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Transdermal Drug Delivery System: Review and Future

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Abstract:

Transdermal drug delivery system (TDDS) comes under the controlled drug release category with a basic principle of delivering the drug molecule permeate through skin. TDDS are more or less upper hand to conventional tablet, injection and capsule. Conventional formulation sometimes becomes non-compliant because of its frequent dosing, pain during administration, fast pass metabolism of the drug and various others. On the other side, TDDS can nullify all these problems by avoiding fast pass metabolism, single dosing effective for 1 to 7 days. For the permeation of drug through the skin layers like epidermis and dermis can be barriers. TDDS are designed in a way that they can bypass these barriers by permeating through the skin using the routes like appendageal, transcellular and other routes. Some factors which effect skin permeation are physicochemical, biological and other factors. TDDS have some basic components like polymer matrix, adhesive, backing laminate etc. which forms the transdermal device. Transdermal devices are generally classified into four types of polymer membrane permeation-controlled TDDS, adhesive diffusion-controlled TDDS and others. Various evaluation techniques are available for its evaluation, E.g. folding endurance, probe tack test, rolling ball tack test and many more. Some recent advancements in TDDS are transdermal protein delivery, diabetic monitoring patch and nanotechnology in TDDS. Some recent technologies have been invented to enhance transdermal delivery of a drug, which are electrically-based enhancement technology, structure-based enhancement technology, and others. In the recent past patient, compliance has been one of the prime goals of TDDS, which is the focus of all researchers.

Keywords: Transdermal Devices, TDDS, Permeation, Conventional, Enhancement Technology, Fast Pass Metabolism

Introduction:

Innovations in the area of drug delivery for more patient compliance get increased at a much faster rate as compared from the previous two decades. One of those approaches, transdermal drug delivery system in short TDDS, uses human skin as a port for systemic delivery of drug molecules.Transdermal drug delivery systems, also known as “patches”, comes into the controlled drug delivery category, in that the goal is to transport the drug through the ‘intact’ skin in a Controlled and predetermined and rate. TDDS are drug and adhesive

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containing devices with a limited surface area which sends a particular amount of medicine to the surface of intact skin in a limited rate to the systemic circulation.Conventional medication which requires multi-dose therapy have various problems and complications. The conventional dosage forms, either a tablet, capsule or injection to deliver the drug at the right amount to the specific target site becomes tough. (Rastogi V et al.,2012)Where TDDS gives a better choice over routes of oral and intravenous by increasing compliance of patients by nullifying first-pass metabolism, reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma drug levels.The transdermal products have the aim of dosage form design is to maximum the flux throughout the skin to the blood circulation and also minimizing the metabolism and deposition of the drug in the skin.(Tiwari R et al.,2013) TDDS not only gives controlled and constant drug administration also allows short biological half-live drug input continuously. From one to seven days, even more, TDDS can administer drug properly.TDDS were entered development in the 1970s and in 1979 FDA approved first TDDS scopolamine for motion sickness treatment. Then in 1981 nitroglycerin patches were approved and nowadays there are various patches present such as fentanyl, clonidine, nicotine, lidocaine, oestradiol and testosterone.(Patel DM et al.,2011)

Advantages & Disadvantages:

Advantages

1. Patient compliance
2. The administration is painless, cause it uses non-invasive way to deliver drug molecule in the body
3. Easy to use and self-administrable
4. TDDS is better suitable for those drugs which broken-down by the stomach acids, not well-absorbedfrom the gut, highly degraded by the liver
5. TDDS gives a controlled and steady delivery of drug for long periods of time
6. Avoid the first-pass metabolism of a drug
7. In one time application, it provided an extended period of therapy
8. Gastrointestinal drug absorption difficulties like gastrointestinal pH, enzymatic activity and drug interaction with food can be avoided by using TDDS
9. Drug therapy can’t be effected to the patient having vomiting or diarrhoea
10. Dosing frequency gets decreased
11. Gastrointestinal irritation of a drug can be avoided
12. No chance of toxicity
13. Drug therapy can be stopped rapidly by removal of a patch(Patel D et al.,2012)

Disadvantages:

1. Currently, an only small lipophilic drug can be used in TDDS

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2. Drug with the high large molecular size is not suitable
3. Not suitable for high dose drugs
4. Sweat, water can remove a patch from the skin
5. Hypersensitivity and skin irritation can be happen
6. For long time use, it can be uncomfortable
7. Long time adhesion is difficult
8. Ionic drug can't be delivered
9. Sometimes not economical (Mali AD et al.,2015)

Anatomy of Skin:

The main aim of TDD S is a transfer of medicine to desire area of the body through the skin. Human skin is the largest and fasted growing organ that makes a protective layer that prevents any trauma to internal organs from outside. It makes a barrier for UV rays, microorganism, and toxic chemicals and from higher heat exposer. The main aim of TDDS is throughout the skin because to avoid the first-pass metabolismSkin divided into three major parts epidermis, dermis, and hypodermis. (**fig. 1**)

