Journal of Positive School Psychology http://journalppw.com
2022, Vol. 6, No. 8, 8882-8892

Review Article: Recent Advancement In Transdermal Drug Delivery System (Tdds)

Kajal*[1], Dev Raj Sharma[2], Vinay Pandit[3], M.S. Ashawat[4]

*[1]*Research scholar, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India.*

[2]*Assistant Professor, Department of Pharmaceutics, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India.*

[3]*Head of Department, Department of Pharmaceutics, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India.*

[4]*Director cum Principal, Department of Pharmaceutics, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India.*

***Corresponding author:** Kajal*[1]
[1]Research scholar, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Himachal Pradesh 176031, India.
Email: kajalmandyal22@gmail.com,

ABSTRACT:
TDDS is the best and easily self-administered system. It interacts with the skin and delivers the medicament in a controlled manner into the systemic circulation. It reduces/avoids the side effect related to oral therapy, like- hepatic first-pass metabolism, GIT irritation, etc. The skin infusion enhancer technique has been advanced to improve the bioavailability of the drugs. So various Transdermal dosage forms have been prepared like: Transdermal patches, Gel, Cream, Ointments, etc. The Transdermal route is a viable option to enhance the variety of drugs. Transdermal drug delivery has become the primary route of delivery for a variety of medications that would otherwise be difficult to supply. There are some advantages to Transdermal medicine administration. Primarily to prevent first-pass metabolism and a stomach environment that would render the drug inactive in pharmaceuticals used to treat skin problems as well as for systemic effects to treat ailments of other organs. The therapy of hormone replacement, pain management, smoking cessation, neurological illnesses and angina pectoris like as Parkinson's ailment are all examples of Transdermal products and applications. Formulated to distribute the medicine into the systemic circulation at an optimal pace, it must stick to the skin for the desired period and not cause sensitization or skin irritation. By-passing first-pass metabolism to enhance bioavailability Keeping pharmacokinetic peaks and troughs to a minimum, Tolerance and dosage are being improved. In Continuous Delivery, increasing patient compliance is important.

KEYWORDS: Patches, Permeation, skin, stratum corneum, drug, Transdermal, delivery

INTRODUCTION:

Oral administration is the frequent method of medication distribution with significant demerits such as reduced bioavailability as a result of hepatic first-pass metabolism and a proclivity for causing oscillations in blood level (both for low and high). To address these issues, a novel drug delivery mechanism must be developed that avoids first-pass metabolism, reduces stomach discomfort, and boosts drug bioavailability. As a result, a system for Transdermal drug delivery has been created..(1)

These are self-administered systems in which medications are distributed to the blood circulation through the skin in a controlled way.(2) Because only a few medications can be given through the skin and the topical formulation must remain intact with the skin surface, the use of Transdermal patches has recently been limited..(3)

The medicine is permeated through multiple layers of skin(as shown in fig(a)) by a different method than the systemic circulation in the prime organ of the human body.(4)

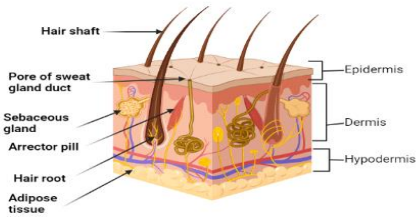


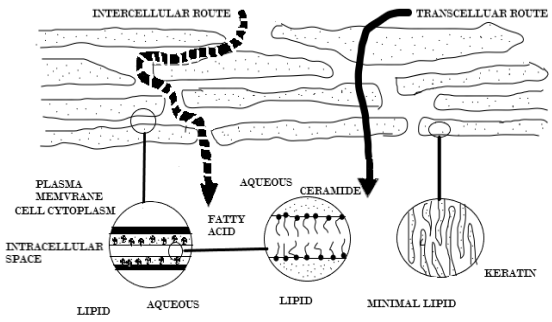
Fig (a): Skin Cross-Section

PATHWAY OF DRUG PERMEATION THROUGH THE SKIN: (as shown in fig(b))

1.Paracellular/ Intercellular route: The drug across epithelium membrane by transfer to the

systemic circulation through the tight junction or intracellular spaces.(5)

2.Transcellular/Intracellular route: The drug pass through both apical membrane and basolateral membrane.(6)



Fig(b): Permeation pathway

ADVANTAGES OF TDDS:

- Avoid first-pass metabolism. Transdermal medicine offers a continuous permeation of a substance over a long period of time.(7)
- Patient compliance is increased
- Adverse events are reduced Intra &inter-patient variability is reduced as a result of the shortened medication regimen.(8)
- No interference with the liquids in the intestines and stomach.(9)
- Maintains blood levels that are stable, constant, and under control for a longer period of time.(10)

DISADVANTAGES OF TDDS:

- It's possible that the area where the application is made will become inflamed. Problems like local edema and erythema can be caused by either the medication or some other additives in the patch formulation.(11)
- Many hydrophilic medicines slowly penetrate the skin and offer little therapeutic efficacy. On the other hand lipophilic drugs are more suited for Transdermal delivery.(12)
- The role of skin's barrier changes from a region to the next on the similar human, from patient to patient with age.(13)
- TDDS are not able to attain maximum drug concentrations in the plasma or blood.(14)

METHODS TO IMPROVE DRUG DELIVERY THROUGH SKIN:-

Various methods involve improving the drug delivery through the skin which is shown below:

