TRANSDERMAL DRUG DELIVERY SYSTEM

AIM

To study about the transdermal drug delivery system using the type of vehicle.

INTRODUCTION

Oral administration of drugs has been practiced for centuries and most recently, through tablets and capsules. Injectable came into being approximately 130 years ago, but have only become acceptable since the development of a better understanding of sterilization. Topical application has also been used for centuries, predominantly in the treatment of localized skin diseases. Oral delivery is by far the easiest and most convenient way of delivering drugs especially when repeated and routine administration is required. Therefore, to achieve as well as to maintain the drug concentration within therapeutically effective range needed for treatment. This results in significant fluctuations in plasma drug concentration levels leading to marked side effects in some cases.

MODIFIED RELEASE DRUG DELIVERY SYSTEM CAN BE DIVIDED INTO FOUR CATEGORIES

a) **Delayed release:**

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric coated tablets where timed release is achieved by a barrier coating.

b) **Sustained release:**

The term "sustained release" describes a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/ or prolonged.

c) **Site specific targeting**:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

d) **Receptor targeting:**

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. [3]

Controlled drug delivery systems:

In the mid to late 1960s, the term "controlled drug delivery '' came into being to describe new concepts of dosage form design. The primary objectives of a controlled -release systems have been to enhance safety and extend duration of action Controlled drug delivery systems hold the major credibility because of its obvious advantages of

a) Increase in patient compliance.
b) Reduction in total dose administered.
c) Improve efficiency in treatment.

Some of the disadvantages of controlled drug delivery systems are as follows,

- Longer time to achieve therapeutic blood concentration.
- Dose dumping.
- Lack of dosage flexibility.
- Enhanced first pass effect.

Various forms of controlled drug delivery systems are,

- Oral drug delivery systems.
- Mucosal drug delivery systems.
- Nasal drug delivery systems.
- Ocular drug delivery systems.
- Transdermal drug delivery systems.
- Parenteral drug delivery systems.
- Vaginal drug delivery systems.
- Systemic delivery of peptide based pharmaceuticals.[1]

SKIN – AN EFFECTIVE BARRIER FOR PERMEATION

Skin is the largest organ of the body. The skin an average adult body is about 20square feet and it received about one third of total available blood. The skin completely covers the body and is continues with the membranes lining the body orifice.

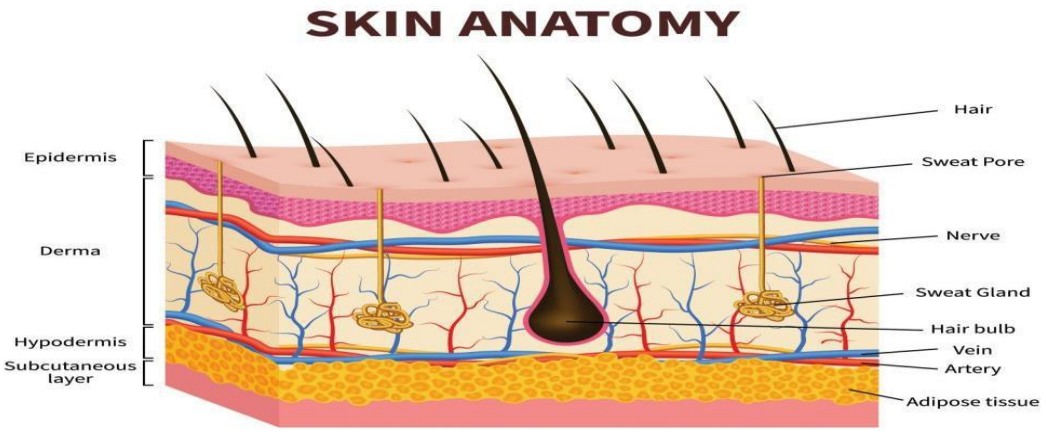

Figure:no: 1(structure of the skin)

The skin is multi- layered organ composed of three histological tissue:

The outermost layer of skin, epidermis is which provides a waterproof barrier and creates our skin tone.Dermis beneath epidermis, contain tough connective tissue, hair follicles, and sweat glands.Deeper subcutaneous tissue (hypodermis) is mode of fat and connective tissue.[5]

Stratum corneum or horny layer is the outermost layer of epidermis, which restricts the inward and outward movement of chemical substance. These are compacted ,flattened, dehydrated and keratinized cells which are physiologically inactive.

