IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT:

Transdermal films and patches are pharmaceutical preparations designed to prolong drug delivery to the skin to achieve a systemic or local effect respectively. Transdermal patches provide a wide range of advantages over oral and intravenous drug delivery and provide controlled drug delivery. Although the transdermal drug delivery system provides various advantages it has to face a strong barrier of skin *stratum corneum*. The current review concisely discusses the *stratum corneum* barrier, Polymers in the transdermal drug delivery system, Penetration enhancers, and evaluation of transdermal patches.

KEYWORDS: Transdermal drug Delivery, Stratum corneum, Polymers, Penetration enhancer, Matrix, Reservoir.

I. INTRODUCTION:

Skin has an area of 1.5 -2.0 m^2 in adults and is the largest organ in the human body by mass (Pastore *et al.*, 2015). Skin has the great advantage for both local and systemic administration (Pireddu *et al.*, 2018). Transdermal route has been used to treat several diseases and therapeutic administration of active pharmaceutical ingredient. The common use of transdermal delivery system was started at later third of the 20^{th} century (Table 1). Transdermal route is one of the novel routes for therapeutic administration through skin and provide several advantages over conventional drug delivery system (Saleem, Idris, 2016).The ultimate goal of this design is to reduce drug's systemic toxicity, increase flux through the skin, improved bioavailability of drugs degradable in gastro-intestinal tract, and overcome the first pass metabolism (Pireddu *et al.*, 2018, Nayak *et al.*, 2018)

Although transdermal delivery provides various advantages the drug has to pass through Stratum corneum which acts as the main protective barrier and slows down the permeation of drug as well as exogenous substances across the skin (Singh *et al.*, 2018).

In transdermal delivery of drug, stratum corneum allow only lipophilic drugs having small molecular weight (<500 Da) to attain therapeutically effective concentration via passive diffusion. This results why only limited numbers of transdermal therapeutic systems are available commercially (Parhi, Suresh, 2016).

Although the skin is powerful barrier, there are several approaches to overcome the barrier and attained therapeutically effective concentration across the skin like use of Penetration enhancers, Micro-needle array, ballistic liquid jet, high velocity particles, ultrasound waves, electric current abrasion, ablation, lasers, pressure waves, radiofrequency, thermal ablation, magnetophores is of diamagnetic solutes and thermophoresis which

used mechanical, electrical, magnetic or thermal energy source to promote transport of macromolecules by disrupting the skin membrane for increasing transport of molecules across the skin (Rajurkar *et al.*, 2015).

Table 1: History of Transdermal Drug Delivery System

Year	History of transdermal drug delivery system (Pastore *et al.*, 2015)
1979	First transdermal Scopolamine patch marketed (Transdermal Scop® by Alza Corporation
1973	US patent filled by Alza corporation for Nitro-glycerine patch
1981	Transdermal-Nitro® by Ciba Pharmaceuticals Company Nitro-Dur® by Key Pharmaceuticals Nitro disc® by Searle Laboratories was marketed.
1983	US patent disclosed bandage of esterediol
1984	US FDA approved Clonidine patch
1984	Transdermal Esterdiol system were in US Market
1984	Fentanyl patch marketed by Alza corporation Duragesic®
1986	US patent disclosed various free base narcotic fentanyl Transdermal Delivery System
1991-92	Nicotine patch were approved by us patent Harbitrol®,Nicoderm®,Nicotrol®
2006	Alza Corporation's Fentanyl patch patent expired
2005	US FDA approved Mylan Fentanyl Matrix patch

It was stated that, the estimated worldwide market for transdermal product were around US $ 6 billion in 2009, Europe 32 % Japan 7% and USA 56 % shearing market for transdermal drug delivery system. In 2015 it was reached to $ 10 billion and even more in 2020 (Saleem, Idris, 2016).

II. STRATUM CORNEUM: A BARRIER TO TRANSDERMAL DRUG DELIVERY SYSYTEM:

Transdermal drug delivery system provides several advantages, However for effective drug delivery system the drug has to pass most effective barrier of the skin known as Stratum Corneum. For design of better and effective transdermal drug delivery system one must have to know the anatomy and pathophysiology of the skin (Baroni *et al.*, 2012).

Skin serve as the largest organ in the body which covers the entire external surface and forms first order barrier against pathogens, chemicals and UV light and act as mechanical barrier to injury (Yousef, Sharma, 2017).The main and primary function of the skin is it regulates water repulsion (hydration) and also maintain temperature of the body.

The structure of skin has two main structural compartments as shown in Figure 1

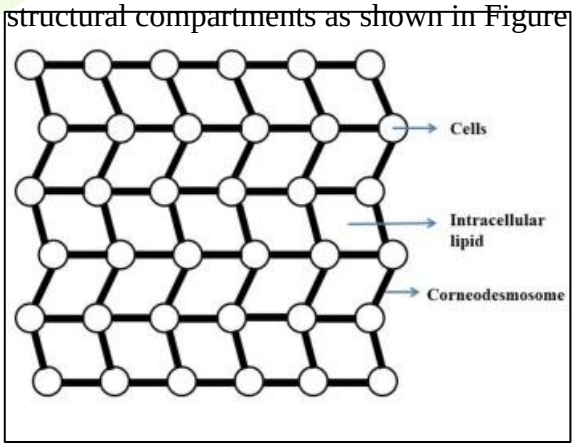


Figure 1: Structure of skin

1) Epidermis or Epithelial component coating over the surface

2) The dermis or Connective component of nutrition (Gladkov *et al.*, 2000)

These both skin compartment epidermis and dermis formed the highly specialized structure, physically separates the two compartments, provide dynamic interface and also stabilise the structure (Baroni*et al.*, 2012).

