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Review on Transdermal Drug Delivery System

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Shaikh Safana*, Sneha Sonawane, Akshay Katkale, Vishvam Kunde, Siddhant Hagavane

SMBT College of Pharmacy, Nandi-Hillis, Dhamangaon, Nashik, Maharashtra-422403, India

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ABSTRACT

Transdermal drug delivery system (TDDS) is generally administered dosage of patches which is delivering drugs by the systemic way at a predetermined and controlled rate. It works in the very simple manner in which a drug is employed inside the patch and patch worn on the skin for long period. Through this process, the drug in form of constant concentration remains in the blood for a significant time duration. Polymer matrix, drug, permeation enhancers are the main elements of TDDS; Polymers include gum Arabic, methylcellulose, starch, shellac, etc. to synthetic are (acetyl copolymer, polyvinyl chloride, polyamide, polyvinyl acetate, etc). TDDS have many types of systems varying from single layer drug in adhesive, multilayer drug in adhesive, and other systems are reservoir and also matrix systems. The market merit of TDDS products is rising rapidly, more than 35 products are permitted for sale in the US, and near about 16 active ingredients are permitted globally for use as a TDDS. Transdermal drug delivery is a recent technology that has a great future and potential to limit the use of needles for presiding various types of drugs but the cost is also an important thing that has to be taken under consideration in developing nations like INDIA that have the second-highest population throughout the world, but due to higher cost TDDS are the hidden part of therapy to be used in. The review article gives an overview of TDDS, advantageous and disadvantageous, fundamental elements, types, evaluation, and recent trends.

INTRODUCTION:

A drug delivery system (DDS) is generally for a series of physicochemical technologies that can control the delivery and release of pharmacologically active substances into cells, tissues, organs, and these active substances could exert desirable effects.[1,2] DDS covers the routes of drug formulations and administration which cause an efficient drug to deliver to maximize therapeutic efficacy also minimizing any side effect [3,5]. Based on the delivery route, there are various types of administration modalities, like mucosal administration, oral administration, transdermal administration, lung inhalation, and intravenous injection from which, the Transdermal.

TDDS is one of the most globally investigated routes for noninvasive drug delivery into the body through the skin, other than conventionally used direct administration routes by use of needle-based injections. TDDS is influencing the delivery of various therapeutic agents significantly, especially in the case of pain management, hormonal, and treatment of diseases like cardiovascular and central nervous systems. [6,9]

TDDS does not involve passage by the gastrointestinal tract; that's why, there is no lost cause of first-pass metabolism, and drugs that can be delivered do not evolve from interference from pH, enzymes, and intestinal bacteria. And also, TDDS may be used to control releasing of drugs per usage restrictions, thereby contributing to high persistence. The most significant thing of TDDS could be a noninvasive administration method that causes minimum pain and burden on the patient, providing thanks to safe and convenient administered medication to children and elders.[10,12]