Epidermis: Epidermis is the uppermost part of the skin. The thickness of epidermis about 0.05 - 1 mm. Epidermis divide into five different layers, from outside to inside stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum.No blood vessels are present in the epidermis layer, and the outermost part of the epidermis is stratum corneum, a dead cell layer, that's why stratum corneum is considered as a rate-limiting barrier for permeation of TDDS. Drug molecule passes that layer through the diffusion mechanism.Stratum corneum is made up with 15-20 keratin filled lipid layers, known as corneocytes. Corneocyte layer has major four characteristic property like they only deliver drug molecule by continuous diffusion pathway, the stratum corneum exists as a multilamellar lipid sheet without hydrophilic bilayer of phospholipids, a unique composition as comparing other biomembranes mostly the phospholipid is absence, the predominantly saturated, tails of long-chain hydrocarbon facilitate a highly ordered, interlinked configuration and gel phase membrane formation changes to a more liquid crystalline membrane system. The vitality is maintained by an epidermal junction.

Dermis: Dermis layer present in between epidermis and hypodermics layer. Hair follicles, blood vessels, lymph vessels, various glands and nerve endings are present in that layer of skin. That is the thickest skin layer, containing fibrous & elastic tissue. That layer gives flexibility and strength of the skin. Sweat produce from sweat glands helps to maintain body temperature and sebum an oily substances secrets from sebum glands that maintain skin miniaturization.

Hypodermis: Lower part of the dermis layer is hypodermics. That also known as a subcutaneous layer of skin. That is too difficult to differentiate the border of the dermis layer and hypodermics layer. Another name of this layer is superficial fascia because of that layer connected with the fascia of bones and muscles. Adipose

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tissue, fibroblast, macrophages, connective tissue, large nerves are present. Adipose tissue is existing on that layer made up with adipocyte cells. Adipocyte cells are store fat. (Hadgraft J.,2004)

Factors Affecting to Transdermal Drug Delivery System

Biological factors:

1.Skin Age: The adult's and young's skin more permeable than older skin. According to the study, the child's skin shows toxic effect due to a bigger surface area as per the weight of the body. Some compound like boric acid, potent steroids and hexachlorophene shows major side effect.

2. Species differences: Skin appendages density, thickness, skin keratinization vary species to species, for that reason can alter the drug penetration from TDDS patch.

A.Skin condition: The skin is weakly acidic, for that reason, weakly acidic drugs are easily penetrate through the skin. Methanol, chloroform and other solvents damage the upper layer of the skin cells then drug molecule penetrate fast.

B.Blood flow: The peripheral blood circulation is a factor of drugs absorption for TDDS. Increase the blood flow causes the fast absorption of TDDS. (Jain NK., 2001)

3.Physiochemical factors:

A. Temperature of Skin: Diffusion coefficient of drug absorption changes with skin temperature. Low temperature causes a low diffusion coefficient, its cause low absorption from TDDS.

B .pH of the skin: Only un-ionized drug molecules can pass easily through lipid membrane of skin. If the skin pH similar as the drug pH, then drug absorption become fast.

C. Drug molecular size: It is very difficult to penetrate the larger molecule size drug. A drug with small molecular size penetrates faster than a large one.

D . Partition coefficient: Partition coefficient is a major physiochemical factor for drug absorption. The optimal partition coefficient is required for good drug absorption; the lower partition coefficient value drugs shows a lower absorption rate from TDDS.

E . Hydration of skin: The skin permeability increased when our skin saturated by water. In saturated condition skin, cells become soft and swell. At that condition, drug molecule can easily pass through the skin membrane. Some moisturizing agents are uses to the formulation of TDDS, like humectant. (Yamamoto T et al.,1990)

Environmental factors:

A . Air Pollution: The air pollutant can form a layer on the surface of the skin; in that condition, the drug release become slower. The bacteria which presence on-air can easily interfere with skin and the presence of a various chemical substance in the air can react with the drug and reduce the effectiveness.

B. Cold season: The cold seasonresults in dry and itchy skin. Skin water content is very low at that moment; moisturizing agents can improve the drying effect of skin as well as increase the permeation of drugs from TDDS.

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C. Sunlight: The blood vessel wall becomes thin when sunlight falls into the skin surface directly. Internally bleeding occur in higher exposer of sunlight. At that moment, drug absorption can change. Higher pigmentation also reduces drug absorption from the skin. Direct sunlight can reduce the stability of the drug. (Shaila L et al.,2006)

Basic Components of TDDS:

Membrane

The membrane may use to enclose the matrix containing drug by forming a pocket or used to form a single layer for the construction of patch. Membranes are used to control drug availability and excipients to the skin by using diffusion property.Examples are ethylene vinyl acetate, polyurethrane, silicone rubber etc.

Permeation Enhancers

To increase the permeability of stratum corneum (SC) layer permeation enhancers are used because of which drug candidate attain higher therapeutic levels. Structural components of stratum corneum like proteins or lipids are gets interacted by permeation enhancers. Where alteration of the protein and lipid packaging of SC happens by the permeation enhancers, so by chemically modifying the skin barrier function leads to uplift permeability.