- **Epidermis:**

The outermost layer of the skin has thickness of about 10 mm approximately. Epidermis of the skin has a tendency of continuous renewing. It is made up of various layers of skin as given in TABLE II(Baroni*et al.*, 2012).

- ***Stratum corneum* (Horney layer):**

The stratum corneum made up of proteins and lipids, which has structural organisation known as bricks and mortar model (Figure 2). The stratum corneum has the protein in the range of 79-90 % and the lipids 5-15 %. The continuous lipid enriched extracellular matrix is the reason for barrier function of stratum corneum (Ng, Lau, 2015, Proksch, 2018, Draize, 1941).

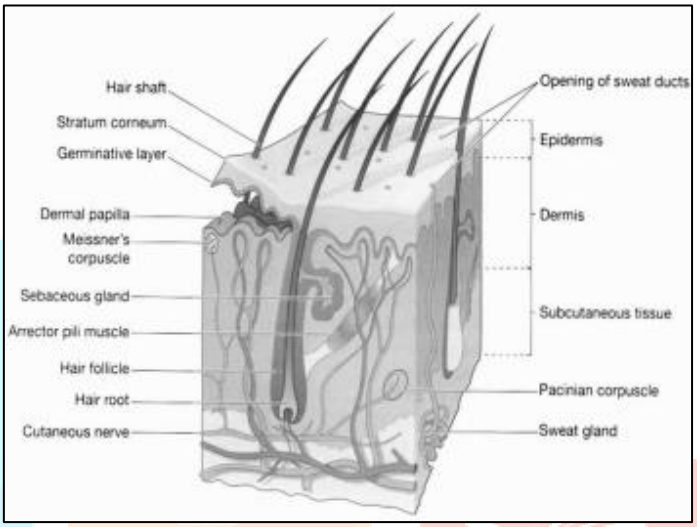


Figure 2: Schematic Representations of Bricks and Mortar Model

Table 2: Layers of Epidermis

Sr. No	Layers of Epidermis	Latin name
1	Basal cell layer	*Stratum Basale*
2	Prickle layer	*S. Spinosum*
3	Granular layer	*S. Granulosum*
4	Clear layer	*S. Lucidum*
5	Horny layer	*S. Corneum*

- **Dermis:**

The dermis is situated next to the epidermis, consist connective tissue having collagen and elastic fibbers. Dermis is highly vascularised tissue and having well network of lymphatic vessels. The dermis is also subdivided into two layers known as;

1. Upper papillary dermis:

Outer layer, thinner and composed of loose connective tissue and contact epidermis

2. Lower reticular dermis:

It is a deeper layer, thicker, less cellular and consist connective tissues.

The dermis has sweat and sebaceous glands and also the hair follicles which extends to dermal side of the dermo epidermal junction. This results into the nutrient and oxygen delivery and also the waste removal from the avascular epidermis to occur by diffusion across the dermo epidermal junction (Marwah*et al.*, 2014, Sharma, Aggarwal, Dhawan, 2010, Aulton, 2007a, Aulton, Taylor, 2013b).

- **Hypodermis:**

The inner layer of the skin has a fat tissue and gives support to membrane for both epidermal and dermal layer of skin (Wickett, Wisscher, 2006)

III. TRANSDERMAL PATCH

Transdermal patches are pharmaceutical preparations designed to provide a prolong delivery of drugs to the skin to achieve a systemic effect (Quaroni *et al.*, 2018).

The first FDA approved Scopolamine patch was developed and marketed in 1980 for the treatment of motion sickness (Prabhakar, Srikanth, Jayaveera, 2013, Amjadi*et al.*, 2018).Later on the clonidine, estradiol, Fentanyl, Nicotine, Testosterone, Seleginine, Buprenorphine are approved for hypertension, Menopausal symptoms, chronic pain, smoking cessesion, testosterone deficiency, Depression and Chronic pain respectively (Dr. Wilson).On the other hand many drugs candidates like insulin, dextromphatamine, loxoprofen, sumatriptan are in clinical trials (Amjadi *et al.*, 2018).

Transdermal passive system is therapeutic system in which the drug is administered through skin with constant rate, predetermined time with effective systemic concentration. The transdermal patch having membrane or matrix creates concentration gradient between the skin layer and dosage form. This is why the passive diffusion takes place with a constant rate at predetermined time.

The transdermal patch are developed in different ways but basically classified into three types likely
1. Reservoir, 2. Polymer Matrix, 3. Micro reservoir

1) Reservoir system:

The reservoir system (Figure 3) consist of three major components
i) The drug reservoir,
ii) The rate controlling membrane
iii) The adhesives (Tanwar, Sachdeva, 2016).

