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Transdermal Patch: An Innovative Technique for Transdermal Drug Delivery System

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ABSTRACT

The transdermal delivery system is the self-contained discrete dosage form which also known as medicated adhesive patch/skin patch. For the delivery of the specific dose of medication through the skin and into the bloodstream, the skin patch or medicated adhesive patch placed on the skin. Skin patch provides a means to control as well as sustained rate when placed above the patient's skin. The transdermal delivery system improves the therapeutic effect of various drugs by reducing the intensity of action and side effects associated with oral therapy many such as gastric irritation, low absorption, pre-systemic metabolism, the formation of toxic metabolites, etc. This review describes mainly the drug delivery prospects, transdermal permeation kinetics, different types of a transdermal patch, permeation enhancement techniques for transdermal delivery, methods and evaluation of transdermal drug delivery, and research on some model drugs.

INTRODUCTION:

Transdermal drug delivery system

Nowadays for drug administration, the transdermal drug delivery system is one of the most promising and effective method[1]. There are large therapeutic agents available to deliver into systemic circulation through skin[2]. For the variety of clinical indications, it is a convenient route of administration. At present marketed product of the transdermal delivery system is available for the treatment of various diseases viz. antifungal disease, Parkinson's disease, anxiety, Alzheimer's etc[3].

The transdermal drug delivery system (TDDS) is a self-contained, discrete dosage form which is also known as medicated adhesive patch/skin patch. Skin patches deliver a therapeutically effective amount of drug at a controlled rate when placed above the patient's skin. The transdermal drug delivery system provides a minimal inter-and intra- patient variation through predetermine rate into the systemic circulation. It is the most promising method for reducing harmful side effects caused by overdose and maximizes patient compliance as well as more important therapeutic benefits. Transdermal patches improve the therapeutic effect of various drugs by avoiding problems such as pre-systemic metabolism, gastrointestinal irritation, the formation of toxic metabolites, low absorption, etc associated with various drugs[4, 5, 6, 7].

Advantages of TDDS[8, 9]

- Delays the gastrointestinal incompatibility
- Decrease undesirable side effects
- Improve stability of drugs which are broken down by stomach acids, degraded by the liver, and not well absorbed by the gut.
- Avoidance of the first-pass metabolism
- For the oral route, TDDS used as a substitute.
- Provides an implementation of drug with short biological half-lives, the narrow therapeutic window.
- Adhesive patches are cost-effective.

- Minimize intra and inter-subject variation

Disadvantages of TDDS[8, 9]

- TDDS cannot deliver ionic drugs.
- Not suitable for drugs that cause skin irritation or sensitization.
- Adhering for a long time is difficult.
- An allergic reaction may develop.
- At the site of application may cause skin irritation.

The rationale of the study

Transdermal delivery is one of the most promising and effective delivery systems for the drugs associated with many problems such as gastric irritation, low absorption, systemic metabolism, the formation of toxic metabolites, etc. Various antifungal diseases are also treated by the transdermal drug delivery system. Clotrimazole and other broad-spectrum antifungal agents inhibit ergosterol synthesis by disturbing the permeability and function of the fungal cell membrane. Clotrimazole has anti-mycotic activity against various Candida species and is used to treat various skin infections. But oral administration of clotrimazole causes many side effects such as gastrointestinal irritation, nausea, vomiting, mouth sensation, etc.

Drug delivery prospects and transdermal route

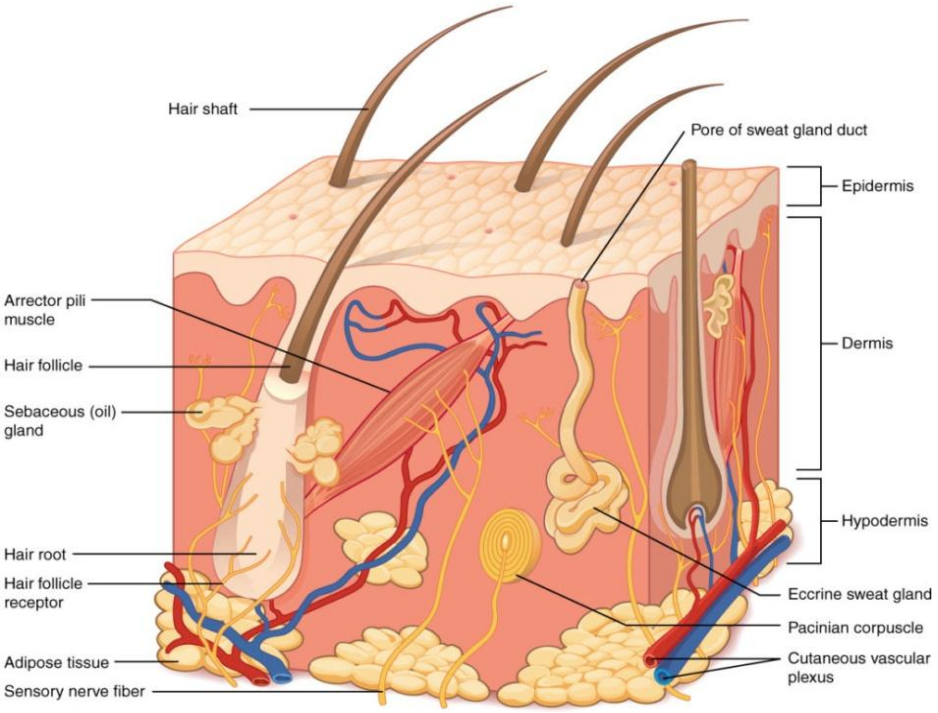

Figure No. 1: Anatomy of Skin[11]

The skin is the most extensive organ of the human body and through the body, it receives about one-third of the blood circulation. Skin covers approximately 2 m^2 surface areas. Various chemical and biological agents that absorb transdermally by the skin serve as a permeability barrier. The skin is also called the integumentary system which helps protect the body, helps to maintain a constant body temperature, and provides sensory information. The skin is the outermost layer of tissue that shows a protective mechanism from the external environment. The skin has a multi-layer structure because of cells and fibers and also has various cellular elements such as melanocytes, erythrocytes, keratinocytes etc[11, 12].

