WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review on Transdermal Drug Delivery-Patches

Miss. Dahatonde Priyanka Sanjay*, Ms. Khandre Rajashree A.*

Pratibhatai Pawar College of Pharmacy, Shrirampur.
priyankadahatonde2000@gmail.com

ABSTRACT:

The human skin is available surface for drug delivery in to systemic circulation. Skin of an average adult body covers a surface of approximately 70 % to 75 % and receives about one-third of the blood circulating through the body. In the past decades, emerging controlled drug delivery has become increasingly important in the pharmaceutical industry. Transdermal drug delivery system (TDDS-Patches),as provides a means to sustain drug release as well reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form. It delivers a drug through intact skin at a controlled rate in-to thesystemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system .It is a sophisticated complex drug delivery system which is difficult to Formulation and development, some advantages and disadvantages also.

Introduction:

Transdermal drug delivery systems (TDDS) commonly known as patches, which are dosage forms devolved for deliver of a therapeutically effective amount of the drug across a human skin. In direction to deliver therapeutic mediators through the human skin for systemic effects, the all-inclusive morphological, biophysical and physicochemical properties of the human skin are considered. Transdermal delivery provides a leading edge over injectable and oral routes by growing patient compliance, avoiding first pass metabolism respectively. (V.Loyd, et al., 2005) Transdermal delivery are not only Provides controlled, constant administration of the drug it also allows continuous input of drugs with short biological Half-lives and eliminates pulsed entry systemic Circulation, which often causes undesirable side effects. Several important advantages of transdermal drug delivery Are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of stable plasma Level of the drug. The first Transdermal system, Transdermal SCOP was approved by Food and drug admiration in 1979 for the inhibition of Nausea and vomiting related with ravel, particularly by Sea.(G.Shingade, et al., 2012),A Transdermal drug delivery systems is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and exact rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a distribution process the drug are pass in the bloodstream directly through the skin. (V.Yadav, et al.,2012).

History:

The first TTDS product containing scopolamine (Name:-Transderm Scop) were marketed in a year 1979. Aninvention was used finished 3 days for the treatment of motion illness at marine. The development of TransdermScōp has confirmed that transdermal distribution of scopolamine could reduce some side effects of Scopolamine, Compared with oral administration. Accordingly, nearly other APIs wasmanufactured into transdermal dosage forms. Following some are the scopolamine-containing product, Catapress-TTS, a clonidine-loaded patch, was released in year 1984 used for treating of hypertension. Supplementary transdermal products was also developed and promotedin year 1986 (Estraderm) and 1990 (Harbitrol and Duragesic). From year 1991 until year 2004, promoted transdermal products was controlled by hormone-contain contraceptives, estradiol, testosterone, ethynyl estradiol, norelgestromine, levonorgestrel. It is suggestin beginning, transdermal products was futuremainly delivery of hydrophobic drugs, composed of sterols.(Prausnitz MR, et al 2009).

Year 2005 until 2013, several altered types of drugs be found also formulated in the transdermal products, such as selegiline, methylphenidate, fentanyl, diclofenac epolamine, with combination of menthol/methylsalycylate, sumatriptan. Positively, Ionsys and Zecuity are main examples of transdermal product which joined with iontophoresis to enhancing drug absorption of transdermal patches. Currently , some transdermal products, such as asenapine for schizophrenia and ethinyl estradiol and levonorgestrel, was approved by US-FDA in year 2019 and year 2020, correspondingly, A development of individually transdermal product has been predeceased with advances knowledge or understanding of transdermal drug delivery, occasioning today, in a wide variety of transdermal products open to patients and clinicians. For ensure development it wascommanding to understand a range of technologies that may be useful for attractive drug immersion via the skin. (FDA, et al 2020).

Advantages Transdermal Drug Delivery System:

- Deterrence of first pass absorption of drugs in to body.
- Reduces the plasma absorption levels of drugs in to the body with lessened side effects.
- Reduction of fluctuations in plasma levels of drugs in to the body, Utilization of drug applicants with short half-life and short therapeutic index.
- Easy exclusion of drug delivery in case of toxicity to patient.
- Reduction of dosing rate an enhancement of patient agreement.
- Transdermal medications deliver a steady mixture of a drug over and extensive period of time. Adverse effects and therapeutic failure frequently associated with intermittent dosing can also be avoided through TDDS.
- Transdermal delivery are improve the therapeutic rate of many drugs via escaping specific problems linked with the drug. Like GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
- Due to above benefit, it is likely that an equivalent therapeutic effect can be prompted via transdermal drug input with a lower day-to-day dose of the drug than is essential, if like the drug is given orally.
- The basic medication routine leads to better patient compliance and compact inter and intra-patient variability.

(Wang M et al 2018).

Disadvantages of Transdermal Drug Delivery System:

- Thedrug that needs high blood levels can-not be controlled and may unfluctuating cause irritation or sensitization of the skin can be occur.
- The bonding agent may not adhere well to different types of skin and may be painful to wear.
- High price of the product is also a chief disadvantage for the extensive acceptance of this product.
- Properties that influence Transdermal Delivery.
- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response.

(Ma et al J. 2017)

Transdermal route and drug delivery views:

- **The largest organ of human Skin:**

The skin amajor organ of the human body which covers a external area of around 2 sq.m. Andaccepts about one third a blood circulation throughout the body. A serves as a penetrabilityblockade against the transdermal absorption of various biochemical, organic agents. A one of the most readily obtainable organs of the human body with a thickness of uncommon millimeters (2.97 to 0.28 mm).

Function of skin:

- Parts the underlying blood circulation system from the outdoor environment.
- Helpsasbarrieragainstphysical or chemical and microbiological outbreaks.
- Performances as a control in retaining body temperature.
- Acting role in the regulation of blood pressure.
- It is help to protects against the penetration of UV rays.
- Skin having main factor to defining the various drug distribution aspects like infusion and absorption of drug through the dermis. A diffusional resistance of the skin a greatly needy on its anatomy and ultrastructure of skin . (H.Tanwar,et al., 2016).

