IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON: TRANSDERMAL PATCHES

Miss. Kaveri Jigjeni* , Mr. Chaitanya Gaikwad , Mr. Darshan Patkar , Ms. Akshada Karad . B .Pharmacy
Prof . Priyanka Panmand .
IVMs, Krishnarao Bhegde Institute of Pharmaceutical Education and Reasearch , Talegaon Dabhade , Pune Maharashtra , 410507.

ABSTRACT :

Transdermal patches have been used for drug delivery to accelerate the wound healing process with minimum negative effect. This study evaluated the wound healing potential of transdermal patches containing Carica papaya, Chromolaena odorata, and Averrhoa bilimbi leaves extract on hyperglycemic rat as a diabetic wound model. For this purpose, a total of 40 Wistar rats aged 2 - 3 months were randomly distributed into 10 groups. The first 5 groups (P1, P2, P3, P4 and P5) consisted of normal rats which received normal dressing, TP Dermafix, TP of C. papaya, TP of C. odorata, and TP of A. bilimbi, respectively. The second 5 groups (P6, P7, P8, P9 and P10) were hyperglycemic rats that received normal dressing, TP Dermafix, TP of C. papaya, TP of C. odorata, and TP of A. bilimbi, respectively. Skin incisions were made perpendicular to the spine in the thickest part of the skin with an incision length of 2cm and a depth of 0.5 cm. Patches were applied to the incisions according to the test group and replaced every 2 days for a period of 13 days. Wound healing activity was determined by evaluating the Clinical Sign of Inflammation (CSI) score, wound closure, TGF-β1 concentration, and histology of skin tissue.Data were analyzed using oneway analysis of variance (ANOVA).

KEYWORDS : Skin incisions , Wound healing , Inflammation , Clinical sign .

INTRODUCTION:

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981 by FDA. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation. Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose . (2) A drug is applied in a relatively high dose inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Transdermal patches were developed in the 1970s and the first was Transderm -SCOP which was approved by the FDA in 1979 for the treatment of motion sickness and nausea.Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively .(9)Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. (8) It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once weekly application. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation.(2) Transdermal patches and medicated plasters (patch) represent well-established prolonged release dosage forms. Even if

satisfactory adhesion to the skin is strictly linked to the efficacy and safety of the therapeutic treatment, nowadays numerous reports of in vivo 'adhesion lacking' are still addressed to regulatory agencies.(15)

IDEAL PROPERTIES OF TRANSDERMAL DRUG DELIVERY SYSTEM :

1.Dose Should be low
2. Half-life in hr Should be 10 or less
3. Molecular weight Should be less than 500
4. Partition coefficient Log P (octanol-water) between –1 and 3
5. Skin permeability coefficient Should be less than 0.5 x10-3cm/hr
6. Skin reaction Should be non-irritating
7. Oral bioavailability Should be low
8. Therapeutic index Should be low
9. Concentration Minute
10. pH of saturated aqueous solubility 5-9
11. Dose deliverable (8)

ADVANTAGES AND DISADVANTAGES :

Advantages:

- They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
- They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.
- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Tradermal clonidine day.
- The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
- Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets. (2)
- First pass metabolism, an additional limitation to oral drug delivery, can be avoided with transdermal administration. (2)

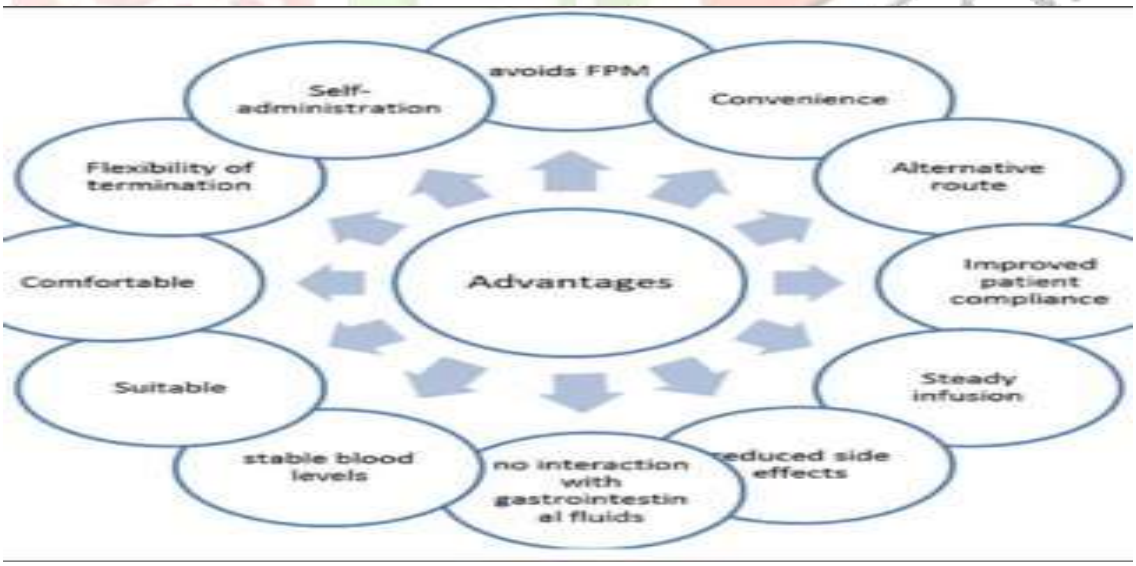

figure no 1:- Advantages of transdermal drug delivery system

Disadvantages:

