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REVIEW PAPER

Transdermal Drug Delivery System: A Systemic Review

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ABSTRACT

The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. It has various advantages like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. The stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules. There are three main routes of drug penetration, which include the appendageal, transcellular and intercellular routes. Skin age, condition, physicochemical factors and environmental factors are some factors that are to be considered while delivering drug through this route. Basic components of TDDS include polymer matrix, membrane, drug, penetration enhancers, pressure-sensitive adhesives, backing laminates, release liner, etc. This review details the progress and current status of the transdermal drug delivery field and describes numerous pharmaceutical developments which have been employed to overcome limitations associated with skin delivery systems. Advantages and disadvantages of the various approaches are detailed commercially marketed products are highlighted and particular attention is paid to the emerging field. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation.

Keywords: - *Transdermal, stratum corneum, transcellular and intercellular routes*

INTRODUCTION

During the past few years, interest in development of novel delivery system for existing drug molecules has been renewed. Development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves. Patient compliance and overall therapeutic benefit to a significant extent. When properly designed and developed for particular drug, novel delivery system can overcome specific hurdles associated with conventional methods of delivery e.g., drugs undergo partial or complete degradation before reaching site of action could be effectively

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delivered with improved bioavailability by using novel concept of time or pulsatile release, or gastro-resistant delivery.[1] During past 20 years, advances in drug formulations and innovative routes of administration have made. Our understanding of drug transport across tissues has increased. While topical products or drug delivery systems have been used for centuries for the treatment of local skin disorders, use of the skin as a route for systemic drug delivery is of relatively recent origin. Administration of drugs by transdermal route offers advantage of being relatively painless. Transdermal delivery has a variety of advantages compared with the oral route. In particular, it is used when there is a significant first-pass effect of the liver that can prematurely metabolize drugs. Transdermal delivery also has advantages over hypodermic injections, which are painful, generate dangerous medical waste and pose the risk of disease transmission by needle re-use, especially in developing countries.(2) Perhaps the greatest challenge for transdermal delivery is that only a limited number of drugs are amenable to administration by this route. With current delivery methods, successful transdermal drugs have molecular masses that are only up to a few hundred Daltons, exhibit octanol water partition coefficients that heavily favor lipids and require doses of milligrams per day or less. (4-7)The primary mode of administering macromolecules is therefore via injection which is not without limitations, such as the invasive nature of injections eliciting pain and lower acceptance/compliance by patients, in addition to the requirement for administration by a trained administrator.(8-10) Rationally, the conventional routes of medication delivery have many inherent limitations which could potentially be overcome by advanced drug delivery methodologies such as transdermal drug delivery (TDD). The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. (11-12)

2. A Brief Review of Skin Structure

2.1 Skin is the most accessible and largest organ of the body with a surface area of 1.7 m2 , compromising 16% of the total body mass of an average person. (13-15) The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the permeation of ultraviolet (UV) radiation, chemicals, allergens and the loss of water. (16) Skin can be divided into three main regions: (1) the outermost layer, the epidermis, which contains the stratum corneum; (2) the middle layer, the dermis and (3) the inner most layer, the hypodermis (Figure 1)

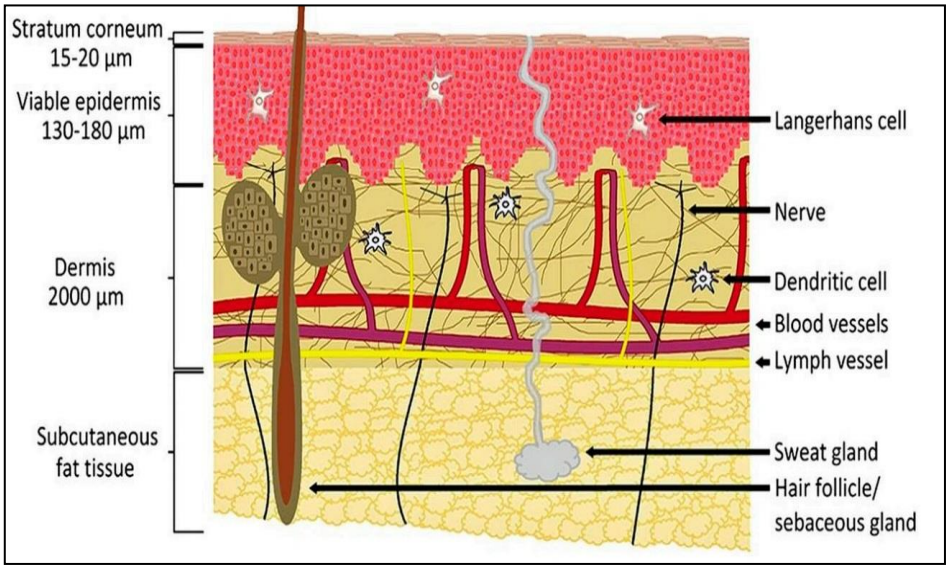

Fig. 1- Anatomy of the skin.

