route. Most molecules pass the *stratum corneum* by both routes.

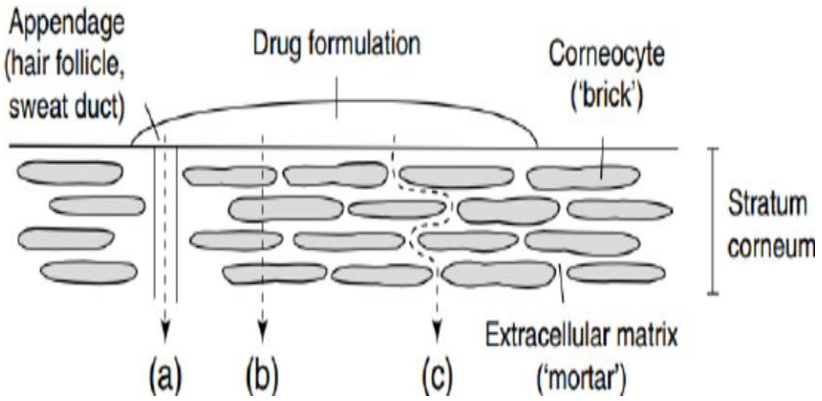


Figure 4: Drug permeation pathways in the skin (stratum corneum shown): (a) the appendageal route, (b) the transcellular route, and (c) the tortuous extracellular route. The transcellular and intercellular routes constitute the transepidermal pathway.

Transfollicular route (Shunt pathway):

This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This route seems to be most important for ions and large polar molecules which hardly permeate through the *stratum corneum.*

Barrier functions of the skin:

The top layer of skin is most important function in maintaining the effectiveness of the barrier. Here the individual cells overlie each other and are tightly packed, preventing bacteria from entry and maintaining the water holding properties of the skin. Stratum corneum mainly consists of the keratinized dead cell and water content is also less as compared to the other skin components. Lipids are secreted by the cells from the base layer of the skin to the top. These lipid molecules join up and form a tough connective network, in effect acting as the mortar between the bricks of a wall.

Basic Principal of Transdermal permeation: Transdermal permeation is based on passive diffusion. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which includes

1) Diffusion of drug from drug to the rate controlling membrane.

2) Dissolution within and release from the formulation.

3) Sorption by stratum corneum and penetration through viable epidermis.

4) Uptake of drug by capillary network in the dermal papillary layer.

5) Effect on the target organ.

6) Partitioning into the skin's outermost layer, the stratum corneum.

7) Diffusion through the stratum corneum, principal via a lipidic intercellular pathway.

Properties that influence transdermal delivery:

1. Release of the medicament from the vehicle
2. Penetration through the skin barrier.
3. Activation of the pharmacological response.

Kinetics of transdermal permeation:

Skin permeation kinetics is important for the successful development of the transdermal systems.

Transdermal permeation of a drug involves the following steps,

- Sorption by *stratum corneum*
- Penetration of drug through viable epidermis
- Uptake of the drug in the dermal papillary layer

The rate of permeation across the skin is given by, (dQ/dt) equation 1

$$\frac{dQ}{dt} = Ps(Cd - Cr) \quad \text{.....1}$$

Where,

Ps is the overall permeability constant of the skin tissue to the penetrant

Cd is concentration of skin penetrant in the donor compartment **(**e.g., on the surface of stratum corneum**)**

Cr is concentration in the receptor compartment **(**e.g., body**)**

$$P_s = \frac{D_{ss}K_s}{h_s} \quad \text{..... 2}$$

Where,

Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium onto the stratum corneum

Dss apparent diffusivity of the penetrant molecule hs overall thickness of skin tissues

As Ks, Dss and hs are constant under given conditions, the permeability coefficient **(**Ps) for a skin penetrant can be considered to be constant

