An Overview on Transdermal Patch

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Abstract: **Transdermal drug delivery systems (TDDS) provide a regulated release of medication directly into the bloodstream, ensuring stable drug concentrations and potentially minimizing systemic side effects while improving efficacy compared to other methods of administration. This non-invasive technique offers a painless and convenient option for patients. The skin is a favorable route for drug delivery due to its large surface area, easy accessibility, and connection to both the circulatory and lymphatic systems, which enable systemic absorption. The primary objective of TDDS is to deliver medication at a consistent rate, reducing both interpatient and intrapatient variability. These systems are increasingly recognized for offering significant therapeutic benefits to patients worldwide.**

Keywords: **Transdermal patches, Controlled release, vapour patches, in vitro permeation study**

INTRODUCTION

Transdermal drug administration typically involves the topical application of substances to healthy, intact skin, either to treat the underlying tissues locally or to provide systemic therapy. The primary aim of dosage design for transdermal products is to optimize the rate of drug penetration through the skin.[1] The concept of delivering medications through the skin is not new, with its use dating back to the 16th century, when castor oil plant husks soaked in water were applied to relieve headaches. Today, transdermal drug delivery is a widely accepted method for administering drugs into the systemic circulation. Until recently, the use of transdermal patches in pharmaceuticals was limited.[2] Non-medicated patches are available for various uses, such as thermal and cold patches, nutrient patches, skincare patches (divided into therapeutic and cosmetic categories), aroma patches, weight loss patches, and others. Currently, transdermal drug delivery systems (TDDS) have gained substantial attention due to their ability to address many of the challenges associated with other antifungal drug delivery methods (e.g., oral or intravenous). The skin, particularly the stratum corneum acts as a barrier to most substances, which has led to the development of gels as semisolid formulations that may be hydrophilic hydrophobic. Recent studies have explored new gel types for dermal drug applications, including Niosomal, Liposomal, Erythrosomal, and microsphere gels.[3] TDDS typically consists of adhesive, drug-containing devices of a specified surface area designed to deliver a predetermined amount of medication through the intact skin at a controlled rate, allowing it to penetrate the skin layers and reach systemic circulation. Today, alongside oral treatments, the transdermal route is one of the most successful and innovative areas of drug delivery research.

SELECTION OF DRUG CANDIDATE FOR TRANSDERMAL DELIVERY:

The transdermal route of administration cannot be employed for a large number of drugs. Judicious choice of the drug substance is the most important decision in the successful development of a transdermal system. The drug candidate should have following ideas characteristics.

- Adequate ability to permeate the skin
- Lower molecular weight to facilitate absorption
- Lower melting point to enhance solubility and diffusion
- Drugs with balanced oil and water solubility
- Sufficient skin acceptability
- Non-irritating substances
- Drugs that do not undergo metabolism
- Sufficient clinical demand
- Balanced lipophilicity
- Melting Point – Drugs with low melting point [4]

BASIC INTRODUCTION OF TRANSDERMAL DRUG DELIVERY SYSTEM: ANATOMY AND PHYSIOLOGY OF SKIN:

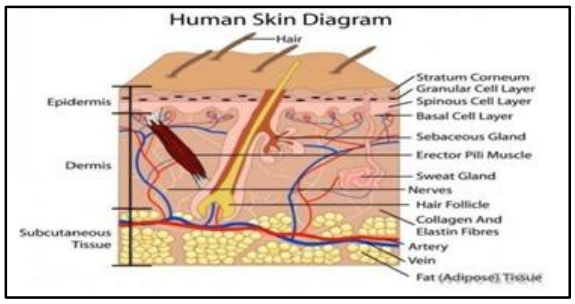

Fig.no.1.Human skin diagram

The skin serves as an effective barrier, safeguarding the body from excessive water loss and preventing the entry of harmful substances, while also helping it withstand various environmental stresses. This protective role is largely due to its structural composition. The stratum corneum, the outermost layer of the skin, acts as the main barrier to the diffusion of most substances. It is made up of flattened, keratin-rich dead cells called corneocytes, surrounded by a lipid matrix containing ceramides, free fatty acids, cholesterol, and cholesterol sulfate. These lipids are organized into bilayer structures, creating a strong barrier.The primary route for molecules to traverse the stratum corneum is through the spaces between the cells. However, this process is slow because of the skin's dense structure and low hydration levels (15–20%), which hinder drug penetration. Furthermore, the continuous renewal of the stratum corneum limits the bioavailability of drugs administered topically or transdermally. Although research has advanced methods to improve skin penetration, challenges like slow absorption, limited dosage options, and the requirement for low-dose drugs remain significant. Beneath the stratum corneum is the viable epidermis, a layer positioned between the dermis and the outer barrier, with a thickness ranging from 50 to 100 µm drugs absorbed through the skin first enter the circulatory system and may later accumulate in the hypodermis, where the fatty tissue can act as a drug reservoir.[5]