2.2 The objective of TDDS is to achieve systemic medication through topical application on intact skin; therefore, it is important to review the structural and biochemical features of the human skin and those characteristics that contribute to the barrier function and the rate of drug access into the body via the skin.Anatomically, the skin can be divided into two layers: epidermis and dermis or corium [Figure 1], penetrated by hair shafts and gland ducts. The skin is one of the most extensive organs of the human body, covering an area of about 2 m2 in an average human adult. The major skin layers, from inside to outside, comprise the fatty subcutaneous layer (hypodermis), the dermis of connective tissue and the stratified avascular cellular epidermis. This multilayered organ receives approximately one-third of all blood circulating through the body. Epidermis results from an active epithelial basal cell population and is approximately 150-µm thick. It is the outermost layer of the skin, and the process of differentiation results in migration of cells from the basal ayer toward the skin surface. The epidermis contains no blood vessels; therefore, nutrients and waste products must diffuse across the dermal–epidermal junction to maintain its vitality. The epidermis consists of five layers, which, from the inside to the outside, are the stratum germinativum (basal layer), stratum spinosum (spinous layer), stratum granulosum (granular layer), stratum lucidum and stratum corneum (SC). Because the SC cells are dead, the epidermis without the SC is usually termed the viable epidermis. The SC is considered as the rate-limiting barrier in transdermal permeation of most molecules. The SC comprises 15–20 layers of keratin-filled corneocytes (terminally differentiated keratinocytes) anchored in a lipophilic matrix. The lipids of this extracellular matrix are distinctive in many respects: (1) they provide the only continuous phase (and diffusion pathway) from the skin surface to the base of the SC; (2) the composition

(ceramides, free fatty acids and cholesterol) is unique among biomembranes and particularly noteworthy is the absence of phospholipids; (3) despite this deficit of polar bilayer-forming lipids, the SC lipids exist as multilamellar sheets; and (4) the predominantly saturated, long-chain hydrocarbon tails.

Table 1- Advantages and disadvantages of TDDS (16-18)

Advantages	Disadvantages
Self-administration is possible and continuous, sustained release of drug	Only small lipophilic drugs can be delivered currently through the skin
Avoids peak and trough drug levels and longer and multiday dosing intervals	Drug molecule must be potent because patch size limits the amount that can be delivered
Avoids first-pass hepatic metabolism and enzymatic degradation by the gastrointestinal tract and also avoids gastrointestinal irritation	Not suitable for high drug doses
Less frequent dosing improves patient compliance	Adhesion may vary with patch type and environmental conditions
Alternate route for patients who are unable to take oral medications	Adhesion may vary with patch type and environmental conditions
Dose delivery unaffected by vomiting or diarrhea	Skin irritation and hypersensitivity reactions may occur

3. FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY

Skin condition-The intact skin itself acts as a barrier, but many agents like acids and alkali cross the barrier cells and penetrate through the skin. Many solvents open the complex dense structure of the horny layer: solvents like methanol and chloroform remove the lipid fraction, forming artificial shunts through which drug molecules can pass easily.(19)

Skin age- It is seen that the skin of adults and young ones is more permeable than that of the older ones. There is no dramatic difference. Children show toxic effects because of the greater surface area per unit body weight. Thus, potent steroids, boric acid and hexachlorophene have produced severe side-effects.

Physicochemical factors-

Hydration of skin-Generally, when water saturates the skin, it swells tissues, softens wrinkles on the skin and its permeability increases for the drug molecules that penetrate through the skin. (20)

Temperature and pH of the skin- The penetration rate varies if the temperature varies and the diffusion coefficient decreases as the temperature falls;, however adequate clothing on the body prevents wide fluctuations in temperature and penetration rates. According to pH, only unionized molecules pass readily across the lipid membrane and weak acids and bases dissociate to different

degrees according to their pH and pKa or pKb values. Thus, the concentration of unionized drug in applied phase will determine the effective membrane gradient, which is directly related to its pH.

Environmental factors-

Sunlight- Because of to sunlight, the walls of blood vessels become thinner, leading to bruising, with only minor trauma in the sun-exposed areas. Also, pigmentation, the most noticeable sun-induced pigment change, is a freckle or solar lentigo. (20)

Cold season- The cold season often results in itchy and dry skin. The skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant. (20)

Air pollution- Dust can clog pores and increase bacteria on the face and the surface of skin, both of which lead to acne or spots, which affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with the skin's natural protection system, breaking down the skin's natural oils that normally trap moisture in the skin and keep it supple. (21)

4. TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM (22)

a) Single layer drug in adhesive- In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi -layer drug in adhesive- This type is also similar to the single layer but it contains an immediate drug-releaselayer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing

c) Vapour patch- The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour. The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system- In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system-

i. Drug-in-adhesive system- This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system- The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Micro reservoir system- The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Micro reservoir system is a combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.

