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DERMAL AND TRANSDERMAL DRUG DELIVERY

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ABSTRACT:

Transdermal drug delivery system (TDDS) offers a number of potential advantages over conventional methods such as injectable and oral delivery. It provides controlled release of drug and avoiding hepatic first pass metabolism. This review focuses on the recent advancements in the TDDS which include how different skin layer and system affects absorption, penetration, and bioavailability of drug molecule. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variations**.**

Keywords: Transdermal, dermal, penetration, dosage form

DERMAL AND TRANSDERMAL DRUG DELIVERY

1.1 INTRODUCTION

In human body, skin is the principal organ [**Gantwerker and Home. 2012**] it acts as a first barrier between the body and the outer environment and protects the body from external harmful effects. [**Lee et al., 2006**]. It acts as a protective barrier against envirmental toxins, microorganisms, and ultraviolet radiations, also it provides important activates of metabolism, sensation, maintains body temperature, and immunity and maintain normal body haemostatic and electrolyte balance. [**Yum et al., 2019**]. The skin thickness on various places of the body varies much, but fundamental structure

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remains the same. Anatomically, the thickness of epidermis is 50–100 μm and the thickness of dermis is 1–2 mm [**SD et al., 1996**]. The most outer layer epidermis is composed of five different layers like; 1) stratum corneum, 2) stratum lucidum, 3) stratum granulosum, 4) stratum spinosum and 5) stratum germinativum this layer mainly contain keratinocytes this layer consists of keratinocytes, which is liable for the biosynthesis of keratin. The drug delivery through skin offers a substitute and smart route of drug delivery more than the oral and parenteral drug delivery. So this route has the greater advantages over oral route of drug administration as it can by-pass hepatic first-pass metabolism and reduce the drug from degradation in GIT. Also it is patient's compliant and more convenient route of drug administration therefore favored against parenteral route. [**Alexander et al., 2012**]. This route has some disadvantages also like poorly water soluble drug cannot easily permeable so it has low bioavailability due to the presence of several skin barriers like- epidermis, dermis, and subdermal region. [**Nastatic et al., 2017**]. Stratum cornrum is the primary barrier for drug permeation. To increase skin permeability, therapeutic efficacy and minimizing possible side effects suitable carrier system is selected like microemulsion, transdermal patches, nanopartical, microneedle, transferosome, etc which is potential drug carrier system for transdermal as well as dermal drug delivery**.[Zhai et al., 2014]**

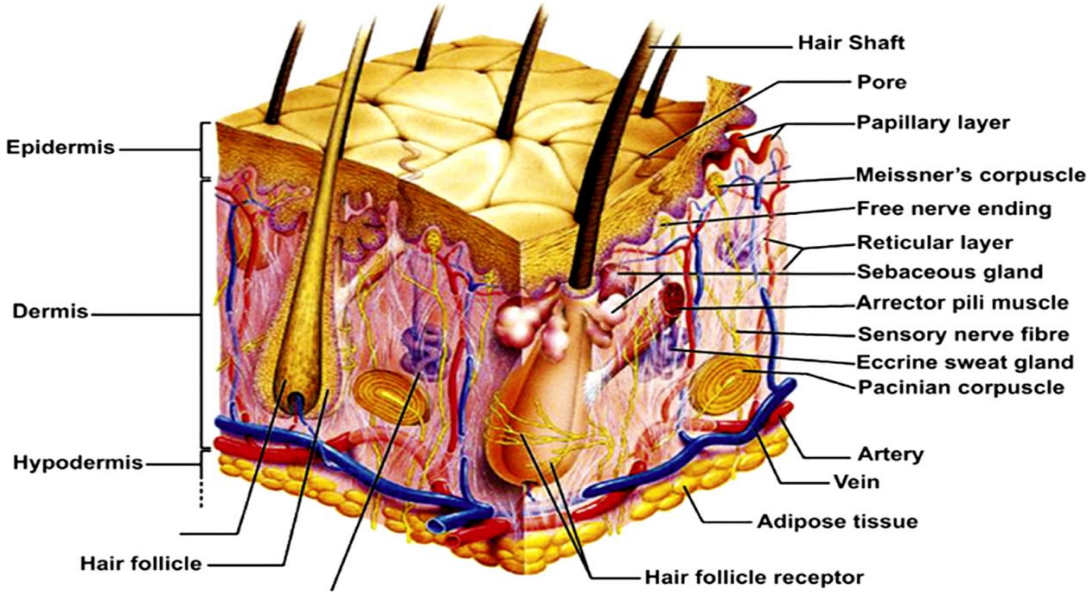

Figure 1: Structure of skin elucidating the main components of the epidermis, dermis, and hypodermis

The first transdermal delivery was- a three day patch make by scopolamine use for treatment of motion sickness. This formulation was accepted in USA in 1979. [**Prausnitz abd Langer., 2008**].

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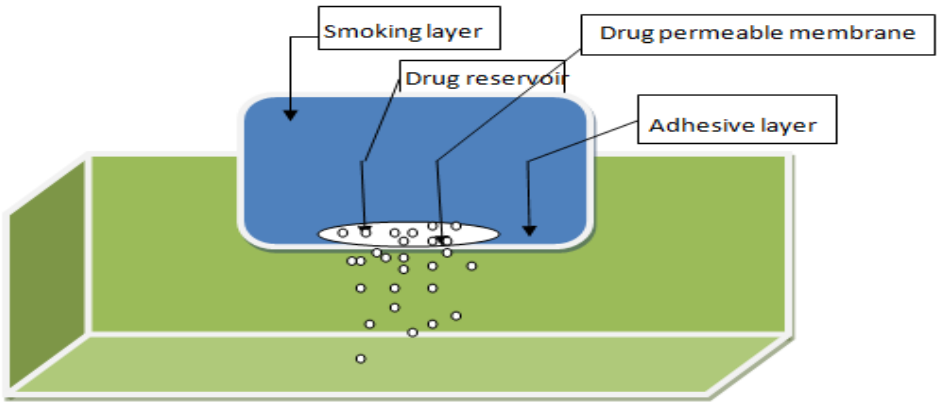

Figure 2: Transdermal patches showing its different components

Transdermal drug delivery has been in clinical use since 1981 [**Davidson et al., 2008**]. One of the vital advantages is that the drug release can be extended over a longer period of time, sometimes hours or even days. The skin serves as a drug pool while reducing gastrointestinal incompatibility and toxicity [**Lee et al., 1998**]. The necessities of drug molecule use for transdermal delivery are having low molecular weight of > 1 kDa and high lipophilicity. Therefore, stratum corneum is a mainly crucial barrier for delivery of drug molecule. The delivery of dermal and trsnsdermal is greatly challenging for dermatopharmaceuticals. [**Mueller bet al., 2006**].