Basically the drug reservoir contains drug and excipients situated in between impervious backing layer and rate controlling membrane. The drug reservoir contain drug in the form of gel, solution or suspension and the microporous or nonporous rate controlling membrane responsible for the release of the drug (Tanwar, Sachdeva, 2016, Rastogi, Yadav, 2012, Sharma, 2018) .One of the important component of reservoir system is adhesive which were situated in between rate controlling membrane and release liner. The adhesive layer act as the immediate release layer as the adhesive is equilibrated with drug. The reservoir type of patch will distributed only after the equilibration of the adhesive layer (Prodduturi *et al.*, 2009). The hypoallergenic polymer was applied over the outer surface of the polymeric membrane. The drug is permeated through the membrane and adhesive to reach the skin (Rani *et al.*, 2011).

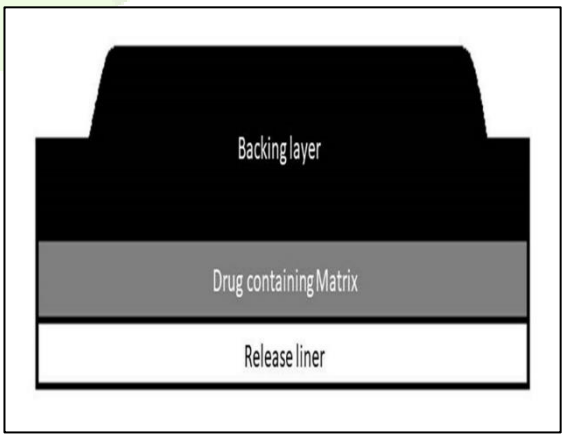


Figure 3: Reservoir System

2) Matrix system or monolithic system:

The matrix system (Figure 4) also called the monolithic system consist of the drug in the form of solution or suspension which is homogeneously dispersed into the hydrophilic or lipophilic polymer which is surrounded by the adhesive layer (Prabhakar, Sreekanth, Jayaveera, 2013, Tanwar, Sachdeva, 2016, Dhiman, Singh, Rehni, 2011)

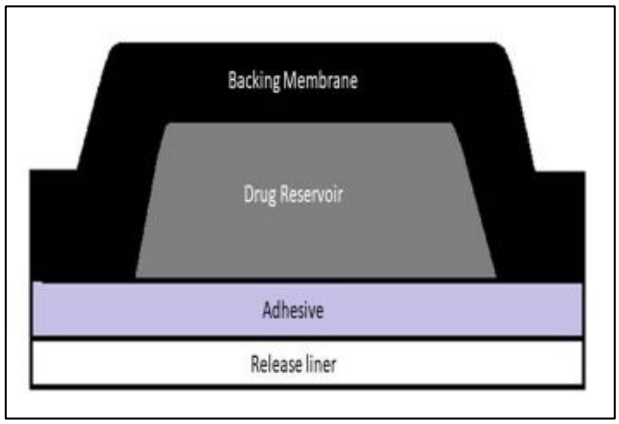


Figure 4: Matrix System

3) Micro-reservoir system:

The reservoir and matrix system are combined to form the micro-reservoir system (Figure 5). In this the drug is first suspended in aqueous polymeric solution and then homogeneously this solution dispersed into lipophilic polymer. This process forms thousands of unleachable and thermodynamically unstable microscopic spheres drug reservoirs. The in situ cross-linking thermodynamically stables the dispersion (Prabhakar, Sreekanth, Jayaveera, 2013, Tanwar, Sachdeva, 2016, Rastogi, Yadav, 2012, Sharma, 2018).

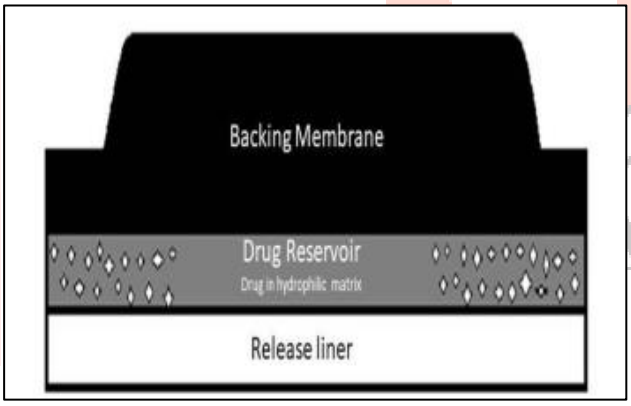


Figure 5: Micro reservoir System

IV. CONTENTS OF TRANSDERMAL PATCH:

- **Drug:**

Selection of drug candidate (Table 3) is crucial factor in case of transdermal delivery system. While selecting of drug there are numerous factors that have to be consider like Molecular weight of drug, Biological half-life, Partition coefficient, aqueous solubility, Drug's bioavailability etc.

Table 3: Ideal Characteristics of Drug Candidate for Transdermal Drug Delivery System

Parameters	**Ideal characteristics**
Molecular weight	≤ 500 Da
Half life	Short half-life (< 10 hrs.)
Partition Coefficient (Log P)	1-4

Dose	< 10 mg/ day
Melting point	< 200°C
Aqueous solubility	>1 mg/mL

The 500 Dalton rule: The inventors of the 500 Dalton rule investigated the molecular weight of allergens that cause allergic contact dermatitis and the most commonly used topical drugs in dermatology. They found that all of allergens and drugs had a molecular weight of less than 500 Daltons. An allergen must be able to penetrate the skin to cause its immune response, same with the topical drugs. Since human skin has effective barrier stratum corneum but it fails to prevent entry of smaller molecules. Therefore, in normal healthy human skin 500 Da is the upper limit of penetration and the molecular weight of drug should be equal or less than 500 Da (Bos, Meinardi, 2000).

