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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**Available online at: <http://www.iajps.com>**Review Article****A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM**

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Dehradun, (248001) Uttarakhand, India**Abstract:**

In today's world about 74% of drugs are taken orally and are found not to be as effective as desired in the present scenario. So to overcome or to improve such character transdermal drug delivery system was emerged in form of transdermal patches. Transdermal drug delivery represents the most rapidly advancing areas of novel drug delivery. To overcome the difficulties of drug delivery through oral route easier way was introduced known as transdermal drug delivery system for example poor bio-availability, first pass metabolism and sometime responsible for rapid blood level.

Keywords: *Transdermal patches, Penetration Enhancers, TDDS.*

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INTRODUCTION:

Transdermal drug delivery system is defined as the topically administered medications which when applied to the skin membrane in the form of patches and delivers the drug, through the skin at a predetermined and controlled rate. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at predetermined and controlled rate. For application of the drug skin is the important site for both systemic and local effect. However, it was in the twentieth century when the skin became used as route for long term drug delivery. Today about two third of drugs (available in market) are taken orally, but these are not as effective as required. To improve upon the features the transdermal drug delivery system was emerged. In transdermal delivery system the drug enters into the bloodstream directly through the skin by a process known as diffusion process. As there is the low concentration in the blood and high concentration on the patch the drug will keep diffusing for a long period by maintaining the constant concentration of drug in the blood [1-5].

Over the last few decades, transdermal delivery system has become an appealing and patient compliance technology as it minimizes and overcomes the limitations concerned with conventional as well as parenteral route of drug administration [6-10].

Physiology of skin [11]:

The skin is the largest organ tissue of the human body. Most of the topical preparations are designed to be useful to the skin. So for scheming topical preparation basic knowledge of the skin and its physiology function are very significant. The skin of an average adult body covers a surface area approximately 2m^2 and receives about one third of the blood circulating through the body. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted also get influence the pH of the skin surface. The skin can be considered to have mainly three distinct layers:

1. Epidermis.
2. Dermis.
3. Subcutaneous connective tissue.

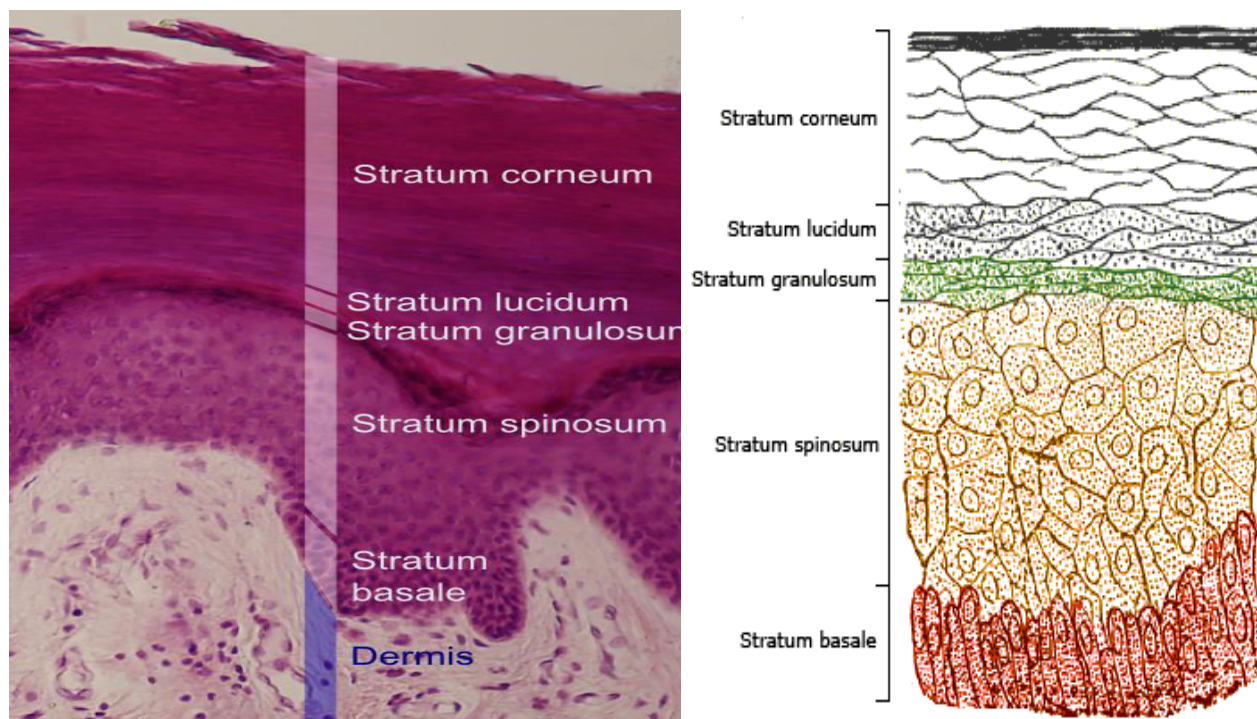


Fig 1: Physiology of skin

1. Epidermis: The multilayered envelope of the epidermis varies in thickness, depending on the cell size and number of cell layers, which ranges from 0.8mm on palms and soles down to 0.06mm on the eyelids. It further consists of two layers:

a) **Stratum corneum:** It is the outermost layer of the skin and also termed as horny layer. It is approx 10mm thick when in dry conditions but swells to several times the thickness when fully hydrated. It is flexible but relatively impermeable and known as the principal barrier for penetration. It constitutes of 75 to 80% proteins, 5 to 15% lipids and 5 to 10% andansteron material on the dry weight basis.

b) **Viable epidermis-** Situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. As we go more deep it consists of few layers as stratum lucidum, stratum basale, stratum spinosum and stratum granulosum.

2. Dermis: Dermis is composed of a matrix of a connective tissue which contains lymphs, blood vessels and nerves and is about 3 to 5mm thick layer. On one hand it provides nutrients and oxygen to the skin and on other hand it removes toxins and waste products too. The blood supply thus keeps dermal concentration of permeation very low, and the resulting concentration difference across the epidermis provides the vital driving force for transdermal permeation.

3. Subcutaneous connective tissue: The subcutaneous fat tissue or hypodermis supports the dermis and epidermis. This layer serves as fat storage area, and helps to regulate temperature and provides nutritional support too. For transdermal drug delivery drug has to penetrate through all the three layers of the skin and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is important and then retention of drug in skin layers is desired.

BASIC COMPONENTS OF TDDS:

Drug

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life. eg fenatyl, nitroglyceriene, etc

Polymer

The polymer controls the release of the drug from the device. The polymer should follow these criteria's:

a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and get released through it.

b) Polymer should be non- toxic.

c) Polymer should be inexpensive.

Types of polymers

a) Natural polymer- Cellulose derivative, Gelatin, waxes, Proteins, etc

b) Synthetic Elastomers- Hydrin rubber, silicone rubber, Neoprene, etc

Penetration Enhancer [12,13]

Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvent, surface active agents and two component systems. E.g. DMSO

Method to Enhance Drug Penetration & Absorption

➤ Chemical enhancement.

➤ Physical enhancement.

➤ Biochemical enhancement.

➤ Super saturation enhancement.

Properties of Penetration Enhancers:

➤ They should be non-toxic, non-irritating & non-allergenic.

➤ They would ideally work rapidly & the activity & duration of effect should be both predictable and reproducible.

➤ They should have no pharmacological activity within the body i.e. should not bind to receptor sites.

➤ They should work unidirectional i.e. avoiding the loss of endogenous material from the body whereas should allow therapeutic agents into the body.

➤ They should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipient and drugs.

➤ They should be cosmetically acceptable with an appropriate skin 'feel'.

Mechanism of Penetration Enhancers:

Penetration enhancers may act by one or more of three main mechanisms:

➤ Disruption of the highly ordered structure of stratum corneum lipid.

➤ Interaction with intercellular protein.

➤ Improved partition of the drug, co enhancer or solvent into the stratum corneum.