1.1.1 Following are some of the Advantages of TDS [Chen et al., 2016]

- To prevent gastrointestinal degradation of active substances.
- Avoidance of first pass hepatic metabolism.
- Have ability to improve bioavailability.
- Continuation of comparatively steady plasma concentrations.
- Low melting point and good solubility.

1.1.2 Disadvantages of transdermal drug delivery [Prausnitz et al., 2004]

- Transdermal drug delivery systems are not able to deliver ionic drugs.
- Unable to provide high systemic availability of drug molecule.
- Drug having high molecular weight are difficult to deliver through this route.
- The drugs which produce skin irritation cannot be delivered through this route.
- Partition coefficient of drug molecule should be between 1-3 for permeation of drug through stratum corneum and underlining layer.

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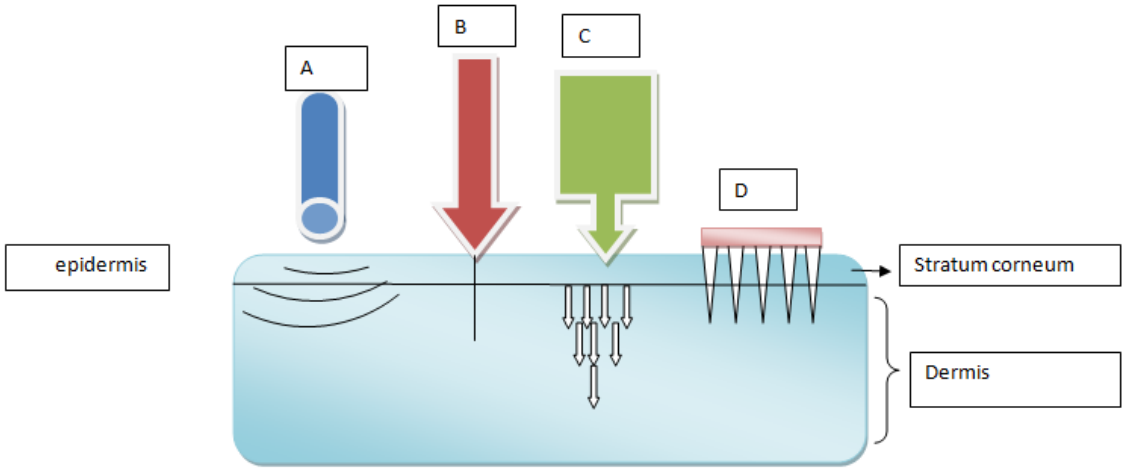

Figure 3: Delivery methods A) Sonophoresis B) Intradermal Injection C) Microjet Injection D) Microneedle Patch

2. PERCUTANEOUS ABSORPTION THROUGH THE SKIN:

When drug formulation applied to the skin it shows either local or systemic biological activity, so obviously drug have to penetrate through the skin first layer through stratum corneum. Percutaneous absorption is defined as the movement of drug particles through different layers of skin and penetrate through the skin and goes into systemic circulation. [**More et al., 2012]** Percutaneous absorption of drug molecules is important phenomena, because drug has to be absorbed in sufficient quantity and rate and helps to maintain uniform systemic drug concentration for prolonged periods of time. In general firstly drug molecule has to pass through stratum corneal barrier, and then goes into deeper tissue where the blood vessels are present and systemic uptake is done and finally goes into systemic circulation. **[Mehta R., 2004].** The release of drug molecules from a delivery system in the skin surface and its movement towards blood circulation is multistep process which is as follows

- Firstly Dissolution of carrier system in the skin surface and release active substance from the formulation.
- Partitioning into the skin's outermost layer, the *stratum corneum*.
- Diffusion of drug molecule through the stratum corneum, principally via intercellular pathway.
- Partitioning starting the *stratum corneum* into the aqueous feasible epidermis, diffusion through the feasible epidermis and goes into the upper dermis, uptake into the papillary dermis (capillary system) and into the microcirculation. **[Ramteke et al., 2012]**

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2.1 Routes of drug diffusion in the course of skin:

For any delivery system applied to the skin has two main route for drug permeation which as follows

Transepidermal route

Transfollicular route

2.2 Transepidermal route:

In transepidermal route transport of drug molecules occurs cross the integral horny layer. Two possible micro routes are available one is endocytosis (or intracellular) and other one is intercellular pathway as shown in **Fig: 4**

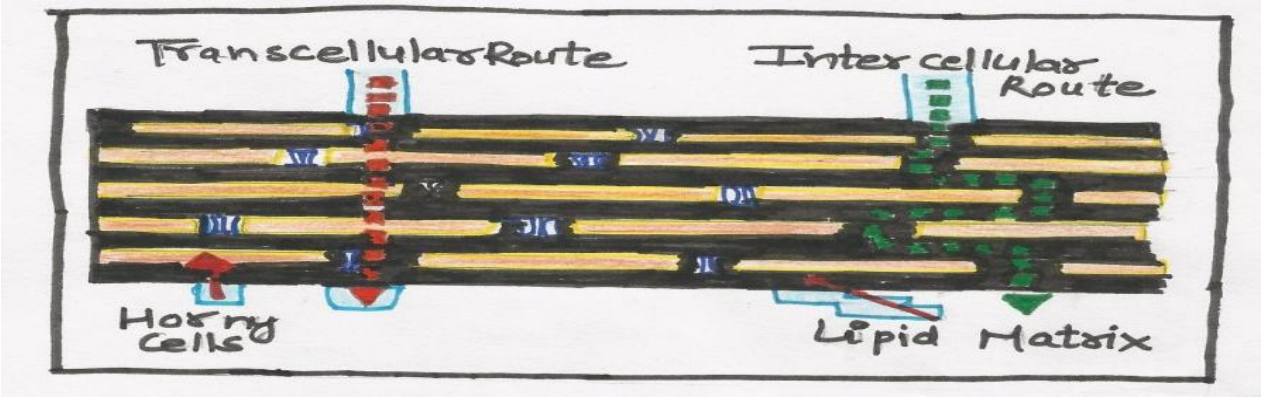

Figure 4: Diagram of transepidermal route

Together polar and non-polar molecules can easily diffuse by means of transcellular and intercellular routes by various mechanisms. The polar molecules basically diffuse to the skin through polar pathway consisting "bound water" within the hydrated *stratum corneum*, where as non-polar molecules diffuse through lipid matrix of stratum corneum. **[More et al., 2012]**