For the administration of transdermal preparation, the skin is a major route and made of three layers.

- Epidermis
- Dermis
- Subcutaneous fat tissue or hypodermis

The Epidermis[12]

The epidermis is a superficial thinner portion and an outermost layer of the skin having a thickness of about 0.2 mm. The epidermis contains four principal types of cells namely keratinocytes, melanocytes, Langerhans cells, and Merkel cells, and also called metabolic active tissue.

The further viable epidermis is classified into five sub-layers and these are:

- Stratum corneum
- Stratum lucidium
- Stratum granulosum
- Stratum spinosum
- Stratum basale

Stratum corneum: It is composed of the outermost layer and consists of 20-30 layers of flattened dead keratinocytes. It is also called a honey layer having a thickness of about 8-15µm. for the water retention, component "ceramide" is contained by this layer. To cross stratum corneum, drug molecule passes through three routes and these are:

- Transfollicular route (through the hair follicles)
- Transcellular route (through the lipid-rich region)
- Intracellular route (between the cells)

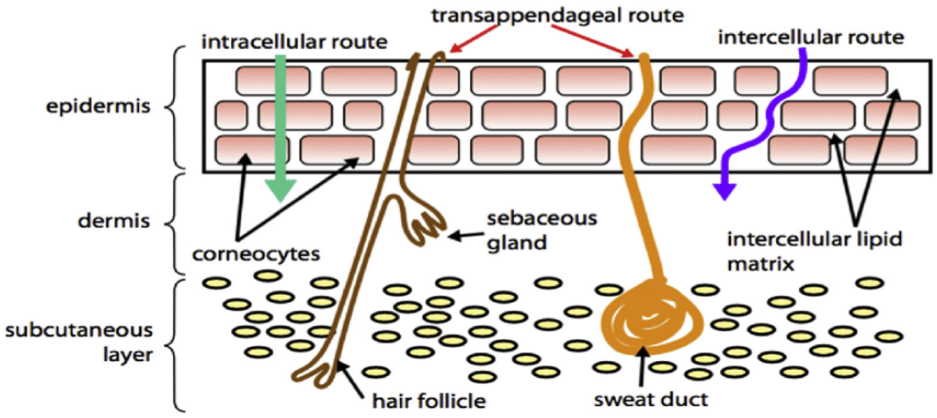

Figure No. 2: Absorption across the skin by intercellular and hair follicular[12]

Stratum lucidum: Stratum lucidum is composed of a thin clear layer of dead skin cells. It is found only in areas of thick skin on the palms of the hands and soles of the feet.

Stratum granulosum: Stratum granulosum is located in the middle of the epidermis having a thickness of 3µm. It consists of 3-5 layers of flattened keratinocytes.

Stratum spinosum: Stratum spinosum consists of several cells and superficial to stratum basale having a thickness from 50-150µm and also called a prickle cell.

Stratum basale: Stratum basale is the deepest layer of the epidermis consists of a single row of cuboidal or columnar keratinocytes. It holds 8% of the water in the epidermis.

Dermis[13]

The middle, deeper and second layer of the skin is the dermis having a thickness from 1-4mm. It is mainly composed of connective tissues, collagen, and elastic fibers. Based on the tissue structure, the dermis layer consists mainly of two regions. These are:

- Papillary region: consists of older tissues and capillaries.
- Reticular region: consists of dense irregular tissues.

The main function of the dermis is to regulate body temperature, remove toxins and waste products from the skin.

Subcutaneous layer

It is the third layer of the skin having thickness usually 4-9mm. It is made of adipose and connective tissues. It is the present bottom side of the skin and for the outer skin, it acts as a protective cushion.

Transdermal permeation kinetics

The development of the transdermal therapeutic system, skin permeation kinetics is important and the drug permeates transdermally by following steps:

1. Drug sorption by stratum corneum
2. Through viable epidermis drug permeation
3. In the dermal papillary layer drug uptake by the capillary network.

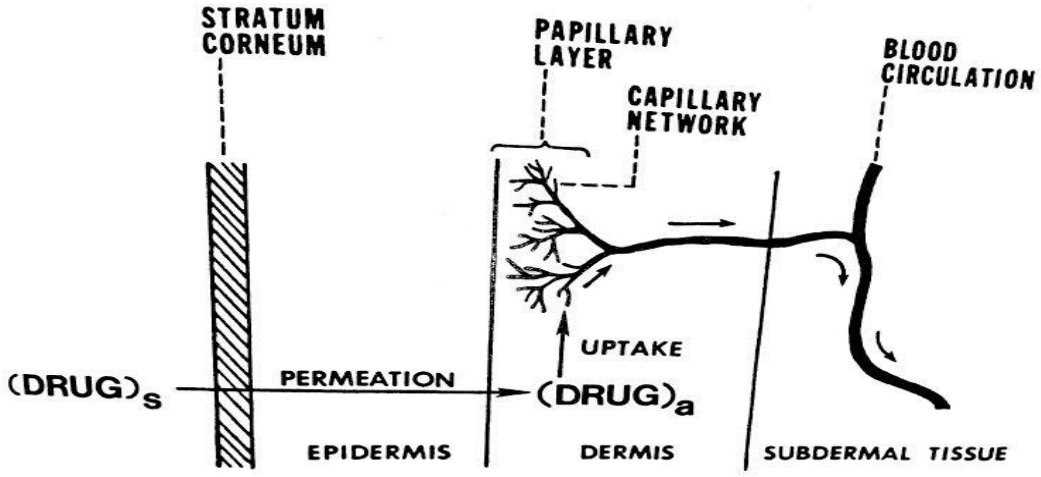

Figure No. 3: A multilayer skin model is showing the sequence of transdermal penetration of drug [21]

Ideal properties of transdermal delivery system[4, 13]

- Shelf life should be up to two year.
- Patch size should be greater than 40cm^2.
- The dosing frequency should be once a day to once a week.
- The melting point of the drug should be < 200^{o}C
- Drugs having a shorter half-life
- Drugs having a molecular weight less than 500 D
- When apply above the skin patch should be non-irritating and non-sensitizing.