Permeation enhancers used for TDDS-

1.Solvents- Methanol, Ethanol, Dimethyl sulfoxide

2.Anionic surfactant- Sodium lauryl sulphate

3.Non-ionic surfactant-Pluronic F68, Pluronic F128

4.Essential oil- Cardamom oil, Caraway oil, Lemon oil, Menthol(Singh MC et al.,2010)

Pressure-sensitive adhesives (PSA)

PSA is used to make the required intimate contact between the transdermal system and surface of the skin. Just by applying finger pressure, it should be adhered to the skin, to be aggressively and long term tacky and show a heavy holding force. Should also able to remove from the skin surface without leaving a little residue. PSA forms an intermolecular and interatomic attractive force at the interface, because of which intimate contact is made. To get this level of contact, the material has to be deformed under little pressure. Adhesion have a fluid-like flow[1], results in wetting of the intact skin surface when pressure is applied and after that when pressure is being removed adhesive sets on the skin. Polyacrylates, silicon and polyisobutylene based adhesives are extensively used in TDDS. Some parameters have to be considered like adhesive must not get effected by drug diffusion. It should not be irritated to skin. It has to be physicochemical and also biologically compatible. Anyhow should not affect drug release. (Aulton ME .,2007)

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Backing laminate

To provide tensile strength and flexibility to the transdermal system, backing laminates are used. Generally, used materials are polyesters, polyolefin's and elastomers. Low-density polyethylene which is elastomers, can withstand more skin movement and gives better adhesion than polyester, which is less compliant materials. Backing material should be non-reactive to drugs and other structural components of the transdermal system. To keep the hydration of the skin backing laminate should have a low rate of water vapor transmission because skin hydration is essential for the permeation of drug.Example of some backing laminates are vinyl, Polyester-polypropylene films, polyester films, Polypropylene resin, and Aluminized plastic laminate.

Release liner

The transdermal system is being covered by a protective layer during packaging, so it's basically a primary packaging material. Before application of TDDS on the skin, this protective layer has been removed and discharged. Hence it's a packing material but as it makes a direct contact with the transdermal system it has to be inert to drug and other components of TDDS.The composition of a protective layer that can be either nonocclusive like paper fabric or occlusive like polyethylene, polyvinyl chloride also silicon or Teflon made release coating layer. Some other materials like polyester foil and metalized laminate used in TDDS release liner.

Other excipients

To prepare drug reservoir chloroform, acetone, methanol, isopropanol and dichloromethane like solvents are used. Also to provide proper plasticity in TDDS triethyl citrate, propylene glycol, polyethylene glycol and dibutylpthalate are added as plasticizers.

Types of TDDS

Polymer membrane permeation-controlled system

In this transdermal system, the drug reservoir is being encapsulated in a narrow space in between backing laminate and rate-controlling membrane. The reservoir is prepared by either dispersing the drug in a solid polymer matrix or dispersing in a viscous, unleachable liquid and form a suspension, solution or gel-like reservoir. Silicon fluid can be used as this medium. The drug release rate gets controlled by the membrane; that's why it is called a membrane rate controlled system. The membrane used here is either nonporous or microporous. Backing laminate used here is made up of drug nonpermeable metallic plastic laminate. Hypoallergenic polymer layer is given in between the release liner and membrane for sticking to the skin. (**Fig. 2**)

Example-Transderm-Nitro (Brown L et al.,1988)

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Adhesive diffusion-controlled system

In this system, a drug reservoir is prepared by dispersing the drug directly to the adhesive and forming a medicated adhesive reservoir. Then this medicated adhesive is spread over drug nonpermeable metallic plastic backing laminate by using the technique of solvent casting or adhesive melting. Then the medicated adhesive layer being covered by another nonmedicated adhesive polymer layer with constant thickness. This nonmedicated second rate controlling adhesive layer provides control over drug release and sticking on the skin. (**fig. 3**)

Example-Deponit, Climara

Matrix diffusion-controlled system

In this system, a drug is dispersed homogeneously in a lipophilic or hydrophilic polymer matrix. Then the medicated polymer matrix is cast over a particular size disk of the occlusive base plate. Then this occlusive base plate is fixed over an absorbent pad and finally fixed over a drug nonpermeable backing laminate. Here adhesive is applying along the system to form an adhesive stripe around the drug reservoir. (**Fig. 4**)

Example- Nitro-Dur

Micro reservoir controlled system

It is considered to be a combined transdermal system of matrix dispersion and reservoir system. Where the drug reservoir is prepared by first dispersing the drug in water-soluble polymer's aqueous solution then in second phase homogeneous dispersion of the solution in a lipophilic polymer is done. Because of this unleachable microscopic globules of drug reservoir is formed and due to the cross-linking of a polymer chain, this dispersion becomes stable. By using this reservoir, a medicated disk is formed and positioned in the middle of the transdermal system rest is covered with adhesive. (**Fig. 5**)