1. **Drug / Prodrug:** The use of a prodrug to mount Transdermal distribution of a medicament with a low partition coefficient value has been recommended.(15). The prodrug is usually attached to the pro moiety to expand the original drug solubility and compound's partition coefficient in the stratum corneum.(16)
2. **Iontophoresis:** In this electrical current should be used which is generally of 500 microamperes cm^2 and it generally increases the flow of drug across skin. The current profile, valency, polarity, and other factors all influence this process.(17)
3. **Eutectic system:** It is the system in which a single chemical compound or element becomes solid at minimum temperature as compared to other composition.(18)
4. **Electroporation:** The medication is injected into the skin using a brief, high-voltage electric current. Due to electric pulses, the small pores can be formed on skin .(19)Commonly used High voltage of 1000v and a short period of milliseconds. Lipophilic medicines with a molecular weight more than 7 kg Dalton are typically tested using this approach.(20)
5. **Chemical Enhancement:** Chemical compounds are employed in this procedure to modify the skin barrier function, allowing the medicine to easily enter throughout the skin & into the systemic circulation.(21).Substances used like amines, alcohol, fatty acids, esters, surfactant, and phospholipids.
6. **Ultrasound:** Small sound frequency waves more than kHz are employed in this, which damage the skin barrier. The range is 20 kHz-10 MHz, with an intensity of up to 3W cm3, and it improves drug Transdermal distribution.(22)

TRANSDERMAL PATCHES:

A Transdermal patch, also known as a skin patch is a medicinal adhesive patch which is applied over the skin to administer a certain quantity of drug directly into stream of blood over the skin.(23).The degree at which the liquid medicine confined in the patch's reservoir can travel over the skin into the stream of blood is controlled by an unique membrane.(24).Some medications must be mixed with other substances, such as alcohol, in order to enter the skin and be utilized in a skin patch.[25](25)

When Transdermal patches are utilized in certain situations:

- If the patient is experiencing unbearable side symptoms such as constipation or dysphagia.
- Where dependable administration could help with pain control.
- Patch can be utilized in conjunction with some other enhancing systems to get collaborative results.

TRANSDERMAL CREAMS:

Creams are consist of medicament which is dissolved or suspended in emollient bases, used to treat skin-related problems and give localized and systemic effects to the skin.(26)
Types of cream:
1.Oil-in-water
2.Water-in-oil

TRANSDERMAL GEL:

Gels are semi-solid dosage form, there is the interaction between colloidal particles in vehicle like:-(27)

- Aqueous
- Hydro-alcoholic
- Alcohol-based
- Non-Aqueous

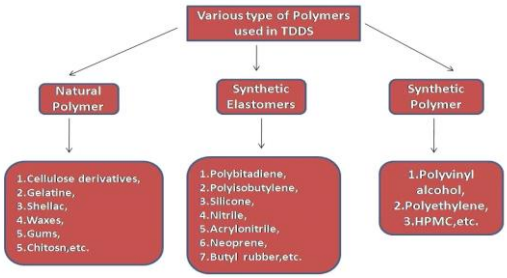
TRANSDERMAL OINTMENT: Ointments are the semi-solid dosage system which is practical over skin, eyes, and mucus membranes and used to treat dry skin to cuts, scrapes, burn, bites, and hemorrhoids.(28)

TABLE (1): FORMULATION PARAMETERS FOR TRANSDERMAL DRUG DELIVERY SYSTEM:

1. Molecular weight	Less than 400 Dalton
2. Elimination half-life	Between 2-6 hours
3. Dose	Should be less than 20mg/day
4. Plasma protein binding	Should not more than 80%
5. Oral bioavailability	Should be minimum

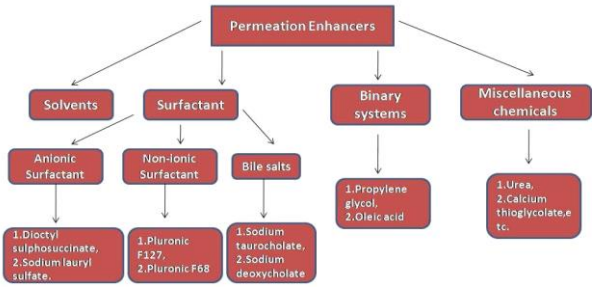
COMPONENTS OF TDDS:

1. **Polymer-matrix:** Polymer should be biologically &chemically compatible with drugs and other excipients like adhesive, permeation enhancer, plasticizer, etc.(29) (Various type of polymer are shown in fig(c))



Fig(c): The polymer most commonly utilized in the manufacture of transdermal medication delivery systems

2. **Adhesive:** It's commonly utilized to secure a Transdermal patch to the skin. The drug generally penetrates through this adhesive layer in a controlled manner.(23)
   Some examples of adhesive generally used in TDDS: Polyacrylates, polyisobutylene, and silicon, etc.
3. **Backing layer:** It is generally used for giving support to patches and giving appearance and flexibility to patch. Mercury is most commonly used as a backing layer in many research works. (30)
   Other backing films are used like - Polyethylene, propylene glycol, polyester film, etc.
4. **Drug:** It is an active ingredient and only a few drugs used in TDDS which follows the criteria/parameters of TDDS.
5. **Permeation enhancer:** These mainly increase skin permeability and change the skin barrier to allow the desired penetrate to pass through.(31) (Various type of permeation enhancer shown in fig (d))



Fig(d): Types of Permeation enhancer

The flux of drug is given by:

$$J = X \times CD$$

- Here D = coefficient of diffusion
- C = diffusing species
- X = spatial coordinate
- **Plasticizers:** It improves polymer brittleness and provides flexibility to patches.(32)

Examples: Glycol derivatives, phosphate esters, etc.