From Equation 1 it is clear that a constant rate of drug permeation can be obtained only when i.e., the drug concentration at the surface of the *stratum corneum* **(**Cd**)** is greater than the drug concentration in the body **(**Cr**)** then Equation.1 becomes, equation 3

$$\frac{dQ}{dt} = C_d P_s \quad \text{.....3}$$

And the rate of skin permeation is constant provided the magnitude of Cd remains fairly constant throughout the course of skin permeation. For keeping Cd constant the drug should be released from the device at a rate Rr i.e. either constant or greater than the rate of skin uptake Ra i.e. . Since Rr >> Ra , the drug concentration on the skin surface Cd is maintained at a level equal to or greater than the equilibrium solubility of the drug in the *stratum corneum* Cs .i.e. Cd>>Cs. Therefore a maximum rate of skin permeation is obtained and is given by the equation, 4

$$\left(\frac{dQ}{dt}\right) m = C_c P_s \text{.....4}$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient Ps and equilibrium solubility in the *stratum corneum* Cs. Thus skin permeation appears to be *stratum corneum* limited The membrane limited flux **(J)** under steady state condition is described by equation, 5

$$J = \frac{DCKo/_w}{h} \text{.....5}$$

Where, J is amount of drug passing through membrane system per unit area per unit time D is diffusion coefficient of drug within the membrane C is concentration gradient across the membrane K is the membrane / vehicle partition coefficient h is the membrane thickness.

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 coefficient. 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:

Fetal 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 moisturizing 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

Formulation of transdermal drug delivery system:

Various components of a transdermal drug delivery system are:

Drug substance:

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 1000 Daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phasea. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
3. The drug should have low melting point.
4. Along with these properties the drug should be potent, having short half life and be non-irritating.

Biological Properties:

1. Drug should be very potent ,i.e. it should be effective in few mg/day

2. The drug should have short biological half life.
3. The drug should not be irritant and non allergic to human skin.
4. The drug should be stable when contact with the skin.
5. They should not stimulate an immune reaction to the skin.
6. Tolerance to the drug must not develop under near zero order release profile of transdermal delivery.
7. Dose is less than 50 mg per day, and ideally less than 10 mg per day.
8. The drug should not get irreversibly bound in the subcutaneous tissue.
9. The drug should not get extensively metabolized in the skin.

Polymer matrix:

Polymers are the backbone of transdermal drug delivery system. System for transdermal delivery are fabricated as multi layered polymeric laminates in which a drug reservoir or a drug polymer matrix is sandwiched between two polymeric layers, an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive, or rate controlled membrane.

Ideal properties of a polymer to be used in a transdermal system:

- Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- The polymer should be stable.
- The polymer should be nontoxic
- The polymer should be easily of manufactured
- The polymer should be inexpensive
- The polymer and its deaggration product must be non toxic or non-antagonistic to the host.
- Large amounts of the active agent are incorporated into it.
- The polymers utilized for TDDS can be classified as:

Natural polymers cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan, starch, etc.

Synthetic elastomers polybutadiene, polyisobutylene, silicon rubber, nitrile, acrylonitrile, styrene-butadiene rubber, neoprene, butylrubber, polysiloxane, etc.

Synthetic polymers polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, epoxy polymethylmethacrylate, ethyl cellulose, hydroxy propyl cellulose etc. The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose and hydroxyl propyl methylcellulose are used as matrix formers for TDDS. Other polymers like EVA (Ethyl vinyl acetate), silicon rubber and polyurethane are used as rate controlling membrane.

Penetration Enhancers:

These are compounds which promote the skin permeability by altering the skin as barrier to the flux of a desired penetrate.

Ideal properties of penetration enhancers:

- Controlled and reversible enhancing action
- Chemical and physical compatibility with drug and other pharmaceutical excipients
- Should not cause loss of body fluids, electrolytes or other endogenous materials
- Non toxic, non allergic, non irritating
- Pharmacological inertness
- Ability to act specifically for predictable duration
- Odorless, colorless, economical and cosmetically acceptable

Surfactants

These are proposed to enhance polar pathway transport especially of hydrophilic drugs. The ability of a surfactant to alter penetration enhancing of a drug.