Example-Nitrodisc(Chien YW et al.,1992)

Recent Advancement in TDDS

1. Transdermal patches using in protein delivery
2. Testosterone transdermal patch used in young women who are suffering from continuous premature ovarian failure
3. Patient compliance diabetic monitoring without pain using Transdermal patch
4. Oxybutynin transdermal patch used in the bladder overactivity, E.g. OXYTROL
5. TDDS use in formulating new pain relief drugs for more patient compliance, E.g. Lidoderm
6. Using nanotechnology in TDDS (Sugibayashi K et al., 1994)

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Future Technology Use to Enhance Transdermal Delivery of Drug

Structure-Based Enhancement Techniques

1.MicrofabricatedMicroneedles: This type of device use the principle of both Hypodermic needle and Transdermal patch, which ultimately helps to transport the drug across the membrane. This device consists of some micro needles and a drug reservoir. Micro needles helps to penetrate the stratum cornea to deliver the drug. (Gordon RA et al.,2003)

2.Metered-Dose Transdermal Spray: This a solution system where a volatile or non-volatile vehicle is used along with the medicaments which is completely dissolved in the liquid preparation. This provides better permeation and sustained delivery of drug through the skin. (Franz TJ.et al.,1991)

3.Macroflux: In such devices, 300 micro needles are being used in an area around $8cm^2$. Generally, three types of macro flux system is used. (Keith AD et al.,1983)

Electrically-Based Enhancement Techniques

1.Iontophoresis: In this system, electrodes has been used which generates an electrical field(few milliamperes) on a certain area of skin. By which drug molecules either positively charged or negatively charged are easily penetrate through stratum cornea and reach to blood circulation. (Kalia NY et al.,2003)

2.Ultrasound: In this method, coupling agents such as gel, cream and ointments are mixed with drug substances, then ultrasonic energy has used to transfer the drug through stratum cornea. In this technique, the lipid layer of stratum cornea will raptured, which will help the drug molecule to cross the skin barrier.

3.Electroporation: In this electrical pulses has been applied to the skin, which will ultimately form small pores on stratum cornea, by this pores, drug diffusion happens in increased rate due to increasing in drug permeability. This method is safe and effective without any pain sensation during drug administration.

4.Electro-Osmosis: In this process, a certain electrical field will be applied because of this voltage difference, a flow of fluid happens. This fluid flow helps to increase the permeability of a drug molecule.

Velocity Based Enhancement Techniques

- **Intraject**
- **Jet Syringe**
- **Mini-ject**
- **Powder Ject Device:** with the help of high-speed gas flow, solid particles of drugs has propelled through skin barriers. Here helium gas is used, the gas from the gas container enters in a chamber where drug powder is stayed between two polycarbonate membranes. After the release, solid drug particles rapture skin barrier layers at a speed of 600-900m/s and cross the barrier.

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Other Enhancement Techniques

Medicated Tattoos: It is a temporary tattoo, which contains the drug in it. It releases a drug molecule in a sustained rate with better penetration. This method is generally used for children who do not like to have traditional dosage forms.

Magnetophoresis: Here magnetic field is applied on skin which will ultimately increase the diffusion of drug substance's flux.

Evaluation of Transdermal Drug Delivery Film

Weight Uniformity: A fully prepared TDDS patch need to dry at 60˚C for 4 h. After cooling that cut a specified area in various parts and weighed with a calibrated digital balance. The values of average weight and standard deviation need to calculate from weights of individual TDDS. (Patel RP et al .,2011)

The thickness of the Patch: A digital micrometre is used to measure the thickness of fully prepared TDDS after that calculate the average value and standard deviation of patches.

Percentage of moisture content: Prepared TDDS patches are individually weighed and calcium chloride loaded desiccator is prepared for kept those patches for 24 h. after 24 h interval, re-weighed the patches for determining percentage moisture content by this formula.

Percentage moisture content = {(initial weight – final weight)/ final weight} × 100(Foco A et al.,2004)

Percentage moisture uptake: pre-weighed patches are needed to kept in a desiccator at room temperature for 24 h, that contains a saturated solution of potassium chloride in order to maintain 84% relative humidity. The patches are re-weighed after 24 h, the percentage moisture uptake calculate by the following formulation.

Percentage moisture uptake= {(Final weight – initial weight)/ initial weight} × 100(Waghulde S et al.,2013)

Drug content test: A suitable solvent need to dissolve the specific part of the patch in a specific volume. After that, the solution filtrate out through a specified filter medium. Then using UV spectroscopy and HPLC techniques analyse drug content on a particular area of the patch.