The drug used in transdermal drug delivery system must have lipophilic as well as hydrophilic properties. As the Stratum corneum is lipoid in nature the drug must have to diffuse through intercellular lipid lamellae and then through aqueous viable epidermis. If the drug is hydrophilic then it won't cross the *stratum corneum*; on the other hand lipophilic drug saturated within *stratum corneum* layers (Naik, Kalia, Guy, 2000, Guy, Hadgraft, 2003, Gorden, Barbra, 1988).

- **Matrix / reservoir forming polymer:**

The matrix forming agent or polymer is another factor which governs the controlled release of the drug through patch. Ideally the polymer should be non-reactive with drug and other excipients, stable throughout self-life of product and consistent drug delivery. The polymers used in transdermal drug delivery system (Table 5) are classified in as

Table 4: Classification of Polymers Used In Transdermal Drug Delivery System

Natural polymers	Cellulose derivatives, Natural rubber, Chitosan, Natural gums. Etc.,
Synthetic elastomers	Acrylonitrile, Polybutadienes, Polyisobutylene etc.,
Synthetic Polymers	Polyvinyl alcohol, Polyethylene, polypropylene. Etc.,

Table 5: Polymers Used in Transdermal Drug Delivery System

Sr. No	Drug	Polymer	Conclusion
1	Ketoprofen, allopurinol (Arshad *et al.*, 2018)	Methocel, Eudragit RL100,	The patch was made with Methocel as primary layer and Eudragit RL 100 as secondary layer. The in vitro study show that increase in concentration of Methocel increased the drug release on the other hand with increase in concentration of Eudragit RL100 decreased the drug release.
2	Dexamethasone (Mukharjee *et al.*, 2005)	Ethylcellulose, Eudragit RL-100, polyvinylpyrrolidone	The transdermal patch of Dexamethasone was prepared with different blends of polymers and found that PVP:EC(1:5) had slowest rate of release and therefore the best suitable polymer for development of transdermal drug delivery system

3	Nicotine (Suksaeree *et al.*, 2018)	pectin isolated from *Cissampelospareira*, Deproteinized natural rubber latex (DNRL)	In this paper the study was carried out patch made with isolated pectin (C. pareira) blended with deprotenized natural ruber latex. The patch made with only pectin are brittle so it is blended with DNRL shows good mechanical strength, flexibility, with proper drug release.
4	4-benzylpiperidine (Ganti *et al.*, 2018)	polyisobutylenes, Silicone adhesive	The patch was successfully made with polyisobutylene and silicon adhesive and found that polyisobutylene patch was have higher drug delivery than silicon adhesive.
5	Glimepiride (Akram *etal., 2018*)	Ammonio Methacrylate Copolymer(Eudragit RL100), Ammonio Methacrylate Copolymer (PhEur RS 100)	In this paper transdermal patch of glimepiride was successfully mad with Eudragit RL100 and Eudargit RS100. With the ratio 7:3 give good transdermal drug delivery system.
6	Simvastatin (Khalid *et al.*, 2015)	Eudragit RSPO, Eudragit RLPO	Simvastatin transdermal patch was made up of Eudragit RLPO and Eudargit RSPO observed that increasing percentage of matrix forming agent increase the thickness on the other hand decrease the permeation.
7	Bisoprolol fumarate (Shabbir *et al.*, 2017)	Eudragit RS100, Methocel E5	In this paper transdermal patch of BISOPROLOL FUMARATE was made with different concentrations of polymer and found that eudragit RS 100: Methocel E5 (8:2) give good transdermal drug delivery system.
8	Diltiazem hydrochloride (Satturwar, Fulzele, Dorle, 2005)	Polymerized Rosin	In this paper study was carried out on the transdermal patch of Diltiazem hydrochloride prepared with polymerized rosin. With PR: PVP (7:3) and DBT 30 % wt/wt produce smooth flexible films and improved tensile strength. Permeation of drug increases with increasing drug and PVP concentration but does not depends upon film thickness.
9	Ibuprofen, flurbiprofen, ketoprofen (Quaroni *et al.*, 2018)	Eudragit® RL	In this paper study carried out on rheological as well as adhesive properties of Eudragit RL. The optimal ratio of polymer/plasticizer had crucial role in development of transdermal drug delivery system.
10	Ketoprofen (Mita, Husni, Setiyowati, 2018)	Ethyl Cellulose (EC), Polyvinyl Pyrrolidone (PVP)	The author formulated patch of ketoprofen with combination of ethyl cellulose and polyvinyl pyrrolidone with different ratio found EC: PVP (1:3) had highest percentage of ketoprofen permeation (93.66%) up to 12 hrs followed zero order kinetics mechanism with AUC 164 um. Hrs/ml