- **Structure of the human Skin:**

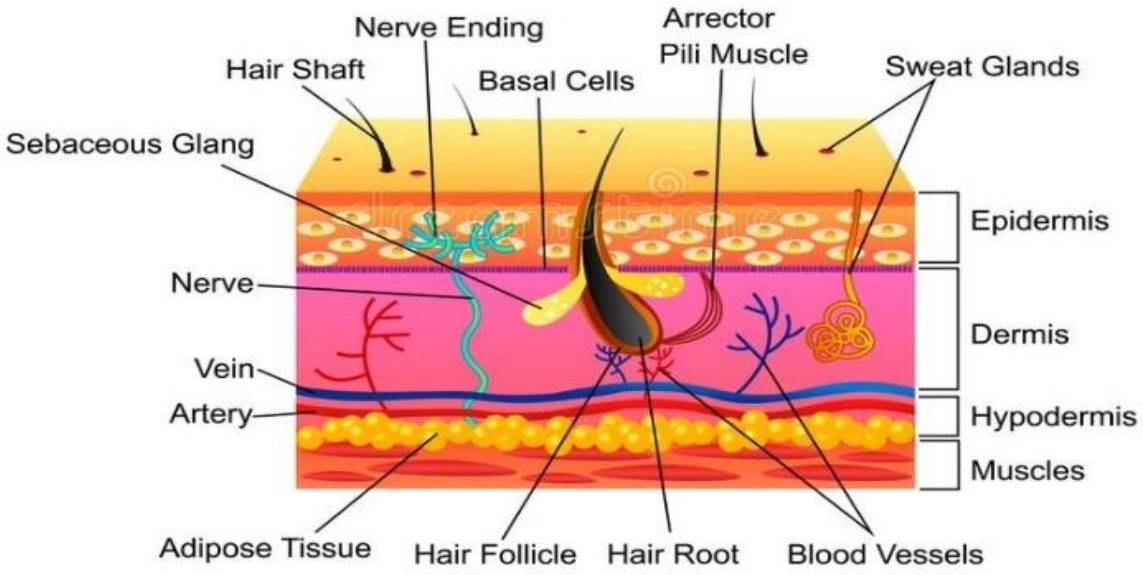


Fig-1: Structure of human Skin

❖ **Anatomy and Physiology of human Skin:**

The building of human skin (fig.2) can be characterized into three layers:

- Epidermis
- Dermis (Derma)
- Hypodermis

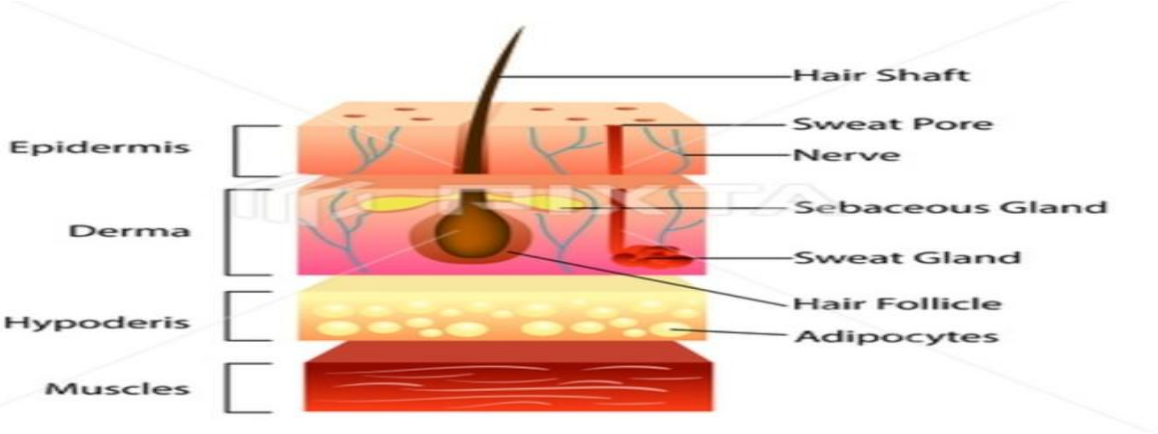


Fig-2: Structure of layers of Skin

❖ **The Epidermis:**

The epidermis stands a continually self-renewing and stratified squamous epithelium cover the entire outside surface of the human body and primarily collected of two parts, the living and viable cells of the Malpighian layer (viable epidermis) & the lifeless cells of the stratum corneum normally referred to as a the horny layer, viable epidermis aadditional. The complex epidermis is a varies in thinness, depending up on the cell size &number of cell layers of epidermis, extending from 0.8 mm on palms and soles downcast to 0.06 mm on the eye-lids. This is the outermost layer in skin likewisenamed as Stratum corneum. About 10 mm thick at what time dry but swells to several periods this thickneswhen completely hydrated. It contains 10 to 25 layers of lifeless, keratinized cells namedas coenocytes. It is flexible then relatively impermeable. The horny layer a principal barrier for diffusion of drug. The construction of horny layer may be modeled like structure. In a model, the keratinized cells meaning as protein "bricks" embedded in lipid "mortar." The lipids are agreed in multiple bilayers. There is adequate amphiphilic substantial in the lipid segment, which as polar free fatty acids, cholesterol, for maintaining a bilayer form. Viable epidermis a situated beneath the stratum corneum and varies in thickness from 0.06 mm eyelids to 0.8 mm in palms. Going inside, it consists of various layers a stratum a lucidum, a stratum granulosum, a stratum spinosumand the stratum basal, In the basal layer, mitosis of the cells continually renews the epidermis and this propagationrewards the loss of lifeless Horney cells from the skin external surface. The cells twistedby the basal layer move externalthey alter morphologically &histochemical, suffering keratinization to form the outmost layer of stratum. (R.Wilson, et al.)

❖ **Classified into four distinct layers**

- A Stratum lucidum.
- A Stratum granulosum.
- A Stratum spinosum.
- A Stratum basale.