Benefits of having transdermal drug delivery system[4, 13]

- Drugs that have a shorter half-life are easily administered by TDDS.
- By simplified medication regimen decreased inter and intrasubject variation.
- For polymedicated patient's transdermal delivery is useful
- Provides safe, convenient, and pain-free self-administration for patients.
- To maintain concentration level of drug provides a constant rate of release of therapeutic substances for a longer period.

- By decreasing specific problems like gastrointestinal irritation, low absorption, the formation of toxic metabolites, patch enhances the therapeutic effects of various drugs.

Transdermal Patch

A transdermal patch or skin patch delivers the drug or specific amount of drug directly into the bloodstream through the skin. For patients, the medicated adhesive patch provides a controlled release medicament[14, 15].

Types of transdermal patch[14, 15]

Single-layer drug-in-adhesive

This adhesive layer holds drugs and drugs are released by this layer. This adhesive layer serves to adhere the various layers together and also along with the entire systems to the skin, temporary liner, and a backing liner outer side of the adhesive layer.

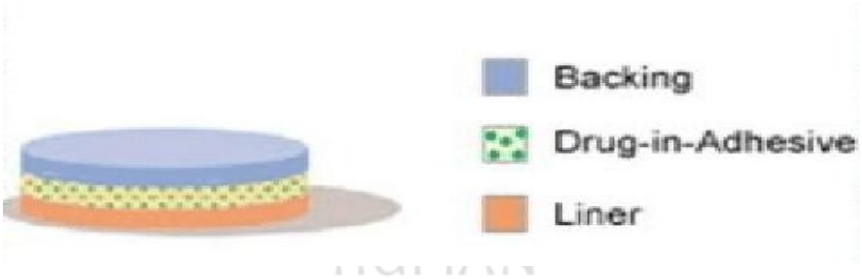

Figure No. 4: Single layer in adhesive[14]

Multi-layer drug-in-adhesive

Releasing of the drug through both adhesive layers is the similarity between the multi-layer and single-layer system. The only difference is the adhesive layer adds another layer of drug-in-adhesive, separated by a membrane (but not in all cases). This patch is also surrounded by a permanent backing and temporary liner-layer membrane permeability and diffusion of the drug molecule is major kinetics for the drug release.

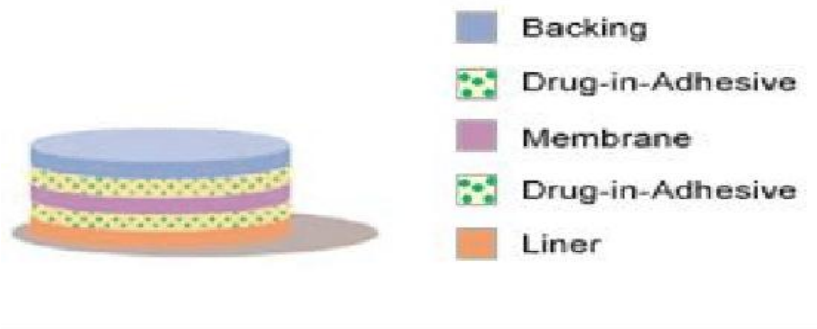

Figure No. 5: Multi-layer drug in adhesive[15]

Reservoir type patch

This type of system has a separate drug layer which is a liquid compartment. The drug can be in the form of a solution, suspension, gel contained by the liquid compartment. Between impervious backing layer and a rate controlling membrane drug reservoir are embedded. The reservoir patch is also backed by a backing layer. This system follows zero-order kinetics.

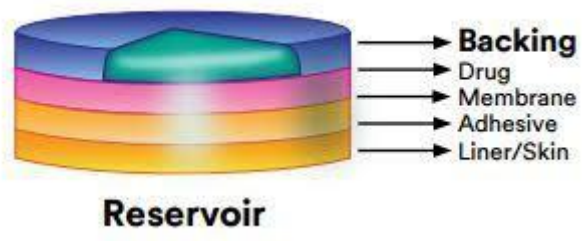

Figure No. 6: Reservoir type patch[14]

Matrix type patch

In this type of system, the drug reservoir in an aqueous solution of water-soluble polymer-drug is suspending and then this solution is dispersed homogeneously in a lipophilic polymer to form unreachable, microscopic spheres which are stabilized by immediately cross-linking of the polymer. Drug delivery is in this type of patch the combination of reservoir and matrix system.

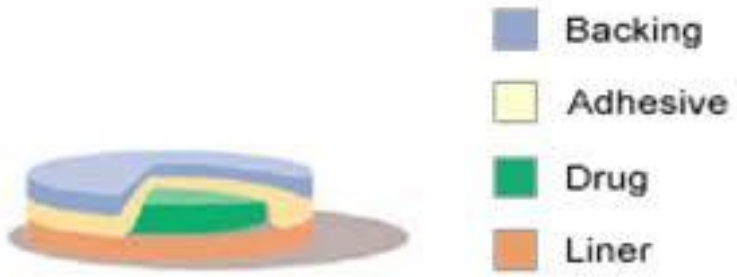

Figure No. 7: Matrix type patch[14]

Vapor patch

In this type of patch adhesive layer release vapor and adhere the various layers together. Essential oil releases by a vapor patch for up to 6hours and used for decongestion.