11	Diltiazem (Anirudhan, Nair, Gopika, 2018)	Cellulose, Sodium Alginate and Polyvinyl Alcohol	In this paper polymers were compared by parameters like thickness, average visible transmittance, water vapour permeability and permeation of drug. It was found that CMC has higher value of thickness, poor transmittance value, grater water retention and also lesser permeation then sodium alginate and PVA. The alginate has the satisfactory results. Whereas PVA had minimum thickness, show better transmittance and higher permeation of drug make it ideal polymer for transdermal drug delivery system.
12	Simvastatin (Parhi Padilam, 2018)	Acrylic adhesives (DURO-TAK® 87-9301, DURO-TAK® 87-4287, DURO-TAK® 87-235A)	The transdermal patch of Simvastatin successfully made with acrylic adhesive. DURO TAK® 87-9301 (93%w/w), Simvastatin (2%w/w), and IPM (5%w/w) shows highest flux for Simvastatin.
13	Piroxicam (Chantasart, 2017)	Eudragit®RL100, Eudragit®RS100	In this paper Eudragit RL 100 and Eudragit RS 100 was used with different ratio and alone for preparation of transdermal patch of piroxicam. Author found that Eudragit RL100 alone (100%) gives softest and toughest film than other also it gives highest release rate as well as increase drug loading and permeation flux across HEM.
14	Ketoprofen (Floriano, 2017)	Natural Rubber Latex	In this paper natural rubber latex was used as matrix forming agent to incorporate Ketoprofen. Study shows that up to 50 hr 60 % drug was released also the drug present on surface responsible for burst release and drug loading has no influence on tensile strength.
15	Ketotifen fumarate (Lefnaoui, 2017)	Chitosan–alginate polyelectrolyte complex	Transdermal films of KF composed with both chitosan and sodium alginate as polymer matrix, and propylene glycol as plasticizer were found transparent films, smooth, flexible with good mechanical strength and high bio adhesiveness. The drug release characteristics provided a release rate for prolonged period of time.

From the Table 5 we see that the concentration of the polymer affects the physical properties (e.g. Thickness, folding endurance etc.) of prepared film which ultimately affects physical appearance as well as the drug release kinetics.

- **Penetration enhancers:**

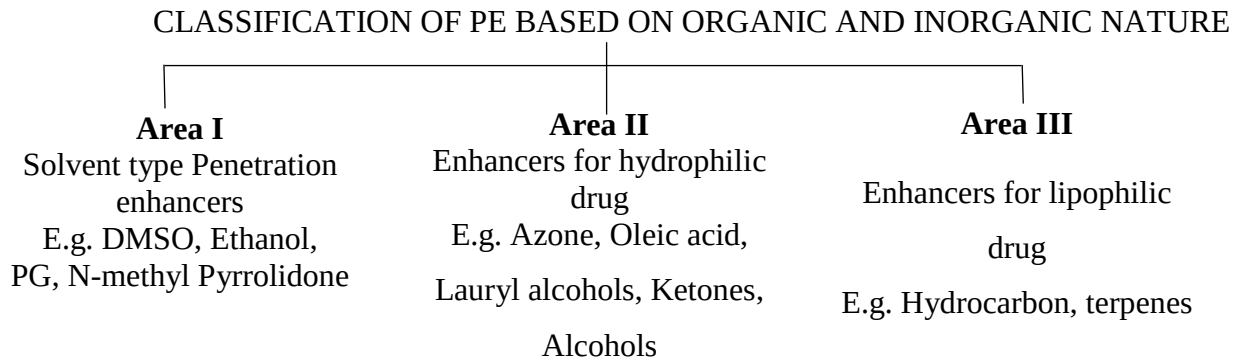
The chemical compound from natural or synthetic origin have an ability to enhance the permeation of drug are known as penetration enhancers. They improve the permeability by interacting with *stratum corneum*. Ideally they should be non-toxic, non-irritating, and non-allergic as well as duration and effect of activity should be predictable and reproducible. eg.Terpenes, alcohol, pyrolidones, surfactants, essential oils. (Sharma, 2018, Dhiman, Singh, Rehni 2011)

V. Classification of penetration enhancers:

Based on organic and inorganic nature of penetration enhancers they are classified into three areas. Also penetration enhancers classified according to their chemical structure (Table 6) and it is consider being most promising system like Sulfoxide (e.g. DMSO, dimethyleacetamide, dimethylformamide etc.), Alcohols (e.g. Ethanol. 1-octanol etc.), Polyols, Fatty acids (e.g.PG, PEG, oleic acid etc.), Azone (e.g. Laurocaprametc.), Surfactants (Tween 80, Tween 20, Sodium lauryl sulphate etc.)

Table 6: Chemical Classification of Penetration Enhancers and Mechanism

Chemical class	Examples	Mechanism of Penetration
Sulfoxides (Pathan, Setty, 2009)	DMSO, Decylmethylsulphoxide	Denature proteins and also make stratum corneum layer more permeable by extracting lipids.
Alcohols (Lane, 2013)	Ethanol, Isopropyl alcohol, Decanol, Hexanol, Lauryl alcohol, Myristyl alcohol, Octanol, Oleyl alcohol	Disturbance of lipid layer resulting into increase lipid fluidity of drug increases drug permeation.
Polyols (Barry, 1987)	PG,PEG	Enhance intracellular transport by reduce drug-tissue binding sites.
Fatty acids & Fatty acid esters (Saruyoo, 2009, Naik, 1995)	Lauric acid, Linoleic acid, Linolenic acid, Myristic acid, Oleic acid	Disrupt intracellular lipid domain by reducing ordered intracellular lipid domain of stratum corneum
Amides (Pathan, Setty, 2009, Lane, 2013, Barry, 1987, Saruyoo, 2009, Naik, 1995)	Azone, Urea, Cyclic amides, etc	Interact with lipids and preventing chain crystallisation and form more fluid environment by hydration of stratum corneum and diffusional resistance of skin reduced.
Surfactants (Pathan, Setty, 2009, Lane, 2013, Barry, 1987)	Sodium lauryl sulphate, Alkyl dimethyl benzyl ammonium halides, Alkyl trimethyl ammonium halides, Alkyl pyridinium halides, Tween 80	Penetrate and interact with the skin and disrupt the entire membrane affecting both protein and lipid structure. The grossly swollen protein domain probably absorbs more water and thus permits drugs to permeate more freely.
Terpenes (Lane, 2013, Chen *et al.*, 2015)	Eugenol, d-Limonene, Menthol, Menthone, Farnesol, Neridol	Extracting stratum corneum lipids and affect both lipoid intercellular as well as transcellular pathway. Terpenes also dissolved in intercellular lipid domain and improved drug partition inti SC