Percutaneous absorption:

Percutaneous absorption involves passive diffusion of substance through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absoption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway absorption). [7]

Transepidermal absorption:

Transepidermal or transcorneal penetration includes intracellular and intercellular penetration ,hydrophilic drugs generally seen to permeate through intracellular pathway. As stratum corneum hydrates , water accumulates near the outer surface of the protein filaments.

Epidermis :

The main sources of resistance to penetration and permeation through the skin is the stratum corneum.It is stratified squamous epithelium layer which is composed primarily of two types of cell dendritic and keratinocytes cells.

Dermis

It provides physiological support for the epidermis. It is typically 3-5mm thick and is the major component of human skin. It is the home for most of the skin's structures including sweat glands and oil glands,hair follicles ,nerve ending, and blood and lymph vessels. The main components of the dermis are collagen and elastin.[6]

Subcutaneous tissue (connective tissue):

The subcutaneous tissue or hypodermis is not actually considered as a true part of the structured connective tissue, which comprises of loose textured ,fibrous, white, connective tissue containing blood and lymph vessels , secretary pores of the sweat gland and the cutaneous nerves .It serves as a fat storage area .

Blood and lymph vessels:

Arterioles form a fine network with capillary branches supplying sweat glands, sebaceous gland, hair follicles, and the dermis. Lymph vessels form a network through the dermis.

Sweat glands:

These are widely distributed throughout the skin .They are formed from epithelial cells. There are two types of sweat gland . The commonest type opens onto the skin surface through tiny pores, and the sweat produced here is clear, watery fluid important in regulating body temperature.

TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal permeation , or percutaneous absorption , can be defined as the passage of a substance such as a drug , from the outside of the skin through its various layers into the bloodstream. Drug delivery to systemic circulation via the application to the skin appears to be a desirable alternative to oral delivery for several good reasons:

- Improved patient compliance.
- Greater flexibility of dosage in that dosing can be easily terminated by removal of the TDDS.
- A controlled delivery of drugs through the skin can provide less fluctuation in the circulating drug levels.

Transdermal drug delivery systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drugs(s), through the skin, at a controlled rate to the systemic circulation. Transdermal drug delivery is a viable administration route for potent, low molecular weight therapeutic agents which cannot withstand the hostile environment of

gastrointestinal tract and /or subject to considerable first- pass metabolism by the liver. Transdermal drug delivery system in which rate of drug absorption increases ultimately bioavailability of drug is increases. A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with predetermined rate of release to reach into the bloodstream.[16]

Drug can penetrate through skin via three pathways-

A) Through hair follicles.

B) Through sebaceous gland

C) Through sweat duct.

Transdermal adsorption occurs through a slow process of diffusion by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin .Thus, The delivery system must be kept in continuous contact with the skin for a considerable time(hours to days).[9]

The worldwide transdermal market approaches 2 billion, yet is based on only ten drugs- scopolamine (hyoscine), nitroglycerine, clonidine, estradiol(with and without norethisterone or levonorgestrel), testosterone, fentanyl and nicotine, with a lidocaine patch soon to be marketed.