The enhancers act by altering one of three pathways. By protein conformational change or solvent swelling the polar pathway is altered. The fluidity of the lipid protein portion of the stratum corneum is increased by fatty acid enhancers. By altering the multi laminate pathway for penetration some enhancers act

on both polar and non-polar pathway. Drug diffusivity through skin proteins is increase by enhancer. On the design and development of the product significant effect is employed by type of enhancer.

Adhesive Layer

Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug.

Backing laminates- should have low modulus or high flexibility. Ex- vinyl, polyethylene.

Release liner- Protects the patch during storage. The liner is removed prior to use.

Other Excipients [14]:

Plasticizers: Plasticizers have been also used in many formulation ranging from 5-20 % (w/w, dry basis) along with brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surface membranes and improvement in strength of film some of its example are glycerol and sorbitol, at 15% w/w (dry basis) phosphate, phthalate ester, fatty acids ester and glycol derivative such as PEG 200 and PEG 400.

Types of transdermal patch [15,16]

1. Single-layer Drug-in-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

2. Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

3. Reservoir

Unlike the Single-layer and Multi-layer Drug-in adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

4. Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The

adhesive layer in this patch surrounds the drug layer partially over laying it.

ADVANTAGES

- They avoid gastrointestinal drug absorption difficulties caused due to gastrointestinal pH, enzymatic activities, etc with foreign particles (food, water, etc) and orally administered drugs.
- They can substitute oral route of administration of drugs which when administered through oral route, as in case of vomiting and diarrhea.
- Avoids first pass effect.
- They are non invasive, avoiding the convenience of parenteral therapy.
- Drug administration can be terminated rapidly by instant removal of its application from the surface of the skin.
- It is also a positive route for the patients who are unconscious.
- They provide extended therapy with a single application, improving compliance over other dosage forms.

DISADVANTAGES

- Its use may be uneconomical.
- The delivery systems can't be used for drug requiring high blood levels.
- May cause allergic reactions.

Factors Affecting Topical Absorption of Drug **Physiological Factors**

1. Skin thickness – It varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100-150µm. Skin on the sole & palm has a high rate of diffusion.
2. Skin pH –The pH of the skin surface is influence by sweat and fatty acid secreted from sebum.
3. Lipid content - It is an effective water barrier, when lipid weight in stratum corneum is low percutaneous penetration increases.
4. Inflammation of skin – that disrupts the continuity of stratum corneum increases permeability.
5. Skin temperature – When temperature is increase the rate of skin permeation is also Increase.
6. Blood flow
7. Hydration of skin
8. Density of hair follicles
9. Density of sweat glands

Physiochemical Factors

1. Partition coefficient – more the value of log p more effortlessly will be the percutaneous absorption of the drug.
2. Molecular weight (< 400 Dalton)
3. Degree of ionization – only unionized drug molecules get absorbed well.

Factors to be considered when choosing a Topical Preparation

- Effect of the vehicle e.g. Penetration of the active ingredient & efficacy is improve by occlusive vehicle. The vehicle itself may have a cooling, drying, emollient or protective action.
- Match the type of preparation with the type of lesions. For example, for acute weepy dermatitis avoid greasy ointments.
- Match the type of preparation with the site.(e.g., gel or lotion for hairy parts)
- Irritation or sensitization potential. Generally, gels are more irritating than ointments and water-in-oil creams. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

EVALUATION PARAMETERS FOR THE FORMULATION:**Thickness of the patch:**

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film [17, 18].

Weight uniformity:

The prepared patches are dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights [18].

Folding endurance:

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance [19].

Percentage Moisture content:

The prepared films are to be weighed individually and to be kept in a desiccators containing fused

calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula [18,21].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Final weight}}$$

Content Uniformity Test:

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test [17, 21].

Moisture Uptake:

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below [17, 18].

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight} \times 100}{\text{Initial weight}}$$

Drug Content:

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV and HPLC technique). Each value represent average of three different sample [17-19].