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.)
- Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable. Long time adhere is difficult. (7)

- May cause allergic reactions.
- Possibility of local irritation at the site of application.
- Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.
- A molecular weight less than 500 Da is essential. Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeate to transverse SC and underlying aqueous layers. (2)

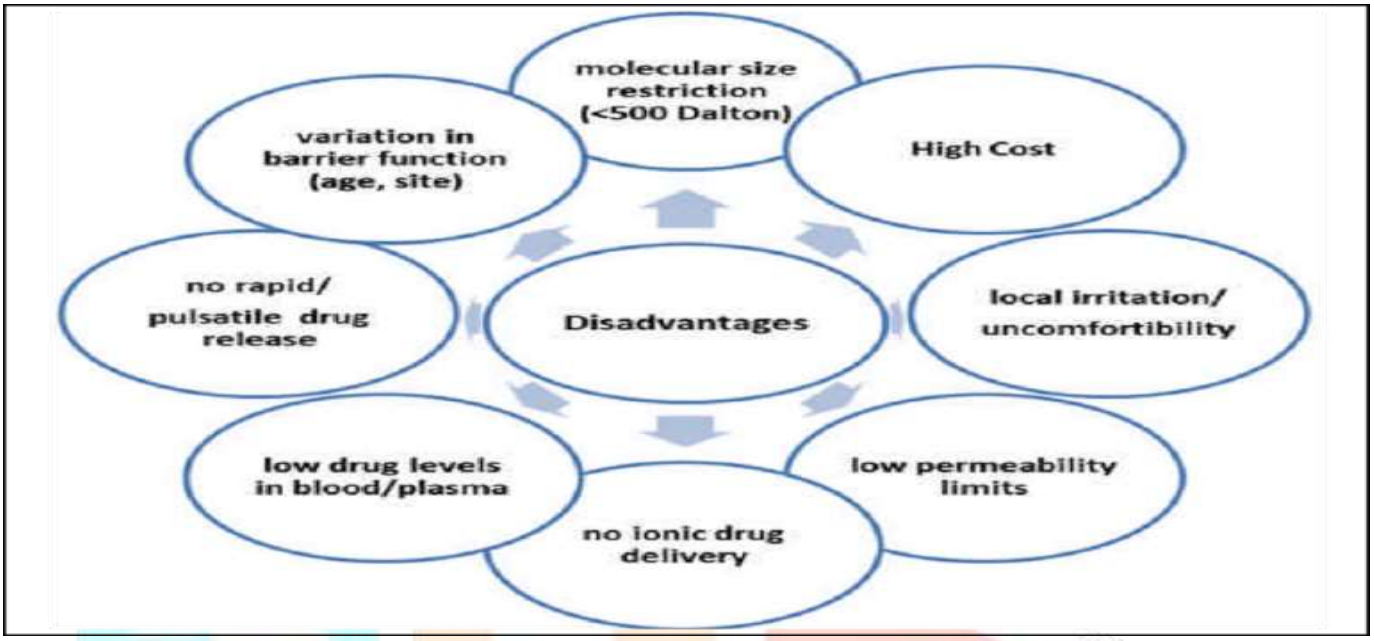

figure no 2:-Disadvantages of transdermal drug delivery system

MAIN COMPONENTS OF TRANSDRMAL PATCHES :

Polymer matrix– Backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate.The following criteria should be satisfied for a polymer to be used in transdermal patches:

a)Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

b)The polymer should be stable.

c)The polymer should be nontoxic

d)The polymer should be easily of manufactured

e)The polymer should be inexpensive

f) The polymer and its deagration product must be non toxic or non-antagonistic to the host.

g) Large amounts of the active agent are incorportaed into it .

Types of polymer: -

a)Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

b)Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

c)Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy. Large amounts of the active agent are incorportaed into it .

Drug- The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life.eg fenatyl, nitroglyceriene etc.

Physiochemical properties of drug : -

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

b)The drug should have affinity for both lipophilic and hydrophilic phases.

c)The drug should have a low melting point.

Biological properties of drug :

a)The drug should be potent with a daily dose of the order of a few mg/day.

b)The half life (t½) of the drug should be short.

c)The drug must not produce allergic response.

d)Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

Permeation enhancers- Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug . These are of three types - lipophilic solvent, surface active agents and two component systems. E.g. DMSO

a)Solvent: - These compounds increase penetration possibly by swelling the polar pathway. **e.g.: Water alcohols**–Methanol & ethanol, / Dimethyl acetemide Propylene glycol and Glycerol.

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

i) Anionic surfactant:- Sodium lauryl sulphate Diacetyl sulphosuccinate

ii) Nonionic Surfactant:- Pluronic F127, Pluronic F68

iii) Bile Salt: - Sodium taurocholate, Sodium deoxycholate.

(c) Miscellaneous Chemicals: - These include urea, a hydrating and keratolytic agent; N, N dimethyl-mtoluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-omethyl-ß-cyclodextrin

(d) Enhance the permeation eg. Urea, calcium thioglycolate.