APPROACHES OF TDDS:

Membrane infusion controlled drug delivery system: A amount controlling membrane of polymer, which can be micro-porous or non-porous, encapsulates the drug reservoir.(33)

Example:

- Nitroglycerine is a Transdermal device that releases nitroglycerine once a day and is used to treat angina pectoris.
- A Transdermal device that releases scopolamine to treat motion sickness.
- Clonidine patch for hypertension.

- **Adhesive dispersion type system:** A drug reservoir can be formulated by the dispersion of drug into an adhesive polymer, hot melting the drug-loaded adhesive, and then attaching it with a plane sheet of medicament-impermissible metallic plastic backing to produce a slim layered reservoir of drug.(34)

For instance

- An Isosorbide dinitrate-releasing Transdermal treatment device is used once a day to treat angina-pectoris.

- **Matrix-diffusion controlled system:-**It is made by dispersion of drug elements uniformly with a liquid polymer (lipophilic) or a viscous base polymer (hydrophilic).(35) It is made using the solvent evaporation approach, which involves dissolving a medicine or polymer in a common solvent at a high temperature or in a vacuum. Then, in compartments to form drug-impermeable plastic baking, the mixture of the drug is mounted onto a base plate, and the adhesive polymer is dispersed around the circumference to create a safety rim around the disc. (36)

Example:

- For the treatment of angina pectoris, a nitroglycerine-releasing transdermal device at a daily dose of 0.5g/cm2 is used.
- Micro reservoir type system: -This system combines matrix and reservoir diffusion drug delivery technologies. This system is formed by suspending the medicament in an aq. solution of a water soluble liquid polymer & then using a high dispersion approach to dissolve the drug suspension consistently in a lipophilic polymer such as silicone elastomers. (37)

example:

- Nitroglycerine is released through a Transdermal device once a day to treat angina pectoris.

TRANSDERMAL DRUG DELIVERY SYSTEMS ARE PREPARED USING THE FOLLOWING METHODS:

1. **Asymmetric TPX membrane method:** TPX (4-methyl-1-pentene) is a polymer. A patch can be constructed for a backing membrane made of type 1009 (heat-sealable polyester film)(3m) with 1cm diameter of concave.(38).The sample of drug is distributed into the membrane, by covering of TPX (asymmetric membrane with an adhesive layer) and sealed.(39)

   TPX asymmetric membrane permeation: A wet inversion method or a dry inversion process is used to make these membranes. In order to make a polymer solution, TPX is typically dissolved in non-solvent additives and a mixture of solvent (9-cyclohexane) at 60°C. And this polymer solution was held at 40°C for one day (24 hours) earlier being spread over a plate of glass with a Gardner knife to determine the predetermined thickness. After the casting film has been evaporated for half minute at 50°C, the plate of glass is directly placed in a 25°C coagulation bath. After the 8-12 minutes of soaking, the membrane can be detached and air dried in a oven at 500°Cup to 12 hours.

2. **Circular-Teflon mold method:** Polymers in different proportion are present in various solutions that are dissolved in an organic solvent. Then figure out how much medication is dissolved in 1/2 liter of the similar solvent. The various permeation enhancers are then dissolved in the other half of the solvent in varying quantities. Then, add Di-N-butyl phthalate, as a plasticizer in the drug solution and polymer. The combination of drug-polymer solution was then agitated for 12 hours earlier being put in the circular Teflon mold. An reversed funnel is used to control vaporization of solvent in a laminar flow hood model with a 0.5m/s airflow rate and 24 hour evaporation period followed. The film is then dried and stored in desiccators containing silica gel at 250.5°C to eliminate ageing effects before being evaluated. Within a week after its production, this style of picture can be appraised.(40)

3. **Mercury-substrate method:** To begin, the medicament is dispersed in a solution of polymer comprising of plasticizer. The solution was then agitated for 10-15 minutes in order to ensure a consistent mixture earlier being added into a flat surface of mercury with covering of reversed funnel to avoid evaporation of solvent.(41)

4. **By using IPM membrane method:** To begin, the medicament is dispersed in a polymer solution comprising of plasticizer. The mixture was then agitated for 10-15 minutes in order to

ensure a standardized mixture before being added into a flat surface of mercury with covering of reversed funnel to avoid evaporation of solvent.(42)

5. **By using the EVAC membrane method:** Propylene-glycol is used in the manufacture of gels when the drug is insoluble in water. The medication is first dissolved in propylene-glycol, and then carbopol resin is included. In order to neutralize the solution, sodium hydroxide 5% w/w was added. The medicine is then poured over the rate-controlling membrane layer, backing layer is placed over the gel, and the borders of the patches can be sealed with heat for leak proof devices.(43)

6. **Aluminum-backed adhesive film method:** The aluminum-backed adhesive film approach is employed for Transdermal systems with loading doses larger than 10mg that produce unstable matrices. Chloroform is utilized in this procedure. After dissolving the medicine in chloroform, the sticky material is added to the solution of drug. Aluminum foil is used to line a custom-made aluminum former, and the split ends are blanked off with securely fitting of cork blocks.(44)