Basic components of transdermal delivery system[16, 17]

Skin patch may include the following compounds:

- Drug
- Polymer matrix
- Penetration enhancers
- Adhesives
- Backing membrane
- Release liner

Drug: For transdermal delivery, the selection of the drug is based on physicochemical and biological properties. Examination of the pharmacokinetic and pharmacodynamics properties of the drug is necessary.

Penetration enhancers

To attain the maximum therapeutic level of the drug, penetration enhancers are used to increase the stratum corneum permeability. Substances that promote the permeation through

the stratum corneum are known as penetration enhancers. Penetration enhancers interact with structural components of the stratum corneum such as protein or lipids.

Ideal properties of penetration enhancers as follows:

- Should be non-toxic and non-allergic.
- Should be non-reactive.
- Cosmetically acceptable with an appropriate skin feel
- Should have no pharmacological activity with the body.
- Should be compatible with both excipients and drugs.

Table No. 1: Categories of penetration enhancers

Category	Penetration Enhancers
➢ Chelators ➢ Surfactants ➢ Bile salts ➢ Fatty acids ➢ Cyclodextrins ➢ Non-surfactants ➢ Vehicles and Adjuvant	EDTA, citric acid, sodium salicylate, methoxy salicylates. Sodium lauryl sulfate, cetyltrimethylammonium bromide, Benzalkonium chloride. Sodium glycocholate, sodium deoxycholate, sodium glycodeoxycholate. Oleic acid, capric acid, lauric acid, propylene glycol, methyl oleate Methylated cyclodextrins, hydroxypropyl cyclodextrin. Unsaturated cyclic urea. Ethanol, propylene glycol.

Polymers

Polymer selection for the transdermal delivery system depends on the following criteria:

- Should be chemically non-reactive.
- Should be none decompose on storage or during the life span.
- Should be biocompatible and non-toxic.
- Easy to manufacture and cost-effective

Polymers used in TDDS are:

Natural polymers are Gelatin, Methylcellulose, Shellac, Zein, Waxes, Gum and their derivatives, etc. Synthetic polymers are Polyethylene, Polyvinylchloride, Polyvinyl acetate.

Adhesive layer

Transdermal patch adheres to the skin surface by pressure-sensitive adhesive layer maintain the patch's position for long as desired, even in the presence of water. Without leaving any residue it is easily removed from the skin surface. Three types of adhesive mainly used are silicon type adhesive, polyisobutylene adhesive, and poly-acrylate based adhesive.

Ideal characteristics of the adhesive layer

- Should be highly biocompatible.
- Should be good adhere to oily, wet, and hairy skin.
- Easily removable from the skin
- Should be non-reactive towards the drug.
- Against water and humidity provide good environmental resistance.

Backing layer

The backing layer is used as a supportive material that must be impermeable to drug and permeation enhancers. The main function of the backing layer is to hold the whole system together and protect the drug reservoir from exposure to the atmosphere ex: - polyester foils and other metabolize laminate.

A desirable feature of transdermal patch [18]

- Avoid drug metabolism / first-pass metabolism
- Direct application on the body
- Should be easily removable
- Provides patients complaints

Conditions in which patch are used

- Patches are used when patients are not able to take oral medication and unable to take self-medication with their analgesia.
- When patients have insufferable side effects and they ask for a different method of drug therapy.
- To produce a synergistic effect, patches are used in combination with other enhancement strategies.

Conditions in which patches are not used: -

- When the necessity of dose is equal to or less than 30 mg/ 24 hours.
- When fast dose titration is required.
- Acute pain cure is required.

Methods and characterization

Following methods are used to prepare transdermal drug delivery system[17, 18]

- Circular Teflon mold method
- Mercury substrate method
- Asymmetric tpx membrane preparations
- By using "evac membrane" method
- By using "ipm membrane" method
- By using the free film method
- Aluminum backed adhesive film method
- TDDS are prepared by using pro-liposomes.

Circular Teflon method[17]

This method contains an organic solvent in which a solution containing polymers in different ratios is used and deliberated amount of drug is dissolved in half of the quantity of the same

organic solvent. The other half organic solvent contains enhancers in different concentrations, plasticizers like Di-N-butyl phthalate are added into the drug-polymer solution. This solution is poured into a circular Teflon mold. Before this, for 24 hours total content are to be stirred. After this, molds are to be set down on a labeled surface and for controlling solvent evaporation, covered by the inverted funnel. The solvent is permitted to evaporate for 24 hours and the dried film is to be stored in desiccators for another 24 hours at room temperature.

Mercury substrate method[17]

In this method, polymer solution together with plasticizer having drug and this solution fabricate a homogeneous dispersion when stirred for 10-15 minutes. And cascade into a leveled mercury surface. To control solvent evaporation the solution is covered by the inverted funnel.

Asymmetric tpx membrane method[18]

In this method, tpx [poly (4-methyl-1-pentene)] asymmetric membrane-covered drug sample is distributed into the concave membrane and secured by an adhesive. A precursor patch can be produced by the poly-ester film which is heat reliable. Concave used as a backing membrane with a diameter of 1cm.

By using "evac membrane" method[17, 18]

In this method, the rate-controlling membrane is made up of 1% carbopol reservoir gel, polyethylene copolymer (evac) membrane, for the targeted transdermal therapeutic system. In propylene glycol drug is dissolved and carbopol resin will be added to this solution. 5% w/w NaOH solution is used to neutralize the above solution. The gel form drug is poured on a backing layer sheet and the rate-controlling membrane will be placed over the gel and for obtaining leak-proof device edges will be sealed.