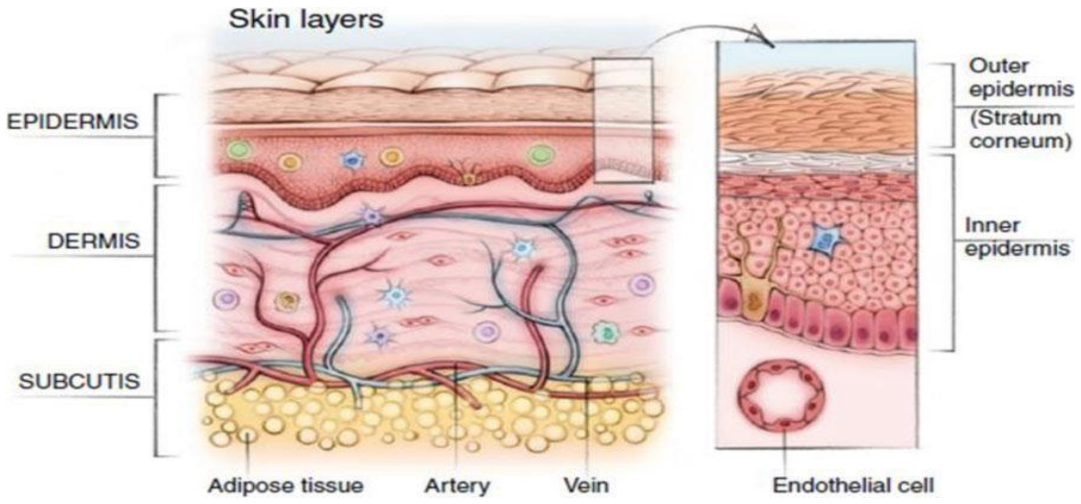


Figure No. 1: Structure of Skin

Even so, it still doesn't utilize its full potential because of the innate skin barrier. The skin is the outermost organ of the body, it contains a multi-layered structure, which plays the role of protection from environmental hazards like chemicals, heat, and toxins to our body. (Figure No.1). Such skin may be divided into the epidermis, which plays the protective role, and also the dermis, which has blood vessels and produces skin cells, and every layer has components that interfere with the transdermal delivery.[13]

Firstly, the skin barrier issue of the epidermis came down in the stratum corneum, the outermost layer, and maybe in property of blocking external substances. The barrier effect is significant for the transport of substances having a large molecular weight. In TDDS, the delivery of substances which has small molecular weights utilizes the intracellular pathway. However, for substances having an oversized mass, methods and various types of mechanisms using the intracellular pathway with additional, intercellular pathways are introduced and used. This can be thankes the skin's structure because of the part "lipid " which contains both cells and hydrophilic substances and hydrophobic substances do have a wonderfully regular position but exist with regularity. These structural attributes are elaborate by physicochemical properties that are used to improve drug delivery through the skin. Next, in the dermal layer, the system can interface TD's therapeutic systems correlations, design, and optimization.

A one-cell-thick layer of endothelial cells is passing within the capillary loops of the superficial arteriovenous plexus close to the dermal-epidermal junction within the upper dermis representing

the interface between the tissues surrounding the skin and also the human vasculature. The role of the endothelium within the skin is like that of the entire body. Which actively reacts to pressure, shear, heat, chemokines, cytokines by modulation of permeability. Therefore, the largest tissue of TDDS is to resolve the barrier effect of the stratum corneum, deliver the drug to the skin tissue, and meet up within the cellular and vascular tissue to succeed in the target tissue. The matter is that only a little amount of the drug may be delivered through the skin tissue. To resolve this problem, different novel TDDS techniques have been intensively developed and have been raised as attractive administration methods. In addition, such development provides a corresponding advantage compared to another drug for the delivered dose, the cost-effectiveness of administration methods. [14]

Figure No. 2: Transdermal drugs (Patches)

Anatomy of Skin:[13]

The structure of human skin (Figure No. 1) can be categorized into four main layers:

The epidermis

1. The viable epidermis
2. A non-viable epidermis (*Stratum corneum*)
3. The overlying dermis
4. The innermost subcutaneous fat layer **(**Hypodermis)[2]

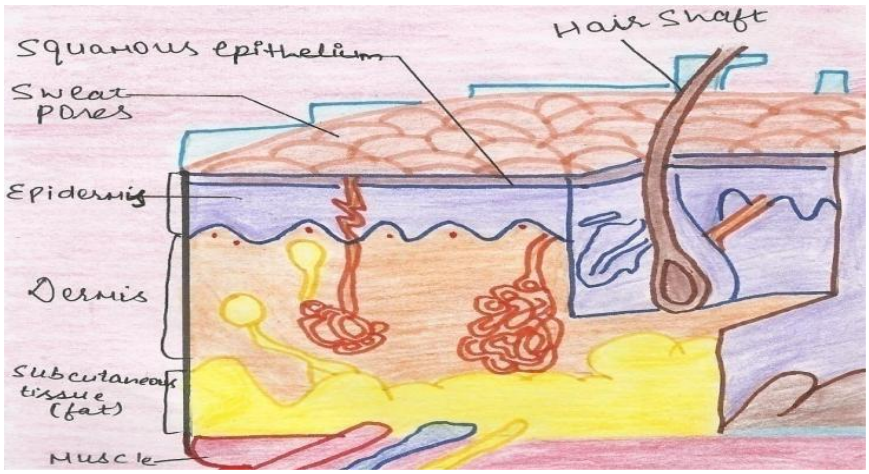


Figure No. 3: Schematic Representation of Skin and its Appendages

Epidermis:

The epidermis is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts: the living or viable cells of the malpighian layer (viable epidermis) and the dead cells of the *stratum corneum* commonly referred to as the horny layer.[2]

Dermis:

The dermis is the layer of skin just beneath the epidermis which is a 3 to 5 mm thick layer and is composed of a matrix of connective tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has an essential function in the regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach within 0.2 mm of the skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water, and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.[5]

Hypodermis:

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all three layers and reach the systemic circulation.[2]

Functions of skin:[13]

- Provides a protective barrier against mechanical, thermal, and physical injury and hazardous substances.
- Prevent the loss of moisture.
- Reduce harmful effects of UV radiation.
- Acts as a sensory organ (touch, detects temperature).
- Helps Regular temperature.
- An immune organ to detect infection etc.
- Production of vitamin D.