2.3 Transfollicular route (Shunt pathway):

In this route, transport of drug molecule occurred by means of the hair follicles with their associated sebaceous glands. Even through this route having high permeability, it is considered as minor route for drug penetration through the skin, due to having small surface area approximately 0.1percent of whole skin. This route is suitable for permeation of drug have large molecular size and polar in nature and ions through the stratum corneum. [**Verma ei al., 2016]**

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3. SOME BASIC COMPONENTS OF TRSNSDERMAL DELIVERY SYSTEM:

3.1 POLYMER MATRIX:

Polymers are used in skin preparations that will acts as a base and strengthen the base of TDDS [**Valenta et al., 2004**]. Choice of polymer and drawing are of main importance in this system. The special concern is required for polymer selection in transdermal delivery system, the polymer having the unique properties that should be stable, non-reactive with the drug and other excepients, simply prepared and made-up into preferred product, and having low cost. Properties of polymers (molecular weight and glass transition temperature and chemical functionality) should be such that the specific drug can easily diffuses properly and get released at the specific site and mechanical characteristics of the polymer should not decline extremely when large quantity of biologically active substances are incorporated into it. Also it should be biocompatible and chemically compatible with drug as well as other components like penetration enhancer should provide consistent and effective delivery of a drug all through the product's life [**Keith AD., 1983**]. Polymers are utilized in transdermal drug delivery system in adjustable manner as well as rate-controlling membranes, adhesives backing layers, and release liners.

TABLE 1: SOME EXAMPLES OF POLYMERS USE IN TRANSDERMAL DELIVERY SYSTEMS [Tanwar and Sachdeva., 2016], [Vyas and khar., 2002], [Srilatha et al., 2018]

Natural polymers	**Synthetic elastomers**	**Synthetic polymers**
Proteins	Neoprppane	Polyamide
Gelatin	Acrylonitrile	Polyacrylattes
Shellac	Cholroprepen	Acetal copolymer
Arabino galactane	Hydrinrubber	Polysterene
Cellulose derivative	Polybutadeine	Polyvinyl alcohol
Zein	Polysioloxane	Polyvinyl chloride
Starch	Silicon rubber	Polysterene

3.2 PENETRATION ENHANCER:

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These are compounds which promote the skin permeability, flexibility by changing the skin as barrier and help to penetrate the drug across the skin layer and deliver into specific site**. [Gupta and Chokshi., 2011]**

3.2.1 SOME OF THE IDEAL PROPERTIES OF PENETRATION ENHANCER

- Should have Controlled and reversible attractive action
- Should be physical and chemically compatible with drug molecule and other excipients.
- Should not cause loss of body fluids, electrolytes or other endogenous materials
- Should be non toxic, non allergic, non irritating
- Should be pharmacologically inert
- Should have ability to show biological activity for specific periods of time.

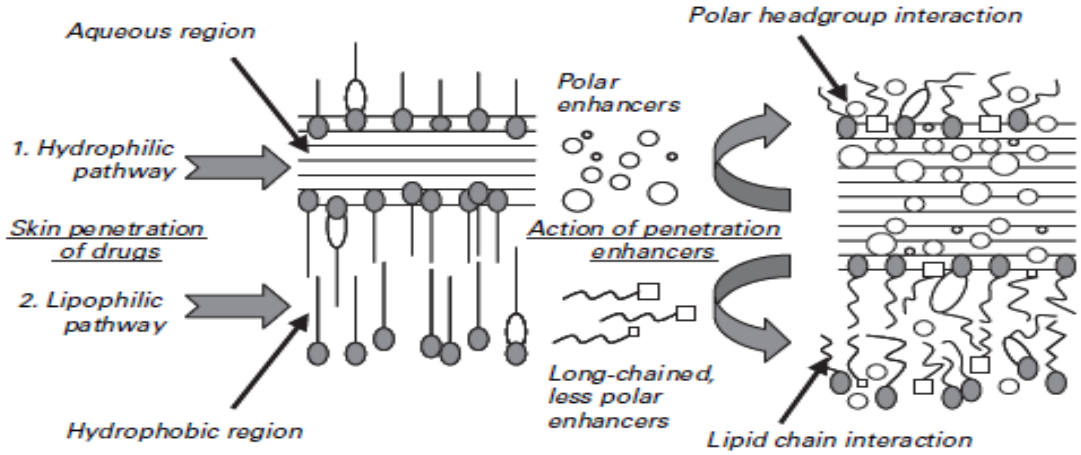

Figure 5: mechanism of action of penetration enhancers.

TABLE 2: EXAMPLES OF PENETRATION ENHANCERS [Tanwar and Sachdey., 2016],[Vyas and khar., 2002], [Srilatha et al.,m 2018]

Class	Examples	Mechanism	Transport pathway
Surfactants	Na- lauryl sulphate Bile salts na-deoxycholate Na-glycocholate	Transcellular Paraacellular	Phospholipid acyl chain perturbation Reduction mucous viscosity

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Chealeting	EDTA Polyacrylates	Transcellular paracellular	Complexatation of Ca2+opening tight junctions
agents Fatty acid	oleic acid	transcellular	Phospholipid acyl chain perturbation
Positively charged polymer	Chitosan Trimethyl chitosan	paracellular	Ionic interactions with negatively charged groups of glycocalix

3.3 DRUG SUBSTANCES: To get potential and successfully transdermal drug delivery system, the selection of drug molecule should be done with grand concern. The drug molecules should have following are important properties used for transdermal drug delivery system. [**Joshi and Selvaduary., 2008]**

3.3.1 Physiological properties:

- Molecular weight of drug molecule should be less than 1000 Daltons.
- The drug should have partition coefficient between 1-3, affinity towards for both lipophilic and hydrophilic phase for potential delivery through the skin.
- The melting point of drug molecule should be low.
- The drug should be potent, having short half life and should be non-irritating.

3.3.2 Biological Properties [Jalwal et al., 2010]

- The drug should be showing biological activity of drug very low concentration.
- Biological half life should be low.

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- The drug should not cause allergic reaction to human skin.
- The drug should be physically and chemically stable when applied to the skin.
- Drug should be non immunogenic.
- The release of drug should follow zero order kinetics.
- The dose of drug should not exceed 50 mg per day, and ideally should be less than 10 mg per day.
- The drug should not get bound to the skin tissues irreversible manner.
- Drug metabolism in the skin should be low.