Adhesive- Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug.

i) It should not be irritant

ii) ii) It should be easily removed

iii) It should not leave an un washable residue on the skin

iv) It should have excellent contact with the skin.

v) Physical & chemical compatibility with the drug

vi) Permeation of drug should not effected.

Backing laminates- Should have low modulus or high flexibility. Eg-vinyl, polyethylene.

Release liner- Protects the patch during storage. The liner is removed prior to use.

Other excipients like plasticizers and solvents. (7)

FACTORS AFFECTING TRANSDERMAL BIOAVAILABILITY

Two major factors affect the bioavailability of the drug via transdermal routes:

Physicochemical factors

Skin hydration

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

Temperature and pH

The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

Diffusion coefficient

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

Drug concentration

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

Partition coefficient

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

Molecular size and shape

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

Biological factors

Skin condition

Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

Skin age

The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.

Blood flow

Changes in peripheral circulation can affect transdermal absorption.

Regional skin sites

Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

Skin metabolism

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

Species differences

The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration (9).

TYPES OF TRANSDERMAL PATCHES :

1. Single-layer Drug-in-Adhesive :

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin .(11) In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing (9)

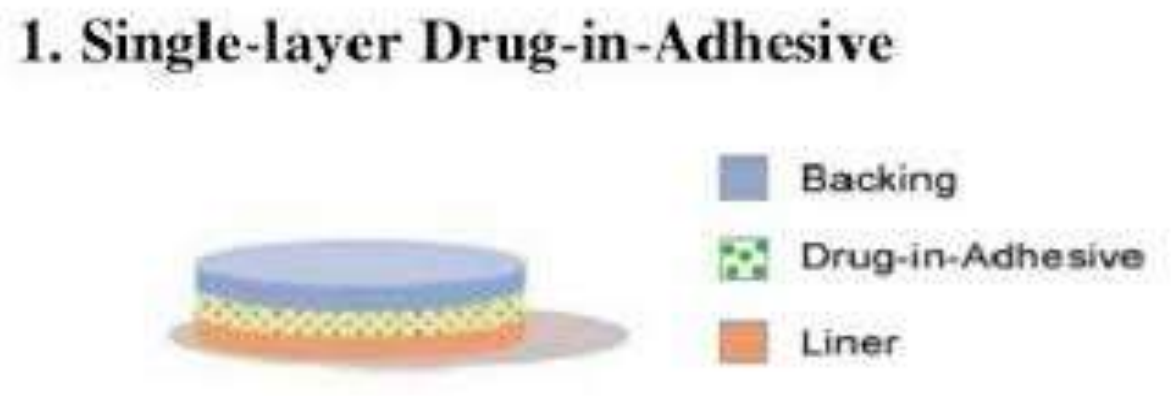

figure no 3:- single layer drug in adhesive .

2 . Multi-layer Drug-in-Adhesive :

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. The multi-layer system is different, however, that it adds another layer of drug-in adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing . (9) Multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.(11)

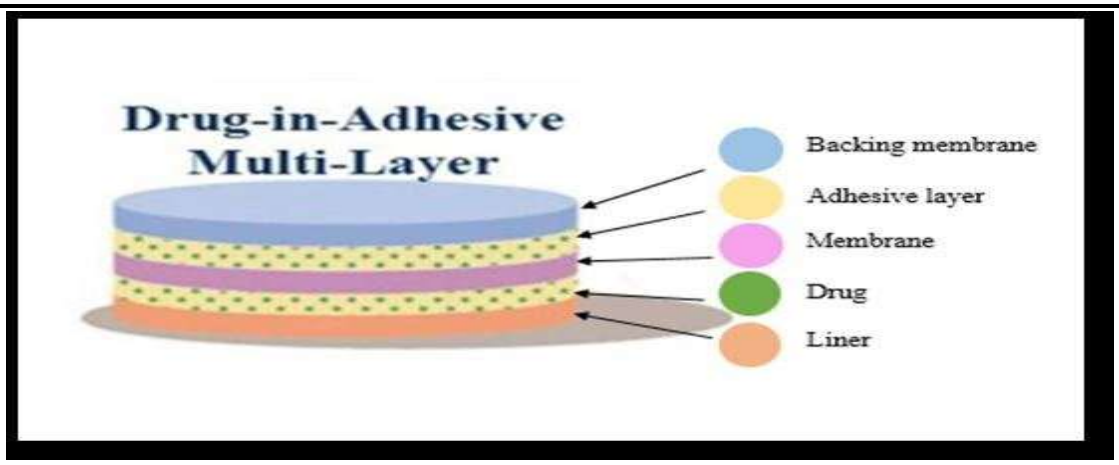

figure no 4:- multi- layer drug in adhesive .

