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A REVIEW ON TRANSDERMAL PATCHES

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ABSTRACT

Transdermal drug delivery (TDDS) is regarding application of drug on the skin surface so that it can permeate through the skin & reaches the systemic circulation at sufficient concentration to ensure therapeutic efficacy. Transdermal drug delivery system has multiple advantages over conventional system; TDDS offers sustained drug release, patient compliance, avoidance of first pass effect, ease of application and removal in case of toxicity as well as decrease in the side effects as compared with conventional therapy. Stratum corneum acts as a barrier that limits the penetration of substances through skin and limitation can be overcome by permeation enhancing techniques. A transdermal patch has several components such as, drug reservoir, adhesive layer, release control membrane, backing membrane and liner etc. This review article offer an overview of TDDS, its advantages over conventional dosage forms, Limitations, various components of transdermal patches, types of patches, and its methods of evaluation and the advancements done in this field.

KEYWORDS: Transdermal drug delivery system, Transdermal patch, Skin, Penetration enhancer.

INTRODUCTION

Transporting medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth or oral route. Patients often forget to take their medicine and also they get tired of swallowing pills. Additionally escaping the gastrointestinal tract would obviate the GI irritation that frequently occurs & avoid partial 1st pass inactivation by the

liver. Further, a steady absorption of drug over hours or days is usually preferable to blood level spikes and troughs presented by oral dosage forms.[3]

TDDS is a viable administration route for potent, low molecular weight therapeutic agents which can't withstand the hostile environment of gastro-intestinal tract and /or are subject to considerable first pass metabolism by the liver. It uses the skin as an substitute route for the delivery of systemically acting drugs. Dermal drug delivery is the topical application of drugs to the skin in the therapy of skin diseases, wherein high concentrations of drugs can be localized at the site of action, therefore reduces the systemic drug levels and side effects.[22] Transdermal delivery has made a major contribution to medical practice but has yet to fully achieve its potential as a substitute to oral delivery and hypodermic injections. The principle of TDDS is that they could provide sustained drug delivery over a prolonged period of time. TDDS can be designed to input drug at proper rate to maintain plasma-drug levels for therapeutic efficacy. The success of all the TDDS depends on the ability of the drug to permeate skin in sufficient quantities to attain its desired therapeutic effect. This review article presents a detailed study of transdermal that is advantage, disadvantages and factors affecting skin permeation and types, mechanism.[3]

These merits are offered by the currently marketed transdermal products. Transdermal drug delivery is defined as self-contained, discrete dosage forms which are applied to intact skin deliver the drug through the skin at controlled rate to the systemic circulation. TDDS settled itself as an integral part of novel drug delivery system. The transdermal patches uses a polymer membrane to modulate the rate at which the drug contained in the reservoir within the patch can pass through the skin and into the blood stream.[3]

The principal of transdermal drug transport is to supply drug across epidermis to achieve systemic effect over a prolonged period of time. The primary objective of controlled drug delivery is to ensure safety, efficacy of the drugs and patients compliance. TDDS is one of the systems lying under the category of controlled drug delivery, in which the focus is to deliver the drug through skin in a predetermined and controlled rate.[9]

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. TDDS delivers a steady infusion of a drug over a prolonged period of time. Adverse effects or therapeutic failures mostly associated with intermittent dosing can also be avoided.[1]

2. The simplified medication regimen leads to enhanced patient compliance and decreased side effects, inter and intra-patient variability.[16]
3. No interference with gastric and intestinal fluids.[16]
4. This route is suitable for the administration of drugs having narrow therapeutic window, very short half-life and poor oral availability.[23]
5. Transdermal route provides convenient and pain-free self-administration for patients, safe.[5]
6. Bypasses the first pass metabolism, avoids inactivation of drugs by pH influences and enzymes present in GI tract, which otherwise occurs on oral administration.[2]
7. Easy elimination of drug delivery in case of toxicity.[42]

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Transdermal drug delivery system cannot deliver ionic drugs.[29]
2. It cannot develop for drugs of large molecular size.[41]
3. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.[17]
4. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.[4]
5. Drugs with very low or high partition coefficient fail to reach blood circulation.[48]
6. Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy.[35]
7. Local irritation may develop at the site of application.[47]

ANATOMY OF THE SKIN[12, 13, 32-34, 44, 43]

The skin of an average adult human comprises a surface area of nearly 2m2 and receives about one-third of the blood circulating through the body. The skin can be considered to have four distinct layers of tissue.