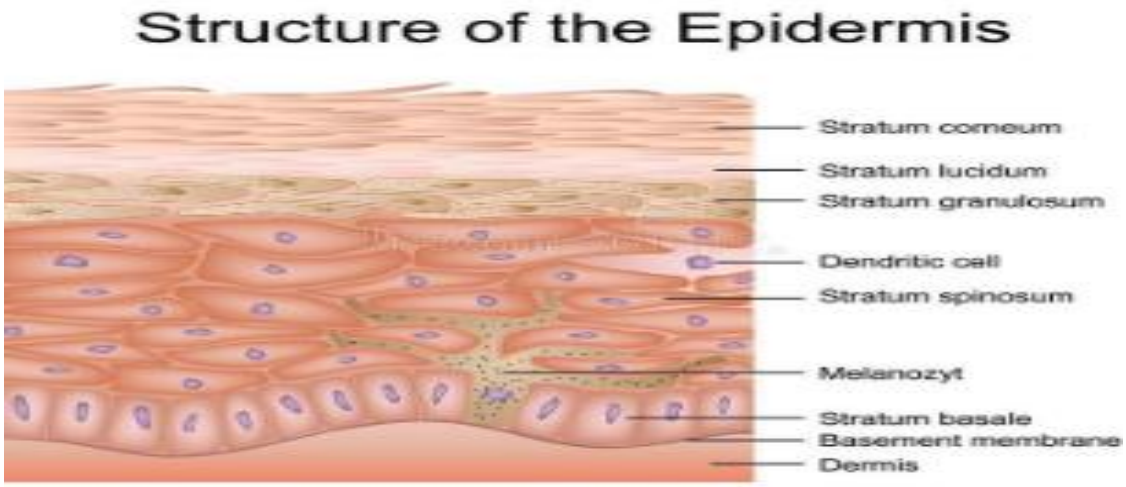


Fig-3: Structure of Epidermis

❖ **A Viable epidermis:**

This is located beneath the stratum corneum & varies in thinness from 0.06 mm on the eyelids 0.8mm on the palms. Going inwardly, it contains of numerous layers as a stratum lucidum, a stratum granulosum, a stratum spinosum, and thestratum basale. on thebasale layer, mitosis cells are constantly renews the epidermis and this propagation compensates the loss of lifeless horny cells from the skin superficial. As cells twisted by the basale layer move outward, they itself change morphologically and histochemical, undergoing keratinization to form the innermost layer of stratum corneum.

❖ **A Stratum corneum:**

It is the outermost layer of human skin called as horny layer. The rate warning barrier that restricts the inner and outer movement of thechemical elements. A barrier nature of the horny layer hinge onjudgmentally on its constituents, 75-80% (Proteins), 5-15% (lipids) and 5-10% (ondansetron) material on a dry weight.Stratum corneum asaround 10.00 mm thick after dry but swells to several periods when it is fully hydrated. It supple but comparativelyresistant. The manner of horny layer may a modeled as a wall like structure with protein bricks and lipid mortar. It isinvolves of horny skin cells,which are linked via desmosomes (protein-rich appendages of the cell membrane). The corneocytes is embedded in a lipid matrix which plays a importanttitle role in defining the penetrability of elementcrossways in the human skin.

❖ **Dermis:**

A Dermis is 3.0 mm to 5.0 mm layer and contains of a medium of connective tissue thatencloses bloodvessels and lymph vessels and nerves. The cutaneous blood amount has essential meaning in regulation of body temperature of body . It furthermoredelivers nutrients and oxygen in skinwhile removing poisons and left-over products. Capillaries reach to within 0.20 mm of skin superficial and provide sink conditions for numerous molecules all-pervading the skin barrier. A blood supply thus retains the dermal attentiveness of a permeate very low and the subsequent concentration change across the epidermis deliversimportantattentiveness gradient for transdermal infusion. (K. Jain et al.,)

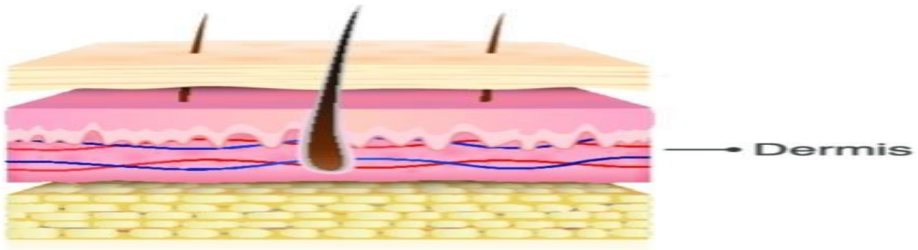


Fig-4: Structureof Dermis

❖ **Hypodermis:**

The hypodermis as subcutaneous fat tissue supports the dermis and epidermis. A serves as a fat storing area. A layer supports to regulate temperature, provides nutritional support and mechanicalsecurity to human body. This layer transports principal blood vessels and nerves to the skin and may encompassphysical pressure organs. For transdermal drug delivery, drug has to enter through all three layers and reach in systemic circulation of human body.(D.Kumar, et al.,).

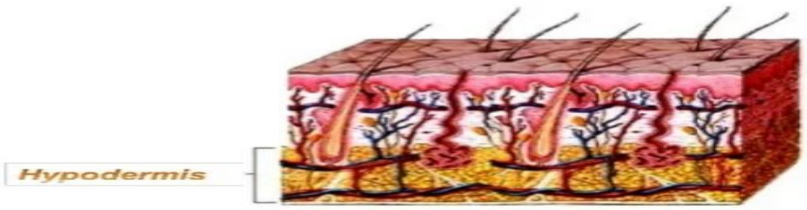


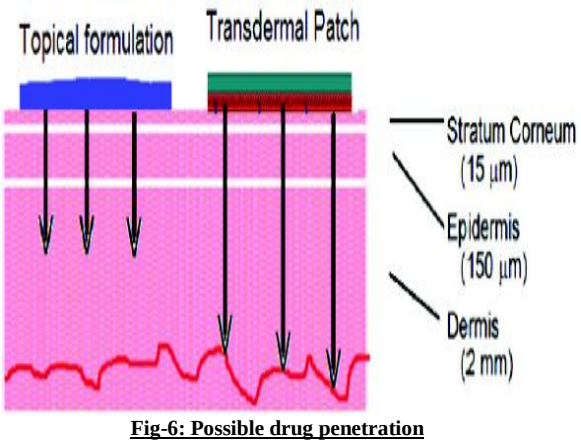
Fig-5: Hypodermis

Basic Principle of Transdermal permeation:

A considerate of the kinetics of the skin infusionit is important for growth of successful Transdermal drug delivery systems. In order to evaluate any Transdermal drug delivery systems, the control of percutaneous involvement of molecules a very important step (Donnelly R.F. et al. 2012). Percutaneous absorption isdiffusion of constituents in a various layers of human skin and infusion across in to the human skin ina systemic passage, percutaneous absorption of particles is a stage wise process connecting.(Dhote V., Bhatnagar P et al. 2012).