7. **By-using the free-film method:** Cellulose acetate-free film is made by pouring chloroform on a surface of mercury. A solution of polymer with a concentration of 2% w/w is made.(45).Plasticizers is added at a 40 % w/w concentration to the polymer weight. Place a glass ring on top of a glass Petri-dish with mercury poured over the surface, then pour a 5ml polymer solution on the glass ring. Then, insert a funnel over a Petri dish to control the pace of solvent evaporation. A slim film formed over the surface of mercury after the solvent was evaporated completely. The dried film was then split and stored into a desiccator between wax paper sheets until needed.(46)

FACTORS AFFECTING TDDS:

- **pH:** The pH of the skin is acidic (4-6). Generally said that the acidic pH of skin provides a defensive mechanism against microbes.(47).The pH of the skin affected the penetration of unionized drugs for absorption. The skin is destroyed if the formulation has a very low or very high pH.(48)

- **Temperature:** When the skin's temperature rises, the medication becomes more permeable to the skin. Heat raises the kinetic energy of proteins, lipids, and carbohydrates in cell membranes across the skin, as well as the kinetic energy of medication molecules. Due to the increase in temperature, the movement of the drug is also increased to the dermis and it decreases the local delivery of the drug. The permeability of the cell membrane changes when the temperature changes by about 5 degrees Celsius.(49)

- **Molecular weight:** The drug's molecular weight is inversely proportional to its skin absorption. The diffusion coefficient is influenced by the drug's molecular weight. Less than 500 Daltons in molecular weight is required. Lesser the molecular weight more the rate of permeation due to increase the concentration of various permeation enhancers.(50)

- **Partition coefficient:** It's indicated by Log P, and it's used to figure out how much of a drug's concentration is distributed in an organic or aqueous solvent.. When the hydrophilic drug is applied topically then they are poorly absorbed because in the stratum corneum the partitioning of the drug is very low.(51).The blood flow clears the absorbed drug rapidly then levels of tissue become low.

- **Biotransformation of the drug in the skin:** It converted the prodrug into an active metabolite, and decreases its bioavailability. In the skin, the biotransformation of the drug is less as compared to observe in the liver.(52)

- **Hydration:** The penetration of medicines into the stratum corneum increases as consequences of hydration. Hydration causes the opening of pores in the stratum corneum and increases the bioavailability of the drug.(53) Hydration occur the flux across the skin, and drug partitioning and transport across the skin.

- **Age:** The pH of your skin varies as you get older. When it comes to hydrophilic drugs, the permeation of the medication through the skin is slowed as people become older, and the amounts of lipids, such as ceramide, decrease as well.(54)

- **Gender:** Because males have a thicker cellular epidermal layer than females, percutaneous penetration is lower in males than in females.(55)

- **Sun exposure:** When the skin exposure to the sun then the stratum corneum has become thinner and in the case of the sun-protected area then the stratum corneum is thicker.(56)
- Blood flow: When the blood flows through the dermis then the absorption of the drug is limited. e.g. if any drug cause constriction of vessels and it is specified by another route, then it affects the blood flow through the skin.(57)

- **Skin condition:** Because the stratum-corneum layer of skin is less water-bound in atopic dermatitis, the skin becomes dry. When compared to healthy skin, the pH of atopic dermatitis patients increased.(58)

EVALUATION OF TDDS:

- **The patch's width:** The width of the patch is calculated by the mean of digital micro-meter, and the standard deviation and average thickness ensure the thickness of the prepared patch.(59).Transdermal film thickness is determined by the screw gauge, microscope dial gauge, or micrometer at different points of film.(60)

- **Weight of uniformity:** The patches were dried for four hours at 60 degrees Celsius before being tested. The patches are divided into sections and weighed using a computerized balance. The average weight and standard deviation data have been derived using individual weights.(61)

- **Folding endurance:** A section of a patch has been chopped off and folded repeatedly in the similar plug until it breaks down. The endurance of patch is measured by the numeral of times we will fold the patch from the same location till it breaks.(62)

- **Percentage Moisture content:** Each patch is weighed separately and maintained at room temperature for 24 hours in desiccators with fused calcium chloride.(63)

The patches are re-weighed after 24 hours and calculated its %age moisture content by the formula: -

$$\textit{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}$$

- **Content uniformity test:** Only 10 patches are chosen from all of the patches, and the content of each patch is determined. If the content uniformity is between 85% to 115% (9 patches out of 10 patches) and for one individual patch content uniformity is within the limit of 75% to 125% then the Transdermal patches pass the content uniformity test.(64). Further test is performed for 20 patches and its limit is in between 85% to 115% then a test is passed.(65)

- **Moisture Uptake:** For 24 hours, all of the patches are maintained in a desiccator (at room temperature). After 24 hours, the patches were removed & subjected to a saturated potassium chloride solution in desiccators at 84 percent relative humidity until they reach a consistent weight..(66)

%Moisture uptake is calculated as: -

$$\textit{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}$$

- **Shear Adhesion test:** This determined the cohesive strength of adhesive polymers. An adhesive film is applied to the stainless-steel plate. And the determination of shear adhesion strength by measuring the time taken to pull the film off from the plate. The longer the time taken greater will be its shear strength.(67)

- **Drug content:** Dissolve a little bit of the patch in a solvent after cutting it. The solution is then filtered by a filter medium, and the content is determined using a suitable technology such as UV or HPLC.(68)
- **Peel Adhesion test:** The power compulsory to eliminate an adhesive covering from a trial substrate is known as peel adhesion. It is influenced by the adhesive polymer's molecular weight. And the test is based on the power necessary to eliminate a single coated film from a substrate at the angle of 180°. (69)(as shown in fig (e))