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

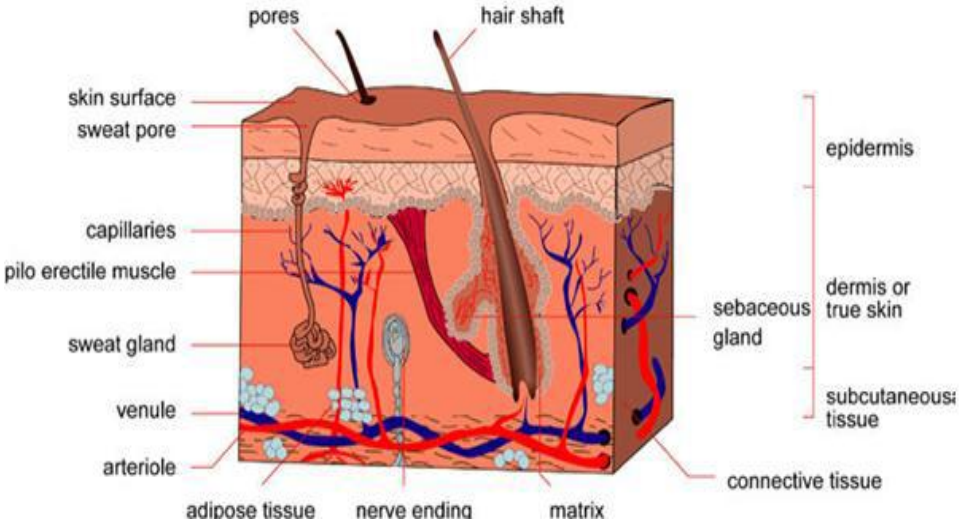

Fig 1: Cross section of skin.

- **Stratum corneum & Epidermis:** The main obstacle to percutaneous absorption: The SC consists of multiple layers of horny dead cells, which are compacted, dehydrated, flattened and keratinized. The horny cells are stacked in highly interdigitated columns with 15-25 cells in the clamp over most of the body. It has a density of 1.55g/cc. The SC has a water content of only 20% as compared to 70 percent present in physiologically active stratum germinativum. It exhibits regional differences over most of the body & is approximately 10-15µm in thickness. However, thickness may be several hundred micrometers (300-400µm) on friction surface such as the palms of the hand and soles of the feet. Keratin present in the cells of the SC is a fibrous protein, which is inferior in sulphur and forms a filamentous network to assure cohesion, flexibility and recovery.

The incredible properties of stability insolubility & resistance observed in the SC are due to the thick cell membrane and cell matrix, which consists of a amorphous proteins rich in sulphur content and lipids with many disulphide linkages. The SC is outlined as the only rate-limiting barrier of the skin with regard to the viable epidermis and dermis. The SC is a heterogeneous membrane having of alternating lipophillic and hydrophilic layers. The pH of the skin surface is between 3 and 4, which is about isoelectric pt. of keratin in the SC layer. Below the SC remains the viable epidermis, a more accommodative of permeant molecules. Viable epidermis is an aqueous solution of protein encapsulated into cellular compartments by a thin cell membranes, which are fused together by tonofibrils.

Viable epidermis has a density close to that of water. The germinal (proliferative) layer above dermis undergoes cell divisions producing an exterior displacement of the cell towards a

surface. As the germinal layer moves upwards, it changes shape into a more rounded form with a thorny projections and appears as a stratum spinosum. After the germinal layer has raised 12-15 layers higher its point of origin, therefore it becomes flattened and the basophilic nuclear material is sprinkle,sprinkled throughout the cells as granules. The layer is introduced to as stratum granulosum. The stratum lucidium layer, which present just below the Stratum corneum , is the site where nuclei disintegrate, keratinization & sulphahydryl-rich matrix formation takes place. Eventually it shifts upwards to form a SC. It should be pointed out that the epidermis consists of no vascular elements. The cells receive nourishment from the capillary beds positioned in the papillary layers of dermis by diffusion of plasma and serum components.

- **Dermis:** The site of systemic absorption is dermis, which is 0.2-0.3 cm thick and is made of a fibrous protein matrix, mainly collagen, elastin & reticulum embedded in an amorphous colloidal ground substance. It is divided into two distinct sections: a superficial finely structured thin papillary layer adjoining to the epidermis and a deeper coarse reticular layer. The dermis is the locus of the blood vessels, sensory nerves segments of the sweat glands & pilosebaceous units. The blood vessels supply blood to the hair.