A transdermal infusionis based on passive spreading. Human skin is the most intensive and readily available organ of the body as individual a fraction of millimeter of tissue separates it is surface from the fundamental capillary network. The release of a therapeutic agent from a formulation applied on to the skin surface and its transport to the systemic circulation is a multi-step process, As per following step are includes in trans dermal penetration.(Wiedersberg S et al. 2013).

- Dispersion of the drug from drug to the rate controlling membrane of skin.
- Dissolution with-in and release from the formulation in to the skin.
- Sorption by stratum corneum &diffusionfrom side to side viable epidermis of skin.
- Acceptance of drug by the cell and capillary network in the dermal papillary layer.
- Outcome on the target organ of body.
- Dividing into the skin's outermost layer, the stratum corneum.
- Dispersion through the stratum corneum, principal via a lipidic intercellular pathway.



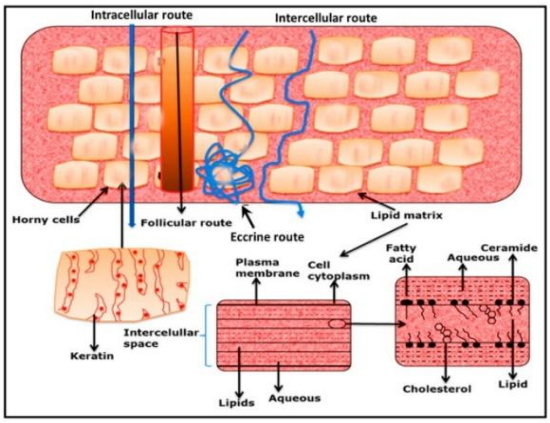
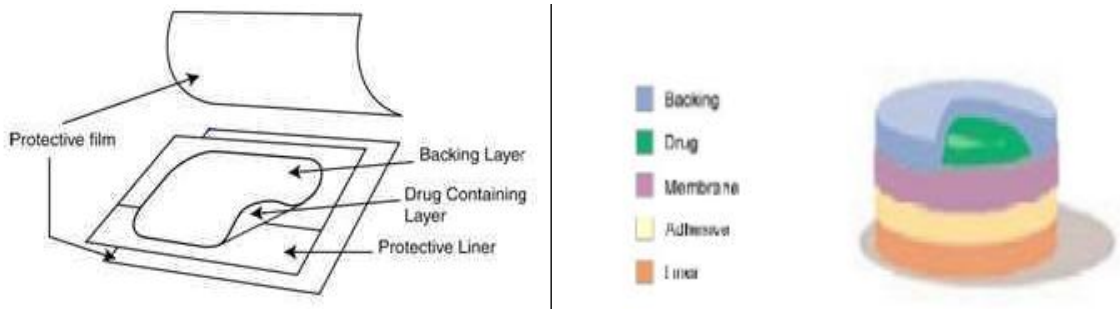


Fig-6: Possible drug penetration

TDDS Patches:

❖ **Components to a transdermal patch are following:**

- **Liner/ Protecting Film** - Defends the patch during storage. Ainsert is detachedbefore to application on site.
- **Drug** –A drug are the solution in direct interaction with release liner.
- **Adhesive** - Serves to stick to the mechanisms of the patch composedsideways with stick to the patch to the human skin.
- **Membrane** - Wheels the release of the drug from the reservoir and multi-layer patches.
- **Backing Film–**It help to protects patch from the outer/external environment.
- **Permeation Enhancer** – This is the infusionorganizers for drugs, which is increase delivery of drug in to human skin.
- **Matrix Filler** - Make available bulk to the matrix, and approximately act as matrix solidifying agents.
- **Other components include**: Stabilizer (anti-oxidants), Preservatives are used to improving the life cycle of drug.



❖ **Types of trans dermal patches :**

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

A adhesive layer of this classification also contains the drugs. A type of patch the adhesive layer not only serves to stick to the various layers composed, along with acomplete system of the skin it is also liable for the discharging of the drug in to human skin. The adhesive layer enclosed by a temporary liner and backing. It characterizedin to inclusion of the drug nonstop within the skin-contacting adhesive placed on--to the epidermis.(Willams and Barry, et al 2004)