ADVANTAGES:

- Transdermal medication provides a continuous release of the drug over an extended period, helping to prevent side effects and therapeutic failures often linked to intermittent dosing.
- It offers an alternative administration method for patients who cannot tolerate oral medications, such as those experiencing vomiting.
- Enhances the therapeutic effectiveness of many drugs by addressing issues like gastrointestinal irritation, poor absorption, and interactions with food, beverages, or other drugs.
- Avoids first-pass metabolism since it bypasses the liver.

DISADVANTAGES:

- Drugs larger than 500 Daltons are unsuitable for transdermal drug delivery systems (TDDS).
- High drug concentrations can lead to skin irritation.
- Achieving high plasma drug levels is challenging.
- Extended use may cause discomfort for patients.
- Drugs with extremely low or high partition coefficients may not successfully enter systemic circulation.[6]

LIMITATIONS OF TDDS:

- The drug or its formulation may cause irritation or allergic reactions.
- It is impractical for drugs that undergo significant metabolism in the skin or have a molecular size too large to pass through the skin.
- Not ideal for drugs lacking a suitable oil/water partition coefficient.
- The skin's barrier properties vary between different areas of the same person, between individuals, and with age.[7]

A COMPREHENSIVE STUDY ON TRANSDERMAL PATCHES:

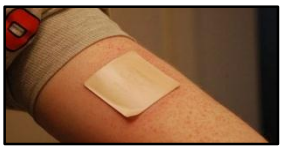

Fig. no 2. Transdermal patch

Fig. no 3. Patch of Administration date.

DEFINATION:

A transdermal patch is an adhesive, drug-infused patch applied to the skin, intended to deliver a controlled amount of medication through the skin into the bloodstream.

MECHANISM OF ACTION:

RELEASE FROM THE BASE MATERIAL OF THE PATCH

DIFFUSION TO THE STRATIUM CORNEUM

DIFFUSION TO THE EPIDERMIS

MIGRATION TO THE CAPILLARY VESSELS

MIGRATION TO THE AFFECTED AREA

PRINCIPLE OF THE TRANSDERMAL PERMEATION:

Initially regarded as an impermeable barrier, the skin's potential for systemic drug delivery has been revealed through research. As the body's largest and most accessible organ, the skin is only separated from the underlying capillaries by a thin layer of tissue, making it suitable for drug absorption. The journey of a drug from a patch to the bloodstream involves several essential stages

- Release from the Reservoir: The drug travels from the reservoir to the rate-controlling membrane.
- Entry into the Stratum Corneum: The drug moves through the rate-controlling membrane and into the stratum corneum.
- Absorption and Penetration: The stratum corneum absorbs the drug, which then penetrates the viable epidermis.
- Absorption by Capillaries: The drug is taken up by the capillary network in the dermal papillary layer.
- Effect on the Target Organ: The drug reaches the target organ and exerts its therapeutic effect.

FACTORS AFFECTING PERMEABILITY:

- The stratum corneum, the outermost layer of the skin
- The precise anatomical site of application
- The overall health and condition of the skin, including any underlying conditions
- The patient's age
- Metabolic activity in the skin[8]

BIOPHARMACEUTICAL PARAMETERS IN DRUG SELECTION OF TRANDERMAL PATCHE:

- The drug should have a daily dosage of less than 100 mg.
- Its half-life should be 12 hours or less.
- The molecular weight must be under 400.
- The partition coefficient (Log P) between octanol and water should be between 1.0 and 3.0.
- The skin permeability coefficient should not exceed 0.5 x 10^-3 cm/h.[9]

BASIC COMPONENTS OF TDDS:

A. Polymer matrix / Drug reservoir

B. Drug

C. Permeation enhancers

D. Pressure sensitive adhesive (PSA)

A) Polymer matrix:

Polymers are the key materials used in transdermal drug delivery systems. These systems are generally structured as multilayer polymer laminates, with a drug reservoir or drug-polymer matrix positioned between two polymer layers: an outer impermeable backing layer that prevents drug loss and an inner polymer layer that functions as an adhesive and/or controls the rate of drug release. To develop efficient transdermal systems, selecting the right polymers and designing them appropriately is crucial to meet fabrication needs. A major challenge is creating a suitable polymer matrix and optimizing the drug-loaded matrix to achieve not only the desired release profile but also an appropriate balance between adhesion and cohesion, along with the necessary physicochemical properties and compatibility with both the other system components and the skin.

a. Natural Polymers: Examples include cellulose derivatives, zein, gelatin, shellac, waxes, proteins, gums and their derivatives, natural rubber, starch, etc.

b. Synthetic Elastomers: Examples include polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, nitrile, acrylonitrile, butyl rubber, styrene-butadiene rubber, neoprene, etc.

c. Synthetic Polymers: Examples include polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, polymethylmethacrylate, epoxy resins, etc.

❖ Polymer Criteria:

- ✓ The polymer must be chemically stable or act as an inert carrier for the drug.
- ✓ It should remain stable, without decomposition, during storage and throughout its intended use, ensuring proper adhesion of the patch to the skin.
- ❖ Adhesion is influenced by three main factors:
- ✓ Peel: The resistance to separation of the adhesive bond.
- ✓ Tack: The ability of the polymer to adhere to a surface with minimal pressure.
- ✓ Creep: The gradual weakening of the adhesive bond under shear stress.

B) Drug substance

Physiochemical properties:

- The drug should be soluble in both water and oil, ideally with a solubility greater than 1 mg/ml.
- The melting point of the drug should be under 200°F. The concentration gradient across the membrane is affected by the drug's solubility in the lipid phase, which is inversely related to its melting point. Hence, drugs with lower melting points are better suited for transdermal delivery.
- The molecular weight of the drug should ideally be less than 1000 daltons.
- The pH of a saturated aqueous solution of the drug should range from 5 to 9. Drugs that are too acidic or alkaline tend to ionize at physiological pH, reducing their ability to penetrate the skin

Biological Properties:

- The drug must be highly potent, requiring less than 25 mg per day to achieve its therapeutic effect.
- It should have a short half-life in the body.
- The drug should not cause irritation or allergic reactions when applied to the skin.
- It must remain stable upon contact with the skin.
- The drug should not provoke an immune response in the skin.[10]

APPROACHES USED IN DEVELOPMENT OF TRANSDEMAL PATCH:

A. Membrane moderated systems
B. Adhesion controlled system
C. Matrix dispersion

A.Membrane moderated systems:

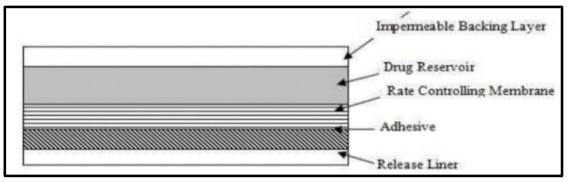

Fig no 4. Membrane moderated systems

In this system, the drug reservoir is fully enclosed within a shallow compartment made from a drug-impermeable metallic plastic laminate and a polymeric membrane that controls the rate of release. The drug within the reservoir can be either incorporated into a solid polymer matrix or suspended in a non-leachable, viscous medium, such as silicone fluid. The release-controlling membrane can be either micro-porous or non-porous, like ethylene vinyl acetate copolymer, positioned on the outer surface. A hypoallergenic adhesive polymer layer may be added to ensure proper contact between the transdermal drug delivery system (TDDS) and the skin.

Marketed systems include:

Transderm - Nitro system for once-daily use.

Transderm- Scop system for multiple days of medication.

Catapres- TTS system for weekly treatment.