Anionic surfactants

Sodium lauryl sulphate, Decodecylmethylsulphoxide, DMSO etc.

Nonionic surfactants

Pluronic F 127, Pluronic F68 etc. Enhancer actions can be classified by lipid-protein partitioning concept. This hypothesis suggests that enhancers act by one or more ways selected from three main possibilities.

Lipid action

Some enhancers interact with the organized intracellular lipid structure of the stratum corneum so as to disrupt it and make it more permeable to drug molecules. Some solvents act by extracting the lipid components and thus make the horny layer more permeable.

Protein modification

Ionic surface active molecules in particular tend to interact well with the keratin in the corneocytes, to open up the dense keratin structure and make it more permeable. The intracellular route is not usually prominent in drug permeation, although drastic reductions to this route could open up an alternative path for drug penetration.

Partitioning promotion

Many solvents can enter the stratum corneum, change its solvent properties and thus increase the partitioning of a second molecule into the horny layer. This molecule may be a drug, a co enhancer or a co-solvent. e.g. Ethanol has been used to increase the penetration of the drug molecules nitroglycerin and estradiol.

Other excipients: Various solvents such as chloroform, methanol, acetone, isopropananol, and dichloromethane, are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, propylene glycol are added to provide plasticity to the transdermal patch.

Pressure sensitive adhesive:

A Pressure Sensitive Adhesive (PSA) is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanentaly tachy, exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue 7 e.g.: polyacrylamates, polyacrylates, polyisobutylene, silicone based adhesive. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemical and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device or in the back of the device and extending peripherally.

Backing laminates:

While designing a backing layer the consideration of chemical resistance and excipients may compatible because the prolonged contact between the backing layer and the excipients, drug or penetration enhancer through the layer. They should a low moisture vapour transmission rate. They must have optimal elasticity, flexibility and tensile strength. eg: aluminium vapour coated layer, a plastic film and heat real layer.

Release linear: During storage release linear prevents the loss of drug that has migrated into the adhesive layer and contamination. However, as the linear is inintimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water.

Plasticizer and solvents

Plasticizer

In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility. They are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces. Many of polymers used in pharmaceutical formulations are brittle and require the addition of plasticizer into the formulation. The plasticizers with lower molecular weight have more molecules per unit weight compared to the plasticizers with higher molecular weight. These molecules can more easily penetrate between the polymer chains of the film forming agent and can interact with the specific functional groups of the polymer. By adding

plasticizer to a polymeric material, elongation at break, toughness and flexibility are expected to increase; on the other hand, tensile stress, hardness, electrostatic chargeability, and glass transition temperature (Tg) are expected to decrease.

Solvents

Various solvents are used to solve or disperse the polymer and adhesive or drug used in preparation of transdermal system. Among those chloroform, methanol, acetone, iso propanol and dichloromethane are used frequently.

Major transdermal systems:

Drug in adhesive system:

Single layer drug in adhesive:

The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the entire the various layers together, along with system to the skin, but is also responsible for releasing of the drug. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The adhesive layer is surrounded by a temporary linear and a backing layer.

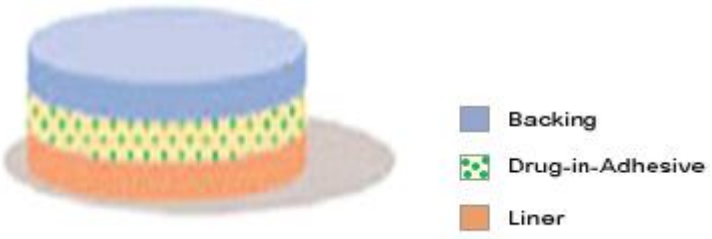


Figure 5: Single layer adhesive transdermal delivery system

Multi layer drug in adhesion:

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug shown in Figure.6 . One of the layer is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi layer patch also has a temporary linear layer and a permanent backing.