Barrier functions of the skin:

The top layer of skin is the most important function in maintaining the effectiveness of the barrier. Here the individual cells overlie each other and are tightly packed, preventing bacteria from entering and maintaining the water-holding properties of the skin. The stratum corneum mainly consists of the keratinized dead cell and water content is also less as compared to the other skin components.[15] Lipids are secreted by the cells from the base layer of the skin to the top. These lipid molecules join up and form a tough connective network, in effect acting as the mortar between the bricks of a wall.[2]

Routes of drug penetration through the skin:

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands as shown in Figure No. 4**.** In the initial transient diffusion stage, drug molecules may penetrate the skin along with the hair follicles or sweat ducts and then be absorbed through the follicular epithelium and the sebaceous glands. When a steady-state has been reached the diffusion through the intact *Stratum corneum* becomes the primary pathway for transdermal permeation.[2]

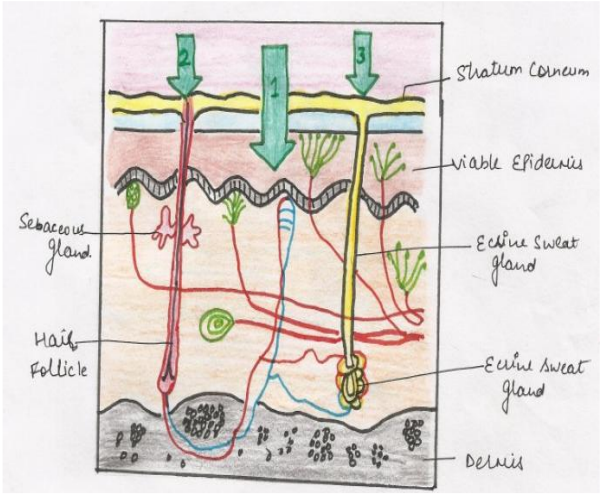


Figure No. 4: Possible Macro Routes for Drug Penetration

1) INTACT HORNY LAYER, 2) HAIR FOLLICLES AND 3) ECCRINE SWEAT GLANDS

For any molecules applied to the skin, two main routes of skin permeation can be defined:

- Transepidermal route
- Trans follicular route

Transepidermal route:

In Transepidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the Transcellular (or intracellular) and the intercellular pathway as shown in Figure No. 5.

Both polar and non-polar substances diffuse via Transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated *stratum corneum* whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the *stratum corneum*. Thus the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permanents (octanol/water log K > 2) traverse the *stratum corneum* via the intercellular route. Most molecules pass the *stratum corneum* by both routes.[5,2]

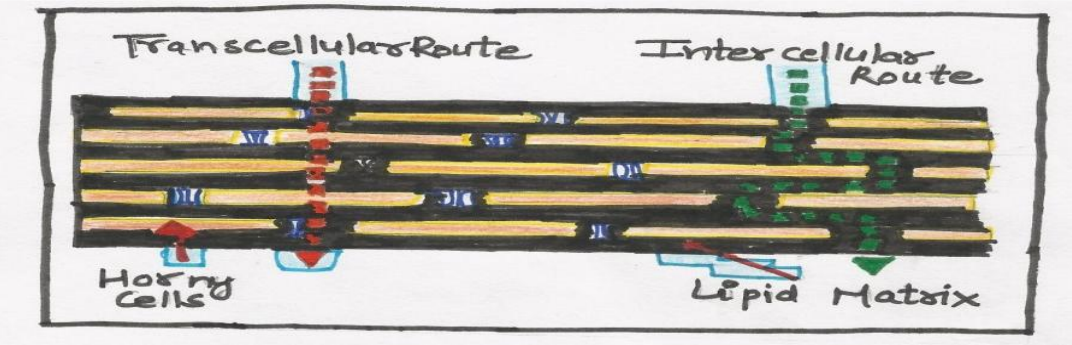


Figure No. 5: Schematic Representation of Transepidermal Route

Trans follicular route (Shunt pathway):