Shear Adhesion Test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a1 direction parallel to the plate. Shear adhesion strength is determined by measuring the time it take to pull the tape off the plate the longer the time take for removal, grater is the shear strength [20].

Flatness:

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the center and two from each side of patches. The length of each strip is measured and variation in length is measured

by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{(L_1 - L_2) \times 10}{L_1}$$

L_2 = Final length of each strip

L_1 = Initial length of each strip

Tensile Strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

'F' is the force required to break; 'a' is width of film; 'b' is thickness of film; 'L' is length of film; 'l' is elongation of film at break point.

In another study, tensile strength of the film was determined with the help of texture analyzer.

The force and elongation were measured when the films broke [21].

CONCLUSION:

Transdermal drug delivery is most applicable route of drug administration, which is used to deliver the drug into the site of action at the predetermined and control rate. Through this route drug can be applied in the form of thick transdermal patch that's why the drug release easily from the patch and maintain therapeutic effect. The main purpose of making transdermal patches is to overcome the steps present in oral drug delivery like first pass metabolism, GI irritation, etc.

REFERENCES:

1. Kshirsagar N A. Drug Delivery Systems. *Ind. J. Pharmacol.* 2000; 32:S54- S61.
2. Sharma S. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. *Pharmaceutical reviews* 2008; 6:1
3. Stanos SP. Topical Agents for the Management of Musculoskeletal Pain. *J Pain Symptom Manage* March 2007; 33.
4. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal Drug Delivery System: A Review. *AJPCR* 2009; 2: 14-20.
5. Subranayam N, Ghosal SK, Moulik SP. Enhanced *In-Vitro* Percutaneous Absorption & *In-Vivo* Anti-Inflammatory Effect of a Selective Cyclooxygenase

Inhibitor Using Microemulsion. *Drug Dev. & Industrial Pharm.*, 2005.

6. Pathan, I.B.; Setty, C.M. Chemical penetration enhancers for transdermal drug delivery systems. *Trop J Pharm Res.* April 2009; 8:173-179.

7. Curr AEB. *Transdermal Drug Delivery: Penetration Enhancement Techniques* Heather. *Drug Deliv*, 5(2):23-33, (2005).

8. Rutter N, Drug absorption through the skin: a mixed blessing. *Arch Dis Child*, 62:220- 221, (1987).

9. Swarbrick, J. *Encyclopedia of pharmaceutical technology*, 3rd ed., 1551.

10. WB Saunders Co. Philadelphia, 1970, 55-60.

11. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. *Int J Drug Del*, 1(3): 41 – 51, (2009).

12. Jones DB, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. *Int J Pharm*, 151:223–33, (1997).

13. *Transdermal Drug Delivery Technology Revisited: Recent Advances.*

14. Arabi H, Hashemi SA, Ajdari N. Preparation of a transdermal delivery system and effect of membrane type for scopolamine drug. *Iranian Polymer J.* 2002; 11(4): 245- 249.

15. Singh MC, Naik AS and Sawant SD. Transdermal Drug Delivery Systems with major emphasis on Transdermal patches : A Review. *Journal of Pharmacy Research* 2010; 3(10): 2537-2543

16. Tortora G, Grabowski S. (2006). The Integumentary system. In: *Principles of Anatomy and Physiology*. 9th edition. John Wiley and Sons Inc. pp.150-151.

17. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal Drug Delivery System –design and Evaluation. *International Journal of Advances in Pharmaceutical Sciences*. 2010; 1:201-211

18. Rhaghuram RK, Muttalik S, Reddy S. Once – daily sustained release matrix tablets of nicorandil: formulation and *invitro* evaluation. *AAPS Pharm.SciTech.* 2003; 4(4):480–488.

19. Shaila L, Pandey S, Udupa N. Design and evaluation of matrix type membrane controlled

20. Transdermal drug delivery system of nicotin suitable for use in smoking cessation. *Indian Journal of pharmaceutical sciences*. 2006; 68:179-184.

21. Aggarwal G, Dhawan S. Development, Fabrication and Evaluation of Transdermal Drug Delivery System - A Review.