B. Adhesive controlled system:

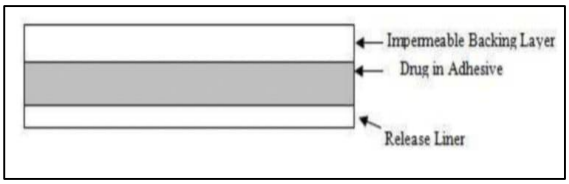

Fig no 5 Adhesive controlled system

This is a basic form of membrane-controlled drug delivery system. In this method, the drug is directly dispersed within an adhesive polymer, which is then applied onto a drug-impermeable metallic plastic backing through solvent casting to form a thin layer. To regulate the drug release rate, non-medicated adhesive polymer layers of uniform thickness are applied above the reservoir layer. The drug-in-adhesive patch can be designed as a single-layer or multi-layer system. In the multi-layer version, an additional drug-in-adhesive layer is typically separated by a membrane. These drug-in-adhesive patches improve patient compliance by simplifying the application process (often requiring weekly

changes), while also enhancing cosmetic appeal and ensuring better adhesion.[11]

Marketed devices:

* Climara®

* Nicotrol®

* Deponit®

TYPES OF TRANSDERMAL PATCHES:

A. Single layer drug in adhesive

B. Multilayer drug in adhesive

C. Drug reservoir in adhesive

A. Single layer drug in adhesive:

In this system, the drug is integrated into the adhesive layer itself. The adhesive not only bonds the layers together and holds the system in place on the skin but also regulates the release of the drug. The adhesive layer is positioned between a temporary liner and a backing layer.

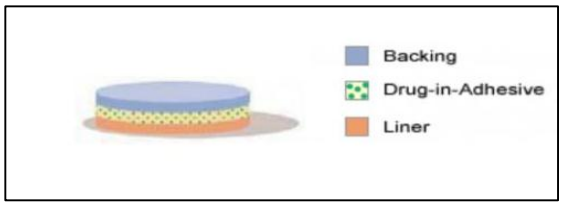

Fig no 6. Single layer drug in adhesive

B. Multilayer drug in adhesive:

The multi-layer drug-in-adhesive patch is similar to the single-layer system, but it features an additional drug-in-adhesive layer, often separated by a membrane (though this is not always the case). One layer is designed for immediate drug release, while the other provides controlled release from the reservoir. The patch also includes a temporary liner and a permanent backing. Drug release is governed by the membrane's permeability and the diffusion of the drug molecules. In this system, both the drug and excipients are incorporated into the adhesive, with two adhesive layers separated by a single membrane layer. Drug release occurs through diffusion.

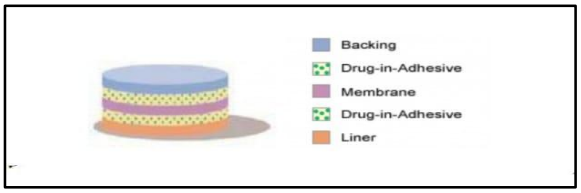

Fig no.7. Multilayer drug in adhesive

C. Drug reservoir in adhesive:

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems, the reservoir transdermal system has a separate drug layer. This layer contains a liquid compartment that holds either a drug solution or suspension, and it is isolated from the adhesive layer. The system is also reinforced by a backing layer.[12]

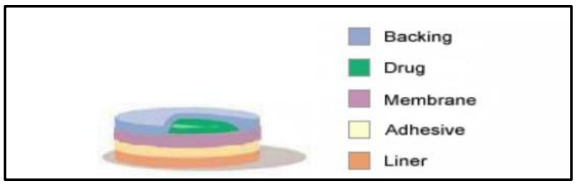

Fig no. 8 Drug reservoir in adhesive

VARIOUS METHODS FOR PREPARATION OF TDDS PATCHES:

A. A Solvent casting technique
B. Asymmetric tpx membrane method
C. Asymmetric tpx membrane preparation
D. Circular teflon mould method

A. Solvent casting technique

In the solvent casting method, transdermal patches are prepared by incorporating glycerin (15% w/w of the dry polymer) as a plasticizer and polyethylene glycol 400 (PEG 400, 10% w/w of the dry polymer) as a permeation enhancer. The polymeric solution is made by dissolving hydroxypropyl methylcellulose (HPMC) in a 1:1 mixture of chloroform and methanol, which is stirred with a magnetic stirrer. Glycerin and PEG 400 are then added to this solution. Afterward, 50 mg of the drug is gradually added and dissolved with continuous stirring for 30 minutes. The prepared solution is poured into custom molds and placed on a flat surface, covered with an inverted funnel to control evaporation. The solution is left to dry for 24 hours, after which the films or patches are cut into 1 cm^2 sections. These patches are stored in a desiccator until testing, and a thin layer of hypoallergenic adhesive is applied to the outer surface to ensure proper adhesion to the skin.