This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This route seems to be most important for ions and large polar molecules which hardly permeate through the *stratum corneum*.[2]

Properties that influence transdermal delivery:[2]

1. Release of the medicament from the vehicle

2. Penetration through the skin barrier.

3. Activation of the pharmacological response

Advantages of TDDS[1,8,16]

- Prevent from risk and slightness of intravenous therapy (noninvasive).
- Prevent first-pass hepatic metabolism (avoiding the deactivation by digestive and liver enzymes) and enhance the bioavailability, efficiency of drugs.
- Not gastrointestinal degradation (pH, enzymatic activity, drug reaction with food, drink, and other orally taken drugs).
- Optional for oral administration of medication when that route is not suitable, has vomiting and diarrhea.
- Extensive therapy avoids frequent use of dose administration.

Disadvantages ofTDD[8,17]

- Limited skin permeability.
- Restricted to the potent drug.
- Cannot be used for large relative molecular weight (>500Dalton).
- Significant lagtime.
- Skin irritation and allergic responses.

Tolerance inducing drugs or those (e.g., hormones) requiring chronopharmacological management.

Basic Components of TDDS:

Matrix patches, as well as liquid reservoir patches, consist of a large number of factors. Some of these are the same in both classes, while others are class-specific. Those are common in both are as follows:

- Backing films.
- Release liners.

- Pressure-sensitive adhesives.
- Permeation enhancers.
- Microporous or semi-permeable membranes.
- Pouching materials.

Backing Films: [17]

Backing films have to play a very critical role in the TDDS (when they are packaged in their pouch), and also during the use of the system. And the function of a film is to protect the active layer, the system's stability, and also impact skin permeation and tolerance, the basis on occlusion or breathability. Because of the large categories of ingredients, the release liner should be fully inert to the ingredients in arrange for avoiding any type of incompatibility. It should show flexibility as well as comfortableness and must present good affinity with the adhesive and excellent printability. The most usual materials used for releasing liners are polypropylene, saran, polyesters, PVC, and nylon.

Release Liners:

A release liner is a film overlapped with help of an anti-adherent coating. The function of the release liner is during it is in the package gives protect the system, as well as remove almost the adhesion of the TDDS to the skin. Release liners play a critical function in the product stability, in its safe and functional use. The release liner should a proper release liner doesn't allow the easy release of the patch, and also interfere with the active(s) or other components, hence reducing its shelf life. The General films used in release liners are paper-oriented plastic film-based and composite films.

Pressure-Sensitive Adhesives:

In both classes of TDDS, pressure-sensitive adhesives (PSAs) have a major function, which serves to the matrix that carries all active (which are additives, permeation enhancers) and the important for creating the patch stick to the skin. There are three large families of PSAs those are: rubber-based PSAs, acrylic PSAs in acrylic solutions state, emulsion polymers or hot melts,

and silicon PSAs. In every family of adhesives, more sub-categories provide desired flexibility to the formulator.

Every activity is not the same and also the choice of the adhesive is complex for the desirable result of the final product.

Penetration Enhancers:[8]

Penetration Enhancers are related to a global family of chemically several substances each having the same properties – they smoothly penetrate actives with the help of the skin, raising the permeation rate by many times. This is very essential corresponding to the feasibility of a system because all the actives don't pass into the skin, the required dosage from a relatively tinny area. Sometimes a combination of ingredients is the desire to make the correct enhancement effect.

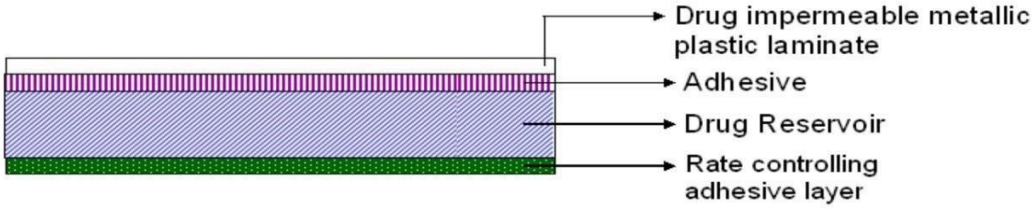
Microporous:

The porous membrane is a particular type of plastic film, usually used in each liquid reservoir patch and several matrix patches. Its function is to limit the flow of the semi-solid content from the liquid reservoir, and/or to behave like a rate-limiting membrane for liquid reservoir and matrix systems. The function relay on the system design, active factor's size, and the requirement to have a rate-limiting factor to satisfy the release and absorption properties of the system. The chemical compound of these membranes is a major factor in their permeability.