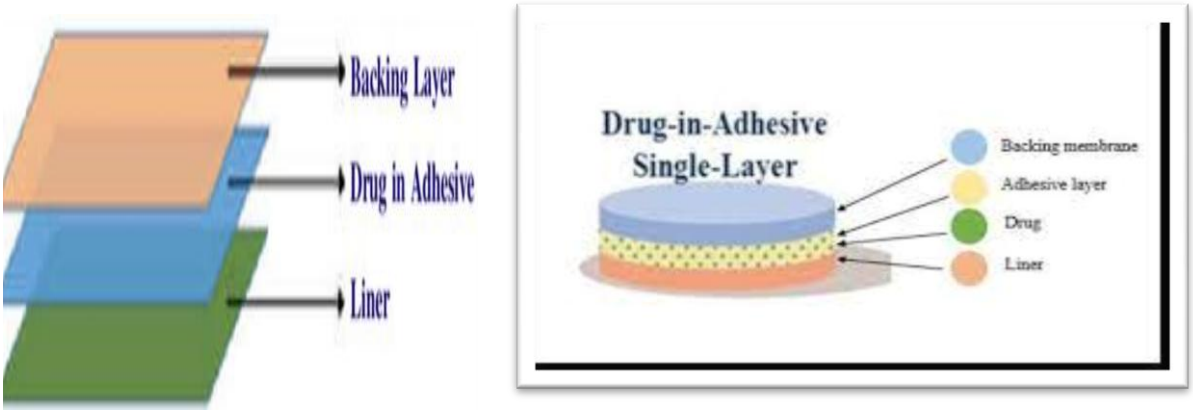


Fig-8: Single-layer Drug-in-Adhesive

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

The multi-layer drug-in-adhesive patch are similar with the single-layer system, the multi-layer system is dissimilar, however, in that it adds another layer of drug-in-adhesive, typicallyparted by a membrane one of the layers is for instant release of the drug and additional layer is for regulator release of drug from the reservoir. A patch also has a impermanent liner-layer and a permanent backing. The drug release from this be subject to on membrane penetrability and dispersal of drug molecules and formulation.(Pellet et al., 2003).

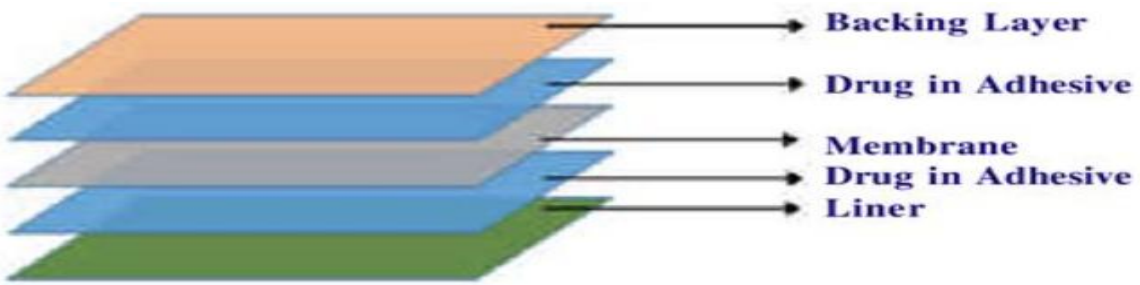


Fig-9:Multi-layer Drug-in-Adhesive

- **Reservoir/membrane controlled:**

It is different than the single-layer and multi-layer drug-in-adhesive systems, the reservoir transdermal system hasisolated drug layer. The drug layer is a liquid sectionholdingthe drug solution and suspensionparted by the glue layer. A drug reservoir is completelysummarized in a shallow sectionshaped from a drug-impermeable metallic or plastic laminate, with a rate-controlling membrane made of a polymer alike vinyl acetate on the external.This patch is also backed by the assistance layer. In this type of system the rate of release is zero order drug release. (Nahid Newaz et al 2013).

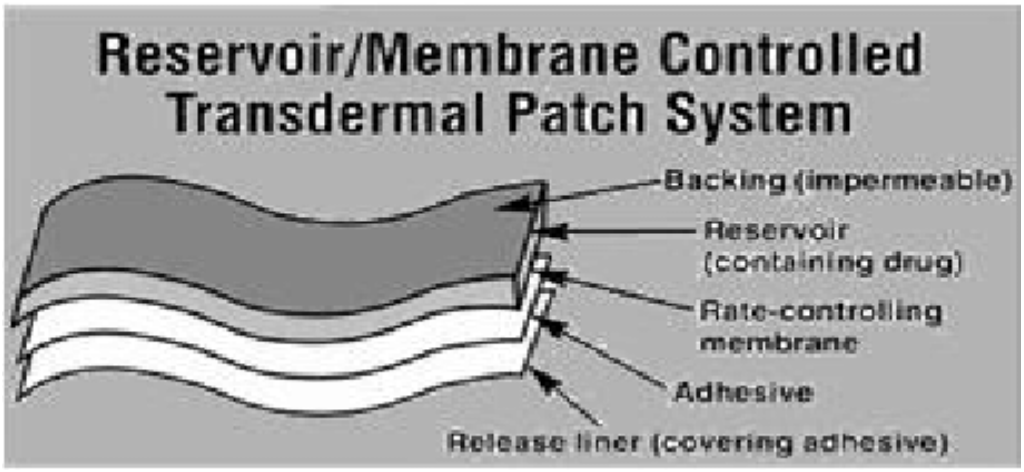


Fig-10:Reservoir/membrane controlled

- **Matrix:**

A Matrix is the systemincludes a drug layer of a semisolid matrix encompassing a drug resolution and suspension. A adhesive layer in this patch surrounds the drug layer partly covering it,(Pellet et al., 2003).

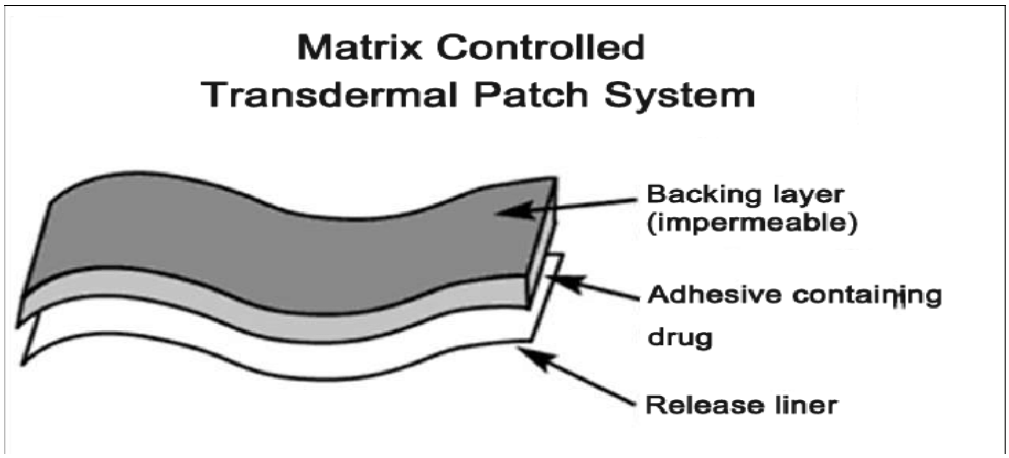


Fig-11: Matrix

- **Drug-in-adhesive system:**
In drug-in-adhesive system drug reservoir is made by dispersing the medication in an adhesive polymer hence spreading of the medicated adhesive polymer by solvent forming or melting on an impervious backing layer. On top of the reservoir, instant adhesive polymer layers are applied for protection purpose.(Brown and Jones, et al 2000).