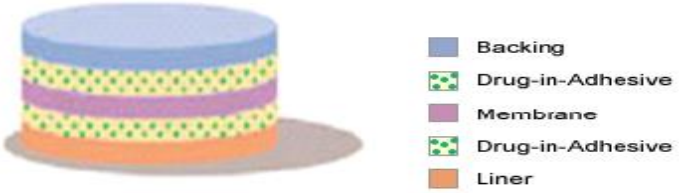


Figure 6: multilayered drug in adhesive transdermal system.

Reservoir:

Unlike the single layer and multilayer drug in adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or

suspension separated by the adhesive layer. This patch is also backed by the backing layer, in Figure: 7**.** In this type of system the rate of release is zero order.

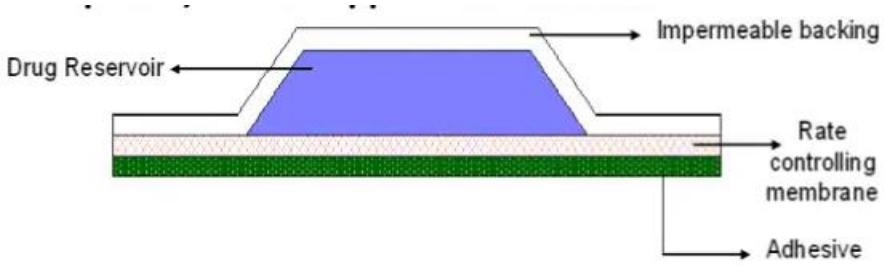


Figure 7: Schematic representation of reservoir transdermal delivery system.

Matrix:

The Matrix system design as shown in Figure: 8 has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlying it. These type of patches are also known as monolithic device.

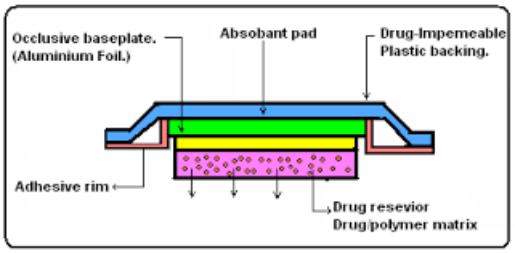


Figure: 8. Matrix system design

Vapour Patch:

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour . The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controlled vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigrate that one smokes in a mouth are also available on the market.

Structure-Based Enhancement Techniques

Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation. An adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the "stickyness" of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again. Several pharmaceuticals

usually combined with substances, like alcohol, within the patch to improve their penetration via skin in order to improve absorption.

Components of Transdermal Patches:

1. Liner - Protects the patch during storage. The liner should be removed before its use.
2. Drug-Drug solution is in direct contact with release liner.
3. Adhesive- It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g. - Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).
4. Membrane- It controls the release of the drug from the reservoir and multi-layer patches.
5. Backing- The film protects the patch from the outer environment

Microfabricated Microneedles These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane. The systems consists of a drug reservoir and some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug.NG TDDS Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment. Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

- Biodegradable microneedles: Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- Hollow microneedles: Involves injecting the drug through the needle with a hollow bore.

Macroflux

These are devices having an area of around 8cm as well as 300 micro projections per cm2 with the length of individual micro projection less than 200Î¼m. Three types of Macroflux have been designed. They include, Dry-Coated Macroflux system-this is used for short period delivery that consists micro projection array coated with medicament that adhered to a elastic polymer adhesive backing.

Metered-Dose Transdermal Spray (MDTS)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin.

The MDTS has the following potential advantages:

- Improves delivery potential without skin irritation due to its non-occlusive nature.

- Increased acceptability.
- Dose flexibility
- Simple manufacture

Electrically-Based Enhancement Techniques

Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia .

Ultrasound

In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

Electroporation

It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.