B. Asymmetric TPX membrane method (Berner and John)

To fabricate a prototype patch, a heat-sealable polyester film (type 1009, 3M) with a 1 cm diameter concave area serves as the backing membrane. The drug is placed into the concave section, covered with an asymmetric TPX (poly (4-methyl-1-pentene)) membrane, and then sealed with an adhesive layer.[13]

C. Asymmetric TPX membrane preparation

These membranes are produced using a dry/wet inversion process. TPX is dissolved in a mixture of cyclohexane (solvent) and nonsolvent additives at 60°C to form a polymer solution. The solution is kept at 40°C for 24 hours before being spread onto a glass plate to the desired thickness using a Gardner knife. The cast film undergoes partial evaporation at 50°C for 30 seconds, followed by immediate immersion in a coagulation bath at 25°C. After 10 minutes of immersion, the membrane is removed and air-dried in a circulating oven at 50°C for 12 hours.

D. Circular Teflon Mold Method (Baker and Heller)

Solutions with varying polymer ratios are prepared using an organic solvent. A measured amount of drug is dissolved in half of the solvent, and then a plasticizer is added. The mixture is stirred well and poured into a circular Teflon mold. To control the solvent evaporation rate, an inverted glass funnel is placed over the mold. The solvent is left to evaporate over 24 hours, and the resulting films are stored in a desiccator.[14]

EVALUATION OF TRANSDERMAL PATCHES:

- Physical Appearance: All prepared patches will be visually examined for color, clarity, uniformity, flexibility, and smoothness.
- Folding Endurance: Folding endurance of the film will be measured manually by folding a small strip repeatedly at the same point until it breaks. The number of folds made before breaking will indicate the folding endurance.[15]
- Flatness: To assess patch flatness, three longitudinal strips—one from the center, one from the left, and one from the right—will be cut. The length of each strip will be measured, and any variation in length due to flatness inconsistencies will be calculated by determining the percent constriction, with 0% constriction representing complete flatness.

Constriction (%) = (l1 - l2) / l1

Where;

l1 = initial length of each strip,

and l2 = final length.

- In Vitro Skin Permeation Studies

In vitro permeation studies can be performed using a diffusion cell setup. Full-thickness abdominal skin from male Wistar rats (weighing between 200-250 g) is typically utilized. The abdominal hair is carefully removed using an electric clipper, and the dermal side of the skin is thoroughly rinsed with distilled water to eliminate any residual tissues or blood vessels. Prior to the experiment, the skin is equilibrated for one hour in a diffusion medium, such as phosphate buffer with a pH of 7.4.

- In Vivo Studies

In vivo evaluations provide a more accurate representation of a drug's performance, addressing variables that cannot be fully assessed during in vitro experiments. These studies can be conducted using both animal models and human volunteers to thoroughly investigate the drug's behavior and effectiveness in a living system.[16]

Advantages of Transdermal Patches:

- Bypasses the first-pass metabolism, thereby improving the bioavailability of the drug.
- Helps in maintaining lower plasma drug concentrations, which reduces the likelihood of side effects.
- Minimizes fluctuations in plasma drug levels, making them ideal for drugs with a short half-life or a narrow therapeutic window.
- Reduces dosing frequency, which can enhance patient adherence to the prescribed regimen

Disadvantages of Transdermal Patches:

- There is a potential for local skin irritation, such as redness, itching, and swelling at the site of application.
- The number of drugs suitable for transdermal administration is limited because of the skin's low permeability.[17]

Limitations of Transdermal Patches:

- Transdermal delivery is not effective for ionic drugs.
- They are not capable of achieving high drug concentrations in the bloodstream or plasma.
- Transdermal patches are not suitable for large molecular weight drugs.
- These systems cannot provide pulsatile drug delivery.[18]

CARE TAKEN WHILE APPLYING TRANDERMAL PATCH:

- Precautions for applying a transdermal patch:

- The skin area where the patch will be applied must be thoroughly cleaned.
- The patch should not be cut, as this can compromise drug delivery.
- Always remove the old patch before applying a new one.
- Avoid touching the adhesive side of the patch with your hands or other objects, as this can affect the release rate and bioavailability.