TABLE 3: SOME IDEAL PROPERTIES OF DRUG USE FOR TRANSDERMAL DRUG DELIVERY SYSTEMS [Kaleb et al 2010], [Archana and Gaikwad., 2013]

Parameters	**Properties**
Halflife	<10 hrs
Molecular weight	<400 dalto
Dose	Less than 20mg/day
Skin reaction	Non irritatin and non sensitizing
Melting point	<200degree c
pH of the aqueous standard solution	5-9
Partition coefficient	1 to 4
Oral bioavailability	Low
Aqueous solubility	>1 mg/ ml

TABLE NO 4: VARIOUS DRUG USE IN TRANSDERMAL DRUG DELIVERY:

Name of Drug	**Class**	**Polymer use**	**Results**	**Reference**
Ethinylestradiol and	hormones	Eudragit RL-100	Successfully	**Agrawal and**

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medroxyprogestrone acetate		Eudragit RS-100	developing and which shows postcoital antifertility Activity.	**Pruthi., 2011**
Tonoxicum	NSAID	Eudragit-130D-55	Sustained release characteristics of drug	. **Demiana and Nesseem., 2011**
Naloxane	Opoid antagonist	HPMC	Safe and effective delivery of drug with minimal possible side effects.	**Panchagnula et al., 2005**
Ketoprofen	NSAID	Na- polyacrylate	Effective transdermal patch	**Shinkai et al., 2008**
Tacrine	Cholinesterase inhibitor	Ethyl cellulose	Increase therapeutic efficacy and flux.	**Sathyan et al., 1995**
Primaquine	Antimalarial	Ethyl cellulose	Increase release of drug and therapeutic efficacy	**Mayorga et al., 1997**
Clonazepam	Anticonvulsant	carbapol	By increased stability of drug we can get more efficacy.	**Shin et al., 2005**

3.4 RELEASE LINERS

During storage of the patch it is necessary to it covered by a protective liner which is removed and discarded before the application to the skin. So, liner is directly get in touch with transdermal drug

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delivery system and should be chemically stable. The release liner is generally composed of a base like (polyethylene, polyvinylchloride) and coating of release layer made up of silicon, Teflon. Other materials are also used for TDDS as a release liner includes polyester foil and metalized laminate **[Kandavilli et al., 2002].**

3.5 BACKING

Backings are the substances which are used to improve appearance, flexibility and occlusion; some of the examples of backings are polyester film, polyethylene film and polyolefin film, and aluminum vapor coated layer **[D'Arcy., 2006]**

3.6 OTHER EXCIPIENTS

Other excipients are also used in the transdermal drug delivery system, solvents like chloroform; methanol, acetone, isopropananol, and dichloromethane are used to dissolve and serve as reservoir of drug molecule. Also plastisizers are used to provide plasticity of transdermal drug delivery**. [Gupta and Chokshi., 2011]**

4. FACTOR AFFECTING TRANSDERMAL DELIVERY SYSTEM: [Ravi et al., 2011], [Srilatha et al., 2016], [Vyas and khar. 2002]

4.1 Skin condition:

Skin is the largest organ in human body, provides ultimate structure of human body. It acts as barrier and prevents permeation of various agents like acids alkali and other toxic substances. But many solvents can be able to open the complex dense structure of the skin and easily pass through the skin. The intact skin itself acts as barrier however several agents like acids, alkali cross the barrier cells and penetrates through the skin. Many solvents open the complex dense structure of stratum corneum. Solvents like methyl alcohol, chloroform take away macromolecule fraction, forming artificial shunts through those drug molecules will pass simply**.**

4.2 Skin age

The skin of young adults is more permeable as compare to adult skin**.** In case of Children, skin shows toxic effects because the skin surface area is greater per unit body weights, thus when potent drug like steroids, boric acid, hexachlorophene are applied into skin it will show more toxic effects.

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4.3 Blood supply

Blood is a connective tissue that circulates around all parts of the body and carries all the blood components from one compartment to another like central compartment to peripheral compartments. As blood circulates in peripheral compartments so it cans affect transdermal drug absorption and biological activity.

4.4 Skin metabolism

Skin also takes parts metabolism of various drugs. Metabolism of drugs by skin is an important parameter for permeation of drugs like steroids, hormones, chemical carcinogen etc.

Physicochemical factors:

4.2.1 Hydration of skin

When skin is allow come in contact with water then the permeability of the skin is increases. So, hydration of skin is most important. To provide skin hydration humactant is use in the transdermal and dermal formulation.

4.2.2 Temperature and pH

Skin permeation can be improved ten times with variation of temperature. If the temperature decreased it will allow to decreased diffusion coefficient. Similarly weak acid and weak bases dissociated depending on PH, pka or pkb. Thus temperature and ph play an important role for skin permeation.

4.2.3 Diffusion coefficient

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

4.2.4 Drug concentration:

If the drug concentration is higher at the barriers site it will allows the concentration gradients high at the barrier site, so more drug diffuse through the skin barrier.

4.2.6 Molecular size and shape:

Absorption of drug molecule is inversely proportional to molecular weight, if the molecule less it can easily penetrate the skin as compare to larger molecule. So, molecular size should be less to get better drug penetration.

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4.3 Environmental factors: [Singh et al., 2010]

4.3.1 Sunlight:

When human skin comes in contact with sunlight in presence of sunlight it can allow the blood vessels to become thinner bad lads to formation of minor trauma.

4.3.2 Cold Season:

In cold seasons, human skin become excessively dry and leads to formation of rashes. Dryness of skin can be prevented by application of moisturizer, sunscreen and taking of large volume of drinking water.

5. VARIOUS APPROCHES USE TO DEVELOPMENT OF TRANSDERMAL DELIVERY SYSTEM

Drug in adhesive system:

5.1 Single layer drug in adhesive: [Mali AD., 2015]

The adhesive layer which is surrounded by linear layer and backing layer is the main part of this system which holds the drug and entire various layers. This layer has greater importance which play important role to release of drug into different layer of skin. Drug release is mainly follow diffusion mechanism through the skin. **[Jatav et al. 2011]**

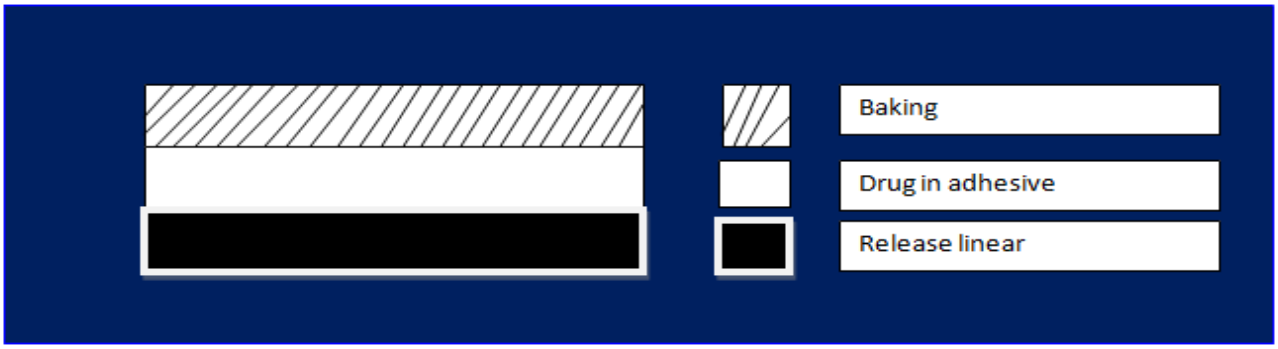

Figure 6: single layer adhesive transdermal delivery system.