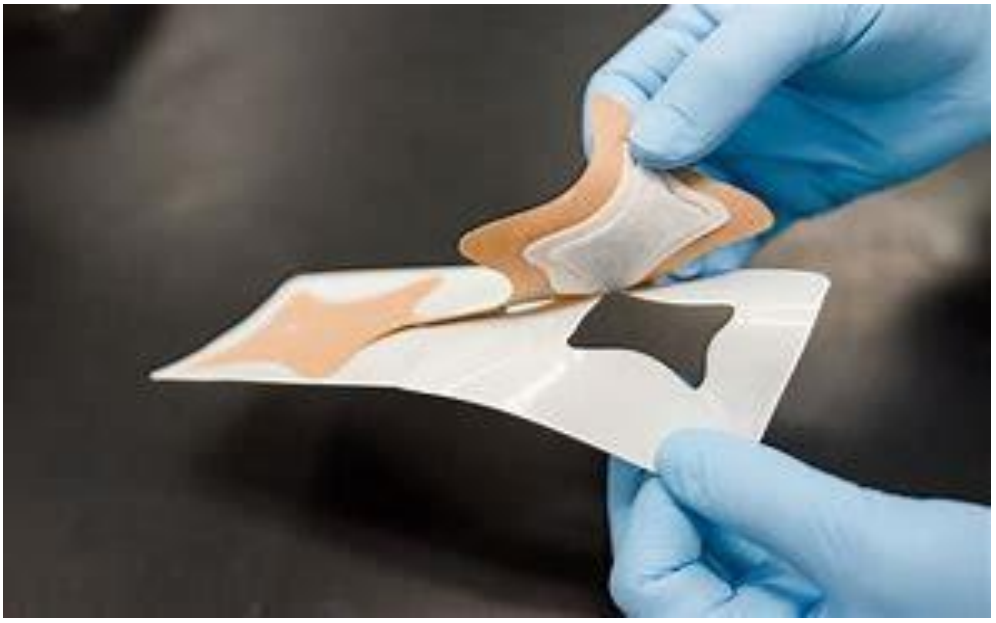

Figure:no:2 (Transdermal patch)

ADVANTAGES

- Improved bioavailability.
- More uniform plasma levels and maintain plasma concentration of potent drugs.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Reduce dosing frequency.
- First pass metabolism of drug get avoided.
- Self –medication is possible.

DISADVANTAGES

- Not suitable for high drug doses.
- Adhesion may vary with patch type and environment conditions.
- Skin irritation and hypersensitivity reactions may occur.
- Long time adhere is difficult.
- Transdermal drug delivery system does not suitable for delivery of ionic drug.

PRINCIPLE OF TRANSDERMAL PERMEATION

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration ,skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separate its surface from underlying capillary network.[8]

MECHANISM OF TRANSDERMAL DRUG PENETRATION OF PATCH

- Release of base material of patch
- Diffusion into stratum corneum
- Diffusion into epidermis
- Diffusion into dermis
- Migration of capillaries
- Migration into lesion.[4]

Pathway of transdermal permeation:

The permeation of drugs through the skin includes the diffusion through intact epidermis and through the intact epidermis and through the skin skin appendages, i.e.,hair follicles and sweat glands, which form shunt pathways through the intact epidermis.

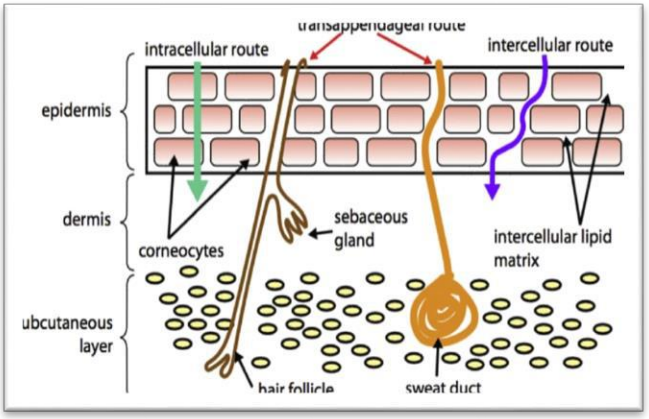

Figure:no:3 (pathway of skin)

Two pathways through the intact barrier may be identified the intercellular lipid route between the corneocytes and the transcellular route crossing through the corneocytes and the intervening lipids that is, in both cases the permeant must diffuse at some point through the intercellular lipid matrix, which is now recognized as the major determinate of percutaneous transport rate.[17]

Kinetics of transdermal permeation:

The knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic system. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of dug through epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical properties. The rate of permeation across the skin is given by

$$Dq/dt = Ps(Cd-Cr) \text{--------- } 1$$

Where the Cd and Cr are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. Ps is the

overall permeability coefficient of the skin tissue to the penetrant . this permeability is given by the relationship

$$P_s = D_{ss}K_s/h_s \text{----------} 2$$

Where Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hg is the overall thickness of skin tissue. As Ks , Dss and hs are constant under given conditions the permeability coefficient Ps for a skin penetrant can e considered to be constant.