3.Reservoir system :

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be porous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix . In this type of system, the rate of release is zero order.(9)The drug release profile follows a

zero order rate of kinetic drug release, maintaining a constant drug level in the plasma. Crosslinking polymeric agents are usually added, since the drug dispersion needs to be thermodynamically stable.(3)

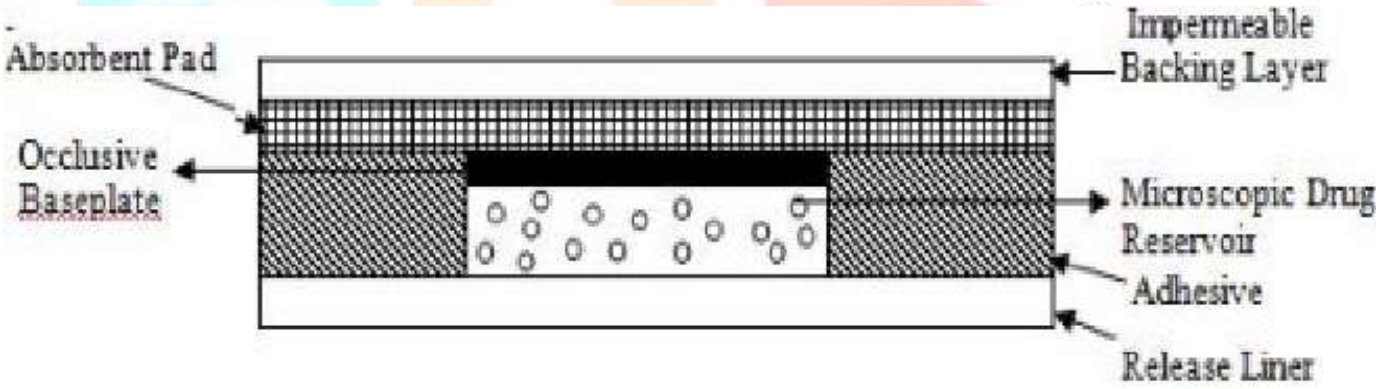

figure no : 5 :-reservoir system.

4. Matrix System :

The Matrix system 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 overlaying it.(7)

i. Drug-in-adhesive system :

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system :

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.(4)

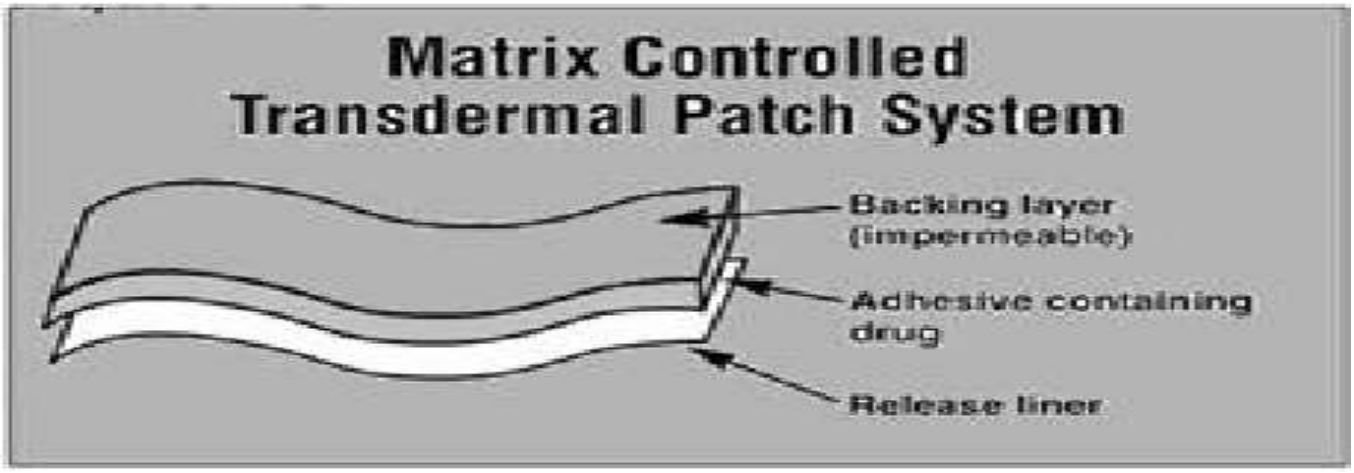

figure no 6:- matrix controlled transdermal patch system.

5. **Microreservoir system**

The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Microreservoir system is a combination of

reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer (4)