- **Subcutaneous fatty tissue:** Cushioning the epidermis & dermis is a subcutaneous tissue or fat layer where fat is manufactured and stored. It acts as a shock absorber and heat insulator. It essentially has no effect on the percutaneous absorption of drugs because it lies below the vascular system.

COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

Fig 2: Components of transdermal patches.

1. **Polymer Matrix[12]:** The polymer monitors the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

- Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses & released through it.
- The polymer should be stable.
- The polymer should be nontoxic.
- The polymer should be easy to manufacture.
- The polymer should be inexpensive.
- The polymer and its degradation product must be non-toxic or non-antagonistic to the host.
- Large amounts of the active agent are incorporated into it.

➢ **Types of polymer.**

- Natural polymers: Gelatin, Cellulose derivative, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.
- Synthetic Elastomers: Hydrin rubber, Nitrile, Acrylonitrile, Neoprene, silicone rubber.
- Synthetic polymers: Polyvinyl alcohol, polyethylene, polypropylene, polyvinyl chloride, polyurea, polyamiode, epoxy.

2. Drug: Transdermal route of administration cannot be applied for all types of drugs. The important drug properties that affect its diffusion from device as well as across the skin include molecular weight, solubility, physical properties and melting point.[37] The most important requirement of drug to be delivered transdermally is demonstrated by need for controlled delivery, such as adverse effect and short half-life associated with other route or a complex oral or I.V. dose regimen.[31] The drug parameter required for ideal drug candidate for transdermal drug delivery can be divided into:

➢ **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 (t½) of the drug should be short.
- The drug must not produce allergic response.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.[25]

3. Permeation Enhancer: Penetration enhancers are the substances used to increase permeation of skin mucosa. Penetration enhancer increases the absorption of penetrant through the skin which is also known as absorption promoter or absorption enhancers. Penetration enhancers used to increase the permeability of drug through skin.[19] The flux J. of drug across the skin can be write as, $J = D\, dc/dx$

Where, J = the Flux

D = diffusion coefficient

C = Concentration of the diffusing spectes

X = Spatial coordinate

Penetration enhancer does.

- enhances the diffusivity of the drug in the skin;
- cause stratum corneum lipid-fluidization, which leads to decreased barrier function;
- increase and optimize the thermodynamic activity of the drug in the vehicle and skin;
- result in a reservoir of drug within a skin;
- Affect the partition coefficient of the drug, increasing its release from formulation into the upper layers of the skin.
- Disrupt the order within and between the corneocyte upon binding to the keratin filament.[46]

➢ **Classification of penetration enhancers[6]**

- Terpenes (essential oils)

E.g. Nerodilol, menthol, 1,8-cineol, limonene, carvone etc

- Pyrrolidones

E.g. N-methyl-2-pyrrolidone (NMP), azone etc

- Fatty acids and esters

E.g. Oleic acid, linoleic acid, lauric acid, capric acid etc

- Sulfoxides and similar compounds

E.g. Dimethyl sulfoxide(DMSO), N,Ndimethyl formamide

- Alcohols, Glycols, and Glycerides

E.g. Ethanol, Propylene glycol, Octyl alcohol etc

- Micellaneous enhancers

E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc

4. Other excipients.

➢ **Adhesives[24]:** The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.

- It should be non-irritant.
- It should be easily removed.
- It should not leave an un-washable residue on the skin.
- It should have excellent contact with the skin.
- Physical & chemical compatibility with the drug
- Permeation of drug should not effect.

➢ **Linear:** During storage a patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore interpreted as a part of the primary packaging material rather than a part of dosage form for delivering of a drug. However, as the liner is in intimate contact with the delivery system, it should follow the specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Basically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive i.e. polyethylene, polyvinylchloride & the release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil & metallized laminates.[36]

➢ **Backing:** Backing laminate function as to provide support. They prevent drug from leaving the dosage form through top. They are impermeable to drugs and also act as permeation enhancers. Baking laminates should chemically compatible with the drug, enhancer, adhesive and other excipients35. Protect the patch from the outer environment.[7]

Approaches To Development Transdermal Therapeutic Systems[14, 36, 40-42]

Various technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of a drugs. These technologies can be classified into two major categories as follows.

A. Rate-programmed transdermal DDS

1. Membrane permeation-controlled systems
2. Adhesive dispersion-type systems.
3. Matrix diffusion-controlled systems.
4. Micro reservoir type or micro sealed dissolution controlled systems.