Uniformity of dosage unit test: A specified part of the patch cut into small peace, then weighed accurately that part of the patch. The drug contains part solubilize to a specific solvent and sonicate for full extraction of a drug. After full extraction, the solution transfers to the specified volume volumetric flask and fill the solution to flask up to mark. The resulting solution keeps 1h for settle and diluted to the desired concentration for analysis with a suitable solvent. The solution was filtrated by using 0.2 micro meter membrane and the filtered part analyse by UV or HPLC technique for calculating drug content per piece.(Yan-yuXet al.,2006)

Shear addition test: This test is mainly based on a measure of cohesive strength of adhesive that used in TDDS patch. The cohesive strength influenced by the degree of cross-linking, molecular weight, the composition of the polymer and the amount of the thick filler agent used to TDDS. A patch applied into the stainless steel plate and a specific weight is hang from the patch in a parallel direction from the stainless plate. Note the time consume to pull the patch totally from the stainless still plate. The shear addition test is

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calculated by this procedure. Greater shear stress is confirmed when it takes a longer time to remove the patch. (Maibach HI et al.,1996)

Thumb tack test: Thumb tack test is a qualitative test for prepared TDDS patch that determined the adhesive strength of patch. Simply the thumb press on the adhesive layer of the patch and track property determined relatively. (Shaila L et al.,2006)

Peel adhesion test: Peel adhesion test is a determination of force that need to remove an adhesive coating from a specific test substrate. The various factors depend on this test like the amount of adhesive polymer used in the patch, the molecular weight of the polymer. A patch applied to a specific stainless plate and pulled one edge of patch 180◦ angle, the required force needed for removal is measured. (**fig. 6**) (Aarti N et al., 1995)

Rolling ball tack test: The rolling ball tack test is a measure of polymer softness that related on talk. A 7/16 inches diameter stainless still ball rolled down from inclined track and contact with patch horizontally on a plane. The adhesive layer of the patch put upward facing on a plane. Then measure the distance the ball travels on the track in inches(**Fig. 7**)

Peel tack test/ Quick stick test: The TDDS patch applied on a specific substrate then pull it at 90◦ angles at speed 12 inches/ min. The peel force is the force that needs to break the bonds between the adhesive layer and surface. The tack value measured and recorded in g/inches width or ounces/inches width. (**Fig. 8**)

Probe tack test: In the probe tack test, a cleaned specific surface roughness probe is used and applied on adhesive surface, after some time when the bonds ate forms between two surfaces then mechanically separate or brake the probe from the adhesive surface of a patch at a fixed rate. The force is calculated in gram that needs to pull the probe the adhesive layer(**Fig. 9**)

Skin irritation study: A healthy rabbit, average weight (1.2-1.5 kg) is used to study the skin irritation and skin sensitization. The hair of the rabbit is cleaned from the dorsal surface about 50 cm^2 by shaving. After that clean, the surface by using rectified spirit and then the TDDS patch apply that part. After 24h remove the patch and observe any skin irritation and any red mark on the skin, then the observations are classified into five grades on the severity of the skin injury.

In-vitro drug release study: In-vitro drug release study for patches done by paddle over disk method that comes under USP apparatus v. At first the dried patches are cut into a defined shape and weigh then attached properly over a glass plate by an adhesive. The glass plate was transferred in a phosphate buffer pH 7.4 or dissolution medium (500 ml), then the apparatus equilibrated to 32 ± 5º C. The paddle fixed at a distance of 2.5 cm from the glass plate and set to 50 rpm. The samples (5ml) are withdrawn from the apparatus at an appropriate time interval and analyse through HPLC or ultraviolet spectrophotometer. The average value obtains from three experiments.

Stability studies: The stability studied are performed as per ICH guidelines. As per guidelines, the TDDS patches are store at 40 ± 0.5º C and 75% ± 5 relative humidity for 6 months. Then the samples are withdrawn 0,30,60,90, and 180 days interval for analysis of stability study for drug content.

The studies of In-vitro skin permeation: Thediffusion cells are uses to studies of in vitro skin permeation. A male Wister rat weight about 200-250 g was selected, also which has full-thickness abdominal skin.

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Abdominal hair removed carefully; after that hairs, adhering tissue are need to be cleaned by distilled water. Equilibrated with specific dissolution medium or by phosphate buffer at pH 7.4 the diffusion uniformly distributed by a magnetic stirrer. Temperature maintained at 32º C ± 0.5º C by using a thermostat heater. Isolated rat's skin properly mounted to diffusion cell with upward epidermis facing into donor compartment. Exact sample volume removed at a proper time interval from receptor compartment & then an equal volume of frees medium replaced to receptor compartment. The removed samples areneed to be filtrated by using the filtered medium. The filtered samples are analysed by using UV-spectrophotometer or by HPLC. Steady-state values of the permeated drug (mg/ cm^2) versus time (h) plotted on a graph paper. The flux calculated from the graph's slope. The permeability coefficients deduced by dividing the flux by initial drug load (mg/cm^2). (Singh J.et al., 1993)

Conclusion :