5.2 Multi layer drug in adhesion:

The multi-layer drug-in adhesive patch is also similar to the single-layer system. In this system having two adhesive layers is the main part of this system which holds the drug and entire various

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layers **Fig-7.** One of the layers provides fast release of the drug and other layer is for sustained release form reservoir**. [Dhiman et al., 2011]**

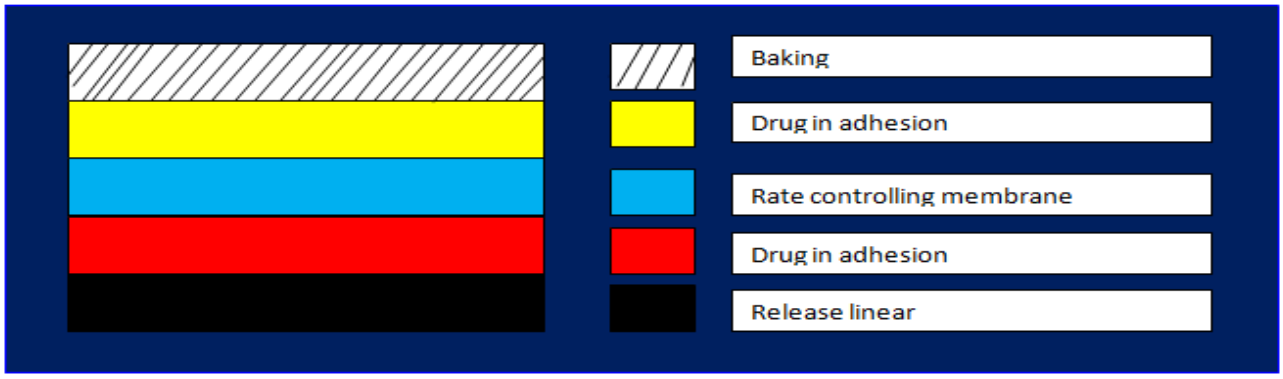

Figure: 7 multi layer adhesive transdermal delivery system.

5.3 Reservoir:

Unlike the single layer and multilayer adhesive systems, the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer, In **Fig-8** in this type of system the rate of release is zero order. **[Joshi et al., 2008]**

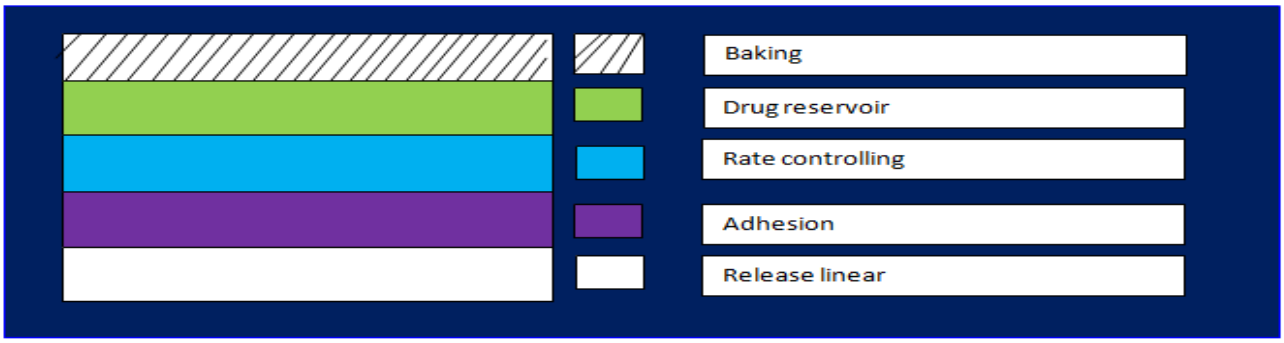

Fig: 8 schematic representation of reservoir transdermal delivery system.

5.4 Matrix:

The Matrix system design as shown in **Fig-9** has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlying it. These types of patches are also known as monolithic device.

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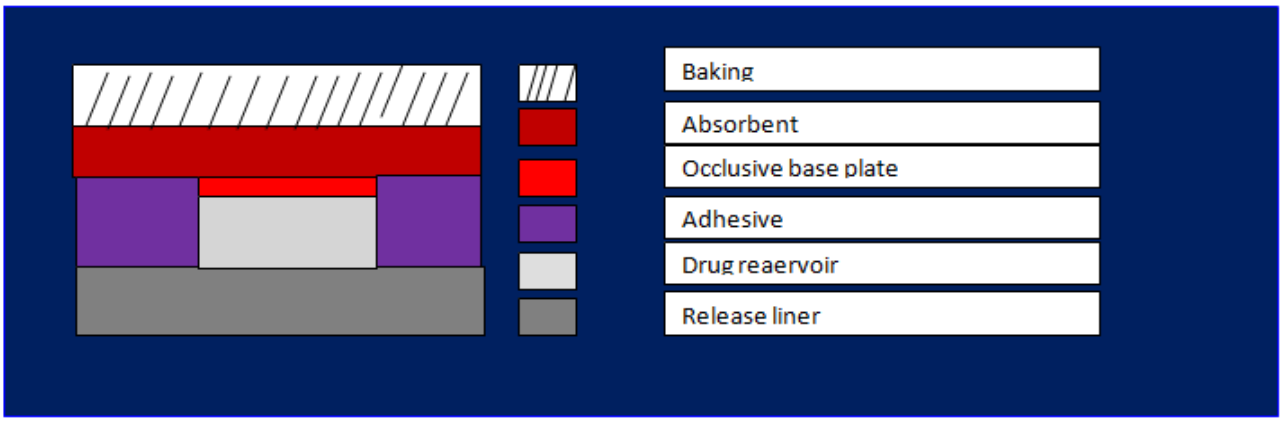

Figure 9: schematic representation of matrix transdermal delivery system.