Finally, ensure that the patch is positioned correctly on the application site.[19]

USES OF TRANSDERMAL PATCHES:

1. This method serves as an alternative for patients experiencing severe side effects, such as constipation, or those who have difficulty swallowing oral medications (dysphagia).
2. It can enhance pain management through consistent drug delivery, which is beneficial for patients with cognitive impairments or those unable to self-administer their pain relief.
3. Additionally, it can be combined with other enhancement techniques to achieve synergistic effects.[20]

RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES:

A) Patch technology for protein delivery

Transdermal delivery of large proteins is a cutting-edge and promising method, though no commercial technologies currently incorporate proteins into transdermal patches. TransPharma has developed a unique printed patch technology that facilitates protein delivery through its ViaDerm system. These patches are designed to hold specific doses of proteins in a dry form. It is believed that water-soluble proteins dissolve when they come into contact with the interstitial fluid from the skin, which is drawn through RF-MicroChannels, creating a concentrated protein solution at the application site. The dissolved proteins are then transported via these RF-MicroChannels into the deeper layers of the skin, where they diffuse across a concentration gradient.

B) Pain-Free Diabetic Monitoring Using Transdermal Patches

The initial prototype patch is a few centimeters in size, made from a combination of polymers and thin metallic films. The sampling array, along with its metallic connections, is clearly visible. When the patch seal is broken, interstitial fluid and its biomolecules are exposed on the surface of the skin. The patch includes micro-heating elements embedded in the layer closest to the skin, which can generate a localized heat pulse to penetrate the stratum corneum. This ablation process raises the skin surface temperature to around 80°C, but the heat quickly dissipates, ensuring no harm to the underlying living tissue or nerve endings. This painless, bloodless method creates a disruption about 50 micrometers in diameter, the size of a hair follicle, enabling the interstitial fluid to interact with the electrode sites on the patch.

C) Pain Relief

Transdermal patch technology is commonly used for pain relief, with the Duragesic patch being one of the most well-known examples. Other options, such as the Lidoderm patch, which contains lidocaine for treating post-herpetic neuralgia, are also available. Significant progress in pain management has been made with the E-Trans fentanyl (Cl) patch. This compact, credit card-sized device contains a self-powered battery that delivers pulses of fentanyl (Cl), a strong opioid. This technology mimics intravenous self-controlled analgesia systems, which are typically expensive, bulky, and require substantial nursing support.[21]

TRANSDERMAL PATCHES AVAILABLE IN THE MARKET CURRENTLY:

Table no. 1 Transdermal patches available in the market currently

Sr. No	PRODUCT NAME	DRUG	MANUFACTURER	INDICATION
1.	Alora	Estradiol	Thera Tech /proctor & Gamble	Postmenstrual syndrome
2.	Androderm	Testosteron	Thera Tech / Glaxo Smith Kline	Hypogonadium (males)
3.	FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
4.	Habitraol	Nicotine	Novartis	Smoking cessation
5.	CatapresTTS	Clonidine	Alza	Hypertension
6.	Combi Patch	Estradiol	Noven	Hormone replacement therapy

7.	Fematrix	Estrogen	Ethical Holding	Postmenstrual syndrome
8.	Deponit	Nitroglycerin	Schwarz-Phrma	Angina pectoris

Fig no 9. Contraceptive patch

Fig no 10. Diabetic patch'

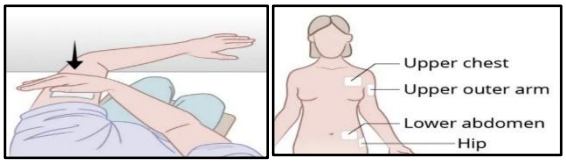

Fig no 11. Transdermal patches: How to apply them

CONCLUSION

The field of transdermal patches has seen significant progress, generating considerable interest among researchers due to the many advantages offered by transdermal drug delivery systems. Ongoing research is focused on integrating new drugs into these systems and creating devices to improve drug absorption and penetration. However, there are still challenges, such as the inability to deliver large molecules, limited dosage capacities, low absorption rates, and the risk of skin irritation, which have hindered the widespread adoption of transdermal systems. Despite these limitations, the development of new devices and drugs compatible with this delivery method is driving the increasing use of transdermal drug delivery systems today.Since its introduction in 1981, the transdermal drug delivery system has proven to be a safe and effective means of medication administration, offering a more convenient and safer alternative to traditional systemic drug delivery methods. This could eventually replace needles for a variety of drugs. This article provides valuable insights into the formulation and evaluation of transdermal patches, addressing the challenges of current drug delivery techniques. Additionally, advancements in transdermal drug delivery systems (TDDS) have established TDDS as the next-generation solution for drug delivery.