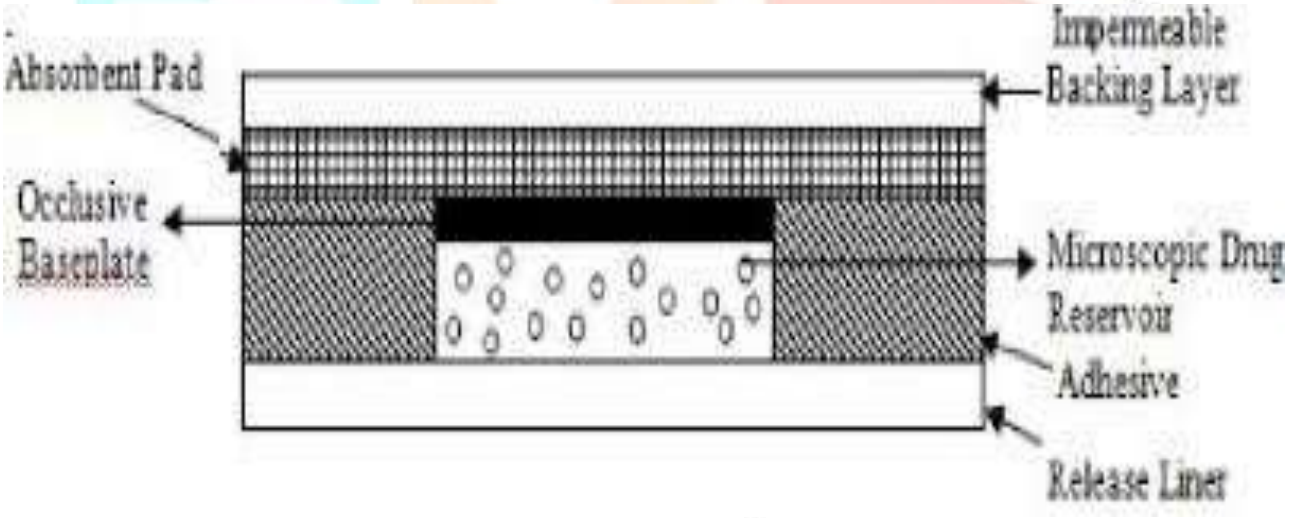

figure no 7:-microreservoir system .

VARIOUS METHODS FOR PREPARATION OF TDDS :

Asymmetric TPX membrane method :

A prototype patch can be fabricated using a heat sealable polyester film (type 1009, 3 m) with a concave of 1 cm diameter will be used as the backing membrane. Drug sample is dispensed into concave membrane, covered by TPX {poly- (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

Circular teflon mould method :

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-Nbutylphthalate is added as a plasticizer into drug polymer solution. The total contents are stirred for 12 h and poured into circular teflon mould. The moulds are placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate

for 24 h. The dried films are stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

Polymer + organic solvents

↓

(divide the solvent mixture into two equal halves)

Calculate the amount of drug in 1and half solvent and enhances in other slovent .

↓ Add drug solvent and plasticizer {Di-N-butylphalate }

Poured in teflon mould covered with inverted funnel .

↓

Evaluated within 1 week of preparation .

Mercury substrate method :

In this method, drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 min to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation .

Drug + polymer solution + Plasticizer .

↓

Poured in levelled surface covered with inverted funnel .

IPM membrane method :

In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

Drug +(water + propylene glycol- carbomer 940 polymer)

↓ Continously 12 hrs in magnetic stirrer .

Neutralised and made viscous by addin Triethanolamine .

↓ Buffer with pH 7.4 used to form gel

Incorporated in isopropyl myristate membrane in a gel form.

EVAC membrane method :

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. 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 backing layer covering the specified area. A rate controlling membrane is placed over the gel and the edges are sealed by heat to obtain a leak proof device.(9)

Aluminium Backed Adhesive Film Method:

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks .(10)

Free film method :

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution .(9)

Proliposome/Proniosome based TDDS :

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference the drug and lecithin ratio (e.g., 0.1:2.0) may be used as an optimized one. The proliposomes are prepared by taking mannitol powder (e.g., 5 mg) in a round bottom flask which is kept on a heating water bath and the flask is rotated. It is followed by vacuum drying. Drug and lecithin are dissolved in a suitable organic solvent mixture. An aliquot (e.g., 0.5 ml) of organic solution is introduced into the round bottomed flask. After complete drying, second aliquot (e.g., 0.5 ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected with a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through suitable mesh. The collected powder is transferred into a glass bottle and stored at freezing temperature until characterization (Deo et al., 1997). Vora et al., (1998) have studied the proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and extensively characterized both in-vitro and in-vivo. The system was evaluated in-vitro for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion across rat skin. The effect of composition of formulation, amount of drug, type of spans, alcohols and sonication time on transdermal permeation profile was observed. The stability studies were performed at 4°C and at room temperature. The biological assay for progestational activity included endometrial assay and inhibition with the formation of corpora lutea. The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception. Alam et al., (2010) have studied the anti-inflammatory effect of celecoxib incorporated in proniosomes. A low dose proniosomal gel containing celecoxib was developed for the treatment of osteoarthritis. All the prepared formulations were subjected to physicochemical evaluations and anti-inflammatory studies. The entrapment efficiency was found to be more than 90%. The vesicle shape was determined with the help of transmission electron microscopy. It showed that the vesicles were spherical and discrete with sharp boundaries. The vesicle size, size-distribution, and polydispersity studies were performed using photon correlation spectroscopy. The niosome vesicles formed from proniosomes had a mean size of 449.4 nm. An admirable uniformity in particle size distribution was obtained as indicated by a low polydispersity index (PI < 1). Anti-inflammatory studies were performed using the rat hind-paw oedema induced by carrageenan (1% w/v) method. The optimized proniosomal gel produced 100% inhibition of paw oedema in rats up to 8 h after carrageenan injection.(4)

APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL PATCH :

A. **Membrane moderated systems:** The system consists of drug reservoir moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane (Figure 2). The drug reservoir compartment contains the drug solids that are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium (e.g.,silicon fluid). The rate controlling membrane can be micro porous or nonporous polymeric membrane e.g., ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo-allergic adhesive polymer may be applied

to achieve an intimate contact of TDDS with skin surface. The membrane moderated transdermal systems are available under the various Catapres- TTS (providing continuous systemic delivery of clonidine for 7 days for the treatment of high blood pressure) rand names including Transderm-Nitro system (once a day provide continuous controlled release of nitroglycerin for the prevention of angina

pectoris due to coronary artery disease), Transderm-Scop system (3 days medication for prevention of nausea and vomiting).