5. BASIC COMPONENT OF TDDS (23)

Both matrix patches and liquid reservoir patches comprise of various components. Some are similar in both classes, while others are type-specific. The common components include

1. Backing Films- Backing films play a vital role in the transdermal patch and also while using the system. The role of the film is to protect the active layer and safeguard the stability of the system, and to affect skin permeation and tolerance, depending on occlusion or breathability. In order to avoid any type of incompatibility the release liner must be fully inert to the ingredients. It must also be flexible, comfortable and must have good affinity with the adhesive and excellent printability. The most common release liners are polypropylene, polyesters, PVC and nylon.

2. Release Liners- An anti-adherent coating will be covering the release liners. The role of the release liner is to protect the system when it is in the package, it will be removed just before the application of TDDS to the skin. Release liners play an important role in the stability, safety and affectivity of the patch. Care should be taken to choose the release liners. An incorrect release liner will not permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its

shelf life. The most common films used as release liners are paper-based, plastic film-based and composite films. The two major classes of coating are silicones and fluoro-polymers.

3. Pressure Sensitive Adhesives- For both types of TDDS, pressure-sensitive adhesive(PSAs)play an important role, by serving as the matrix that carries the active like additives and permeation enhancers and the means for making the patch stick to the skin. There are three categories in PSAs: rubber-based, acrylic in the form of acrylic solutions, emulsion polymers or hot melts, and silicon PSAs. For each category there are several sub-categories that give the required flexibility to the patch.

4. Penetration Enhancers- These are the completely different chemical substances that belong to the same family by characteristics. They increase the permeation rate by several times of the active ingredient through the skin. This enhances the feasibility of a system, because most of the actives do not enter the skin in the required dosage through a relatively small area. Sometimes a combination of these ingredients is needed to create the correct enhancing effect.

5. Micro porous or Semi-Permeable Membranes- Porous membrane is a special type of membrane mostly used in all liquid transdermal patches and some of the matrix type patches. Its role is to regulate the flow of the semisolid content from the liquid reservoir, and to act as a rate limiting membrane for the systems. The ability of the membrane depends on the design of the system, size of the active component and the need to have rate-limiting factor in order to satisfy the release and absorption characteristics of the system. Permeation rate depend on chemical composition. There are two types of porous membranes as shown below.

A. Ethylene Vinyl Acetate Membrane.

B. Micro porous Polyethylene Membrane

6. Pouching Material- Most of the TDDS that are available in the market are packaged as Unit doses in sealed pouches. The pouching material should be inert and should maintain the stability and integrity of the product. When there are two films with similar desired characteristics, the one with the lower cost, better function and printability will be chosen. There are three main layers in the composite materials used for pouches

a) Internal plastic heat sealable layer

b) The aluminum foil layer

c) The external printable layer.

If the film is a lamination, an adhesive is used to keep the layers intact.

a. Heat Sealable Layer- This layer play an important role in the functionality, stability and protection of the patch. Several plastic films or coatings can be used for its formation, including polyethylene.

b. Aluminum Foil Layer- This layer plays an important role in protecting the product from light and oxygen. In ideal conditions the foil needs to have a thickness of more than 1mil or 25 micrometers to be a real barrier. If any less than this thickness level is used, there will always be pinholes reducing the barrier properties.

c. External Layer- The external layer of a composite film is responsible to achieve a better finishing and printing quality. It acts synergistically with the aluminum foil. Paper or polyester film is used as an external layer, but the polyester film creates a better looking pouch and better barrier.

Table 2- Market preparation of TDSS (23)

APPROVAL YEAR	DRUG	INDICATION	PRODUCT NAME	MARKETING COMPANY
1991	Nicotine	Smoking cessation	Nicoderm®, Habitrol®, proStep®	GSK, Novartis, Elan
1993	Testosterone	Testosterone deficiency	Testoderm®	Alza
2001	Estradiol/norelgestromin	Contraception	OrthoEvra®	Ortho-McNell
2005	Lidocaine/tetra Caine	Local dermal analgesia	Synera®	Endo pharmaceuticals
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana®	Shire
2007	Rotigotine	Parkinson's disease	Neupro®	Schwarz pharma
2013	Sumatriptan	Migraine	Zecuity®	Nupathes Inc.