By using "ipm membrane" method[17,18]

In a mixture of propylene glycol and water, the drug is distributed containing 940 polymers and this was stirred for 24 hours. Tri-ethanolamine is added for neutralization of the dispersion and made viscous. For obtaining solution gel buffer pH 7 can be used if in aqueous solution the drug is poorly soluble. Further in ipm membrane prepared gel will be incorporated.

Free film method[17, 18]

Casting on mercury surface cellulose acetate film is formulated. Chloroform is used to prepare 2% w/w polymer solution while a concentration of 40% w/w of polymer weight plasticizer is included. Over the mercury surface, about 5ml of the polymer solution is poured into Petridis and covered by an inverted funnel for controlling the rate of evaporation. After total evaporation, the total film is formed and this dried film is separated and stored in desiccators between the wax paper sheets.

Aluminum backed adhesive film method[18]

In this method in chloroform drug is dissolved and, in this solution, the adhesive material is added. With aluminum foil, a custom-made aluminum former is bound, and with tightly fitted cork blocks the ends are blanked off.

Approaches in the development of TDDS[19, 20]

Polymer membrane permeation-controlled TDDS:

In this system, the drug reservoir inserts between an impervious backing layer and a rate controlling membrane (micro-porous or non-porous), drug release only by a rate controlling membrane. The drug in the form of a solution, suspension, or gel or dispersed in the solid polymer matrix in the drug reservoir compartment a thin layer of drug compatible hydro allergenic adhesive polymer surrounded an outer surface of the polymeric membrane. By changing the composition of polymers, permeability coefficient or thickness of adhesive, and rate-limited membrane the rate of drug release is maintained.

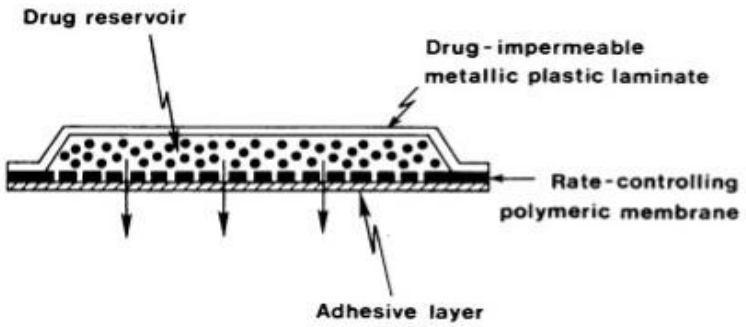

Figure No. 8: Cross-sectional view of Polymer membrane permeation-controlled system[19]

Adhesive diffusion-controlled TDDS: In this technique, a drug reservoir formulates by when a drug is dispersing in an adhesive polymer and then only by solvent casting or melting the medicated polymer adhesive spread and adhesive onto an impervious membrane. Nonreactive rate-controlling membrane-covered reservoir to produce an adhesive diffusion controlling drug delivery system.

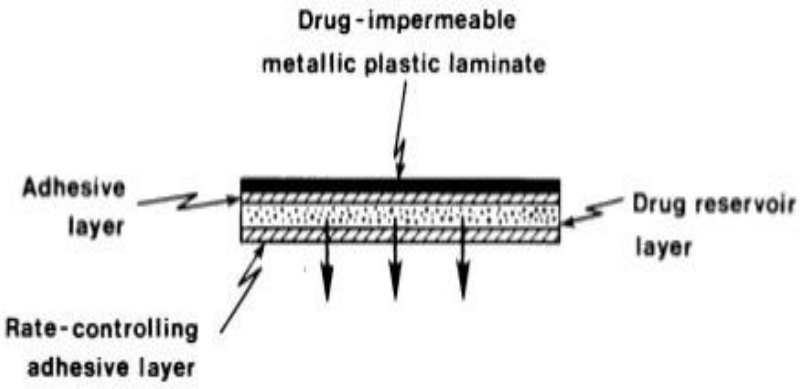

Figure No. 9: Cross-sectional view of adhesive diffusion-controlled system[19]

Matrix diffusion-controlled TDDS:

In this technique, by dispersing uniformly in a hydrophilic or lipophilic polymer matrix, a drug reservoir is formed. Polymer disk then fixed onto an occlusive base plate in compartment produce from a drug-impermeable backing layer. The adhesive is spread along the circumference to form a strip of the adhesive rim instead of applying it on the face of the drug reservoir. Ex- Nitro Dur®.

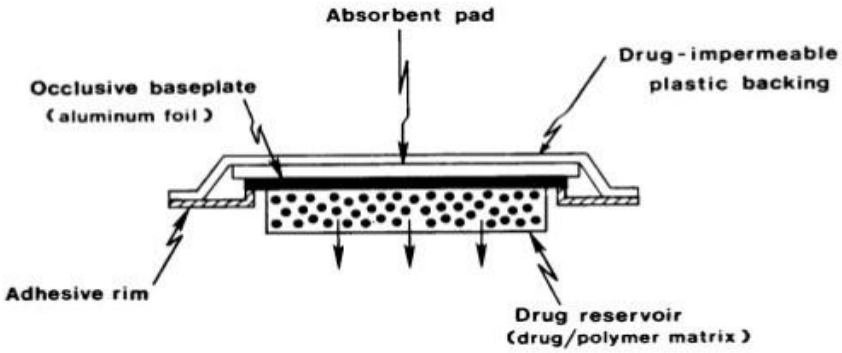

Figure No. 10: Cross-sectional view of matrix diffusion controlled system[19]

Micro reservoir controlled TDDS:

In this approach, drug reservoir prepared by drug suspending firstly in an aqueous solution of polymer (water-soluble) and then uniformly dispersing in the solution of lipophilic polymer to form unreachable microscopic spheres of the drug reservoir. This dispersion is thermodynamically immediately with the polymer in situ mediated disc located at the center and enclosed by an adhesive rim formed transdermal system.