Rather than the conventional method of drug administration like solid oral dosage form and parenteral the TDDS is a quite new approach. But on the other hand, we can see TDDS are more physicochemical and biologically effective, so it has higher patient complains than others. Its capability of bypassing fast pass metabolism, long endurance and minimal side effect makes it unique. For such drugs which need frequent dosing and cause gastric irritation, got a new way to administered in a required patient through TDDS. The TDDSs are highly depends on structural components such as backing laminates, penetration enhancer, plasticizer, adhesive and polymer matrix. Generally, TDDS can be divided into membrane permeation-controlled TDDS, adhesive diffusion-controlled TDDS, and matrix diffusion controlled TDDS and micro reservoir controlled TDDS. As TDDS delivers its drug through the skin, so the skin layers become barer for drug delivery. That's why choosing the proper root in transdermal drug delivery system for drug delivery is highly important. Research and development happening for TDDS gets increased now days then last two decades. The modern technologies, including enhancing transdermal drug delivery, are researched in various parts of the world. As the TDDS overcomes most of the challenges which are faced by conventional dosage form, so it's a high priority topic for researchers.

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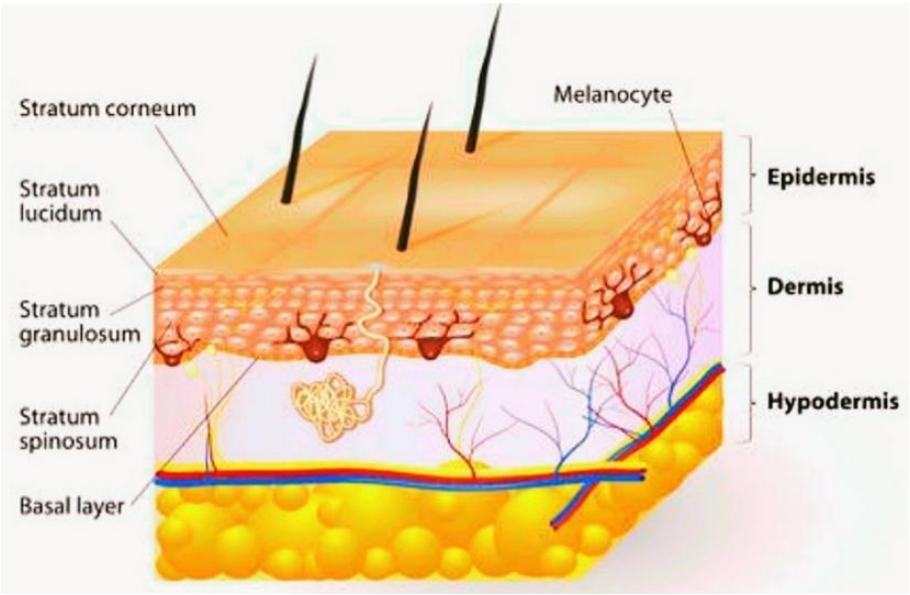

Fig. 1: Layers of human skin

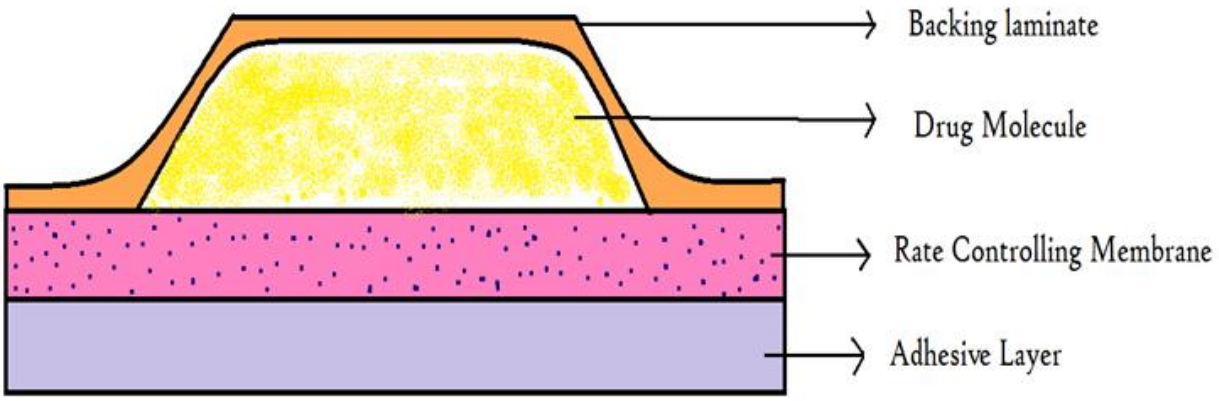

Fig. 2: Polymer membrane permeation-controlled system

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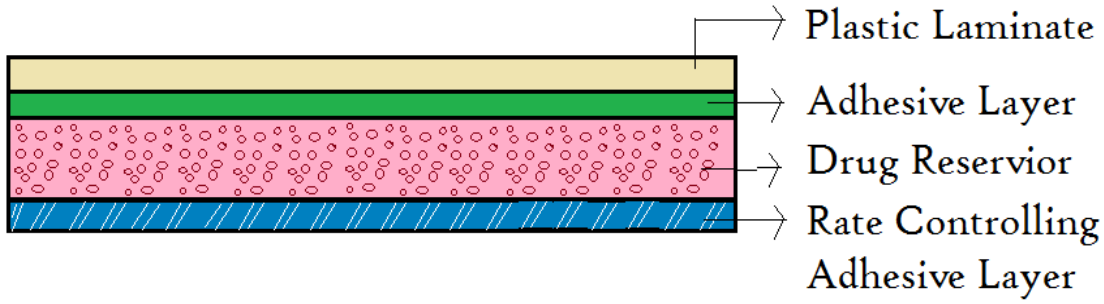