B. **Adhesive diffusion controlled system:** It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non-medicated rate

controlling adhesive polymer of constant thickness are applied (Figure 3). Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion. The system is available under the various brand names including Climara®

(designed to release both estradiol and levonorgestrel for the treatment of moderate to severe vasomotor symptoms associated with menopause and postmenopausal osteoporosis), Nicoderm® (for smoking cessation), and Deponit patches (containing glyceryl trinitrate for the prevention of angina attacks).

C. **Matrix dispersion system:** The drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix (Figure 4). The medicated polymer is then moulded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc; the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no

interference of adhesive. Nitro-Dur® patches provide continuous controlled release of nitroglycerin to help prevent angina attacks.

D. **Microreservoir systems:** These are considered as combination of reservoir and matrix dispersion type. In this the drug reservoir is formed by suspending the drug solids in an aqueous solution of water soluble polymer followed by dispersing the drug suspension homogenously in lipophilic polymer (Figure 5). The dispersion is carried out by high shear mechanical force to form unleachable microscopic spheres of drug reservoir. This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness. The system is available as Nitrodisc® (containing nitroglycerin for the prevention of chest pain (angina) in people with a certain heart condition) in the market. (4)

EVALUATION OF TRANSDERMAL PATCHES :

Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

❖ **Physicochemical evaluation :**

Thickness:

The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film. (5)

Drug Content: A specified area of the patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique).

Weight Uniformity: The prepared patches are to be dried at 60°C for 4 hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight andstandard deviation values are to be calculated from the individual weights37, 38 .

Thickness of the Patch: The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch38-41 .

Flatness Test: Three longitudinal strips are to be cut from each film at different portion like one from thecenter, 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 percent constriction, with 0% constriction equivalent to 100% flatness33 .

Percentage Moisture Uptake: The weighed films are to be kept in desiccators at room temperature for 24 hrs

containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula41, 42 . Percentage moisture uptake = [Final weight-Initial weight/ initial weight] × 100.

Moisture Loss: The prepared films are to be weighed individually and to be kept in a desiccator containing

calcium chloride at 40oC. After 24 hrs the films are to bereweighed and determine the percentage of moisture loss from the below formula .

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

Water Vapor Transmission Rate (WVTR) Studies: Glass vials of equal diameter were used as transmission

cells. These transmission cells were washed thoroughly and dried in oven at 100 oC for some time. About 1g anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after storage. The amount of water vapor transmitted was found using following formula43, 44 . Water Vapor Transmission Rate = Final Weight –Initial Weight/ Time X Area It is expressed as the number of grams of moisture gained/hr/cm.sq

Swellability: The patches of 3.14 cm^2 was weighed and put in a petri dish containing 10 ml of double distilled

water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed45 . The degree of swelling (S) was calculated using the formula,

S (%) = Wt– Wo /Wo × 100 Where S is percent swelling Wt is the weight of patch at time t and Wo is the weight of patch at time zero.

Folding Endurance: A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be fold at the same place without breaking gave the value of the folding endurance 46 .

Polariscope Examination: This test is to be performed to examine the drug crystals from patch by Polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch21 .

Percentage Elongation Break Test: The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula47 . Elongation percentage = [L1-L2 / L2] × 100 Where, L1 is the final length of each strip and L2 is the initial length of each strip.

Tensile Strength: Tensile strength of the film determined with universal strength testing machine. The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one is fixed and upper one is movable. The test film of size (4 × 1 cm2) is fixed between these cell grips and force is gradually applied till the film broke31 . The tensile strength of the film is taken directly from the dial reading in kg. Tensile strength is expressed as follows. Tensile strength =Tensile load at break / Cross section area

Probe Tack test: In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive and when a bond is formed between probe and Adhesive . The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams47 .

Skin Irritation Study: Skin irritation and sensitization testing can be performed on healthy rabbits (average

weight 1.2 to 1.5 kg). The dorsal surface (50 cm 2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hrs and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.(10)

❖ **In vitro permeation studies :**

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature usually for skin and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and

temperature etc. are some variables that may affect the release of drug. So permeation study involvespreparation of skin, mounting of skin on permeation cell, setting of experimental conditions like

temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e., drug permeated per cm/ per second.

❖ **In vivo studies :**

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 :

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.

Human models :

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.(5)

■ VARIOUS TECHNOLOGIES FOR ENHANCEMENT OF DRUG ABSORPTION THROUGH TRANSDERMAL PATCH:

Iontophoresis :

Iontophoresis is a system in which a charged drug molecule is propelled through the skin by applying low electrical current (Pathak *et al* 2006). A typical ionotphoresis device consists of two electrodes, anode (+) in a reservoir containing the positively-charged drug in a solution and cathode (-) in a negatively-chargedsalt solution. When voltage is applied to the electrodes, it creates a mild electrical current that repulses positively charged drug molecules through the skin into the blood stream. The advantage of the system is the controlled delivery of drug and can be turned on and off when required. The limitation of the system is irritation and pain, which limits the dose of the drug. It is currently applied for the rapid delivery of lidocaine for local anaesthesia.