From equation (1) it is clear that a constant rate of drug permeation can be obtained only when Cd>>Cr i.e. the drug concentration at the surface of stratum corneum Cd is consistently and substantially greater than drug concentration in the body Cr.

The equation becomes

$$dQ/dt = P_sC_d \text{----------} 3$$

The rate of skin permeation is constant provided is constant provided the magnitude of Cd remains fairly constant throught the course of skin permeation. For keeping Cd constant the drug should be diffusion from the device at a rate 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;

$$(Dq/dt)_m = P_sC_s \text{----------} 4$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient PS and is equilibrium solubility in the stratum corneum Cs. Thus skin permeation appears to be stratum corneum limited.[18]

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM CAN BE DIVIDED INTO THREE CLASSES

1) BIOLOGICAL FACTORS

pH of the skin:

The pH of the skin is usually acidic i.e., 4-6.

The pH is responsible for regulating permeability of drug.

According to pH – Penetration hypothesis, only the unionized form of drug can permeate through lipid barrier.

Site of application:

The site on which the transdermal patches are applied will affect the permeation.

The thickness of the skin, nature of stratum corneum vary site to site which affects permeation.

Skin age:

It is assumed that skin of young and elderly are more permeable than middle aged persons. In premature infants, stratum corneum is absent and children are more susceptible to toxic effects of drugs through the skin.

Pathological conditions of the skin:

Injuries that disrupt the continuity of the stratum corneum increases permeability due to Lipid film.The lipid film on the skin surface act as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

2) PARTITION COEFFICIENT

The optimal partition coefficient (k) is required for good action. (b/w 1 and 4). Drug with high k are not ready to leave the lipid portion of skin. Also, drugs with low k will not be permeated.

Molecular size and shape:

Drug with high molecular weight have low permeation (less than 400 daltons) **.** Smaller particle size have more permeability than the larger particles.

Drug concentration:

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher, if the concentration of the drug will be more across the barrier.

Stability and half-life:

Drug should be stable when it comes in contact with the skin. It should have low melting point. Half- life of drug should be less than 10 hours.

3) FORMULATION FACTORS

Release characteristics

Solubility of drug in dosage form determines the release time.

pH of the vehicle:

The acidic or alkaline pH may cause irritation to skin and may affect drug release, degree of hydration of polymers, therefore these surface pH of patches was determined to optimized both the drug and adhesion.

Permeation enhancers:

Physical permeation enhancers.

Chemical permeation enhancers.

TYPES OF TRANSDERMAL PATCHES

1) Single layer of drug in adhesive patches: In this systems, the drug is remains in contact with the adhesive layer which is attached to the skin. In the layer of adhesive helps to releasing the drug and also serve to adhere to various layers together along with the skin, but also serves of the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of diffusion of drug from this types of system is dependent on the diffusion across the skin. The intrinsic rate of drug diffusion from this type drug delivery system is defined by

$$dQ/Dt=Cr/(1/Pm+1/P$$

a) Where,

Cr is the drug concentration in the reservoir compartment

Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane.

$$Pm = Km/r\ Dm\ /hm$$
$$Pa = Ka/m.Da/ha$$

Where,

Km/r and Ka/m are the partition coefficients for the interfacial partitioning drug from the reservoir to the membrane and from the membrane to adhesive. Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer. hm and ha are the thickness of the rate controlling membrane and adhesive layer.[14]