Fig. 3: Adhesive diffusion-controlled system

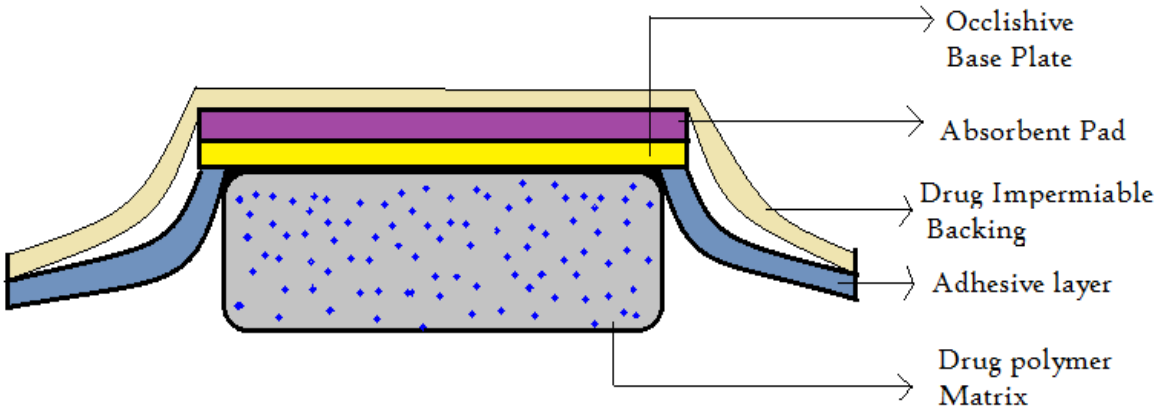

Fig. 4: Matrix diffusion-controlled system

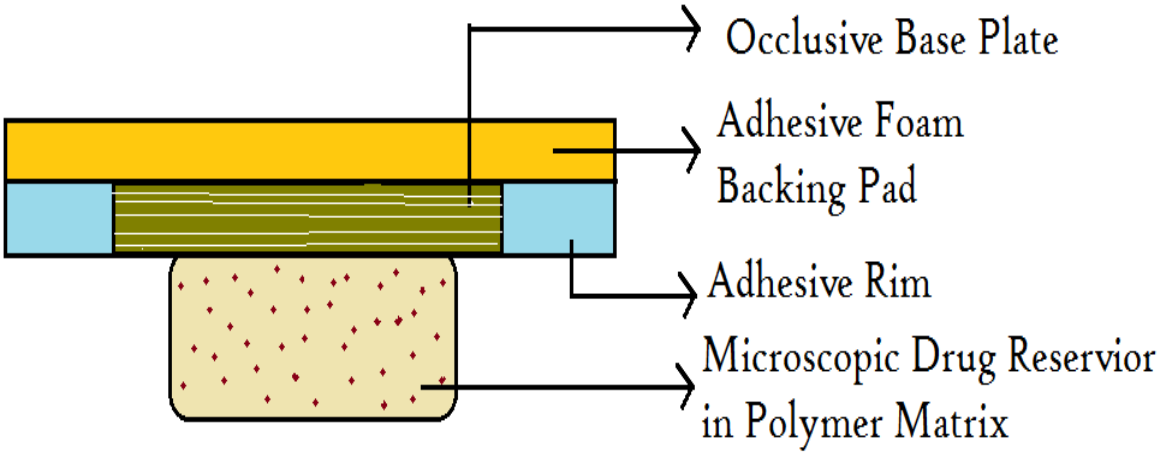

Fig. 5: Micro reservoir controlled system

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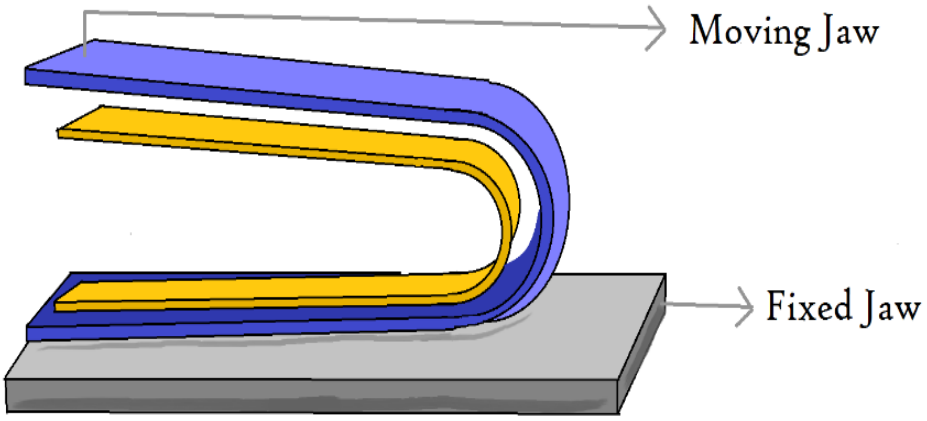