Pouching Materials:

All patches which are imposed in a Transdermal Drug Delivery System are in form of a package and considered as unit doses in packed pouches. Hence the pouching material is difficult for the product's stability as well as integrity. If there are many films with the same positive properties like cheap cost, better mechanism, as well as printable, would be selected.

There are three main layers in the complex materials which are utilized for pouches: the plastic heat-sealable layer, the aluminum foil layer, and last one the external printable layer.



Approaches used in the development of TDDS [19]

Figure No. 6: Matrix System

Matrix System –

The reservoir of the drug is created by dispersing the drug into an adhesive polymer and so spreading the medicated polymer adhesive through solvent casting or melting the adhesive (i.e hotmelt) on an impervious backing layer.[2]

The drug reservoir layer is later overlapped with help of a non-pharmaceutical rate managing adhesive polymer of sustained thickness to provide an adhesive diffusion controlling drug delivery system.

Deponit® (Nitroglycerine) for the once-a-day medication of angina pectoris.

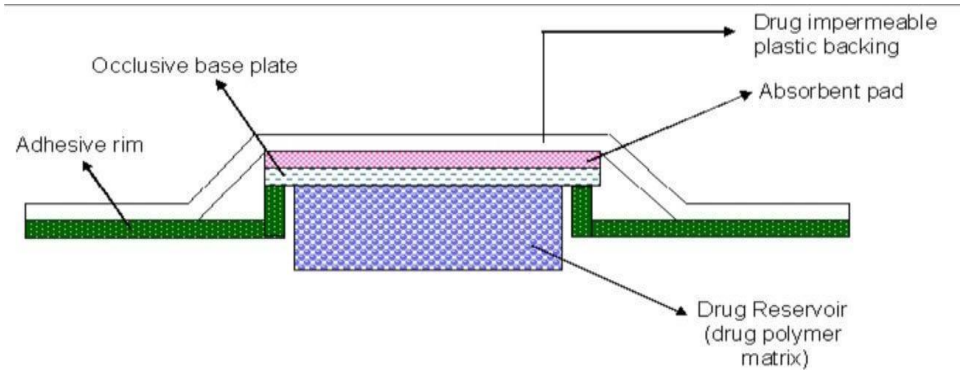


Figure No. 7: Matrix System - Matrix Dispersion System (Matrix Diffusion Controlled System)

The drug is dispersed homogeneously within a hydrophilic or lipophilic polymer matrix. This drug included polymer disk presiding fixed with an occlusive base plate during a compartment fabricated by a drug-impermeable backing layer.

Other than applying the adhesive to the surface of the drug reservoir, it's spread through the circumference to make a strip of the adhesive rim.

Nitro Dur® (Nitroglycerine) is used for once a day medication of angina pectoris.

Reservoir System (Membrane Moderated TDDS):

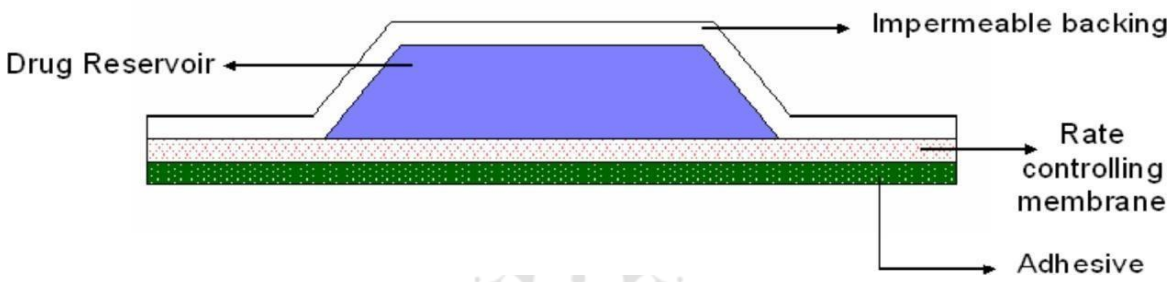


Figure No. 8: Reservoir Transdermal Patch

In the Reservoir system, the drug reservoir is enclosed in-between an impervious backing layer, a rate-controlling membrane. Rate controlling membrane is the only one that releases the drug, it would be microporous or non-porous. In the drug reservoir compartment, the drug may be originated in a solution form, suspension, gel or dispersed in a solid polymer matrix. On the outermost surface area of the polymeric membrane, a thin layer of drug-suitable, hypoallergenic adhesive polymer may be applied. The rate of drug release from this type of TDDS may be tailored by changing the polymer composition, coefficient of permeability, and rate-controlling membrane's thickness Micro reservoir System.[18]