7. DOSAGE FORMS USED FOR TRANSDERMAL AND DERMAL DRUG DELIVERY

a) **TRANSFEROSOMES**

Dosage form	Materials use	Active substances	Results	References
	Sodium citrate, Tween 80, Span 80 HCL and methanol phosphatidylcholine (soya 95%) Sodium hydroxide and potassium dihydrogen phosphate	Sildenafil	*In-vitr* permeation study of drug loaded transferesomes was done and which showed five times more permeation as compare to drug loaded with suspension.	**Tarek and Ahmed., 2014**
	Phosphatidyl choline (Phospholipon 90G), Sodium deoxycholate	Piroxicam	The drug loaded transfersomal gel showed a significantly higher cumulative drug permeation and flux than the drug solution and conventional gel.	**Shaji and Lal., 2014**
	Human insulin, soya lecithin cholesterol,sodium deoxycholate, Tween 80, dimethyl sulfoxide	Insulin	*In-vitro* permeation study Of insulin loaded transferosomal gel was done, Which showed the good skin permeation and use for the treatment of insulin dependent diabetes	**Malakar et al., 2012**

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			mellitus	
	Phospholipids like Phospholipon (90G and 90H) and Lipoid (S-100, E-80), Cholesterol hemisuccinate, Sodium cholate and sodium deoxy cholate, Carbopol 934P, Carbopol 971P and Carbopol 974P	Raloxifene hydrochlorid	Transferosome loaded with sodium cholate which increases the flexibility of transfersomes allow permeating easily through skin. The initial release obtained was faster than later time points.	**Joshi et al., 2018**

across human cadaver skin resulted in enhanced transdermal flux Permeation studies of indinavir across human cadaver skin resulted in enhanced transdermal flux

from ethanolic liposomes that was

b) LIPOSOME:

Dosage form	**Materials**	**Active substance**	**Results**	**References**
	Soya phosphatidylcholine (soya PC) (99% pure) and phosphotungstic acid,triple-distilled water	Indinavir	Indinavir loaded ethanolic liposome shows better skin permeation in human cadaver skin as compare to ethanolic drug solution, conventional liposomes, or plain Drug solution.	**Dubey et al., 2010**
	Soyaphosphatidylcholine (PC), cholesterol, Sephadex-G-50, Triton X-100, Span 40, 60, and 80, Rhodamine red-X 1,2 dihexadecanoyl-sn-glycero-3-phosphoethanolamine trimethylammonium salt and Ethanol, chloroform,	propranolol hydrochloride	Elastic liposomal formulation loaded with propranolol hydrochloride shows better transdermal flux, higher entrapment efficiency, ability to –penetrate easily and increased effectiveness for transdermal	**Mishra et al., 2007**

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	and xylene		delivery as compared to liposomes	

c) ETHOSOME

Dosage forms	Materials	Active substance	Results	Reference
	Ciclopirox olamine,ethanol, Lipoid S PC-3	Ciclopirox olamine	Etosomal formulation loaded with ciclopirox olamine shows better stability and entrapment efficiency and also provide targeted therapy for dermal and transdermal delivery.	**Girhepunje et al., 2010**
	Curcumin, Soya lecithin, Cholesterol and Ethanol	Curcumin	Curcumin loaded ethosomal formulation provides better entrapment efficacy so, manimly use for treatment of pain via transdermal delivery system.	**Pathan et al., 2018**
	Phosphatidylcholine, Absolute ethanol	Valsartan	Valsartan loaded ethosomal hydroalcoholic formulation, showed higher penetration power without rupturing normal skin structure, also *invivo* study prove that it provide better bioavailability.	**Bhosale and Avachat., 2013**
Ethosome	Ranolazine, Phospholipid (Phospholipon 90G),	Ranolazine	Ranolazine loaded ethosomal formulation showed	**Bisht ei al., 2017**

	Absolute ethanol		better skin penetration and therapeutic efficacy as compare to conventional formulation with advantages of lowering frequency of dosing.	
	Soya phosphatidylcholine (99%) and phosphotungstic Acid, Rhodamine Red-X 1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine trimethylammonium salt	Melatonin	Melatonin loaded ethosomal formulation increase transdermal flux, decrees lag time, higher entrapment efficiency and low skin irritation, so this delivery system could be effective transdermal delivery Of melatonin.	**Dubey et al., 2007**

	Vancomycin hydrochloride, phosphatidylcholine and Stearylamine, Potassium dihydrogen phosphate, Disodium hydrogen phosphate and Sodium chloride	Vancomycin hydrochloride	Ethosomal formulation loaded with vancomycin hydrochloride showed better entrapment efficiency and penetration power, so this formulation is good too, for transdermal and dermal delivery.	**Mohammed et al., 2014**
	Cryptotanshinone, Soybean	Cryptotanshinone	Ethosomal formulation	**Yu et al. 2016**

	phosphatidycholine, Oleic acid and Carbomer 974, Polyethylene glycol 400 (PEG-400), Trypsinase		loaded with Cryptotanshinone showed better loading and entrapment efficacy, skin permeation and therapeutic efficacy.	

d) NANOPARTICLES:

Dosage form	**Materials**	**Active substance**	**Results**	**Reference**
Nanoparticles	Poly(lactide-co-glycolide), PLGA, polyvinyl alcohol (PVA), indomethacin, trehalose dehydrate and flufenamic acid, Physiological saline	Indomethacin (IM) and coumarin-6	*In-vivo* study Indomethacin and coumarin-6-loaded PLGA nanoparticles were done which provides more effective delivery to blood , so this formulation can be use for systemic delivery of drug through skin.	**Tomoda et al., 2012**
	Halobetasol propionate,Glycerol monostearate, Isopropyl alcohol, acetonitrile (HPLC grade), triethanolamine, methyl and propyl paraben	Halobetasol propionate	Halobasterol loaded solid lipid nanoparticles showed better skin hydration and skin penetration power.	**Bikkad et al., 2014**
	Flurbiprofen,Trimyristin, Captex 355, Soy phosphatidylcholine, Texturant Systems . Tween 80 and dialysis membrane-70, Carbopol 934, Xanthan gum, hydroxyl propyl	Flurbiprofen	Flubriprofen loaded nanoparticls showed better penetration power and effective delivery through the skin.	**Bhaskar et al., 2009**

	cellulose,Chitosan			
	Sildenafil citrate, Compritol 888 ATO, Precirol ATO 5, Labrasol, Gelucire 44/14 and Sedefos, Plurol stearique, Cholesteryl stearate and Phosphatidylcholine, Stearylamine and dihexadecyl hydrogen Phosphate, Poloxamer 188	Sildenafil citrate	Solid lipid nanoparticles loaded with sildenafil citrate provide sustained drug release with better bioavailability. . .	**Hosny et al., 2015**