Fig. 6: Peel adhesion test

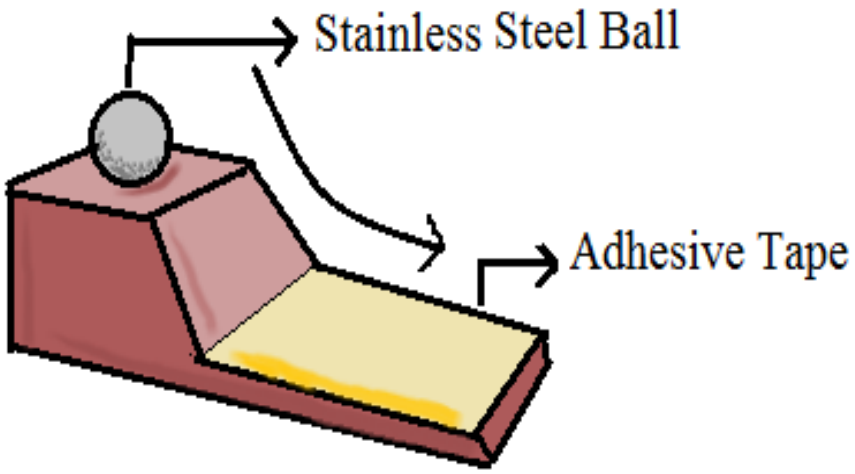

Fig. 7: Rolling ball tack test

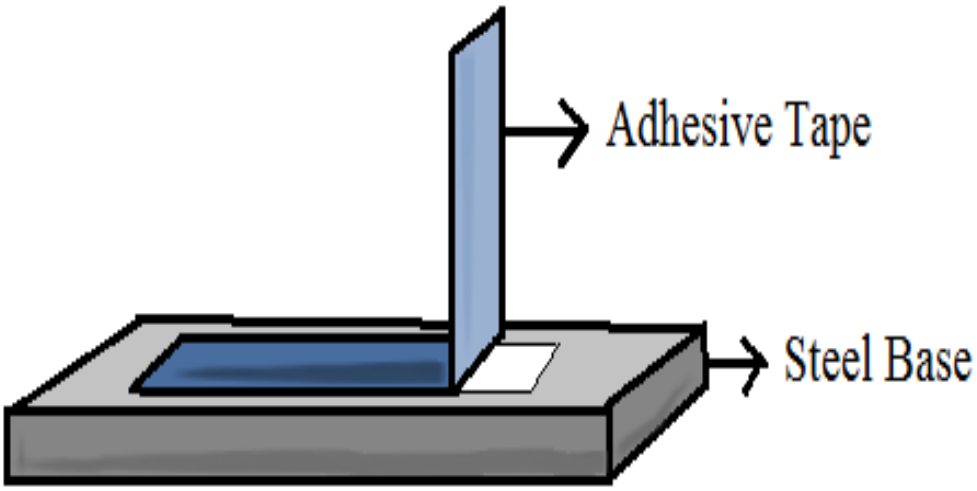

Fig. 8: Peel tack test/ Quick stick test

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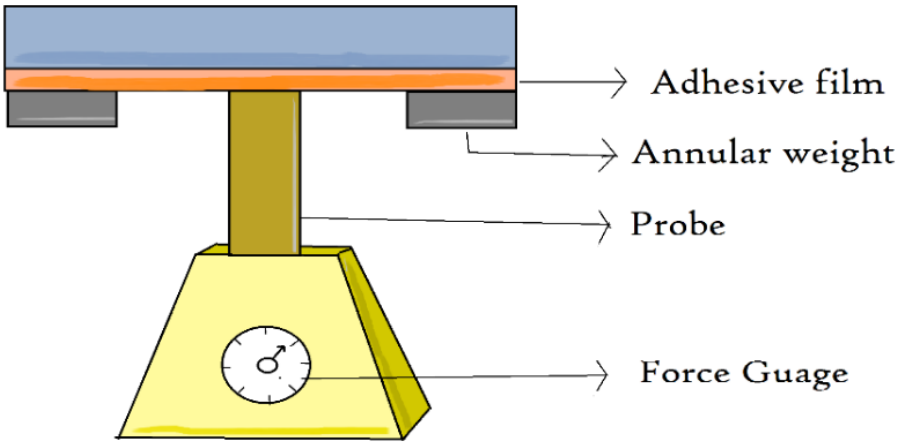

Fig. 9: Probe tack test