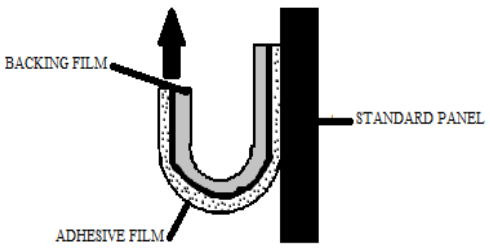
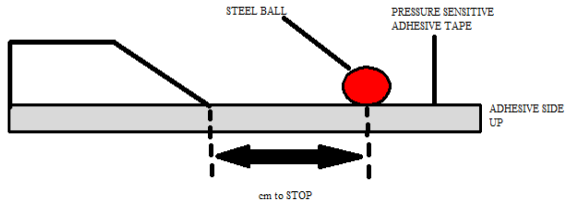


Fig (e): Peel tack test

- **Rolling ball tack test:** It entails measuring the distance covered by a ball of stainless-steel with an upward-facing adhesive; the fewer adhesive

used, the further the ball goes. This test is used to determine how soft a polymer is.(70)(as shown in fig(f))



Fig(f): Rolling ball tack test

- **Quick stick test (peel tack test):** The peel strength is necessary to breakdown the binding between a substrate and an adhesive at 90 degrees at a pace of 12 inches per minute in this test. The tack value is reported in units (ounces per inch width) of force.(71)

- **Probe Tack test:** The probe comes into contact with the glue, forming a bond between the two. A tack is the power necessary to pull a probe far from an adhesive at a constant proportion.(72)(as shown in fig (g))

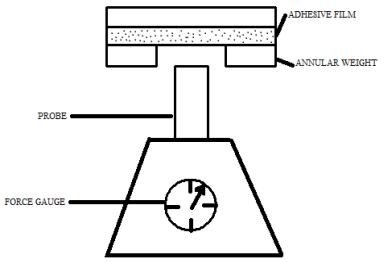


Fig (g): Probe tack test

- **In-vitro drug release study:** The USP apparatus (V) (paddle over-disc method) is utilized to release the medication from the prepared patches in this approach. Patches are cut into precise shapes, weighed, and adhered to a glass plate with glue. After that, the glass plate is submerged in 500ml of dissolving media (phosphate buffer pH 7.4). The paddle is 2.5cm away from the glass plate, and it regulates the speed to 50 rpm. 5ml sample is withdrawn at a specific time interval up to 24 hours and then analyzed on UV spectrophotometer or HPLC.(73)

- **In-vitro skin infusion investigation:** Diffusion cells are utilized to carry it out. Take a skin of a male rat, the weighting rat is 200g to 250g. Hair will be cut from the abdomen region by the electric clipper, and the dermal side of the skin will be washed with water to eliminate sticking blood vessels and tissue. Equilibrated it on dissolution medium for an hour before starting an experiment then placed it on the magnetic stirrer. The thermostatically regulated heater keeps the temperature at 32±0.5 degrees Celsius. The skin of rat is sandwiched between the donor compartment and the compartment of diffusion cell, with the epidermis pointing upward. At various time intervals, a certain volume of the sample is withdrawn from the receptor compartment. Then the sample is filtered out from the filter medium and analyzed by a spectrophotometer or HPLC.(74)(as shown in fig(h))

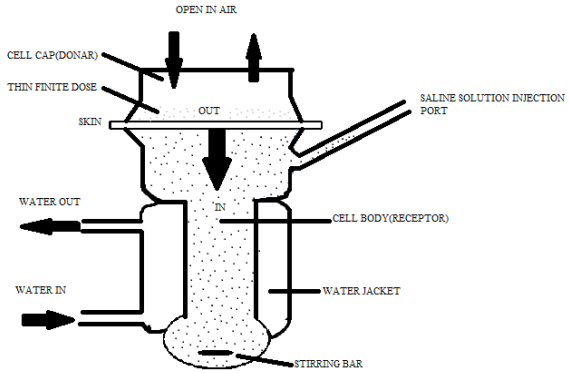


Fig (h): Franz diffusion cell

- **Skin-Irritation study:** Take a well rabbit with having an avg. weight of 1.2kg to 1.5kg. Then remove the hair of the rabbit from the dorsal side and after removal of hair clean the dorsal surface with rectified spirit and apply your formulation or patch on the skin.(75).After 24 hours, the patch is removed. Then, depending on the degree of the skin injury, assess the condition of the skin.

- **Stability studies:** Stability tests are conducted in compliance with ICH guidelines for 6 months, keep the TDDS sample at 75± 5%Rhand40± 5^0C. The samples were taken at various time interludes of days (such as 0, 30, 60, 120 and 180) and the content of drug is analyzed. Stability tests are performed in

accordance with ICH guidelines. FOR 6 MONTHS, keep the TDDS sample at 40± 5°C and 75± 5% Rh. The samples are taken at various time intervals of days (such as 0, 30, 60, 120 and 180) and the drug content is analyzed. (76)

TABLE (2): NEW DRUG APPROVAL FOR TRANSDERMAL DRUG DELIVERY SYSTEM[72]:

S.no.	Drug Name	Marketed company	Formulation	Approval Year	Disease
1.	Twyneo (tretinoin benzoyl peroxide)	Sol-Gel Technologies, Ltd.	Cream	2021	Acne
2.	Fenantyl	SparshaPharma International Pvt. Ltd.	Patch	2021	Pain
3.	Butenafine Hydrochloride	Bayer Healthcare Llc.	Cream	2021	Fungal skin infection
4.	Opzelura (ruxolitinib)	Incyte Corporation	Cream	2021	Atopic Dermatitis
5.	Twirla (ethinylesyradiol and levonoegesterl)	Agile Therapeutics, Inc.	Transdermal system	2020	Birth Control
6.	Phexxi (lactic acid, citric acid, and potassium bitartrate)	Evofem, Inc.	VaginalGel-FormerlyAmphore	2020	Birth Control
7.	Zilxi (minocycline)	Foamix Pharmaceutics Ltd.	Topical foam-formerly FMX103	2020	Rosacea
8.	Wynzora (calcipotriene and betamethasone dipropionate)	MC2Therapeutics	Cream	2020	Plaque Psoriasis
9.	Xeglyze (abametapira) Topical Lotion	Dr.Reddy's Laboratories Ltd.	Topical lotion	2020	Head Lice
10.	Winlevi (clascoterone)	CassiopeaSp	Cream	2020	Acne
11.	Klisyri (tribanibulin)	Athenex, Inc.	Ointment	2020	Actinic Keratosis
12.	Duobrii (halobetasol propionate and tazarotene)	Ortho Dermatologic	Lotion	2019	Plaque Psoriasis
13.	Aklief (trifarotene)	Galderma	Cream	2019	Acne
14.	Secuado (asenapine)	Noven Pharmaceuticals Inc.	Transdermal system	2019	Schizophrenia
15.	Amzeeq	Foamix Pharmaceutic	Topical Foam	2019	Acne
16.	Arazlo (tazarotene)	Bausch Health ompaniesinc	Lotion	2019	Acne

CONCLUSION OR SUMMARY:

TDDS is a suitable, trouble-free and possibly successful technique of delivering a range of medications. Unfortunately, the skin is immune to all but the tiniest molecules when it comes to Transdermal technology. The continual administration of medicine, which results in consistent drug levels, is the key merit of TDDS. Another benefit is the ease of weekly or biweekly application, which encourages patient compliance. Transdermal drug delivery technologies have showed a lot of promise in recent years, and they're becoming more prevalent in health care. As of the existence of a somewhat impermeable thickness of the stratum corneum layer, Transdermal technology has limits in terms of treatment rates. Only lipophilic, low molecular weight powerful drugs can be delivered Transdermal due to the barrier created by human skin.

REFERENCES

[1]. Hafeez A, Singh J, Maurya A, Rana L, Jain U. Recent Advances in Transdermal Drug Delivery System (TDDS): An Overview. J Sci Innov Res [Internet]. 2013;2(3):733–44. Available from: www.jsirjournal.com

[2]. Singh P, Carrier A, Chen Y, Lin S, Wang J, Cui S, et al. Polymeric microneedles for controlled transdermal drug delivery. J Control release. 2019;315:97–113.

[3]. Uchechi O, Ogbonna JDN, Attama AA. Nanoparticles for dermal and transdermal drug delivery. Appl Nanotechnol drug Deliv. 2014;4:193–227.

[4]. Haque T, Talukder MMU. Chemical enhancer: a simplistic way to modulate barrier function of the stratum corneum. Adv Pharm Bull. 2018;8(2):169.

[5]. Sonaje K, Chuang E-Y, Lin K-J, Yen T-C, Su F-Y, Tseng MT, et al. Opening of epithelial tight junctions and enhancement of paracellular permeation by chitosan: microscopic, ultrastructural, and computed-tomographic observations. Mol Pharm. 2012;9(5):1271–9.

[6]. Girardin F. Membrane transporter proteins: a challenge for CNS drug development. Dialogues Clin Neurosci. 2006;8(3):311.

[7]. Zhang Y, Yu J, Kahkoska AR, Wang J, Buse JB, Gu Z. Advances in transdermal insulin delivery. Adv Drug Deliv Rev. 2019;139:51–70.

[8]. Khoury T, Ilan Y. Introducing patterns of variability for overcoming compensatory adaptation of the immune system to immunomodulatory agents: a novel method for improving clinical response to anti-TNF therapies. Front Immunol. 2019;10:2726.

[9]. de Vos P, Faas MM, Spasojevic M, Sikkema J. Encapsulation for preservation of functionality and targeted delivery of bioactive food components. Int dairy J. 2010;20(4):292–302.

[10]. Helfer P, Shultz TR. Coupled feedback loops maintain synaptic long-term potentiation: A computational model of PKMzeta synthesis and AMPA receptor trafficking. PLoS Comput Biol. 2018;14(5):e1006147.

[11]. Gupta J, Thakur A, Thakur S. Transdermal drug delivery system of Metformin Hydrogen Chloride using Two Different Polymeric Combinations. Int J Heal Biol Sci. 2019;2(4):1–5.

[12]. Goyal R, Macri LK, Kaplan HM, Kohn J. Nanoparticles and nanofibers for topical drug delivery. J Control Release. 2016;240:77–92.

[13]. Danby SG. Biological variation in skin barrier function: from A (atopic dermatitis) to X (xerosis). Ski barrier Funct. 2016;49:47–60.

[14]. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: A review. Asian J Pharm Sci. 2020;15(1):13–25.

[15]. Ita KB. Prodrugs for transdermal drug delivery–trends and challenges. J Drug Target. 2016;24(8):671–8.