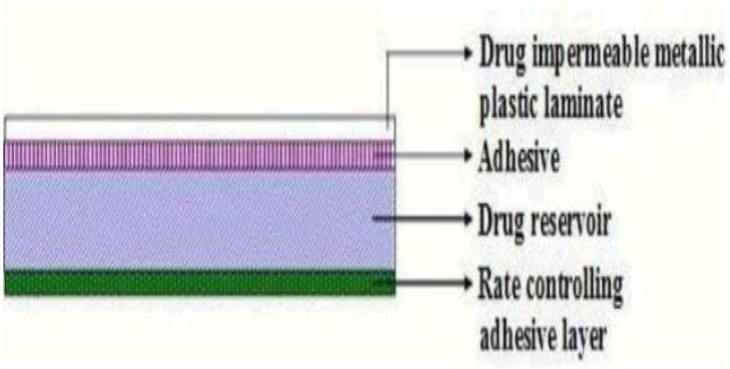


Fig-12: Drug-in-adhesive system:

- **Vapour Patch:**
A avapour patch, the adhesive layer are not only helps to adhere the numerous layers composed but also to release vapour. Vapour patches release important oils for throughout 6 hours and are mostly used for decongestion. Additionalvapour patches on the marketimprove quality of sleep or aid in smoking cessation.

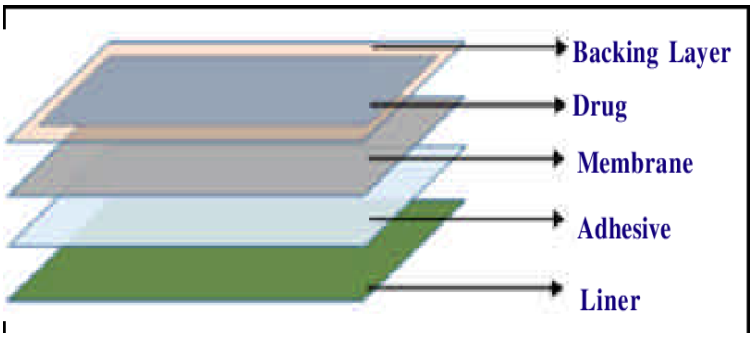


Fig-13: Vapour Patch

- **Micro-resevior system:**
In Micro-resevior systemtype the medication delivery system is a grouping of reservoir and matrix-dispersion system. This the drug reservoir are made by first swinging the drug in a solution of water solvable polymer and so dissolving the solution consistently in a lipophilic polymer to form thousands of unreached microscopic scopes of drug reservoirs. This thermos-dynamically unbalanced dispersion is stable rapidly by promptly cross-linking the complex in situ using cross connecting agents.(Patani and Chien, et al 1999).

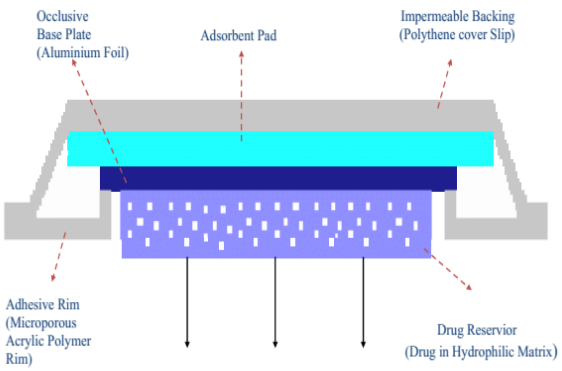


Fig-14: Micro-resevior system

Factors affecting transdermal drug delivery:

A Human skin is awell-organizedshielding barrier. Selecting a candidate drug that is appropriate for creation transdermal preparations can be problematic. Some variables effect the transdermal transport, bioavailability of the drugs as the drug crosses various physical layers of skin. Preferred applicant drugs for transdermal delivery is those with low-slung molecular weight and lipophilicity, which are associate with good solubility and diffusion through the human skin. In addition, drugs that are more unstable and have lower melting points incline to be additional easily formulated into a transdermal patch as (B.Vecchia, et al., 2003). These is partial availability of normally used medications as transdermal preparations. Current advances in approaches for controlling skin diffusion to rise transdermal transport of drugs may permit a wider choice of medications available as TDS. These modulations can be a chemical alteration of the drug molecules or through action on the skin to increaseinfusion. This may involve adjustment of the structure and arrangement of skin lipids and proteins by using methods such as micro needles producing micro abrasions, ultrasound, transdermal drives or delivery through hair follicles. (Benson, et al., 2005; Touitou, et al., 2002).

The operative transdermal drug delivery can be expressed by since three factors as Drug, Skin, and the vehicles. So the factors distressing can be divided in to classes as organic/biological factors and physicochemical factors.