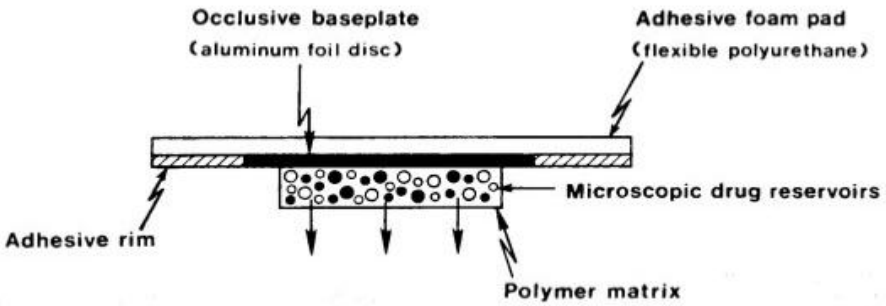

Figure No. 11: Cross-sectional view of Micro reservoir controlled system[19]

The transdermal system characterized in the term of the following parameters[19, 20]

Evaluation:

Thickness: Travelling microscope, dial gauge, screw gauge, or micrometer are used to determine the thickness of drug-loaded patch at different points of the film.

Folding endurance: Folding the film at the same place several times without breaking gave folding endurance value.

Uniformity of weight:-10 randomly selected patches are individually weighed and calculating the average weight by this weight variation was studied. From the average weight, the individual weight should not deviate.

Moisture content: Moisture content was studied by individually weighing prepared film and for 24 hr. the film was kept in a desiccator containing calcium chloride. After a specified interval, the film is reweighted until the shown a constant weight. The formula through which percent moisture content is calculated are:

$$\% \text{ Moisture content} = (\text{initial weight} - \text{final weight}) \times 100$$

Drug content determination: An accurately weighed portion of the film is taken and dissolved in 100 ml of solution in which day is soluble. This solution is stirred continuously for 24 hr in a magnetic stirrer. Before filtration the whole solution is sonicated, then the drug in solution is analyzed spectrophotometrically by suitable dilution.

Moisture uptake: At room temperature for 24hr. weighed films are kept in desiccators and after this those films are taken out and exposed to 84% relative humidity using a saturated solution of KCl in a desiccator until a constant weight is achieved.

$$\% \text{ Moisture uptake} = (\text{final weight} - \text{initial weight}) \times 100$$

Tensile strength: A modified pulley system is used for the study of tensile strength. The force required to break the film is examined as the tensile strength of the film.

$$\text{Tensile strength} = (\text{Break force } (1 + \text{change in length})) / (a \times b \times c)$$

Where a= patch width, b= patch thickness, c = initial length of film

Flatness: The flatness of selected strips is selected as the average % of length calculated from the 7cm strips. Zero % constriction is equal to 100 % flatness shown by the following eq.

$$\% \text{ Constriction} = (\text{initial length} - \text{final length}) / \text{initial length} \times 100$$

Tack properties: Tack property is the ability of the polymer to adhere to the substrate when applying little contact pressure.

Thumbtack test: Tack is measured by force required to remove the thumb from an adhesive.

Quick stick (peel tack) test: In this test, pulling the tape away from the substrate at 90º at a speed of 12inch/min. and the peel force required to break the bond between substrate and adhesive recorded as tack value.

Rolling ball test: In this test, stainless steel ball travels some distance along with an upwards facing adhesive. Through this process distance travel by ball provides a measurement of tack.

Probe tack test: In this test, a probe is pulled away from an adhesive and the force required for this at a constant rate is recorded as a tack.

In vitro skin permeation study[18, 19]

By using an eggshell membrane with a receptor compartment (80ml capacity) in-vitro permeation studies were performed. With the help of a thread, the eggshell membrane was fixed at the end of the hollow tube as a donor compartment, and the beaker present as a receptor compartment. The eggshell membrane and eggshell membrane clamped between the donor and receptor chamber. Receptor compartment filled with phosphate buffer solution pH 7.4 for solubilizing the drug. On the magnetic stirrer, the whole assembly was placed and the solution was continuously stirred with the help of a magnetic bead. The temperature was maintained at 37 ± 0.5 ºC at suitable interval 1ml sample was withdrawn and analyzed for drug content spectrophotometrically at 261nm.

Recent advancement in the field of Transdermal delivery:

Penetration enhancement techniques [22, 23, 24, 25]

- Microneedle: these are either hollow or solid and filled with the desired drug, very small, painless needles. Without causing a painful sensation the microneedles penetrate through the stratum corneum. Its painless nature and ability to deliver high molecular weight compounds are the advantage of this method.

- Iontophoresis: electrical driving force is the main force used to move the substances across the stratum corneum, where via electrophoresis there is charged particle movement. By an electrical current, the rate of drug delivery can be controlled.

- Thermal poration: Generation of small pores in the skin by providing heat to the skin, high molecular weight compounds easily diffuse and cross the stratum corneum.

- Electroporation: providing high electrical voltage to the stratum corneum, also generates small pores for high molecular weight compounds. Due to which compounds easily cross the stratum corneum.

- Conventional enhancers: for increasing the permeability of stratum corneum, a chemical substance applied first to the skin.

- Ultrasound: in this method sound waves are used which disrupts the stratum corneum and increases its permeability.