B. Physical stimuli-activated transdermal DDS

1. Structure based
- Microneedles
- Macroflux
- MDTS

2. Electrically based
- Iontophoresis
- Ultrasound
- Photochemical waves
- Electroporation
- Electroosmosis

3. Velocity based
- Powder jet
- Needle free injection

4. Others
- Transferosomes
- Medicated tattoos
- Skin abrasion
- Heat
- Laser radiation
- Magnetophoresis

A. Rate-programmed transdermal DDS

1. Membrane permeation-controlled systems

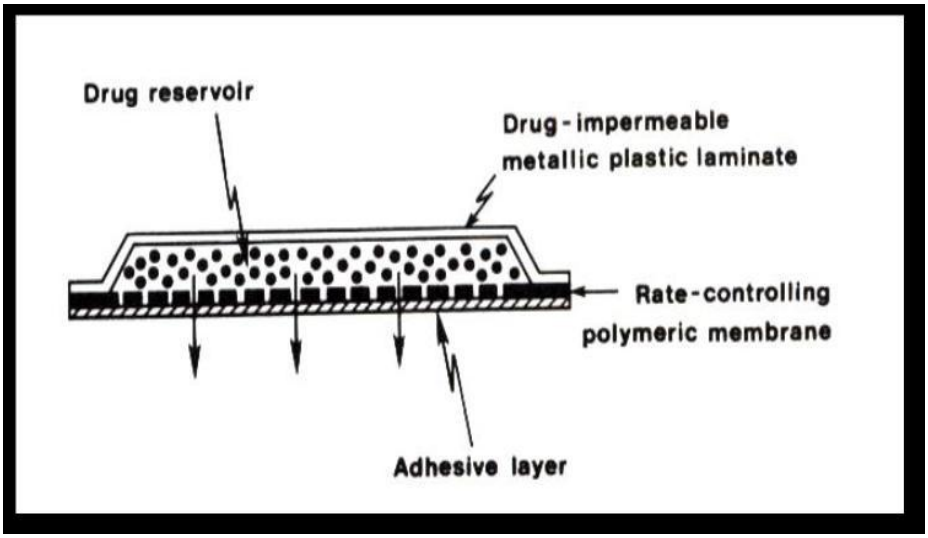

Fig 3: Membrane permeation controlled system.

In this system, drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminat & a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are allowed to release only through a rate-controlling membrane. In the drug reservoir compartment, the drug solid matterials are either scattered homogenously in the solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, viscous liquid medium to form a paste like suspension. The rate of drug release from this type of system can be tailored by changing the polymer composition, permeability coefficient and thickness of the rate limiting membrane & adhesive. The constant release rate of the drug is the major merit of membrane permeation controlled system. However, a rare fear also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or rapid release of entire drug content. Examples of this system are,

- **Transderm-Nitro**

Nitroglycerin- releasing transdermal system for once a day medication in angina pectoris.

- **Transderm-Scop**

Scopolamine- releasing transdermal system for 72 hrs. prophylaxis of motion sickness.

- **Catapres**

Clonidine- releasing transdermal system for 7 day therapy of hypertension.

- **Estraderm**

Estradiol – releasing transdermal system for treatment of menopausal syndrome for 3 – 4 days. The membrane permeation-controlled technology has also been used for controlled percutaneous absorption of prostaglandin derivatives.

- **Single-layer Drug-in-Adhesive**

This type of system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this TDDS design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation containing drug & all other excipients under a single backing film. The rate of release of drug from Single-layer Drug-in-Adhesive system is dependent on the diffusion of drug across the skin. The intrinsic rate of drug release from this system is defined by

$dQ/dT = Cr/1/Pm + 1/Pa$

Where Cr is drug concentration in the reservoir compartment Pa and P m are permeability coefficients of adhesive layer & rate controlling membrane, Pm is sum of permeability coefficients simultaneous penetrations across the pores & polymeric material. Pm and Pa, respectively, are defined as follows.

$Pm = Km/r. Dm/hm$

$Pa = Ka/m. Da/ha$

Where Km/r and Ka/m are partition coefficients of interfacial partitioning of drug from the reservoir to the membrane & from membrane to adhesive respectively; Dm and Da are the diffusion coefficients in the rate controlling membrane & adhesive layer, respectively; and hm and ha are thicknesses of the rate controlling membrane and adhesive layer.