8. SOME MARKETED FORMULATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Product name	**Drug**	**Manufacturer**	**Indication**	**References**
Habitraol	Nicotine	Novartis	Smoking cessation	**Kharat and bath ., 2016, srilatha et al., 2018**
Catapress-TTS	Clonidine	Alza/Boehinger ingelheim	Hypertension	
Butrans	Buprenorphine	Mundi pharma	Opiod analgesic	
Ortro evra	Estradiol	Orthro-Mencil Phrmctls	Birth control	
Combipatch	Estradiol	Noven Inc/ Aventis	Harmone replacement therapy	
Climara	Estradiol	3M Pharmaceuticals/ Berlex Labs	Postmenstrual Syndrome	
Fem Patch	Estradiol	Parke-Davis	Postmenstrual syndrome	
Prostep	Nicotine	Elan corp	smoking cessation	

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CONCLUSION:

To overcome the problems associated with the oral delivery route, transdermal drug delivery systems are utterly used as an alternative route especially focusing improvements in the elegance, dosage flexibility and patient compliance. This scenario surely remains continued in the future and hence leads to more advancement of modern techniques involved for loading a bioactive in TDDS for overcoming the problems associated with the barrier properties of the skin.

REFERENCE:

1. Gantwerker EA, Hom DB. Skin: histology and physiology of wound healing. Clinics in plastic surgery. 2012;39:85-97.
2. Lee SH, Jeong SK, Ahn SK. An update of the defensive barrier functions of skin. Yonsei medical journal. 2006 Jun 30;47(3):293-306.
3. Yun MY, Bae EY, Lee SW, Yim SH, Ly SY, Choi HJ. Anti-photoaging effect of skin cream manufactured with ziyuglycoside I isolated from Sanguisorba officinalis on ultraviolet B-induced hairless mice. Bioscience, biotechnology, and biochemistry. 2019 Apr 20:1-8.
4. Roy SD, Gutierrez M, Flynn GL, Cleary GW. Controlled transdermal delivery of fentanyl: Characterizations of pressure-sensitive adhesives for matrix patch design. Journal of pharmaceutical sciences. 1996 May;85(5):491-5.
5. Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of Controlled Release. 2012 Nov 28;164(1):26-40.
6. Nastiti C, Ponto T, Abd E, Grice J, Benson H, Roberts M. Topical nano and microemulsions for skin delivery. Pharmaceutics. 2017;9(4):37.
7. Zhai Y, Zhai G. Advances in lipid-based colloid systems as drug carrier for topic delivery. Journal of controlled release. 2014 Nov 10;193:90-9.
8. .Prausnitz MR, Langer R. Transdermal drug delivery. Nature biotechnology. 2008 Nov;26(11):1261..

9. Davidson A, Al-Qallaf B, Das DB. Transdermal drug delivery by coated microneedles: Geometry effects on effective skin thickness and drug permeability. Chemical Engineering Research and Design. 2008 Nov 1;86(11):1196-206.
10. Lee S, McAuliffe DJ, Flotte TJ, Kollias N, Doukas AG. Photomechanical transcutaneous delivery of macromolecules. Journal of investigative dermatology. 1998 Dec 1;111(6):925-9.
11. Mueller J, Oliveira JS, Barker R, Trapp M, Schroeter A, Brezesinski G, Neubert RH. The effect of urea and taurine as hydrophilic penetration enhancers on stratum corneum lipid models. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2016 Sep 1;1858(9):2006-18.
12. Chen W, Li H, Shi D, Liu Z, Yuan W. Microneedles as a delivery system for gene therapy. Frontiers in pharmacology. 2016 May 26;7:137
13. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nature reviews Drug discovery. 2004 Feb;3(2):115.
14. More, S., Inde, A., Jadhav, A. and Jadhav, A., 2012. Journal of Pharma Research
15. Mehta R. Topical and transdermal drug delivery: What a pharmacist needs to know. Inet Continuing education, InetCE. com. 2004:1-0.
16. Ramteke KH, Dhole SN, Patil SV. Transdermal drug delivery system: a review. Journal of Advanced Scientific Research. 2012;3(1):22-35.
17. Verma A, Jain A, Hurkat P, Jain SK. Transfollicular drug delivery: current perspectives. Research and Reports in Transdermal Drug Delivery. 2016; 5:1.
18. Valenta C, Auner BG. The use of polymers for dermal and transdermal delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2004 Sep 1;58(2):279-89.
19. Keith AD. Polymer matrix considerations for transdermal devices. Drug development and industrial pharmacy. 1983 Jan 1;9(4):605-25.
20. TABLE –POLYMER
21. Tanwar H, Sachdeva R. Transdermal drug delivery system: A review. Int. J. Pharm. Sci. Res. 2016 Jun 1;7:2274-90
22. . Vyas SP, Khar RK. Submicron emulsions in targeted and controlled drug delivery, Novel Carrier Systems.
23. Malvey S, Rao JV, Arumugam KM. Transdermal drug delivery system: A mini review. Pharma Innov. 2019;8:181-97..

24. Gupta IK, Chokshi MM. Transdermal drug delivery system: an overview. Asian J Pharm Sci. Clinical Res. 2011;1(1):25-43.
25. Joshi K, Selvaduary G. Transdermal drug delivery systems and their use of polymers. San Jose State University, California. Submitted in partial fulfillment of course requirements for MatE 175–Biomaterials.. 2008 Nov 26.
26. Jalwal P, Jangra A, Dahiya L, Sangwan Y, Saroha R. A review on transdermal patches. The Pharma Research. 2010;3:139-49.
27. Keleb E, Sharma RK, Mosa EB, Aljahwi AA. Transdermal drug delivery system-design and evaluation. International Journal of Advances in Pharmaceutical Sciences. 2010 Jul 1;1(3).
28. Table of drug
29. Gaikwad AK. Transdermal drug delivery system: Formulation aspects and evaluation. Comprehensive Journal of Pharmaceutical Sciences. 2013 Feb;1(1):1-0.
30. Agrawal SS, Pruthi JK. Development and evaluation of matrix type transdermal patch of ethinylestradiol and medroxyprogesterone acetate for anti-implantation activity in female Wistar rats. Contraception. 2011 Nov 1;84(5):533-8.
31. Demiana I, Nesseem SF, Eid SS. Development of novel transdermal self-adhesive films for tenoxicam, an anti-inflammatory. Drug Life Sci 2011; 89: 430. 2011;438.
32. Panchagnula R, Bokalial R, Sharma P, Khandavilli S. Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies. International journal of pharmaceutics. 2005 Apr 11;293(1-2):213-23.
33. Shinkai N, Korenaga K, Mizu H, Yamauchi H. Intra-articular penetration of ketoprofen and analgesic effects after topical patch application in rats. Journal of Controlled Release. 2008 Oct 21;131(2):107-12.
34. Sathyan, G., Ritschel, W.A. and Hussain, A.S., 1995. Transdermal delivery of tacrine: I. Identification of a suitable delivery vehicle. *International journal of pharmaceutics*, *114*(1), pp.75-83.
35. Mayorga P, Deharo E, Puisieux F, Couarraze G. Interpretation and prediction of plasma levels of primaquine following transdermal delivery in Swiss mice. International journal of pharmaceutics. 1997 Sep 12;155(1):99-107.