Electroporation :

Electroporation is the creation of aqueous pores in the lipid bilayers by the application of short electrical pulses. Electroporation may combine with iontophoresis to enhance the permeation of peptides such as vasopressin, calcitonin and neurotensin.

Sonophorosis :

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis.

Microporation :

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. Microporation is a process by which micro-pores or channels are created in the skin which then can facilitate the transport for drug molecules across the stratum corneum. There are several methods to create these microchannels, the most prominent includes mechanical microneedles, thermal or radiofrequency ablation and laser ablation.

Microneedles :

An array of microscopic needles made from metal, polymers, silicon or glass can be used to create pathways of microdimension in the skin. The drug can be delivered by variety of mechanisms including:

· directly coating on solid microneedles
· delivering drug through hollow microneedles
· incorporating the drug inside the needle during fabrication.

Thermal or radiofrequency ablation:

Exposure of skin to short, high temperature pulses cause structure disruption of stratum corneum without significantly heating or damaging the deeper tissues. This creates micropores in the skin very similar to created by micro needles.

Laser ablation :

Skin ablation can also be achieved by the application of laser rays of specific defined wavelength which are directly absorbed by the skin. Pulse laser energy causes the water in the outer skin layer to superheat and evaporate. The resulting micro-explosion results in tissue ablation (9)

❖ GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDS:

The patient should be advised of the following general guidelines. Rotating of site of application is important to allow the skin to regain its normal permeability and to prevent skin irritation15 .

- TDDS should be applied to clean, dry skin relatively free of hair and not oily, inflamed, Irritated, broken. Wet or moist skin can accelerate drug permeation time.
- Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.
- Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug. Patient should not physically alter TDDS, since this destroys integrity of the system.
- The protecting backing should be removed with cannot to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds.
- A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing or swimming.
- A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system.
- The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system.
- If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.
- Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets. Use of transdermal patch It is important to use a different application site everyday to avoid skin irritation. Suggested rotation is: Day 1 – Upper right arm, Day 2 – upper right chest, Day 3 – Upper left chest, Day 4 – Upper left arm, then repeat from Day 1.

❖ CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED:

- Transdermal patch is used when: When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia33, 34 .

❖ CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED:

The use of transdermal patch is not suitable when:

(1) Cure for acute pain is required.
(2) Where rapid dose titration is required.
(3) Where requirement of dose is equal to or less than 30 mg/24 hrs.(10)

❖ LIMITATIONS FOR SELECTION OF TDDS:

All types of drugs cannot be administered through this route; the drug must have some desirable Physico Chemical properties. 11

- Not suitable for drugs that require high plasma levels.
- Not suitable for drugs that produce skin irritation and contact dermatitis.
- Not suitable for drugs with high molecular weight.
- Not suitable for drugs that undergo metabolism during the passage through the skin.
- The Transdermal route cannot be employed for a large number of drugs, as the skin is a very efficient barrier for penetration of drugs. Only with low dose can be administered.(10)

❖ APPLICATIONS :

- For the treatment of Angina pectoris.
- Contraceptive
- Anti-inflammatory
- Anti-emetics
- Cosmetics
- Smoking cessation (3)

CONCLUSION :

Transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs; the pain and inconvenience of injections. The successes of first generation transdermal patches, second generation chemical enhancers, and iontophoresis are expanding delivery capabilities for small molecules, whereas third generation physical enhancers could enable transdermal delivery of macromolecules and vaccines. A further major step forward will be production of total dissolved solids units delivering peptide and even protein substances including insulin and growth hormone. The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase.Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. TDDS are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy. It offers the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. This may be achieved by by-passing the hepatic first metabolism. Almost all major and minor pharmaceutical companies are developing TDDS. Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug.

REFERNCES :

1. Wound Healing Activity of Transdermal Patches of Carica Papaya,Chromolaena Odorata, and Averrhoa Bilimbi Leaves on Incision Wounds of Hyperglycemic Rat Tahara Dilla Santi1,2, Tongku Nizwan Siregar3 , Amalia Sutriana4,*Rita Andini5 and Aditya Candra1,6 .

2. TRANSDERMAL PATCHES: A RECENT APPROCH TO NEW DRUG DELIVERY SYSTEM
SONIA DHIMAN*, THAKUR GURJEET SINGH AND ASHISH KUMAR REHNI .

3 . OTHMAN A. AL HANBALI1,2* HAJI MUHAMMAD SHOAIB KHAN3 MUHAMMAD SARFRAZ4,5 MOSAB ARAFAT4 SHAKEEL IJAZ3 ABDUL HAMEED .Transdermal patches: Design and current approaches to painless drug delivery .Accepted November 7, 2018 Published online November 28, 2018 .