Electro-Osmosis

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

Velocity Based Enhancement Techniques

Needle-Free Injections

- Intraject
- Implaject
- Jet Syringe
- Iject

- Mini-ject

Powder Ject Device

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

Other Enhancement Techniques

Transfersomes

This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

Medicated Tattoos

Medical Tattoos is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

Skin Abrasion

This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules are generally known as Microscissuining.

Controlled Heat Aided Drug Delivery (CHADD) System

It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

Laser Radiation

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

Magnetophoresis

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

Evaluation of transdermal patches:

The transdermal patches can be characterized in terms of following parameters

1. Physicochemical evaluation
2. *In vitro* evaluation
3. *In vivo* evaluation

Physicochemical evaluation:

Transdermal patches can be physicochemically evaluated in terms of these parameters:

Thickness:

The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight:

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination:

An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test:

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content:

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content = Initial weight – Final weight X 100

Moisture Uptake:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.35 %

Moisture uptake = Final weight – Initial weight X 100

Flatness:

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip.

Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

Tack properties:

It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

Thumb tack test:

The force required to remove thumb from adhesive is a measure of tack.

Rolling ball test:

This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (Peel tack) test:

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inch/min.

Probe tack test:

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

***In vitro* release studies:**

Transdermal patches can be *in vitro* evaluated in terms of Franz diffusion cell the cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm^2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds th**e** receptor compartment. The drug content is analyzed using suitable method, maintenance of sink condition is essential.33

***In vivo* Studies:**

Transdermal patches can be *in vivo* evaluated in terms of *In vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using animal models human volunteers.

Animal models:

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal

species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted leads to a conclusion that hairless animals are preferred over hairy animals in both *in vitro* and *in vivo* experiments. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man.

Human model

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources best to assess the performance of the drug.

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 systems 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 totreat 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:

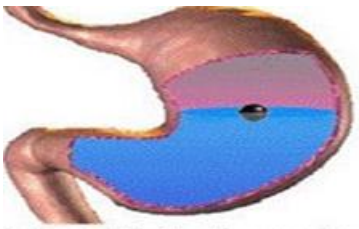
- This system should be administered with plenty of water.
- Drugs with solubility or stability problem in GIT can't be administered.
- Drugs, which undergoes first pass metabolism, are not suitable. e.g. Nifedipine.
- Drugs which are irritant to gastric mucosa are not suitable. E.g. Aspirin & NSAID.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

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 fromthe 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.



Intragastric floating system
(density < 1 g.cm^{-3})

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,

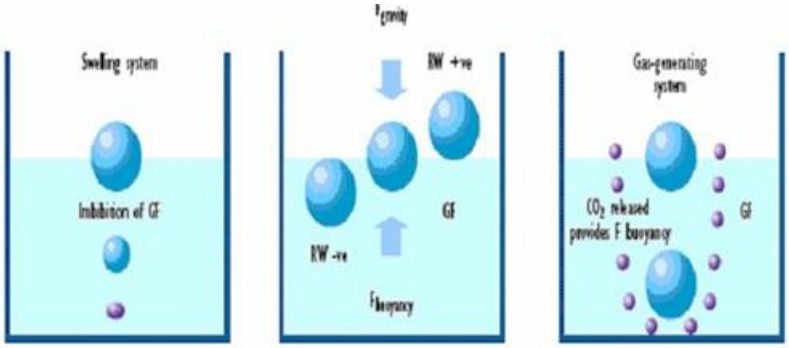
RW = total vertical force,Df = fluid density,

Ds = object density,

V = volume and

g = acceleration due to gravity.