[16]. Subedi RK, Oh SY, Chun MK, Choi HK. Recent advances in transdermal drug delivery. Arch Pharm Res. 2010;33(3):339–51.

[17]. Yu Y-Q, Yang X, Wu X-F, Fan Y-B. Enhancing Permeation of Drug Molecules Across the Skin via Delivery in Nanocarriers: Novel Strategies for Effective Transdermal

Applications. Front Bioeng Biotechnol. 2021;9:200.
[18].Yeh J-W. Alloy design strategies and future trends in high-entropy alloys. Jom. 2013;65(12):1759–71.
[19].Panda AK, Basu B. Biomaterials-based bioengineering strategies for bioelectronic medicine. Mater Sci Eng R Reports. 2021;146:100630.
[20].Donnelly RF, Singh TRR. Novel delivery systems for transdermal and intradermal drug delivery. John Wiley & Sons; 2015.
[21].Bolzinger M-A, Briançon S, Pelletier J, Chevalier Y. Penetration of drugs through skin, a complex rate-controlling membrane. Curr Opin Colloid Interface Sci. 2012;17(3):156–65.
[22].KOST J, LANGER R. Transdermal Drug Delivery. Top Drug Bioavailability, Bioequivalence, Penetration. 2013;91.
[23].Hwang I, Kim HN, Seong M, Lee S, Kang M, Yi H, et al. Multifunctional smart skin adhesive patches for advanced health care. Adv Healthc Mater. 2018;7(15):1800275.
[24].Saroha K, Yadav B, Sharma B. Transdermal patch: A discrete dosage form. Int J Curr Pharm Res. 2011;3(3):98–108.
[25].Bhowmik D. Recent advances in novel topical drug delivery system. Pharma Innov. 2012;1(9).
[26].Roberts MS, Cheruvu HS, Mangion SE, Alinaghi A, Benson HAE, Mohammed Y, et al. Topical drug delivery: History, percutaneous absorption, and product development. Adv Drug Deliv Rev. 2021; 177:113929.
[27].Bora A, Deshmukh S, Swain K. Recent advances in semisolid dosage form. Int J Pharm Sci Res. 2014;5(9):3596.
[28].Chauhan L, Gupta S. Creams: A Review on Classification, Preparation Methods, Evaluation and its Applications. J Drug Deliv Ther. 2020;10(5-s):281–9.
[29].Ghosh S, Das S, Singh A, Gupta S. Applicability Of Natural Polymer And Natural Permeation Enhancer In Transdermal Drug Delivery System: A Detailed Review. Int J Innov Pharm Sci Res. 2021;9(08):1–24.
[30].Banerjee S, Chattopadhyay P, Ghosh A, Datta P, Veer V. Aspect of adhesives in transdermal drug delivery systems. Int J Adhes Adhes. 2014;50:70–84.
[31].Desai P, Patlolla RR, Singh M. Interaction of nanoparticles and cell-penetrating peptides with skin for transdermal drug delivery. Mol Membr Biol. 2010;27(7):247–59.
[32].Suksaeree J, Karnsopa P, Wannaphruek N, Prasomkij J, Panrat K, Monton C, et al. Use of isolated pectin from a cissampelos pareira-based polymer blend matrix for the transdermal delivery of nicotine. J Polym Environ. 2018;26(9):3531–9.
[33].Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. J Control Release. 2012;164(1):26–40.
[34].Mishra B, Bonde GV. Transdermal drug delivery. In: Controlled Drug Delivery Systems. CRC Press; 2020. p. 239–75.
[35].Liu W, Yang X-L, Ho WSW. Preparation of uniform-sized multiple emulsions and micro/nano particulates for drug delivery by membrane emulsification. J Pharm Sci. 2011;100(1):75–93.
[36].Larraneta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Mater Sci Eng R Reports. 2016;104:1–32.
[37].John L. Review on transdermal drug delivery system. Int J Pharm Res Heal Sci. 2014;2(4):261–72.
[38].Halder S, Chakraborty P, Pradhan D, Bagchi A. Recent advancement in the method of transdermal drug delivery system: A review. J Appl Pharm Res. 2021;9(2):6–9.
[39].Rao TV, Kiran OR. Transdermal patch. Res J Pharm Dos Forms Technol. 2013;5(1):12–6.
[40].Devarakonda B. Poly (amidoamine)(PAMAM) dendrimers as solubility and permeation enhancers. University of Louisiana at Monroe; 2005.
[41].Alam MI, Alam N, Singh V, Alam MS, Ali MS, Anwer T, et al. Type, preparation and evaluation of transdermal patch: A review. World J Pharm Pharm Sci. 2013;2(4):2199–233.
[42].Karadzovska D, Riviere JE. Assessing vehicle effects on skin absorption using artificial membrane assays. Eur J Pharm Sci. 2013;50(5):569–76.
[43].Ranjan A, Sahu A, Yadav A, Payasi A, Jaiswal A, Kumar A, et al. A Short Review on the Formulation of Transdermal Dermal Drug Delivery System (TDDS). Res J Pharm Dos Forms Technol. 2018;10(2):90–4.
[44].Khalaf-HN-Al-Jabiry A. Studies on biologically active natural products and synthesis of fluorinated heterocyclic drug scaffolds using SNAr substitution reactions. Loughborough University; 2018.