CONCLUSION

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Transdermal drug delivery offers controlled release of the drug into the patient it enables a steady blood level profile, resulting in reduced systemic side effect and sometimes, and improved efficacy over other dosage form. It offers the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. Transdermal patches have become a proven technology that offers variety of significant clinical benefits over other dosage form. TDD sector continues to grow and develop with rapid expansion in fundamental knowledge feeding industrial development. In time, it is hoped that technological advancements in TDD will lead to enhanced disease prevention, diagnosis and control,

with concomitant improvement in health-related quality of life for patients worldwide. To this end, this review has charted the development of numerous novel TDD methodologies, highlighting the advantages and disadvantages of each approach. Due to the exponential growth in investment and interest in MN technologies and the numerous associated advantages of this approach, particular attention was paid to this TDD system.

REFERENCES

[1] Anjali V. Patel and Biren N. Shah. TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW. AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES. 2018.9 (1): 378-390.
[2] Pawan Jaiswal, "A review on transdermal patches." The pharma research, a journal, Jun 2010, 3, 139-149.
[3] Miller, M.A. & Pisani, E. The cost of unsafe injections. Bull. World Health Organ. 77, 808–811 (1999)
[4] Guy, R.H. & Hadgraft, J. (eds.) Transdermal Drug Delivery (Marcel Dekker, New York; 2003).
[5] Williams, A. Transdermal and Topical Drug Delivery (Pharmaceutical Press, London; 2003).
[6] Prausnitz, M.R., Mitragotri, S. & Langer, R. Current status and future potential of transdermal drug delivery. Nat. Rev. Drug Discov. 3, 115–124 (2004).
[7] Bronaugh, R.L. & Maibach, H.I. (eds.) Percutaneous Absorption, edn. 4 (Marcel Dekker, New York; 2005).
[8] Schoellhammer, C.M.; Blankschtein, D.; Langer, R. Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects. Expert Opin. Drug Deliv. 2014, 11, 393–407.
[9] McCrudden, M.T.; Singh, T.R.R.; Migalska, K.; Donnelly, R.F. Strategies for Enhanced Peptide and Protein Delivery. Ther. Deliv. 2013, 4, 593–614.
[10] Kermode, M. Unsafe Injections in Low-Income Country Health Settings: Need for Injection Safety Promotion to Prevent the Spread of Blood-Borne Viruses. Health. Promot. Int. 2004, 19, 95–103
[11] . Donnelly, R.F.; Singh, T.R.R.; Morrow, D.I.; Woolfson, A.D. Microneedle-Mediated Transdermal and Intradermal Drug Delivery; Wiley: Hoboken, NJ, USA, 2012.
[12] Kretsos, K.; Kasting, G.B. A Geometrical Model of Dermal Capillary Clearance. Math. Biosci. 2007, 208, 430–453.
[13] Menon, G.K. New Insights into Skin Structure: Scratching the Surface. Adv. Drug Deliv. Rev. 2002, 54, S3–S17.
[14] Liu, X.; Kruger, P.; Maibach, H.; Colditz, P.B.; Roberts, M.S. Using Skin for Drug Delivery and Diagnosis in the Critically Ill. Adv. Drug Deliv. Rev. 2014, 77, 40–49.
[15] Williams, A.C.; Barry, B.W. Penetration Enhancers. Adv. Drug Deliv. Rev. 2012, 64, 128–137.
[16] Benson, H.A.; Watkinson, A.C. Topical and Transdermal Drug Delivery: Principles and Practice; Wiley: Hoboken, NJ, USA, 2012.

[17] Merkle HP. Transdermal delivery systems. Methods Find Exp Clin Pharmacol 1989;11:135-53.12.

[18] Brown L and Langer R. Transdermal delivery of drugs. Annu Rev Med 1988;39:221-9.

[19] Singh MC, Naik AS, Sawant SD. Transdermal drug delivery systems with major emphasis on Transdermal Patches: A review. J Pharm Res 2010;3:2537-43.17.

[20] Aulton ME. Aulton's Pharmaceutics The design and manufacture of medicine. 3rd ed. Churchill Livingstone: Elsevier; 2007. p. 567-8.18. Jain NK. Controlled and Novel Drug Delivery. New Delhi: CBS Publishers and Distributors; 2002. p. 107.19

[21] Arunachalam A, Karthikeyan M, Kumar DV, Prathap M, Sethuram S, Kumar AS. Transdermal drug delivery system: A review. Curr Pharma Res 2010;1:70-81.

[22] Pravin C., "A novel approach on transdermal drug delivery system [TDDS]", World journal of pharmacy and pharmaceutical sciences, 2016 Vol. 5, Issue 4, 932-958.

[23] Arti K., "Theoretical aspects of transdermal drug delivery system." Bulletin of pharmaceutical research 2013; 3(2): 78-89.