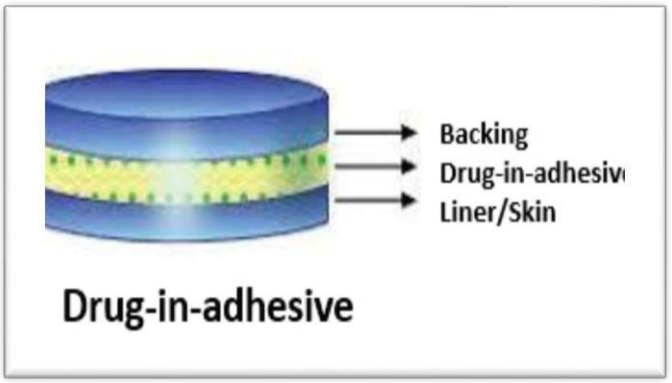

Fig no:4 (Single layer of drug in adhesive)

2) Multi- layer Drug- in -Adhesive: The multi- layer Drug-in-adhesive is similar to the single-layer drug-in-adhesive in that the drug is incorporation directly into the adhesive. However, the multi-layer encompasses either the addiction of a membrane between two distinct drug- in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

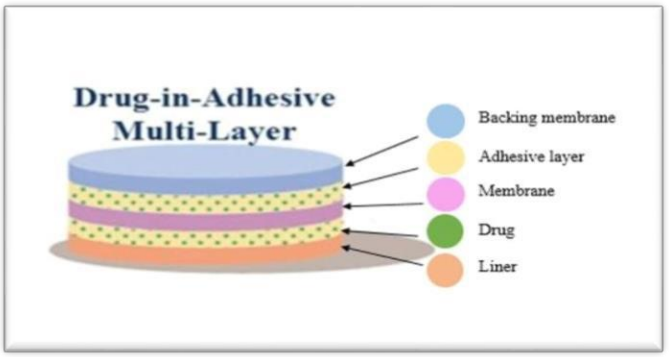

Fig no:5 (Multi-layer drug in adhesive)

The rate of drug diffusion in this system is defined by:

$$Dq/dt=Ka/r.Da/ha(cr)$$

Where,

Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

3) Reservoir type patches: The reservoir transdermal system has a separate drug layer unlike the single layer drug in adhesive and multilayer drug in adhesive system. In this system it include compartment for liquid that contains a solution or suspension of drugs separated from the liner by a membrane adhesive.[15]

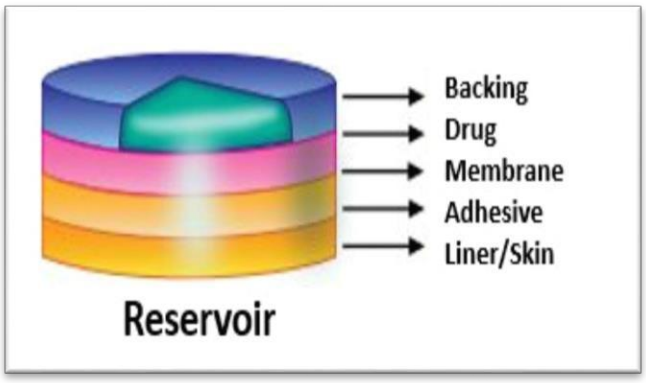

Figure no:6 (Reservoir type patches)

4) Matrix type patches: The matrix system consists a medicament layer of a semisolid matrix that contains a drug as a solution or suspension, that is direct contact with the liner layer. In this device the adhesive layer surrounds the drug layer partially overlaying it.

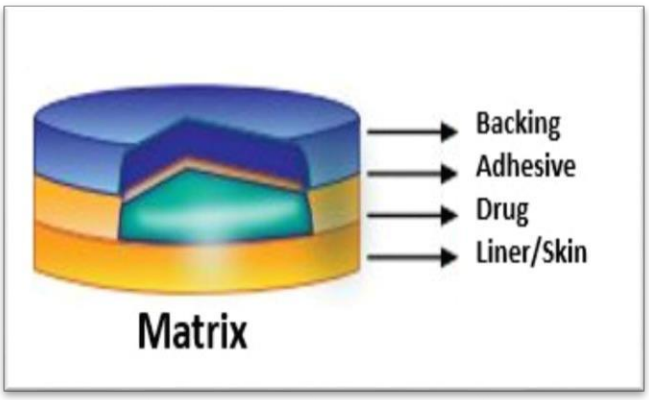

Figure no:7 (matrix type patches)

5) Vapour patches: In this type of patch system the adhesive layer not only serves to adhere the various layers together but also releases vapour. This patches are new to the market, and commonly used for releasing of essentials oils for up to 6hrs.These patches release essential oils and are used in cases of decongestion mainly. Many types of vapour patches are available in the market which are used to improve the quantity of sleep and reduces the cigarette smoking condition.