Gf= gastric fluid



Mechanism of Floating Systems

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

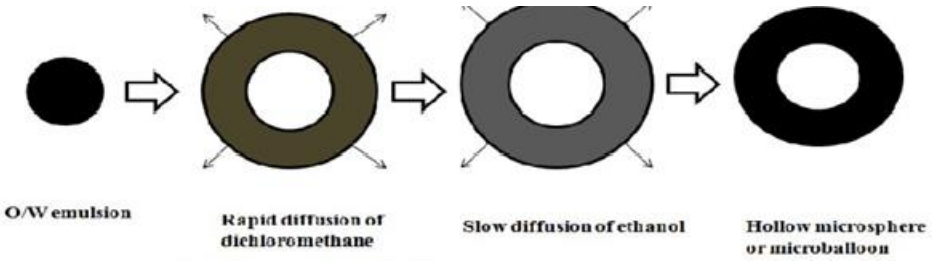
The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio-adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent. FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol).

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.

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:

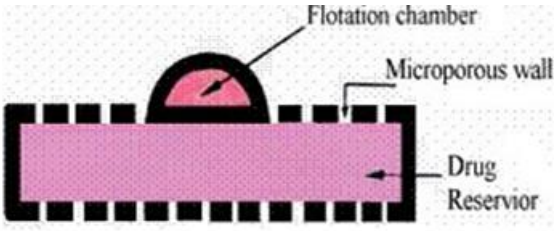
a. Volatile liquid or vacuum containing systems.

b. 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

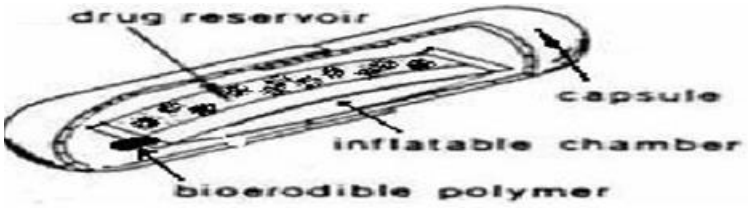


Intragastric floating gastrointestinal drug delivery device

(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 System 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

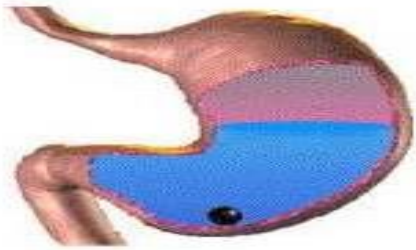
carboxylic groups.

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 ongastric 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:

- ***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.
- ***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.
- ***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.
- ***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.

- **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.

NASO-PULMONARY DRUG DELIVERY SYSTEM:

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

- Drug degradation that is observed in the gastrointestinal tract is absent.

- Hepatic first pass metabolism is avoided.
- Rapid drug absorption and quick onset of action can be achieved.
- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- The nasal bioavailability for smaller drug molecules is good.
- Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drugdelivery.
- Studies so far carried out indicate that the nasal route is an alternate to parenteral route,especially, for protein and peptide drugs.
- Convenient for the patients, especially for those on long term therapy, when compared withparenteral medication.
- Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
- Polar compounds exhibiting poor oral absorption may be particularly suited for this route ofdelivery.

Limitations

- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yetclearly established.
- Relatively inconvenient to patients when compared to oral delivery systems since there is apossibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.
- 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.
- Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane inhigh concentration.
- There could be a mechanical loss of the dosage form into the other parts of the respiratorytract 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:

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 molecularweight greater than 1000 Daltons having drugs shows poor bioavailability.

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

1. **Nasal Effect**
   - Membrane permeability.
   - Environmental pH
   - Muco-ciliary clearance
   - Cold, rhinitis.
   - Blood flow
2. **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

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.

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.

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.

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.

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.

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.

Bioadhesive polymers: Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods is calledas 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.

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:

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 systemsare known to be able to simply deliver the drug to the required site in the body directly or toother 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 efficacyof 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:

- Pulmonary drug delivery having very negligible side effects since rest of body is notexposed to drug.
- Onset of action is very quick with pulmonary drug delivery.
- Degradation of drug by liver is avoided in pulmonary drug delivery.
- 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.
- Increased drug delivery efficacy due to size-stable aerosol droplets with reduced hygroscopic growth and evaporative shrinkage.
- Liposomal drug formulations remain stable, when nebulized.
- Ability to nebulizer protein-containing solutions.
- Inhaled drug delivery puts drug where it is needed.