- **Multi-layer Drug-in-Adhesive**

In this system drug is directly incorporated into the adhesive. However, the multi-layer encompasses either addition of a membrane between 2 distinct drug-in adhesive layers or the addition of multiple drug-in-adhesive layers under single backing film. The rate of drug release in this type of system is defined by,

$dQ/dt = Ka/r. Da Cr/ha$

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

2. Adhesive Dispersion-Type Systems

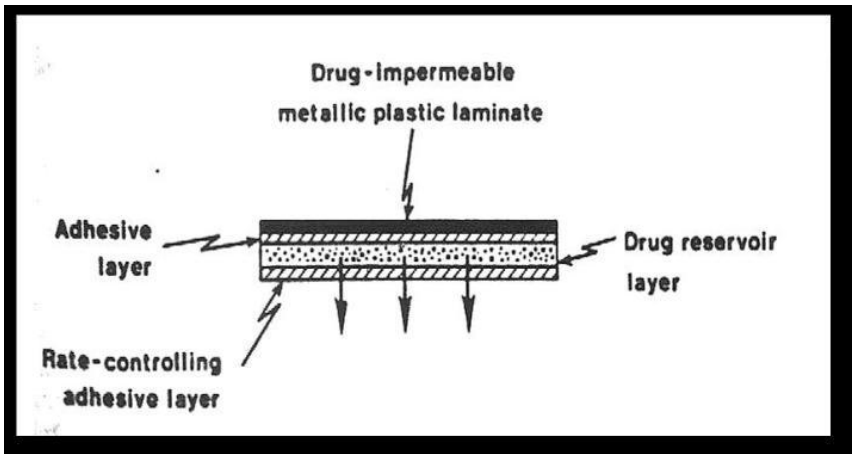

Fig 4: Adhesive dispersion type system.

This is a simplified form of membrane permeation controlled system. The drug reservoir is formulated by directly dispersing drug in an adhesive polymer e.g. poly (acrylate) or Poly(isobutylene) adhesive and then spreading the medicated adhesive, by hot melt or solvent casting, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a specific permeability & constant thickness are applied to manufacture an adhesive diffusion-controlled delivery system.

- **Frandol tape**

Releases of Isosorbide dinitrate for once-a-day medication of angina pectoris

This system is characterized by the inclusion of a liquid compartment containing a drug suspension or solution separated from release liner by a semi-permeable membrane and adhesive. The adhesive component of product responsible for skin adhesion can either incorporated as a continuous layer between the membrane and release liner or in concentric configuration around membrane. The rate of drug release from this system is given by,

$dQ/dt = Ka/r.\ Da\ A\ (\ ha\ )/ha\ (\ t\ )$

In the above equation,the thickness of adhesive layer for drug molecules to diffuse through enhances with time ha (t). To compensate this time dependent increase in diffusional path due to the depletion of drug dose by release, drug loading level is also enhanced with the thickness of diffusional path A (ha). In the above equation, thickness of adhesive layer to diffuse through enhances with time ha (t).

3. Matrix diffusion controlled systems.

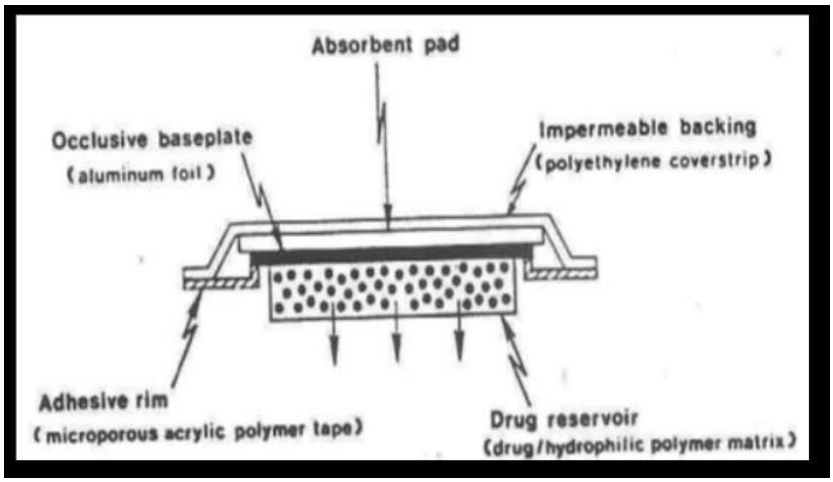

Fig 5: Matrix diffusion controlled system.