VI. Mechanism of action of penetration enhancers (Lundborg *et al.,* 2018):

1] Changes the solubility properties of stratum corneum

2] Altering solubility of drug in donor phase

3] Modifying the thermodynamic activity of drug

4] Promoting transport by dragging the permeant through the skin

5] Perturbation of skin barrier lipid organisation

In following Table 7 effect of natural and chemical penetration enhancers were discussed on the permeation of drug

Table 7: Penetration Enhancers Used In Transdermal Drug Delivery System

Sr. no.	Drug	Penetration enhancer	Conclusion
1	Tetrametylepyrazine (Teng *et al.*, 2013)	Eucalyptus oil (2.5%) Azone (2.5%) Menthol (2.5%)	All three enhancers significantly increase permeation but the highest permeation was found with eucalyptus oil (410.6 ±ug/cm2/h), 3-4 fold increase, also various combinations (EO+menthol, EO+Az) but it significantly lower than EO.
2	Heparin sodium (Patel, Gaikwad, Patel, 2014)	Oleic acid Iso Propyl myristate	Formulation containing 10 % oleic acid with 10 % IPM gave better penetration of HS through rat skin (93.06%).
3	Hydralazine Hydrochloride (Mannam, Yallamalli, 2017)	Azone Isopropyle Myristate Menthol	IPM was have higher flux value which is increased with concentration from 10-15 % (64.168) further increase in concentration does not show any effect. Ex-vivo study shows no significant difference with (60.487 ug/cm^2/h) drug release.
4	Diclofenac sodium (Rajput *et al.*, 2014)	Karanj oil	In the present study various formulations prepared by using Karanj oil *(Pongamiaglabra)* as one of the component (vehicle) to evaluate its effect on in enhancement and drug permeability. Maximum drug diffused from the formulation no F3 (51.42%) contains ethanol. It was also observed that formulation F2 (44.44%) had shown better permeation. It contain glycerol. This shows additive enhancement effect of glycerol with Karanjoil *(Pongamiaglabra)* in topical drug delivery system.
5	Lornoxican (Saleh *et al.*, 2014)	Propyene glycol Ethanol HP B-CD BB CD Tween 80 Oleic acid	In this study carbopol containing PG, HP BCD could be promicing carrier for Lonoxicam

6	Terbinafine (Rajurkar *et al.*, 2015)	DMSO di-n-butyle-phtalate	In this study the patch is formulated using different polymers with DMSO as penetration enhancer and PEG as plasticizer. The formulation containing HPMC E5, PVP K25, shows the 92.56 % drug release at the end of 6 hrs.
7	Ketoprofen (Zakir *et al.*, 2015)	DMSO	The different polymeric concentration of HPMC and EC was studied alone and in combination with DMSO as penetration enhancer.
8	Glibenclamide (Rastogi *et al.*, 2015)	Olive Oil Mustard Oil	Significant effect of vegetable oils on the lipid and protein framework of the skin was seen which results in approximately 1.3 fold times increase of Glibenclamide flux.
9	Ligustrazinre hydriochloride (Wang *et al.*, 2016)	Menthol Menthone Azone	Both menthol (6.30 ug/cm^2/h) and Menthone (5.37 ug/cm^2/h) has more permeation flux then azone. Also it was absorved that menthol had a longer lag time then menthone and azone and there were larger incerese in Kp of menthol (200.75/h) than Menthone (171/h) and Azone (27.20/h)
10	Indomethacin Lidocain Asprin Antipyrine Tegafur 5-fluorouracil (Xie *et al.*, 2016)	Camphor	The in-vitro skin permeation studies showed that camphor could markedly enhance the transdermal permeation of drug with differing lipophilicity, meanwhile camphor had greater efficiency for transdermal permeation of weak lipophilic or hydrophilic drugs.
11	Benazepril hydrochloride (Jain, Dubey, Mishra, 2016)	Span 80 Tween 80 Methanol Water	In this study the transdermal patch of Benzaeperil hydrochloride was made and found that the formulation containing Acryle S100 and HPMC had a 97.770 % drug content with 89.58 % drug permeation through the skin at the end of 10 hrs.
12	5-Fluorouracil Antipyrine Aspirin Salicylic acid Ibuprofen (Yi *et al.*, 2016)	Borneol Azone	Borneol significantly enhanced the transdermal permeation of five model drugs with wide range of Log P value. Berneol achieve optimum permeation-enhancing effect for moderately hydrophilic drugs (-0.5-0.5)
13	Fluoxetine (Eunjae *et al.*, 2015)	IPM, Limonene, Oleic Acid, Tween 20	The selected penetration enhancer did not show any enhancing effect significantly.
14	Repaglinide Ramipril (Zaman *et al.* 2017)	Oleic Acid, PG	Was found that combination of HPMC K4M along with Ethyl Cellulose are suitable polymers as well as Oleic acid and Propylene Glycol show good effect in Permeation of both drugs. It was noted that percentage of drug permeated directly proportion to HPMC K4M & inversely proportional to Ethyl Cellulose.