Limitations:

- The oropharyngeal settlement may give local adverse effects.
- Patients may have trouble using the delivery devices correctly.
- 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.
- Drug absorption may be limited due to the barrier action of the mucus and the drug–mucusinteractions.
- Mucociliary clearance diminishes the retention time of drugs within the lungs that may affectthe pharmacological efficacy of the slowly absorbed drugs.
- The lungs are not an easily reachable surface for drug delivery, and complex delivery devicesare 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:

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 drugis 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;

API Production

The important requirement of API in case of DPI is particle size. Particle size of drug shouldbe 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 rangeof 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.

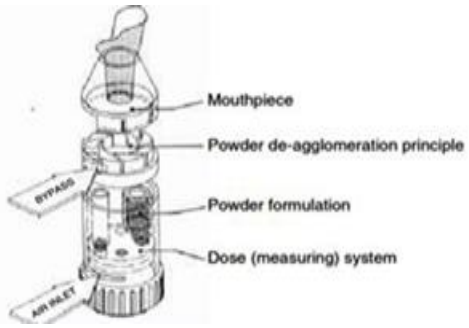
Formulation of API with or without carriers.

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.

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.

Formulation of Pressurized Metered Dose Inhalers:

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medicationto 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.

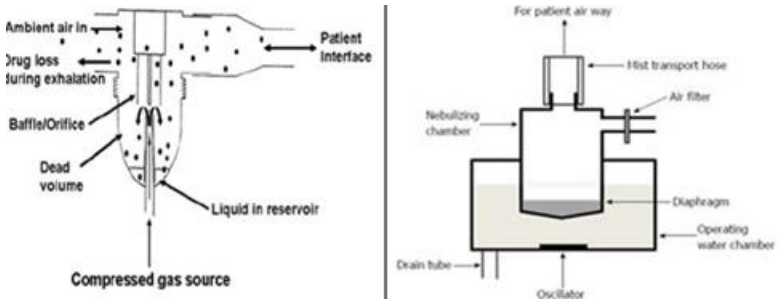
In cold filling , active compound , excipients and propellant are chilled and filling at about-60^{o}c. additional propellant is then added at the same temperature and the canister sealed with the valve. In pressure filling, a drug/propellant concentrate is produced and filled at effectively room temperature 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 inhalationaerosols.

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 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.

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.

QUESTION BANK

SHORT ANSWERS (2MARKS)

1. Write the excipients in nasal spray formulation.
2. Write polymers used as backing layer in Transdermal drug delivery
3. Write advantage of Nasal drug delivery.
4. Enlist excipients used in nasal spray
5. Enlist the types of nebulisers.
6. State basic components of transdermal drug delivery.
7. What are the factors affecting gastric retention in gastrorententive drug delivery
8. State various system of transdermal drug delivery
9. Advantages of Metered dose inhalers

LONG ANSWER (5MARKS)

1. Describe in detail about of gastrorententive drug delivery system with advantages and disadvantages.
2. Explain different formulation approaches of Transdermal drug delivery system.
3. What are gastrorententive drug delivery systems? Explain various approaches of gastrorententive drug delivery system.
4. Discuss in detailed about gastrorententive floating drug delivery systems.
5. Describe in detail about formulations aspects of Nasal Spray
6. What is a pulmonary route of administration? Explain in detail about drug powder inhalers
7. Describe in detail about formulations aspects of Nasal Spray

Very Long answer (10marks)

1. Define Transdermal drug delivery system (TDDS)? Give advantages and disadvantages. Describe permeation enhancer with examples.
2. Define Transdermal drug delivery system (TDDS)? Describe various basic components of TDDS.
3. Discuss gastroadhesive drug delivery systems and its applications
4. Write in details about Dry powder inhalers
5. Write short note on nebulizer.