4.Md. Intakhab Alam1 , Nawazish Alam*2 , Vikramjit Singh2 , Md. Sarfaraz Alam1 , Md. Sajid Ali1 , Tarique Anwer1 , Mohammed M. Safhi TYPE, PREPARATION AND EVALUATION OF TRANSDERMAL PATCH: A REVIEW Article Received on 21 May 2013, Revised on 27 June 2013, Accepted on 30 July 2013

5.KAMAL SAROHA, BHAVNA YADAV* , BENIKA SHARMATRANSDERMAL PATCH: A DISCRETE DOSAGE FORM Vol 3, Issue 3, 2011 .

6. Bhupendra Koul 1,* , Baveesh Pudhuvai 2 , Chelsi Sharma 1 , Arvind Kumar 3 , Vinay Sharma 4 , Dhananjay Yadav 5,* and Jun-O Jin 5,**Carica papaya* L.: A Tropical Fruit with Benefits beyond the Tropics Received: 27 July 2022 Accepted: 17 August 2022 Published: 20 August 2022.

7 .Audumbar Digambar Mali* , Ritesh Bathe and Manojkumar Patil An updated review on transdermal drug delivery systems *International Journal of Advances in Scientific Research* ISSN: 2395-3616 (Online)
Journal DOI: 10.7439/ijasr.

8.Gayatri Patel; Dr. Kantilal Narkhede; Dr. Anuradha Prajapati; Dr. Sachin Narkhede A Comprehensive Review Article on Transdermal Patch . International Journal of Pharmaceutical Sciences & Medicine (IJPSM),
Vol.8 Issue. 3, March- 2023, pg. 77-81 .

9. Arti Kesarwani*, Ajit Kumar Yadav, Sunil Singh, Hemendra Gautam, Haribansh N. Singh, Anamika Sharma, Chitresh Yadav THEORETICAL ASPECTS OF TRANSDERMAL DRUG DELIVERY SYSTEM , Received: May 09, 2013 / Revised: August 27, 2013 / Accepted: August 28, 2013 .

10 . D. Prabhakar1 , J. Sreekanth2 , K.N. Jayaveera , TRANSDERMAL DRUG DELIVERY PATCHES: A REVIEW Journal of Drug Delivery & Therapeutics; 2013, 3(4), 213-221 .

11 . Sakalle Parivesh1*, Dwivedi Sumeet2 and Dwivedi Abhishek , Design, Evaluation, Parameters and Marketed Products of transdermal patches: A Review ,Received on: 20-10-2009; Revised on: 16-12-2009; Accepted on:07-01 2010 .

12 . LEYA MATHEWS, ANITHA ROY . MANAGEMENT OF PAIN USING TRANSDERMAL PATCHES - A REVIEW Vol 9, Issue 6, 2016.

13 . Anjali V. Patel*1 and Biren N. Shah TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW PHARMA SCIENCE MONITOR AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES Jan-Mar 2018 .

14 .* 1A.Arunachalam, 2M.Karthikeyan, 3D.Vinay Kumar, 3 Prathap. M, 4 S. Sethuraman, 2 S.Ashutoshkumar,
2 S.Manidipa. Transdermal Drug Delivery System: A Review, Vol. 1, Issue 1, October-December 2010 .

15 .Francesco Cilurzo, Chiara G M Gennari & Paola Minghetti , Adhesive properties: a critical issue in transdermal patch development .Published : 16 Dec 2011.

16 . Won Fen Wong 1 , Kuan Ping Ang 2 , Gautam Sethi 3,* and Chung Yeng Looi 4, *Review* Recent Advancement of Medical Patch for Transdermal Drug Delivery Published: 17 April 2023 .

17. Eylul Gulsen Yilmaz 1,2,†, Emre Ece 1,2,†, Özgecan Erdem 1 , Ismail E¸s 1 and Fatih Inci 1,2, *Review* A Sustainable Solution to Skin Diseases: Ecofriendly Transdermal Patches, Published: 8 February 2023.

18 . T. Tanner and R. Marks Simbec Research Ltd, Merthyr Tydfil, UK , Review Delivering drugs by the transdermal route: review and comment , Accepted for publication 30 December 2007.

19 . Katz NP, Gammaitoni AR, Davis MW, Dworkin RH, Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial, Pain Med, 2002,3(4),324-32.

20 .Jacoby DB, Youngson RM, Marshall Cavendish Corporation, Encyclopedia Of Family Health, Published by Marshall Cavendish, 2004,2259.

21. Liao, Z.; Dong, F.; Liu, J.; Xu, L.; Marshall-Colon, A.; Ming, R. Gene regulation network analyses of pistil development in papaya. *BMC Genom.* 2022, *23*, 8.

22 .Wai, C.M.; Ming, R.; Moore, P.H.; Paull, R.E.; Yu, Q. Development of chromosome-specific cytogenetic markers and merging of
linkage fragments in papaya. *Trop. Plant Biol.* 2010, *3* .

23 .. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system- A review. Asian Journal of Pharmaceutical and Clinical Research. 2009; 2:14-20 .

24. Aggarwal G, Dhawan S. Development, Fabrication and Evaluation of Transdermal Drug Delivery System - A Review. Pharmainfo.net. 2009; 7(5).

25 . Heather AE. Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery. 2005; 2:23-33. Dhiman et al. Int J Pharm Pharm Sci, Vol 3, Suppl 5, 26-34 34.