15	Dimethyl Fumarate (Ameen, Michniak-Kohn, 2017)	Polysorbate 80 (T80), N-methyl pyrilidone (NMP), Laurocapram (AZ), Transccutol P (TC), Terpineol (TERP), Cineole (CIN).	The flux and the amount permeated were significantly increased with the incorporation of PEs, PEs were most effective at highest conc. used and 5% v/v Cineole in PG was the best vehicle to deliver DMF.
16	Palonosetron (Nair *et al*., 2018)	Oleic acid Propylene glycol Diethylene glycol monomethyl ether Tween80	The patch is formulated with different PSA and found that highest drug level was incorporated in Duro-Tak 87-9301.Furter addition of PE the Propylene glycol shows significant increase in flux then other PE
17	Ibuprofen (Tombs *et al.*, 2017)	Combination of DEGEE, PG, Octadecenol, Oleic acid	In this study the solvent free TEPI membrane was used for drug reservoir. It was observed that drug is easily released and penetrate trough human skin.
18	Flurbiprofen (Akhlaq *et al.* 2017)	Thistle oil	The diffusion study was conducted on artificial membrane, rabbit, rat, pig dog and human skin. The physicochemical parameters and *invitro* drug permeation data showed that the formulation containing 5-10% milk thistle oil exhibited enhanced drug release.
19	Dihydroquercetin (Cizinauskas *et al.*, 2017)	Soybean oil Olive oil Avocado oil sea-buckthorn pulp, raspberry seed oil and coconut oils	Soybean and olive oils efficiently increase the penetration of DHQ into the skin layers and can be used as skin penetration enhancers.
20	Trans-Resveratrol (Liu *et al.*, 2018)	Pomegranate seed oil Isopropyl palmitate	The permeation study shows that IP 2.5 % and 5.0% accelerate the permeation but not no effect on cumulative percutaneous amount. IP 10% improved total transdermal absorption but no impact on speeding up the absorption while PSO has more potent ability in enhancing the percutaneous absorption as well as accelerating the transdermal process. The cumulative permeation amount of reservetrol with 10 % PSO was 3.14 fold that of Resevertrol alone.
21	Glimepride (Akram *et al.*, 2018)	IPM Span 80 Tween 20 Limonene Eucalyaptus oil	The patch is subjected for effect of five PE with three concentration level and found that IPM at 10% showed 5.75 times increased in permeation flux.
22	Diclofenac (Pireddu *et al.*, 2018)	Diethylene glycol monoethyle ether	In this study the two approaches namely size reduction and inclusion of PE were studied and found that Nano sizing the particles was increase the skin permeation whereas increase permeation was reduced dramatically by increasing concentration of PE (TCP).

23	Ligustrazine (Dai *et al*., 2018*)*	Berneol Menthol	In this study the permeation effect of Berneol and Menthol was studied and found that at low concentration (0-0.5 %) the enhancing ratio was higher than berneol, meanwhile at higher concentration (>0.5 %) berneol also form water channels and improve the permeation.
24	5-Fluorouracil Lidocaine Ibuprofen (Singh *et al.,* 2018)	Crude Palm Oil TRF Refined palm oil	In this study the RPO are used as negative control. The flux of 5-FU and Lidocaine was not significantly different then RPO. The flux of Ibuprofen was grether then RPO. Permeation of three Drugs increased followed by CPO

- **Plasticizers:**

Transdermal patch with hardness should also possess the flexibility; hence plasticizers such as dibutylphtalate, triethylcitrate, polyethyleneglycol and propylene glycol are used as plasticizers which give plasticity to transdermal patch (Arunachalam *et al.,* 2010).

- **Pressure sensitive adhesive:**

The adherence of transdermal patch to skin surface is governed by pressure sensitive adhesive. One of main aspect in transdermal treatment is that the patch has to maintain complete skin contact during required period of time to ensure efficient and desired drug delivery. It can be removed easily and does not leave residue over the skin. E.g. Poly isobutylene, Silicone based adhesives, Acrylic adhesives. (Sharma, 2018, Banerjee *et al.,* 2014)

- **Backing layer:**

Backing laminate hold the entire system together also protects it from environment during application. It also gives appearance as well as flexibility. While selecting of backing laminate the chemical resistance and excipients compatibility has to be considered, cause prolong contact between backing layer and excipients results into leaching out or may leads to diffusion of excipients. The most appropriate and suitable backing may consist lowest modules or high flexibility, good oxygen transmission and high moisture vapour transmission rate. E.g. Co-tran 9701, 9702, 9706, 9720, 9722, Scotchpack 1006 etc. (Rastogi, Yadav, 2012, Banerjee *et al.,* 2014)

- **Release liner:**

Protection of transdermal patch during long-term storage is main function of release liner. Release liner does not come in contact with skin, but is in direct contact with drug hence the properties of materials are important. The material used for release liner should not react with drug; the drug should not leach out into release liner and should not absorb water. Release liner has to be removed before use of patch. (Rani *et al.,* 2011, Banerjee *et al.,* 2014)