REFERENCES

[1] Rathore R P S, Chauhan C S, Naruka P S, Tan war Y S, Chauhan L S. Transdermal Formula tion of Terbutaline Sulphate. Pharmacy onlin e.2006

[2] Bouwstra JA, Cooris CS, Vander spek JA, Bras W, Structural investigation of human stratum corneum by small angle x-ray scattering, J Invest Dermatol 1991,97,1005-12.

[3] Segal, Marian, Patches, Pumps and Timed Release: New Ways to Deliver Drugs, Food and Drug Administration. Retrieved on 2007-02-24.

[4] Berner B, John VA, Pharmacokinetic characterization of Transdermal delivery systems, J Clin Pharmacokin, 1994,26 (2),121-34.

[5] Aggarwal G. Development, Fabrication and Evaluation of Transdermal Drug Delivery-A Review, Pharmainfo.net, 2009.

[6] Ranade VV, Drug delivery systems, Transdermal drug delivery, J ClinPharmacol, 1991,31(5),401-18.

[7] Jacoby DB, Youngson RM, Marshall Cavendish Corporation, Encyclopedia Of Family Health, Published by Marshall Cavendish, 2004,2259.

[8] Barry BW, William AC, Encyclopedia of pharmaceutical technology, Marcel Dekker, New York,1995,Vol. II,49-93.

[9] Barry BW, Dermatological formulation: percutaneous absorption, Marcel Dekker, New York, 1983.

[10] Alexander A, Dwivedi S, Ajazuddin, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. J Control Rel 2012:164;26–40.

[11] Flaynn CL, Bronaugh RL and Maibach HI, Percutaneous absorption, Marcel Dekker, New York, 1985,17-52.

[12] Chakrabarty Tulasi, Sani Vipin, Sharma sakshi, kaur Baljot, Dhingra Garima, IJOF; antifungal gel for different rout of administration and different drug delivery system, 2014; 5(3): 230-240.

[13] Crawford RR and Esmerian OK, Effect of plasticizers on some physical properties of cellulose acetate phthalate films, J. Pharm. Sci, 1997; 60: 312-314.

[14] Deo MR, Sant VP, Parekh SR, Khopade AJ and Banker UV, Proliposome-based transdermal delivery of levonorgesterol, J. Biomat. Appl, 1997; 12: 77-88.

[15] Devi Kusum V; Saisivam S; Maria GR, and Deept P.V; "Desine and evaluation of matrix diffusion controlled transdermal patches of

Verapamil Hydrochloxide" J Drug Dev .Ind. pharm, 2003; 29(5): 495-203.

[16] Dr. S.J.Shankar., P. Kapadiya Palak., Prabhu Makaranda., Prarthan B. Raju., Formulation and Evaluation of an Anti-Diabetic drug of GLIBENCLAMIDE, World J of pharmaceutical sciences and research, 2015; 3: 522-541.

[17] Franz TJ. Transdermal Delivery. In: Kydonieus A, ed Treatise on controlled drug delivery: fundamentals, optimization, application. New York, Marcel Dekkar Inc, 1991;341-421.

[18] Pokala M, Pawarkar K, Tammira KR, Mamidi P, Racha U, Samudrala L. Formulation and evaluation of transdermal patches of salbutamol.world journal of pharmacy and pharmaceutical sciences .2016

[19] 19.Vyas SP, Khar RK. Targetted and controlled Drug Delivery Novel carrier system. 2002, 411- 447.

[20] Ganga Bhavani PP, Kumar RP, Ravi SK, Santosh T. Formulation and evaluation studies on transdermal dosage forms of diclofenac sodium.World Journal of Pharmacy and Pharmaceutical Sciences. 2014; 4(3):1054.

[21] Verma N, Deshwal S. Design and in vitro evaluation of transdermal patches containing ketoprofen. World Journal of Pharmaceutical Research. 2014; 3(3):3935.