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM:

1) Polymer matrix / drug reservoir:

Polymers of the backbone of the TDDS, which control the release of the drug from the device. It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. Polymer used in TDDS should have biocompatibility and chemical compatibility with the drug and other component of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product shelf life and should be of safe.

Considerations for polymer selection in transdermal system:

- Should be stable and non- reactive with the drug moiety.
- Should provide consistent release of drug throughout the life of system.
- Mechanical properties should not change if large amount of drug incorporate.
- The polymer and its degradation product must be non- toxic to the host.

The polymer used in transdermal system are:

- **Natural polymers:** Eg. Zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes and chitosan etc.
- **Synthetic Elastomers:** Eg. Hydrin rubber, polysiobutylene, polybutadiene, silicon rubber, nitrile, neoprene, butyl-rubber, acrylonitrile etc.
- **Synthetic polymer:** Eg. Polyvinychloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethaacrylate etc.

2) Drug:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer more benefits to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half-life which causes non-compliance due to frequent dosing.

Physiochemical properties:

- The drug should have a molecular weight less than 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.

Biological properties:

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half-life (t1/2) of the drug should be short.
- The drug must not produce allergic response.

3) Permeation enhancer:

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. penetration enhancers interact with structural components of stratum corneum via proteins or lipids .they alter the protein and lipid packing stratum corneum, thus chemically modifying the barrier functions leading to increased permeability. [19]

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

J= D dc/dx

J= the flux

D= diffusion coefficient

C=concentration of the diffusing spectes

X=spatial coordinate

Solvent: These compounds increase penetration possibly by swelling the polar pathway. Eg) Water alcohol methanol and ethanol, dimethyl acetemide propylene glycol and glycerol.

Surfactants: The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

- Anionic surfactant: sodium lauryl sulphate diacetyl sulphoccinate.
- Nonionic surfactant: pluronic F127,pluronic F68.
- Bile salt: sodium taurocholate, sodium deoxycholate .

Miscellaneous chemicals: These include urea ,a hydrating and keratolytic agent N,N dimethyl-m-toluamide calcium thioglycolate anticholinergic agents. some potential permeation enhacers have recently been described but the available data on their effectiveness sparse.

Enhance the permeation: eg . urea ,calcium, thioglycolate.

4) Pressure sensitive adhesive (PSA):

It helps to increase the adherence of transdermal patch to the skin surface. It can easily remove from the smooth surface without leaving a residue on it.

Polyacrylates: In general, all acrylic adhesive are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of poly acrylate matrices.

Poly isobutylenes (PIBs): Poly isobutylenes (PIBs), in contrast, are characterized by a low solvent capacity for drugs. PIBs are often used in membrane-controlled systems where the initial burst of drug released from the adhesive layer should be limited. PIBs-based adhesive are mixtures of high and low molecular weight polymers, which provide cohesion and tackiness, respectively.

Silicone: Silicone , adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicone, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups.

5) Hot Melt Pressure Sensitive Adhesives (HMPSA)

Melt to a viscosity suitable for coating, but when they are cooled they are cooled they generally stay in a flow less state. They are thermoplastic in nature.Compounded HMPSA,Ethylene vinyl acetate copolymers,Paraffin waxes,Low density polypropylene,Styrene-butadiene copolymers.

Backing laminates: The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through top. They must be impermeable to drugs and permeation enhancers. They should a low moisture vapor transmission rate.