In this system, drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix. The resultant polymer with drug is then molded into a medicated disc with a controlled thickness & defined surface area. The dispersion of drug particles in polymer matrix can be accomplished by either homogeneously mixing finely ground drug with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogeneously blending drugs with a rubbery polymer at an elevated temperature. The drug reservoir can be formed by dissolving drug & polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in compartment fabricated from drug impermeable plastic backing membrane. The polymer is spread along the circumference of the patch to form an adhesive rim around the medicated disc. E.g. Nitro-Dur; delivers nitroglycerin for the treatment of angina pectoris. The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug suspension or solution which is in direct contact with the release liner. The component responsible for skin adhesion is consolidated in an overlay & forms a concentric configuration around the semisolid matrix. The rate of drug release from this system is defined as,

$dQ/dt = \sqrt{(ACpDp/2t)}$

Where A is the initial drug loading dose dispersed in polymer matrix and Cp and Dp are solubility and diffusivity of drug in polymer respectively. Since, only drug species dissolved in polymer can release, Cp is equal to CR, where CR is drug concentration in the reservoir compartment.

4. **Micro reservoir type or Micro sealed Dissolution:**

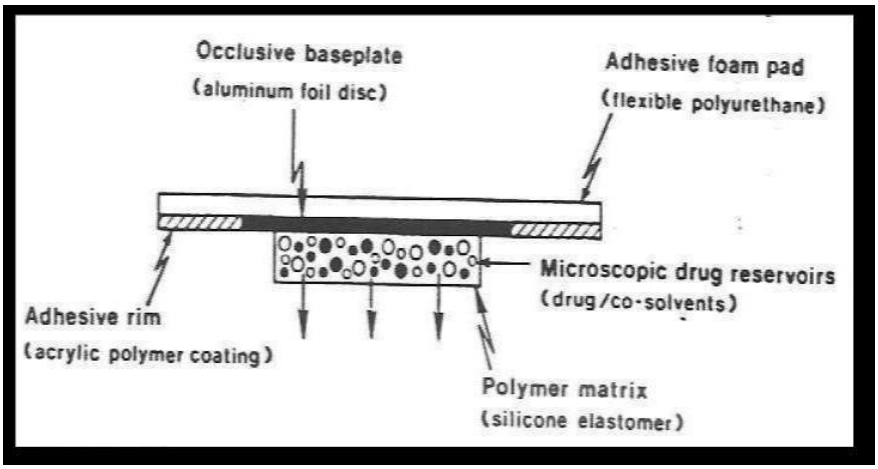

Fig 6: Micro reservoir type controlled system.

The micro reservoir system can be considered a combination of the reservoir and matrix diffusion drug delivery systems. In this, drug reservoir is formed by 1st suspending the drug solids in the aqueous solution of water soluble liquid polymer e.g. PEG and then dispersing the drug suspension homogeneously in the lipophilic polymer viz. silicone elastomers by the high energy dispersion technique to form several discrete, unleachable micro spheres of drug. This thermodynamically unstable dispersion is readily stabilized by immediately cross-linking polymer chains in-situ, which produces a drug polymer disc with constant surface area & fixed thickness. A transdermal delivery system is then produced by positioning the medicated disc at center and surrounding it with an adhesive rim. E.g. Nitroglycerin: Releasing transdermal therapeutic system for once-a day treatment of angina pectoris.

EVALUATION PARAMETER

1. **Physical appearance:**[22] The prepared patches were physically examined for color, clarity and surface texture.
2. **Thickness:**[20] The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines average thickness and standard deviation for the same to ensure the thickness of the prepared patch.
3. **Weight uniformity:**[27] The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of patch & weigh in digital balance. The average weight and standard deviation values are to be calculated from individual weights.

4. **Folding endurance:**[10] A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of time film could be folded at the same place without breaking gives the value of the folding endurance.
5. **Percentage moisture content:**[20] The prepared films are weighed individually and kept in a desiccators containing CaCl2 at RT for 24 hrs. The films are weighed again after a specific interval until they show a constant weight.
6. **Percentage moisture uptake:**[20] The weighed films are to be kept in a desiccator at RT for 24 hrs containing saturated solution of KCl in order to maintain 84% RH. After 24 hrs films are to be reweighed and determine % moisture uptake from the below mentioned formula.
7. **Water vapor transmission rate (WVTR):**[50] Water vapour permeability can be determined with foam dressing method air forced oven is replaced by the natural air circulation oven. The WVP can be determined by following formula

WVP=W/A

Where, WVP is expressed in gm/m2 per 24hrs, W is amt. of vapour permeated through patch expressed in gm/24hrs and A is surface area of the exposure samples expressed in m2.