- **Bio chemical factors affecting on TDDS:**
  - **Skin condition/ Skin nature:**Many solvents like chloroform methanol impairment the skin cells and stimulate penetration like Acids and alkalis,Contaminated state of patient alters the skin situations. The undamaged skin is recovering barrier but the above said conditions affect diffusion.
  - **Age of the skin:** Theolder skin is less permeable than young skin. Children are extra sensitive for the skin absorption of the toxins material, hence skin age is the factors disturbing penetration of drug in TDDS.
  - **Blood Circulation:**Blood circulation cam changes in peripheral circulation blood circulation which may affect to transdermal absorption and if outcome.
  - **Application Location/Area:**Nature of stratum corneum, thinness of the skin and vary location to location. These factors affect expressivelydiffusion.
  - **Metabolism of the Skin:** Skin digestshormones, steroids, biochemical carcinogens components and exceptional drugs. On that skin metabolism regulates efficacy of drug infusedover the skin.
  - **Species differences:**A skin thinness, density of adjuncts, and keratinization of skin differclass to class, so disturbs the diffusion. (Deshwal and Verma, et al 2012).
- **Physicochemical factors affecting on TDDS:**
  - **Hydration of skin:**Contact with water the penetrability of skin risesexpressively. Hydration are highestsignificantinfluence increasing the saturation of skin. Hence of humectants are done in transdermal delivery.
  - **Temperature and pH of body:**The infusion of drug rise with temperature deviation. The dispersionnumberreductions as temperature falls. Weak acids and bases dissociate reliant on the pH values. The amount of unionized drug controls the drug absorption in skin. Hence temperature and pH are important factors disturbing drug diffusion.
  - **Dispersioncoefficient:**Saturation of drug may depends on diffusion coefficient of the drug. At asame temperature the diffusion coefficient drug which are depends on properties of the drug, diffusion medium and interaction between them.
  - **Concentrationof the Drug:**The changeare comparative to the concentration gradient across the barrier, concentration gradient which becomplex if the concentration of drug will be additional across the barrier.
  - **Partitioncoefficient:** The optimal K, partition coefficient is essential for respectable action. Drugs through high K are not prepared to leave the lipid helping of skin. drugs with low K is not be permeated.
  - **Molecular Size andshape:** Drug absorption arecontrariwise related to molecular weight, small molecules penetrated faster than largeparticles. Because of barrier coefficient domination, the effect of molecular size is not identified. (Deshwal and Verma, et al 2012).

RECENT RESEARCH DONE IN THE FIELD:

From the snice of the yearlong research activity was carried out and are few are successful on in this field. Limited of the latest research done in the field of transdermal patches:

- **Pain-free monitoring using transdermal patches for diabetic:**
  A first example patch actions about 1cm and arefinishedby means of polymers and thin metal films. 5 cm ×5cmsample array can be clearly seen, their metallic interconnections. When the seal is negotiated, the interstitial liquid, and the biomolecules controlled therein, developsavailable on the skin apparent. Using micro heating elements combined into the physical layer of the patch nearby to the skin surface, a high-temperature warmth pulse can be functional locally, breaking the stratum corneum. During this ablation of process, the skin surface involvements temperatures for small duration. A temperature reducesquickly from the skin superficial and neither the living tissue nor the nerve finishes are affected. This easy and bloodless process results in disruption of a 40–50μm region of the lifeless skin layer, almost the size of ahair follicle, allowing the interstitial fluid to interrelate with the patch's conductorlocations.

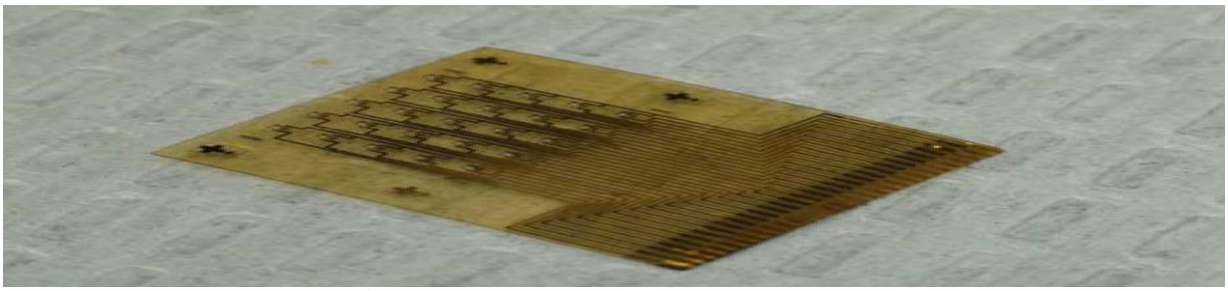


Fig-15:Pain-free diabetic monitoring using transdermal patches

- **Transdermal Patch of used in overactive Bladder:**

  Ainventionare a transdermal patch having Oxybutynin HCl and is permitted in US below the brand title of Oxytrol and in Europe under the brand name of Kentera. OXYTROL are the thin, flexible and clear patch that is functional to the stomach, hip or buttock twice weekly and make available continuous and reliable delivery of oxybutynin over a three to four day intermission. OXYTROL suggestions OAB patient's continuous operative bladder regulator with little side effects, such as dry mouth and constipation encountered with and oral preparation. In maximum patients these side effects however are not a worrying.

- **Transdermal Patch:**

  A patch are up to 4.5 square centimeters in size with three layers, the inside release liner which should be detached before apply, a layer encompassing hormones, and an outside polyester shielding layer. The patch contains about 6 milligram of progestin, Norelgestromin 0.75 milligram of Ethinyle Estradiol. The patch is applied on the skin through which the hormones are engrossed in instruction to provide nonstop flow of hormones during menstrual cycle. The patch are marketed Ortho McNeil Pharmaceutical with the product name Ortho Evra.

- **Rotigotine transdermal patch:**

  Arotigotine transdermal patch is used for symptom control of the Parkinson's syndrome. This patches is operative in dropping the symptoms of initial Parkinson's syndrome, and in dropping "off" time in progressive Parkinson's disease. It is available in market under the product name of NeuproR. (Shakya Pragati et al 2012)

MARKETED FORMULATIONS:

1. **Transdermal Patches withcontaining Nitroglycerine:** Transderm-Nitro (Alza), Nitro dur (Key Pharmaceuticals), Nitro disc (Searle,USA), Deponit (Schwarz Pharma), Minitran (3M Pharmaceuticals).
2. **Transdermal Patch with containing Scopolamine:** Transderm-Scop (Alza).
3. **Transdermal Patch containing Clonidine:** Catapres TTS (Alza).
4. **Transdermal Patchwith containing Estradiol:** Climara (3M Pharmaceuticals), Estraderm (Alza).
5. **Transdermal Patchwith containing Nicotine:** Nicoderm (Alza).
6. **Transdermal Patch withcontaining Testosterone:** Testoderm (Alza).
7. **Transdermal Patch withcontaining Insulin:** U-Strip (Dermisonics).