36. Shin SC, Kim HJ, Oh IJ, Cho CW, Yang KH. Development of tretinoin gels for enhanced transdermal delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2005 May 1;60(1):67-71.
37. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems. Pharmaceutical technology. 2002 May;26(5):62-81.
38. D'Arcy Y. Treatment strategies for low back pain relief. The Nurse Practitioner. 2006 Apr 1;31(4):16-25.
39. Gupta IK, Chokshi MM. Transdermal drug delivery system: an overview. Asian J Pharm Sci. Clinical Res. 2011;1(1):25-43.
40. Ravi S, Sharma PK, Bansal MA. Review: Transdermal Drug Delivery of Nicotine. Int J Drug Dev Res. 2011; 3:01-8.
41. Singh MC, Naik AS, Sawant SD. Transdermal drug delivery systems with major emphasis on transdermal patches: A review. J Pharm Res. 2010 Oct; 3(10):2537-43.
42. Mali AD. An updated review on transdermal drug delivery systems. Skin. 2015;8(9).
43. Jatav VS, Saggu JS, Jat RK, Sharma AK, Singh RP. Recent advances in development of transdermal patches. Pharmacophore (An international research journal). 2011 Nov 1;2:287-97.
44. Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int J Pharm Pharm Sci. 2011;3(5):26-34.
45. Joshi K, Selvaduary G. Transdermal drug delivery systems and their use of polymers. San Jose State University, California. Submitted in partial fulfillment of course requirements for MatE 175–Biomaterials... 2008 Nov 26.
46. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The pharma innovation. 2012 Jun 1;1(4):66-75.
47. Ahmed TA. Preparation of transfersomes encapsulating sildenafil aimed for transdermal drug delivery: Plackett–Burman design and characterization. Journal of liposome research. 2015 Jan 2;25(1):1-0.
48. Shaji JE, Lal M. Preparation, optimization and evaluation of transferosomal formulation for enhanced transdermal delivery of a COX-2 inhibitor. Int J Pharm Pharm Sci. 2014;6(1):467-77.
49. Malakar J, Sen SO, Nayak AK, Sen KK. Formulation, optimization and evaluation of transferosomal gel for transdermal insulin delivery. Saudi pharmaceutical journal. 2012 Oct 1;20(4):355-63.

50. Joshi A, Kaur J, Kulkarni R, Chaudhari R. In-vitro and Ex-vivo evaluation of Raloxifene hydrochloride delivery using nano-transfersome based formulations. Journal of Drug Delivery Science and Technology. 2018 Jun 1;45:151-8.
51. Dubey V, Mishra D, Nahar M, Jain V, Jain NK. Enhanced transdermal delivery of an anti-HIV agent via ethanolic liposomes. Nanomedicine: Nanotechnology, Biology and Medicine. 2010 Aug 1;6(4):590-6.
52. Mishra D, Garg M, Dubey V, Jain S, Jain NK. Elastic liposomes mediated transdermal deliveryof an anti-hypertensive agent: propranolol hydrochloride. Journal of pharmaceutical sciences. 2007 Jan 1;96(1):145-55.
53. Dubey V, Mishra D, Jain NK. Melatonin loaded ethanolic liposomes: physicochemical characterization and enhanced transdermal delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2007 Sep 1;67(2):398-405.
54. Girhepunje K, Pal R, Gevariya H, Behera A, Thirumoorthy N. Ethosomes: A novel vesicular carrier for enhanced dermal delivery of Ciclopiroxolamine. Der Pharm Lett. 2010;2(1):360-367.
55. Pathan IB, Jaware BP, Shelke S, Ambekar W. Curcumin loaded ethosomes for transdermal application: Formulation, optimization, in-vitro and in-vivo study. Journal of Drug Delivery Science and Technology. 2018 Apr 1;44:49-57.
56. Bhosale SS, Avachat AM. Design and development of ethosomal transdermal drug delivery system of valsartan with preclinical assessment in Wistar albino rats. Journal of liposome research. 2013 Jun 1;23(2):119-25.
57. Bisht D, Verma D, Mirza MA, Anwer MK, Iqbal Z. Development of ethosomal gel of ranolazine for improved topical delivery: In vitro and ex vivo evaluation. Journal of Molecular Liquids. 2017 Jan 1; 225:475-81.
58. Mohammed MI, Makky AM, Abdellatif MM. Formulation and characterization of ethosomes bearing vancomycin hydrochloride for transdermal delivery. Int J Pharm Pharm Sci. 2014;6:190-4.
59. Yu Z, Lv H, Han G, Ma K. Ethosomes loaded with cryptotanshinone for acne treatment through topical gel formulation. PloS one. 2016 Jul 21;11(7):e0159967.
60. Nanoparticles:

61. Tomoda K, Terashima H, Suzuki K, Inagi T, Terada H, Makino K. Enhanced transdermal delivery of indomethacin using combination of PLGA nanoparticles and iontophoresis in vivo. Colloids and Surfaces B: Biointerfaces. 2012 Apr 1;92:50-4.
62. Bikkad ML, Nathani AH, Mandlik SK, Shrotriya SN, Ranpise NS. Halobetasol propionate-loaded solid lipid nanoparticles (SLN) for skin targeting by topical delivery. Journal of liposome research. 2014 Jun 1;24(2):113-23.
63. Bhaskar K, Anbu J, Ravichandiran V, Venkateswarlu V, Rao YM. Lipid nanoparticles for transdermal delivery of flurbiprofen: formulation, in vitro, ex vivo and in vivo studies. Lipids in health and disease. 2009 Dec;8(1):6.
64. Hosny KM, Aljaeid BM. Sildenafil citrate as oral solid lipid nanoparticles: a novel formula with higher bioavailability and sustained action for treatment of erectile dysfunction. Expert opinion on drug delivery. 2014 Jul 1;11(7):1015-22.

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