3. **Drug content:**[50] 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 analyses the drugs contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

4. **Flatness test:**[15] Flatness test is performed to determine the smoothness of the film. Three strips of the film one from the center and two from the both sides of the film are to be cut and measured length wise. Variation in length is measured by finding out % constriction. Zero percent constriction is considered equivalent to 100% flatness.

9. **Thumb tack test:**[8] Thumb tack test is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on adhesive & relative tack property is detected.

10. **Shear Adhesion test:**[5] The cohesive strength of an adhesive polymer is measured by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An

adhesive coated patch is stacked on plate which is made of stainless steel and specified weight hung from the patch parallel to this plat. The time taken to pull off patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength.

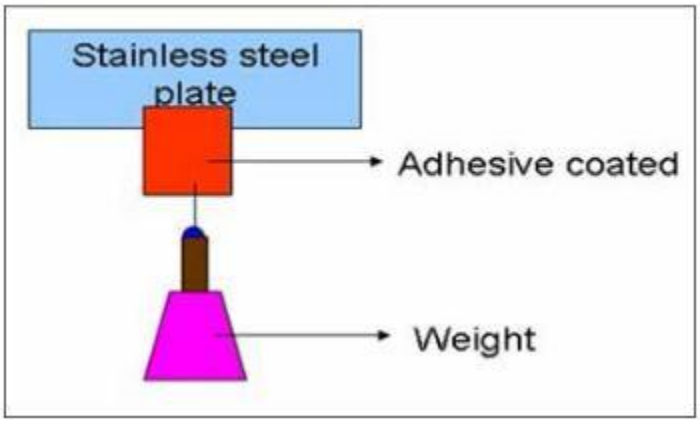

Fig.7: Shear strength test.

11. Peel Adhesion test:[18] In this test, force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a plate of stainless steel or a backing membrane of choice and then tape is pulled from substrate at a 180 angle, and force required for tape removed is measured. Peel adhesion is force required to remove an adhesive coating from the test substrate. Adhesive should provide adequate contact of device with the skin and should not damage skin on removal. Peel adhesion properties are affected by the molecular wt. of adhesive polymer, type and amt. of additives, and polymer composition. It is tested by measuring force required to pull a single coated tape, applied to a substrate, at a 180 angle. No residue on the substrate stipulates 'adhesive failure' which is desirable for transdermal devices. Remnants on substrate indicate 'cohesive failure' signifying a deficit of cohesive strength in the coating.

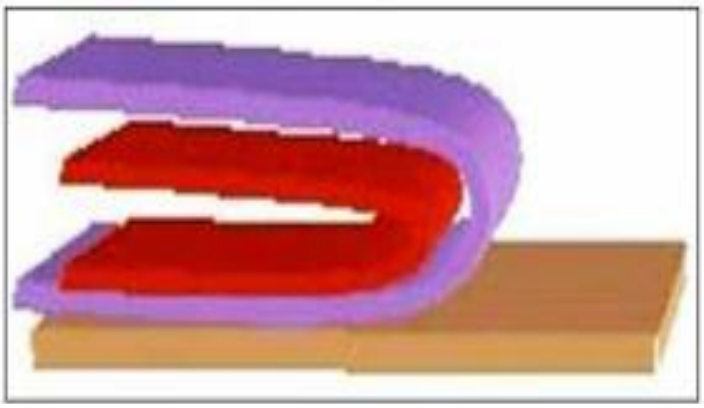

Fig 8: Peel adhesion test.