Release liner: The patch is covered by protective liner during storage until it is used. The release liner removed and discarded just before the application of patch over the skin since release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert. The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g polyethylene , polyvinylchloride) and a release coating layer made up of silicon or Teflon.[2]

EVALUATION METHODS:

The evaluation methods for transdermal dosage form can be classified into types:

- Physiochemical evaluation
- In vitro evaluation
- In vivo evaluation [13]

PHYSIOCHEMICAL EVALUATION:

1.Interaction studies:

The drugs and excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients after the bioavailability and stability of the drug. If the excipients are new and have not been used in formulation containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima.

2. Thickness of the patch:

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and this determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. Weight uniformity:

The prepared patches are to be dried at 60°C for 4 h before testing. A specified area of patch is to be cut in different parts of the patch and weighed in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. Folding endurance:

A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.

5. Percentage moisture content:

The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 h, the films are to be reweighed and the percentage moisture content determined by below formula,

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

6. Percentage moisture uptake:

The prepared patches are to be weighed individually and to be kept in a desiccators containing saturated solution of potassium chloride in order to maintain 84% Rhesus factor (RH). After 24 h, the films are to be reweighed and the percentage moisture uptake determined by the formula.

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

7. Water vapour permeability (wvp) evaluation:

Water vapour permeability can be determined by a natural air circulation oven. The WVP can be determined by the following formula.

$$WVP = W/A$$

Where WVP is expressed in g/m2 per 24 h, W is the amount of vapour permeated through the patch expressed in g/24 h, A is the surface area of the exposure samples expressed in m.

8. Drug content:

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then, the solution is to be filtered through a filter medium and the drug content analyzed with the suitable method (UV or HPLC technique).Then, the average of three different samples is taken.

9. Content uniformity test :

Ten (10) patches were selected and content 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 to 125% 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.

10. Flatness test :

Three longitudinal strips were cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured, and the variation in length because of non-uniformity in flatness was measured by determining percentage constriction, with 0% constriction equivalent to 100%

. Flatness Constriction (%) = I1 - I2 × 100 I1

Where, I1 = initial length of each strip. I2 = final length of each strip.

11. Percentage elongation break test:

The percentage elongation break was determined by noting the length just before the break point and determined from the formula.

Elongation percentages = L1 - L2 / L2 × 100

Where L1 = final length of each strip L2 = initial length of each strip

12. Peel Adhesion Properties

Peel adhesion is the force required to remove all adhesive coating from test substrate, its important in transdermal devices because the adhesive should provide adequate contact of device with the skin of the adhesive polymer, the type and amount of adhesive and polymer composition. It's tested by measuring the force required to pull a single coated tape, applied to substrate, at a 180º angle, Signifying a deficit of cohesive strength in the coating.

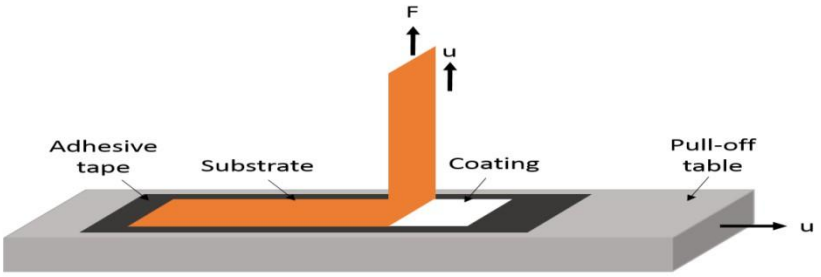

Figure no:8 (Peel adhesion)

13.Tack Properties:

Tack is the ability of a polymer to adhere to substrate with little contact pressure. It is important in transdermal devices which are applied with finger pressure. Tack is dependent on the molecular weight and composition of polymer as well as use tackifying resins in the polymer.

IN VITRO EVALUATION OF TDDS :

In vitro drug diffusion studies**:** The paddle over disc method (USP apparatus) can be employed for assessment of the diffusion of the drug from the prepared patches. Dry films of known thickness were cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500 ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment was performed in triplicate and the mean value calculated.

Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm2) versus time in hours, and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm2).