Micro Reservoir System:

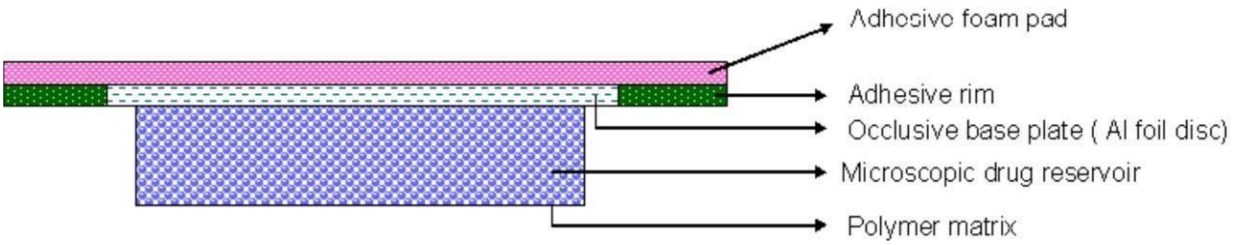


Figure No. 9: Micro reservoir System

Drug delivery systems have a reservoir and matrix-dispersion systems are included with respective ratios. The drug reservoir is created through a process, in which first the drug is suspended with an aqueous solution of water-soluble polymer and later on dispersing a solution homogeneously within a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. And therefore the thermodynamically unstable dispersion is stabilized instant by immediate cross-linking the polymer. A TDS therapeutic system hence made sort of a medicated disc located at the centre and surrounded by an adhesive rim. Nitro-dur® System (Nitroglycerin) for each daily treatment of angina pectoris[19].

Factors affecting transdermal permeation[2]

- **Biological factor: [1,17]**

Skin conditions:

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

Skin age:

It is seen that the skin of adults and young ones are more permeable than the older ones but there is no dramatic difference. Children show toxic effects because of the greater surface area per unit

body weight. Thus potent steroids, boric acid, hexachlorophene have produced severe side effects.

Blood Supply:

Changes in peripheral circulation can affect transdermal absorption.

Regional skin site:

The thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significantly penetration.

Skin metabolism:

Skin metabolizes steroids, hormones, chemical carcinogens, and some drugs. So skin metabolism determines the efficacy of drugs permeated through the skin.

Species differences:

The skin thickness, density of appendages, and keratinization of skin vary from species to species, so affects the penetration.

- **Physicochemical factors:**[14]

Skin hydration:

In contact with water, the permeability of skin increases significantly. Hydration is the most important factor in increasing the permeation of skin. So the use of humectant is done in transdermal delivery.

Temperature and pH:

The permeation of the drug increases ten folds with temperature variation. The diffusion coefficient decreases as the temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drugs determines the drug concentration in the skin. Thus, temperature and pH are important factors affecting drug penetration.

Diffusion coefficient:

Penetration of a drug depends on the diffusion coefficient of a drug. At a constant temperature, the diffusion coefficient of the drug depends on the properties of the drug, diffusion medium, and interaction between them.

Drug concentration:

The flux is proportional to the concentration gradient across the barrier and the concentration gradient will be higher if the concentration of the drug will be more across the barrier.

Partition coefficient:

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of the skin. Also, drugs with low K will not be permeated.

Molecular size and shape:

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

- **Environmental factors:**[20]

Sunlight:

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

Cold Season:

Often result in itchy, dry skin. 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.

Air Pollution:

Dust can clog pores and increase bacteria on the face and surface of the skin, both of which lead to acne or spots. This affects drug delivery through the skin.

Evaluation of transdermal patches:[18]

The transdermal patches can be characterized in terms of the following parameters.

- Physicochemical evaluation.
- *In vitro* evaluation.
- *In vivo* evaluation.