Table No. 2: Research on model drugs of the transdermal patch

Drugs	System	Work done	reference
Ampicillin	Membrane type	Membrane moderated transdermal system of ampicillin sodium: formulation development and in vitro, in vivo evaluation	26
Atenolol&Metoprolol	Matrix-type	By using HPMC, PVP, Ethylcellulose, and cellulose acetate phthalate patch of atenolol and metoprolol were prepared.	27
Aspirin	Matrix-type	Inhibition of platelet aggregation and reduction of serum lipid peroxides by matrix type aspirin transdermal patch	28
Celecoxib		Celecoxib patch: formulation and evaluation (to achieve prolonged drug level)	29
Diltiazem	Matrix-type	Formulation and evaluation of polymerized rosin for the development of the transdermal delivery system by diltiazem patch	30
Fentanyl	Reservoir-type	Effect of the transdermal patch on skin permeation and drug release by reservoir based fentanyl transdermal patch	31
Furosemide	Film-type	Development and evaluation of ethyl cellulose-based transdermal films of furosemide for improved in vitro skin permeation.	32
Gliclazide	Matrix-type	By film casting technique transdermal patch was prepared and evaluated.	33

Haloperidol	Matrix-type	By using ethyl cellulose and povidone as a film former, haloperidol lactate transdermal patch was prepared and evaluated.	34
Insulin	Microneedle type	Novel microneedle patches for active insulin delivery are efficient in maintaining glycaemic control by an initial comparison with subcutaneous administration.	35
Lercanidipine	Matrix-type	Development of transdermal drug delivery of lercanidipine and to determine the effect of a penetration enhancer, limonene on drug permeation.	36
Naltrexon	Matrix-type	In vitro/in vivo correlation of transdermal naltrexone prodrugs in hairless guinea pigs.	37
Parathyroid hormone	Microneedle-type	Pharmacokinetic and pharmacodynamic parathyroid hormone coated microneedle patch for the treatment of osteoporosis.	38
Tramadol	Matrix-type	Polymeric matrix system for prolonged delivery of tramadol HCl.	39
Sinomenine	Matrix-type	Development and evaluation of transdermal patch of sinomenine	40
Papaverine	Matrix-type	Formulation and evaluation of papaverine transdermal patch.	41
Nicorandil	Matrix-type	Formulation, characterization, and in-vitro evaluation of nicorandil patch prepared by different grades of HPMC	42
Ketorolac	Reservoir-type	Effect of pH, alcohol, and permeation enhancers on in vitro	43

		permeation of reservoir type ketorolac patch.	
Dexamethasone	Matrix-type	Comparative studies between povidone ethyl-cellulose and povidone-eudragit transdermal dexamethasone patch based on in-vitro skin permeation.	44
Aceclofenac	Matrix-type	Evlaluation and evaluation of aceclofenac transdermal patch.	45

CONCLUSION:

In the field of a skin patch or a medicated adhesive patch, a lot of research has been done. Many scientist and researcher have shown their interest in the transdermal delivery system because the transdermal delivery system has lots of advantages. Via this system, many researchers are incorporate newer drugs. Transdermal delivery is one of the most promising and effective delivery systems for the drugs associated with many problems such as gastric irritation, low absorption, systemic metabolism, the formation of toxic metabolites, etc. Various antifungal diseases are also treated by the transdermal drug delivery system. By using various permeability enhancement techniques, we can enhance the permeability of various poorly permeable drugs.

REFERENCES:

1. Nanda S, Saroha K, Yadav B, Sharma B. Formulation and characterization of transdermal patch of amlodipine besylate. IJPCS. 2012;1(3):953-969.
2. Fathima S.A, Begum S, Fathima S.S. Transdermal drug delivery system. IJPCR. 2017; 9(1):35-43.
3. Ramesh P. Transdermal delivery of drugs. Indian Journal of Pharmacology. 1997;29:140-156.
4. Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm res. J. 2010; 3: 139-149.
5. Bhowmik D, Chiranjib, Chandira M, Jayakar B, Sampath K. Recent advances in transdermal drug delivery system. IJPTR. 2010; 2(1): 68-87
6. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in Transdermal Drug Delivery System: An overview. Der Pharmacia Sinica, 2011; 2(5):17-29.
7. Jain N.K. Controlled and novel drug delivery. 1st, CBS Publisher and Distributers new Delhi. 2001:100-129.
8. https://www.pharmatutor.org/article/detail-information-on-transdermal-patches
9. Gupta I.K, Chokshi M.M. Transdermal drug delivery system: An overview. AJPS. Clinical research. 2011; 1(1):25-43.
10. Sharma A, Saini S, Rana A.C. Transdermal drug delivery system: A review. JRPBS. 2013; 4(1):286-292.
11. Ramteke K.H, Dhole S.N, Patil S. Transdermal drug delivery system: A review. Journal of Advanced Scientific Research-Science. 2012; 3(8):22-35.