[45].Kadam AS, Ratnaparkhi MP, Chaudhary SP. Transdermal drug delivery: An overview. Int J Res Dev Pharm Life Sci. 2014;3(4):1042–53.
[46].Sanderson J. Biological microtechnique. Garland Science; 2020.
[47].Percival SL, Emanuel C, Cutting KF, Williams DW. Microbiology of the skin and the role of biofilms in infection. Int Wound J. 2012;9(1):14–32.
[48].Coderch L, Collini I, Carrer V, Barba C, Alonso C. Assessment of finite and infinite dose in vitro experiments in transdermal drug delivery. Pharmaceutics. 2021;13(3):364.
[49].Akhtar N, Singh V, Yusuf M, Khan RA. Non-invasive drug delivery technology: development and current status of transdermal drug delivery devices, techniques and biomedical applications. Biomed Eng Tech. 2020;65(3):243–72.
[50].Roy N, Agrawal M, Chaudhary S, Tirkey V, Dhwaj A, Mishra N. Review article on permeation enhancers: a major breakthrough in drug delivery technology. Int J Pharm Sci Res. 2017;8(3):1001.
[51].Prausnitz MR, Elias PM, Franz TJ, Schmuth M, Tsai J-C, Menon GK, et al. Skin barrier and transdermal drug delivery. Dermatology. 2012;3:2065–73.
[52].Zhang Z, Tang W. Drug metabolism in drug discovery and development. Acta Pharm Sin B. 2018;8(5):721–32.
[53].Pawar AY. Transfersome: A novel technique which improves transdermal permeability. Asian J Pharm Free full text Artic from Asian J Pharm. 2016;10(04).
[54].Elias PM, Holleran WM, Feingold KR, Tsai J, Menon GK. The potential of metabolic interventions to enhance transdermal drug delivery. In: Journal of Investigative Dermatology Symposium Proceedings. Elsevier; 2002. p. 79–85.
[55].Singh I, Morris AP. Performance of transdermal therapeutic systems: Effects of biological factors. Int J Pharm Investig. 2011;1(1):4.
[56].Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (I): blood flow, pH, thickness, and ultrasound echogenicity. Ski Res Technol. 2005;11(4):221–35.
[57].Newton DJ, Burke D, Khan F, McLeod GA, Belch JJF, McKenzie M, et al. Skin blood flow changes in response to intradermal injection of bupivacaine and levobupivacaine, assessed by laser Doppler imaging. Reg Anesth Pain Med. 2000;25(6):626–31.
[58].Bala P, Jathar S, Kale S, Pal K. Transdermal drug delivery system (TDDS)-a multifaceted approach for drug delivery. J Pharm Res. 2014;8(12):1805–35.
[59].Darwhekar G, Jain DK, Patidar VK. Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate. Asian J Pharm Life Sci ISSN. 2011; 2231:4423.
[60].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.
[61].Gaikwad AK. Transdermal drug delivery system: Formulation aspects and evaluation. Compr J Pharm Sci. 2013;1(1):1–10.
[62].Patel RP, Patel G, Patel H, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Res J Pharm Dos Forms Technol. 2009;1(2):108–15.
[63].Jamakandi VG, Mulla JS, Vinay BL, Shivakumar HN. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian J Pharm Free full text Artic from Asian J Pharm. 2014;3(1).
[64].Parivesh S, Sumeet D, Abhishek D. Design, evaluation, parameters and marketed products of transdermal patches: A review. J Pharm Res. 2010;3(2):235–40.
[65].Tyagi S, Goyal K. Transdermal drug delivery system: Quality approaches and evaluation. Innov Int J Med Pharm Sci. 2017;2(3).
[66].Arora P, Mukherjee B. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci. 2002;91(9):2076–89.
[67].Zhou L, Huang W, Xiao F, Lv Q. Shear adhesion evaluation of various modified asphalt binders by an innovative testing method. Constr Build Mater. 2018;183:253–63.
[68].Rastogi V, Yadav P. Transdermal drug delivery system: An overview. Asian J Pharm Free full text Artic from Asian J Pharm. 2014;6(3).
[69].Rawat A, Bhatt GK, Kothiyal P. Review on transdermal drug delivery system. Indo Am J Pharm Sci. 2016;3:423–8.
[70].Semwal R, Semwal RB, Semwal DK. Mucoadhesive assessment–An encyclopedic review. Curr Med Drug Res. 2018;2(2):187.
[71].Hanumanaik M, Patil U, Kumar G, Patel SK, Singh I, Jadatkar K. Design, evaluation and recent trends in transdermal drug delivery system: a review. Int J Pharm Sci Res. 2012;3(8):2393.

[72].Mohammed IK, Charalambides MN, Kinloch AJ. Modelling the interfacial peeling of pressure-sensitive adhesives. J Nonnewton Fluid Mech. 2015;222:141–50.
[73].Wake PS, Kshirsagar MD. Compatibility study In-vitro drug release Study of Solid Lipid Nanoparticle Based Transdermal Drug Delivery System for Rasagiline Mesylate. Asian J Res Pharm Sci. 2017;7(2):92–6.
[74].Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Characterization and in vitro skin permeation of meloxicam-loaded liposomes versus transfersomes. J Drug Deliv. 2011;2011.
[75].Sachan R, Bajpai M. Transdermal drug delivery system: a review. Int J Res Dev Pharm Life Sci. 2013;3(1):773–90.
[76].Dave V, Pareek A, Paliwal S. Ethosome: A novel approach of transdermal drug delivery system. Int J Adv Res Pharm Bio Sci. 2012;2(1):439–53.
https://www.drugs.com/newdrugs-archive/july-2020.html list of FDA approval drug 2021.