Physicochemical evaluation:

Transdermal patches can be physicochemically evaluated in terms of these parameters:

- **Thickness:**

The thickness of the transdermal film is determined by a travelling microscope, dial gauge, screw gauge, or micrometer at different points of the film.[4].

- **Uniformity of weight:**

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

- **Drug content determination:**

An accurately weighed portion of the film (about 100 mg) is dissolved in 100 mL of suitable solvent in which the drug is soluble and then the solution is shaken continuously for 24 h in a shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, the drug in solution is estimated spectrophotometrically by appropriate dilution.[4,8].

- **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% to125% 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 ranged from 85% to 115%, then the transdermal patches pass the test.[4].

- **Moisture content:**

The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using the following formula.

***In vitro* release studies:**

Transdermal patches can be *in vitro* evaluated in terms of Franz diffusion cell. The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5 - 12 ml and an effective surface area of 1-5 cm^2. The diffusion buffer is continuously stirred at 600 rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds th**e** receptor compartment. The drug content is analyzed using a suitable method, maintenance of sink condition is essential

***In vivo* studies:**

Transdermal patches can be *in vivo* evaluated in terms of *in vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using animal models and human volunteers.

CONCLUSION

Taking into consideration the benefits of TDDS, it is an ideal replacement for drugs whose pitfall in performance enteral as well as parenteral dosages and also in patient's treatment. By sorting

the recently existing outcomes TDDS can surely introduce new improvements within this sector field of drug delivery.

This review work has been concluding that older drugs through formulating them in new dosage forms have generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs so reinforce their performance by reducing their dose, increasing absorption, delivering to the target site, etc. The patented inventions in the transdermal drug delivery system era aim at these goals. Therefore the final words, test that an innovative technique should pass relates to its successful performance.

REFERENCES

1. Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm Res. J. 2010; 3:139-149.
2. Himanshi Tanwar,Ruchika sachdeva. Transdermal drug delivery system: a review. IJPSR. 2016; 7(6):2274-2290.
3. Kumar A, Pullankandam N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. Int. J Pharm Sci. Review Res. 2010; 3(2):49-54.
4. Divya A, Rao MK, Gnanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. A review on the current scenario of transdermal drug delivery system. Int. J Res. Pharm Sci. 2012; 3(4):494-502.
5. Jain NK, Controlled and novel drug delivery. 1st Ed., CBS Publisher and Distributors, New Delhi. 2001:100-129.
6. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. Plegia Res. Lib. 2011; 2(5):17-29.
7. Dhawan S, Aggarwal G. Development, fabrication and evaluation of transdermal drug delivery system- a review. Pharm info.net. 2009:1-25.
8. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovation. 2012; 1(4):66-75.
9. Mehta R. Topical and transdermal drug delivery: what a pharmacist needs to know. InetCE. 1st Ed., Arizona; 2004:1-10.
10. Loyd V, Allen Jr, Nicholas G, Popovich, Howard C, Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers, New Delhi;2005:298-299.
11. Jain NK. Pharmaceutical product development. 1st Ed. CBS Publisher and Distributors. New Delhi. 2002:221-228.
12. Robinson JR, Lee VH. Controlled drug delivery fundamentals and applications. 2nd Ed. New York. 2005:523-536.
13. Wilson R, Waugh A, Grant A. Anatomy and physiology in health and illness. 9th Ed. 2001 pg. 363-366.
14. Kumar D, Sharma N, Rana AC, Agarwal G, Bhat ZA. A review: transdermal drug delivery system: tools for novel drug delivery system. Int. J Drug Dev. Res. 2011; 3(3):70-84.
15. Ramteke KH, Dhole SN, Patil SV. Transdermal drug delivery system: a review. J Advanced Sci. Res. 2012; 3(1):22-35.
16. Yadav V. Transdermal drug delivery system: a review. Int. J Pharm Sci. Res. 2012; 3(2):376-382.
17. Dhiman S, Thakur GS, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int. J Pharmacy Pharm Sci. 2011; 3(5):26-34.

18. Sharma RK, Keleb E, Mosa EB, Aljahwi AAZ. Transdermal drug delivery system- design and evaluation. Int. J Advances Pharm Sci. 2010; 1:201-211.
19. Rohit Tiwari, Manish Jaimini, schailender Mohan, Sanjay Sharma A. Transdermal drug delivery system. Int. J The. App 2013 ;(14):22-28.
20. Singh MC, Nasik AS, Sawant SD. Transdermal drug delivery system with major emphasis on transdermal.