BIOPHARMACUETICAL PARAMETERS IN DRUG SELECTION FOR TRANSDERMAL PATCH:

- Dose should be low i.e <20mg/ day.
- Half -life should be 10 h or less.
- Molecular weight be <400.
- Partition coefficient should be log p octanol-water) between 1.0 and 4.
- Skin permeability coefficient should be <0.5 x 10-3/h.
- Drug should be non- irritating and non- sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.[11]

APPLICATION OF TRANSDERAMAL PATCHES:

1) Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
2) Nitroglycerine patches are also sometimes prescribed for the treatment of angina.
3) Clonidine the anti-hypertensive drug and ketoprofen, the non- steroidal anti -inflammatory drug are also available in the forms of transdermal patches.
4) Transdermal form of the MOAI selegiline became the first transdermal delivery agent for an antidepressant.
5) Transdermal delivery agent for the attention deficit hyperactivity disorder.[20]

METHOD OF PREPARATION OF TDDS :

Asymmetric TPEX membrane method:

This method was discovered by berner and john in 1994. By this method prototype patch can be prepared by using heat sealable polyester film (film 1009,3m) with a concave of 1cm diameter as the backing membrane. Drug dispersed on concave membrane, covered by a TPEX [poly (4-methyl-1–pentene)] asymmetric membrane, and sealed by a adhesive.

Mercury substrate method:

In this method drug and plasticizers get dissolved in polymeric solution.it stirred for 10-15 mins to produce homogenous dispersion then it is poured into leveled mercury surface, covered with inverc ted funnel to control solvent evaporation

IPM membrane method:

In the mixture of water and polymer (propylene glycol containing carbomer 940 polymer).Drug get dispersed and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. If the drug solubility in aqueous solution is very poor then solution gel is obtained by using buffer pH 7.4. The formed gel will be incorporated in the IPM membrane.

EVAC membrane methods:

For the preparation of TDS,1% carbopol reservior gel,polyethylene (PE),ethylene vinyl acetate co polymer(EVAC) membrane is needed as rate control membrane.if the drug is insoluble in water the use propylene glycol for gel preparation.drug is dissolved in propylene glycol,carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution.the drug (in gel form) is placed on a sheet of packing layer .

Circular Teflon mould method:

Solution containing polymers in various ratio are used in an organic solvent. Calculated amount of drug is dissolved in half of the quantity of same organic solvent enchancers is different concentration dissolved in the other half of the organic solvent and the added. Di-N butyl phthalate is adhesive, material in the added to the drug solution and dissolved. A custom made aluminum former is lined with aluminum foil and the ends blanked of with tightly fitting cork blocks.

Free film method:

In this process firstly cellulose acetate free film is prepared by casting it on mercury surface. And 2% w/w polymer solution is prepared by using chloroform. Plasticizers are to be added at a concentration of 40% w/w of polymer weight. Then 5 ml of polymer solution is poured in a glass ring which is placed over the mercury surface in a glass petridish . The rate of evaporation of the solvent can be controlled by placing an inverted funnel over the petridish. The film formation is noted observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between this sheets of wax paper in a desiccator until use. By this process we can prepare free films of different thickness can be prepared by changing the volume of the polymer solution.[10]

Preparation of TDDS by using proliposomes transdermal patches:

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0:1:2:0 can be used as an optimized one. The proliposomes are prepared by taking 5 mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70^0 C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 mins. After drying,the temperature of the water bath is adjusted to 20 -30^o C. drug and lecithin are dissolved in suitable organic solvent mixture, a 0.5 ml aliquots (0.5ml)of the organic solution is introduced into the round bottom flask at 37^{0}C.after the complete drying second aliquots of the solution to be added. After the last loading. The flask containing proliposomes are connected in a lyophilizer and subsequenty drug loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization and stored at the freeze temperature until characterization.

CONCLUSION:

Transdermal drug delivery is a painless,convenient and potentially effective way to delivery regular doses of many medication .wide range of drugs can be delivered improved drug uptake minimal complication, side effects, low cost and easy to use. Transdermal drug delivery technologies are becoming one of the fastest growing sectors within the pharmaceutical industry. Despite some disadvantages, transdermal drug delivery offers many advantages capable of improving patient health and quality of life. Now a days transdermal drug delivery system are used for hormonal and insulin.

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