VII. EVALUATION:

- **Drug excipients interaction**:

Differential scanning calorimetry&Fourier-transform infrared spectroscopy were used for studying drug excipient compatibility. (Malaiya *et al.,* 2018)

- **Thickness:**

The thickness uniformity was measured at different site by using Vernier calliper and the average values and standard deviation were determined. (Saleem, Idris, 2016)

- **Folding endurance**:

The folding endurance was performed manually on the strip of patch (4 x 2 cm) reputedly folding at same place until it breaks. Folding endurance is defined as number of times of the film folding at same place until it breaks or cracks. (Chandak, Verma, 2008)

- **Weight variation**:

Films are weighed individually and also the average weight is measured. The difference between individual and average weight gives weight variation. (Mutalik, Udupa, 2004)

- **Drug content**:

Patch (1 X 1 cm^2) from different formulations were cut and dissolved in solvent and allowed for continuous stirring up to 24 h using magnetic stirrer. The solution was filtered and diluted further with solvent and percent drug content was measured. (Cherukuri *et al.,* 2017)

- **Percentage moisture absorption**:

The films are weighed before keeping into desiccator. Then the weighed films should be subjected to desiccator at room temperature (24 h) containing saturated solution of potassium chloride to maintain 84 % RH. After 24 h films are reweighed and percent moisture uptake is determined by following formula (Mamatha *et al.,* 2010)

$$\%\text{Moisture Uptake} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{initial weight}} \times 100$$

- **Percentage moisture content/loss**:

The films are weighed individually and subjected to desiccator with fused Calcium chloride or activated silica at room temperature for 24 h. After 24 h films are reweighed and determine percentage moisture content/loss by following formula (Vishwakarma *et al.,* 2012)

$$\%\ \text{Moisture Loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Final weight}} \times 100$$

- **Swelling index**:

Pre-weighed films are totally deep in 50 ml beaker having 25 ml phosphate buffer pH 7.4 maintain 25° using water bath. Then at specified interval of time the swollen films are reweighed after removal of excess water by light blotting with filter paper. The swelling index is calculated by following formula (Ramadan *et al.,* 2018)

$$\text{Swelling index} = \frac{(\text{Weight after time intervals} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

- **Flatness:**

Longitudinal strips are cut out from right, left and middle of the prepared patch and length of each strip was measured and variation in length due to flatness also measured, by determining percent constriction. Zero percent constriction consider as hundred percent flatness (Arora, Mukherjee, 2002).

- **Tensile strength:**

Three strips are cut off from prepared patch (2 X 1 cm^2). Pulley system is used for the measurement. Weights in pan were gradually added until patch was broken. The distance travelled by pointer before brake of patch was noted with the help of magnifying glass on the graph paper. Tensile strength was measured in Kg/cm^2. (Lefnaoui *et al.,* 2017, Patel, Gaikwad, Patel, 2014)

- ***In vitro* permeation study:**

In vitro permeation study can be carried out by using Franz diffusion cell with the help of diffusion membrane e.g. artificial diffusion membrane, egg shell membrane, skin of dorsal region of *Swiss albino mice*, pork ear skin etc. in phosphate buffer solution pH 7.4 with continuous shaken using magnetic stirrer. The phosphate buffer used was isotonic solution and resembles pH 7.4 as same body fluid. (Saleem, Idris, 2016, Parhi, Suresh, 2016, Mita, Husni, Setiyowati, 2018, Jain, Dubey, Mishra, 2016, Arun, 2014)

- ***In vivo study:***

In vivo evaluation of formulation is carried out in animal model e.g. Sprague-Dawley rat, human cadaver skin etc. The abdominal hairs of animals were removed with the help of electric clipper or hair removing cream and skin is observed for any damage. The patch was applied over shaved skin and fixes using adhesives tapes. Then blood samples were collected at predetermined time interval and subjected to UV or HPLC analysis. (Eunjae*et al.*, 2015, Panchgnula *et al.*, 2005)

- **Irritancy test**:

The skin irritancy test was performed on animals like rats. The aqueous solution of formalin was used as standard irritant. After 24 h patch was removed and examine for development of edema or erythema (Table 8). (Patel, Gaikwad, Patel, 2014, Panchgnula *et al.*, 2005, Mehta, Rathod, 2017)

Table 8: Standard Irritancy Values

(A)Erythema and Eschar formation	Standard score	(B)Edema formation	Standard score
Very slight erythema	1	Very slight edema	1
Well defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema	4	Severe edema	4

- **Stability test**:

The stability of prepared patch is studied according to ICH guideline for 6 months. The conditions are maintained 40 ± 2° temp and 75 ±5% RH using stability chamber. (Madi shetti *et al.*, 2010)

VIII. CONCLUSION:

Transdermal drug delivery is the best alternative drug delivery but despite the fact various formulation factors affects the flux across the skin as well as the release of drug. Polymers used in the transdermal drug delivery affects the drug release which was depends upon the thickness of polymer which is result of concentration of polymer in formulation. Transdermal flux or diffusion across the skin is limiting factor in transdermal drug delivery. Penetration enhancers natural and synthetic sufficiently enhance the drug diffusion across the skin. As we increase the concentration of penetration enhancers it will influence the diffusion of drug.

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