Conclusion :

This article is provides a valuable data about the transdermal drug delivery systems. TDDS is exact helpful to the patients who are suffering from the dreadful diseases, somewhere the localization of the specific target becomes problematicthroughouttreatment. This evaluation review article are provides valuable information regarding the transdermal patches &valuationmethodspecifics as a ready reference for the research scientists who are involvd in TDDS and evaluation process. The previous shows that TDDS have great abilities, being able to usage for both hydrophobic and hydrophilic active substance into promising deliverable drugs.

Throughout the historical period, the numeral of drugs formulation in the patches was increased, and there has been small alteration in the structure of the patch systems. Changes have been mostly limited to modifications of the materials used. The reason is the individual a limited number of drugs fit the molecular weight, and potency supplies for transdermal absorption.

In this article review was carried on some factors are affected on the absorption of drug and some advantages and some disadvantages of TDDS.

References:

1. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers,New Delhi, 2005 pp. 298-299.
2. Shingade GM, Aamer Quazi1, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL. Review on: recent trend on transdermal drug delivery system, Journal of Drug Delivery & Therapeutics; 2012, 2(1).
3. Donnelly R.F., Singh T.R.R., Morrow D.I., Woolfson A.D. *Microneedle-Mediated Transdermal and Intradermal Drug Delivery*. Wiley; Hoboken, NJ, USA: 2012.
4. Ansel.H.C, Loyd.A.V, Popovich.N.G, Pharmaceutical dosage forms and drug delivery systems, Seventh edition, Lippincott Williams and Willkins publication.
5. Yadav V, TRANSDERMAL DRUG DELIVERY SYSTEM: REVIEW, International Journal Pharmaceutical Research; 2012,Vol. 3(2)
6. Tanwar.H, Sachdeva.R, Transdermal drug delivery systems:A Review, International Journal Pharmaceutical Research2016, Vol 7(6) 2274-2290
7. Robinson JR, Lee VH. Controlled drug delivery fundamentals and applications. 2nd Ed. New York. 2005:523-536.
8. Dhote V., Bhatnagar P., Mishra P.K., Mahajan S.C., Mishra D.K. Iontophoresis: A Potential Emergence of a Transdermal Drug Delivery System. *Sci. Pharm.* 2012
9. Wilson R, Waugh A, Grant A. Anatomy and physiology inhealth andillness.9thEd. 2001pg. 363-366.
10. Jain NK, Controlled and novel drug delivery. 1st Ed., CBSPublisherand Distributors, NewDelhi. 2001:100-129.
11. Kumar D, Sharma N, Rana AC, Agarwal G, Bhat ZA. Areview: transdermal drug delivery system: a tools for noveldrug delivery sestem. Int. J Drug Dev. Res. 2011;3(3):70-84.)
12. JulianaMattosCorrêa,MatsuyoshiMori,HeloísaLajasSanches,AdrianaDibodaCruz,EdgardPoiateJr.andIsisAndréaVenturiniPolaPoiate. SilverNanoparticlesinDentalBiomaterials.International JournalofBiomaterial
13. GomesBPFA,LilleyJD,DruckerDB.Clinicalsignificanceofdentalrootcanalmicroflora.JDent1996;24:47-55.)
14. Molander A, Reit C, Dahlen G, Kvist T. Microbiological status of root-filled teeth with apical periodontitis.IntEndodJ1998;31(1):1-7
15. Ansel.H.C,Loyd.A.V,Popovich.N.G,Pharmaceuticaldosageforms and drug delivery systems, Seventh edition, LippincottWilliamsandWillkinspublication.
16. Tanwar.H, Sachdeva.R, Transdermal drug delivery systems:A Review, International Journal Pharmaceutical Research2016, Vol 7(6) 2274-2290
17. Robinson JR, Lee VH. Controlled drug delivery fundamentals and applications. 2nd Ed. New York. 2005:523-536.
18. Subramony J.A. Needle Free Parenteral Drug Delivery: Leveraging active transdermal technologies for pediatric use. Int. J. Pharm. 2013;455:14–18. doi: 10.1016/j.ijpharm.2013.07.055.
19. Deshwal S, Verma N. Optimiation techniques in Transdermal Drug Delivery System. International Journal of Pharmaceutical Sciences and Research, 2012; 3(8): 2362-237.
20. Willams AC, Barry BW. Penetration Enhancers. Advanced Drug Delivery Reviews, 2004; 56(11): 603-618.
21. Pellet M, Raghavan SL, Hadgraft J, Davis AF. The application of supersaturated systems to percutaneous drug delivery. In Guy RH, Hadgraft J, Editors. Drug Delivery Systems. Marcel Dekker, NY: CRC Press, 2003, pp 305-326.
22. A project report submitted to the Department of Pharmacy, University of Asia Pacific, for partial fulfillment of the requirements for the degree of Master of Science in Pharmaceutical Technology. Name: Nahid Newaz Registration No.: 12207035 2013.
23. Brown MB, Jones SA. Hyaluronic acid: a unique topical vehicle for localized drug delivery of drugs to the skin. Journal of the European Academy of Dermatology and Venereology, 2000; 19(3): 308-318.
24. Patani GA, Chien YW. Transdermal drug delivery devices: system design and composition. In Swarbrick J, Boylan JC, Editors. Encyclopedia of Pharmaceutical Technology. Marcel Dekker, NY: CRC Press, 1999; pp 309–337.
25. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2009;26:1261–8.
26. Food and Drug Administration Drugs. FDA: FDA-Approved Drugs.2020.
27. Wang M, Li L, Xie J, Sun Y, Ling G, He Z. Transdermal adhesive patches loaded with ketoprofen evaluated by dynamic detection of percutaneous absorption. AAPS pharmscitech. 2017 Aug;18.
28. Ma J, Gao Y, Sun Y, Ding D, Zhang Q, Sun B, Wang M, Sun J, He Z. Tissue distribution and dermal drug determination of indomethacin transdermal absorption patches. Drug delivery and translational research. 2017.
29. TRANSDERMAL PATCHES-Shakya Pragati 2012.