12. Mali A.D, Bathe R, Patil M.K. An advanced review on transdermal drug delivery systems. IJASR. 2015; 1(16):244-254.
13. Divya A, Rao M.K, Gaanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. A review on the current scenario of transdermal drug delivery system. IJRPS. 2012; 3(4):494-502.
14. Kadhim M.J, Kaizal A.F, Hameed I.H. Medicinal plant used for the treatment of rheumatoid arthritis: A review. IJPCR. 2016; 8(12):1685-1694.
15. Kadam A.S, Ratnaparkhi M.P, Chaudhary S.P. Transdermal drug delivery: An overview. International Journal of Research and Development in Pharmacy and Life Sciences. 2014; 3(4):1042-1053.
16. Kaur A, Kumar S.L. Controlled drug delivery approaches for rheumatoid arthritis. Journal of Applied Pharmaceutical Sciences. 2012; 2(8):21-32.
17. Rindfleisch J.A. Diagnosis and management of rheumatoid arthritis. American Family Physician. 2005; 72(6):1037-1047.
18. Sachan R, Bajpai M. Transdermal drug delivery system: A review. International Journal of Research and Development in Pharmacy and Life Sciences. 2013; 3(1):748-765.
19. Hafeez A, Jain U, Singh J, Maurya A. Recent advance in transdermal drug delivery system: An overview. Journal of Scientific and Innovative Research. 2013;2(3):695-709.
20. Tiwari R, Jaimini, Mohan S, Sharma S. Transdermal drug delivery system: A review. International Journal of Therapeutic Applications. 2013; 14:22-28.
21. Chien Y.W. Logics of transdermal controlled drug administration. Drug Delivery Industry Pharmacy 1983; 9:497-520.
22. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005 Jan;2(1):23-33.
23. Prausnitz MR, Langer R. Transdermal drug delivery. Nat. Biotechnol. 2008 Nov;26(11):1261-8.
24. Walter JR, Xu S. Therapeutic transdermal drug innovation from 2000 to 2014: current status and outlook. Drug Discov. Today. 2015 Nov;20(11):1293-9.
25. Hupfeld S, Gravem H. [Transdermal therapeutic systems for drug administration]. Tidsskr. Nor. Laegeforen. 2009 Mar 12;129(6):532-3.
26. Janardhanan Bagyalakshmi, Ramachandra Purapu Vamsikrishna, Rajappan Manavalan, Thengungal Kochupappy Ravi, and Probal Kumar Manna. Formulation Development and In Vitro and In Vivo Evaluation of Membrane- Moderated Transdermal Systems of Ampicillin Sodium in Ethanol: pH 4.7 Buffer Solvent System. AAPS PharmSciTech. 2007; 8 (1): E1- E6
27. Aggarwal S S, MunjalPriya. Permeation Studies of Atenolol and Metoprolol Tartrate from Three Different Matrices for Transdermal Delivery. Indian J. Pharm. Sci. 2007; 69(4): 535- 539.
28. Krishna D R, Shrinivas A G, Shrinivas A. Transdermal Aspirin: Influence of platelet Aggregation and Serum Lipid Peroxide. Indian J. Pharm. Sci. 2000; 62(3): 200- 204.
29. Jayaprakas S, Halith S M, FirthousePu M and Y, Nagarajan M. Preparation and Evaluation of Celecoxib Transdermal Patches. Pak. J. Pharm. Sci. 2010; 23(3): 279- 283.
30. Satturwar PM, Fulzele S V, Dorle A K. Evaluation of Polymerized Rosin for the Formulation and Development of Transdermal Drug Delivery System: A Technical Note. AAPS PharmSciTech. 2005; 6 (4): E649- E654.
31. Prodduturi et al. Reservoir Based Fentanyl Transdermal Drug Delivery Systems: Effect of Patch Age on Drug Release and Skin Permeation. Pharmaceutical Research. 2009; 26(6): 1344- 1354.
32. Patel et al. Development and Evaluation of Ethyl Cellulose- Based Transdermal Films of Furosemide for Improved In Vitro Skin Permeation. AAPS PharmSciTech. 2009; 10(2): 437 - 442.
33. Shinde et al. Design and evaluation of transdermal drug delivery system of gliclazide. Asian Journal of Pharmaceutics. 2010; 121- 129.
34. 25. Sadashivaiah R, Dinesh BM, Patil U A, Desai BG, Raghu K S. Design and *in vitro* evaluation of haloperidol lactate transdermal patch containing ethyl cellulose- povidone as film formers. Asian Journal of Pharmaceutics. 2008; 43- 50.
35. Nordquist L, Roxhed N, Griss P, Stemme G. Novel Microneedle Patches for Active Insulin Delivery are Efficient in Maintaining Glycaemic Control: An Initial Comparison with Subcutaneous Administration. Pharmaceutical Research, 2007; 24(7): 1381- 1389.

36. Mamatha T, Venkateswara Rao J, Mukkanti K, Ramesh G**.** Development of matrix type transdermal patches of lercanidipine hydrochloride: physicochemical and in- vitro characterization. DARU. 2010;18(1): 9- 16.
37. Valiveti et al. In Vitro / in Vivo Correlation of Transdermal Naltrexone Prodrugs in Hairless Guinea Pigs. Pharmaceutical Research. 2005; 22(6): 981- 989.
38. Daddona P E, Matriano J A, Mandema J, Maa Y F. Parathyroid Hormone (1- 34)- Coated Microneedle Patch System: Clinical Pharmacokinetics and Pharmacodynamics for Treatment of Osteoporosis. Pharm Res. 2010.
39. Ammar H O, Ghorab M, Nahhas S A, Kamel R. Polymeric Matrix System for Prolonged Delivery of Tramadol Hydrochloride, Part II: Biological Evaluation. AAPS PharmSciTech, 2009;10(3): 1065- 1070.
40. Ye et al. Development and Evaluation of the Sinomenine Transdermal Patch**.** Pak. J. Pharm. Sci. 2008; 21(4): 407- 410.
41. Shah SS, Joshi R, Prabhu P. Formulation and evaluation of transdermal patches of papaverine hydrochloride. Asian Journal of Pharmaceutics. 2010; 79- 87.
42. Jamakandi V J, Mulla J S, Vinay B L, Shivakumar H N. Formulation, characterization, evaluation of matrix- type transdermal patch of model antihypertensive drug. Asian Journal of Pharmaceutics. 2009; 59- 66.
43. Chandra A, Kumar PK, Irchhiyana R. Effect of alcohols and enhancers on permeation enhancement of ketorolac. Asian Journal of Pharmaceutics. 2009; 37- 42.
44. Rathore R P S, Chauhan C S, Naruka P S, Tanwar Y S, Chauhan L S. Transdermal Formulation of Terbutaline Sulphate. Pharmacy online. 2006.
45. Patel et al. Formulation and evaluation of transdermal patch of Aceclofenac. International Journal of Drug Delivery.2009; 1: 41- 51.

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