12. **Rolling ball tack test:**[14] This test measures softness of a polymer that relates to talk. In this test, stainless steel ball whose diameter is 7/16 inches is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

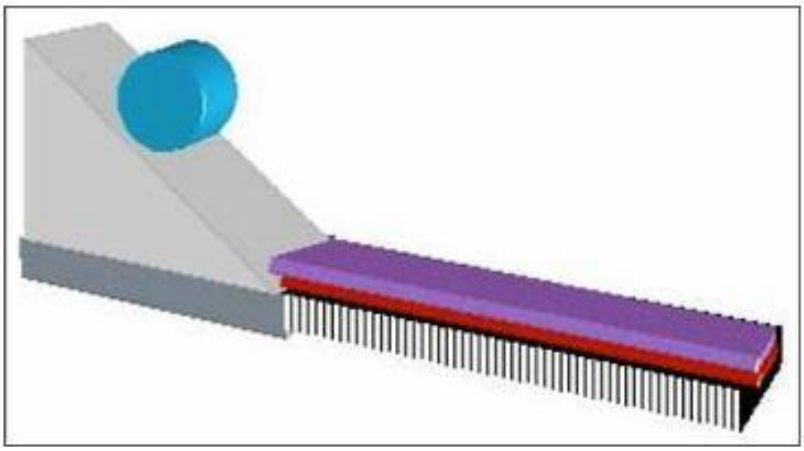

Fig 9: Rolling Ball Tack Test.

13. **Quick Stick (peel-tack) test:**[8] The peel force required breaking bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 900 at the speed of 12 inch/min.

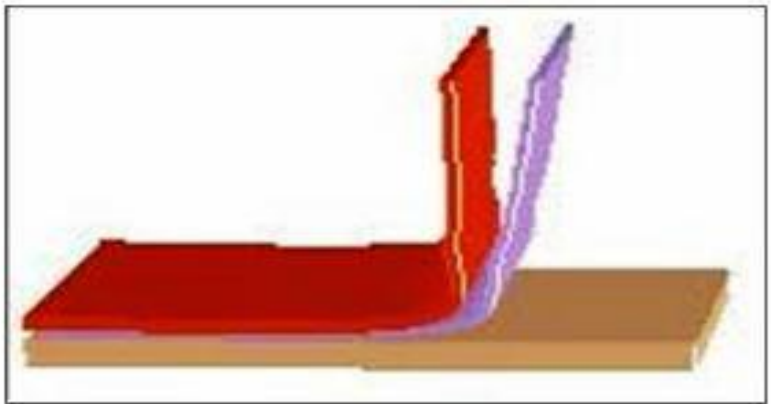

Fig 10: Peel tack test.

14. **Uniformity of dosage unit test:**[27, 51] An accurately weighed portion of patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent & sonicate for complete extraction of drug from the patch and made up to mark with same. Then resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give desired concentration with suitable solvent. Solution was filtered using 0.2m membrane filter and analyzed by suitable analytical method (UV or HPLC) and the drug content per piece will be calculated.

15. **Polariscope examination:**[18] This test is performed to examine drug crystals from patch by polariscope. A specific surface area of the piece is kept on the object slide and observed for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

16. **Skin Irritation study:**[20] Skin permeation and sensitization testing can be performed on healthy rabbits. The dorsal surface of the rabbit is to be cleaned and remove hair from the clean dorsal surface by using rectified spirit and the representative formulations can be applied over skin. The patch is to be removed after 24hrs and the skin is to be observed and classified into 5 grades on the basis of severity of skin injury.

17. ***In vitro* drug release studies:**[28] The USP apparatus V i.e. paddle over disc method can be employed for assessment of the release of the drug from the prepared patches. Dry films of known the thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was filled with a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate & 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 HPLC or UV spectrophotometer. The experiment is to be performed in triplicate and the mean value can be calculated.

18. **Stability studies:**[45] Stability studies are to be conducted according to ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. Samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

Applications of Transdermal Patches[28, 30]

- Transdermal patch of nicotine, releases nicotine in controlled doses to help with cessation of tobacco smoking.
- 2 opioid drugs used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) & Buprenorphine (marketed as Bu Trans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms, post-menopausal osteoporosis.
- Clonidine, Anti-hypertensive drug and ketoprofen, the non-steroidal anti-inflammatory drug are also available in form of transdermal patches.

- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills
- Transdermal form of the MAOI selegiline, became the first TDDS agent for an antidepressant.
- Transdermal delivery agent for Attention Deficit Hyperactivity Disorder (ADHD).

CONCLUSION

This article provides valuable information regarding transdermal drug delivery systems, different type of patches, components and its evaluation parameters. The foregoing shows that TDDS have great potentials, being able to use for both lipophilic and lyophobic active substance into promising deliverable drugs. Many drugs have been formulated in TDDS form, such as hormonal therapy, wide range of analgesics, drugs of heart diseases, for avoiding GI effects and first pass metabolism. The better understanding of the skin physiology and anatomy helps us in further development in this field. To optimize transdermal drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required.