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RECENT TREND ON TRANSDERMAL DRUG DELIVERY SYSTEM AND ADVANCEMENTS IN DRUG DELIVERY THROUGH SKIN

Nitin Saini[1]*, Anshul Bajaj[2]

1. Department of Pharmaceutics, M.M. College of Pharmacy, M.M. University, Mullana-Ambala
2. Department of Pharmaceutics, Manav Bharti University, Solan, Himachal Pradesh

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For Correspondence:

Nitin Saini

Department of Pharmaceutics, M.M. College of Pharmacy, M.M. University, Mullana-Ambala

E-mail:

nitin.tech88@gmail.com

ABSTRACT

Transdermal drug delivery is the application of drug on the skin surface so that it can permeate through the skin and reaches the systemic circulation at sufficient concentration to ensure therapeutic efficacy. Transdermal drug delivery system (TDDS) has several advantages over conventional system; TDDS offers sustained drug release, avoidance of first pass effect, patient compliance, ease of application and removal in case of toxicity as well as decrease in the side effects as compared with conventional therapy. The stratum corneum acts as a barrier that limits the penetration of substances through the skin and this limitation can be overcome by permeation enhancing techniques. A transdermal patch has several components such as backing membrane, drug reservoir, adhesive layer, release control membrane and liner etc. This review article provides an overview of TDDS, its advantages over conventional dosage forms, Limitations**,** various components of transdermal patches, types of transdermal patches, and its methods of evaluation and the advancements done in this field.

INTRODUCTION

Transdermal drug delivery system (TDDS) is the system which delivers a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Skin provides enormous surface area (approx 2 m^2) for absorption with minimal proteolytic activity. It is composed of three layers, dermis, epidermis and subcutaneous tissue and it is flexible enough to resist permanent distortion from movement and thin enough to allow stimulation. The main barrier for the transdermal delivery is slow diffusion through stratum corneum (SC), which is known to be a dead layer. The physiology of skin illustrates the three feasible pathway exist for passive transport of active through the skin

1. Intercellular diffusion through the lipid lamellae
2. Transcellular diffusion through both the keratinocytes and lipid lamellae
3. Diffusion through hair follicles and sweat ducts,

It is documented that polar molecules mainly permeate through the polar pathway within the hydrated stratum corneum, while non-polar molecules through the lipid matrix of the stratum corneum. **(1,2,3)**

Transdermal patch consists of a special membrane to control the rate at which the drug contained in the reservoir within the patch can pass through the skin and then into the bloodstream. TDDS offers many advantages over conventional injection and oral methods. Transdermal drug delivery increases patient compliance and avoid first pass metabolism over conventional drug delivery. It reduces the load that the oral route commonly places on the digestive tract and liver. It minimizes harmful side effects of a drug caused from temporary overdose. Another advantage is convenience and a simple dosing, especially notable in patches that require only once weekly application which aid in patient adherence to drug therapy.

ADVANTAGES

1. Transdermal drug delivery can be used as an alternative delivery system for patients who cannot tolerate oral dosage forms.

2. Avoid the first pass effect e.g. transdermal nitroglycerin. It is rapidly metabolized by the liver when taken orally.

3. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

4. Self administration is possible with these systems.

5. Improved patient compliance and comfort via non-invasive, painless and simple application.

6. Improved bioavailability.

7. More uniform plasma levels and maintain plasma concentration of potent drugs.

8. Longer duration of action resulting in a reduction in dosing frequency.

9. Transdermal medication delivers a infusion of a drug over an extended period of time.

10. An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, e.g. the drug is given orally.

11. They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.

12. It is of great advantage in patients who are nauseated or unconscious.

13. Drugs that cause gastrointestinal upsets can be good candidates for transdermal delivery because this method avoids direct effects on stomach and intestine.

14. Peaks and troughs in plasma level can be avoided, which reduce the risk of side effects. Thus, drugs that require consistent plasma levels are very good candidates for

transdermal drug delivery.

15. Allows continued drug administration permitting the use of a drug with short biological half-life. [4,5,6]

DISADVANTAGES

1. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level, Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.

2. The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.

3. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

4. Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.

5. Long time adhere is difficult.

6. Difficult to administer large dose i.e. more than 10 mg/ day. Not suitable for high drug doses.

7. Adhesion may vary with patch type and environmental conditions.

8. Drugs that require high blood levels cannot be administered.

9. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product. [4,5,6]

ANATOMY OF THE SKIN

The skin is the largest organ in the body and, on average, accounts for about 6 lbs of our body weight. Skin has as its primary function to keep the body hydrated, or to keep water inside the body and also prevents foreign substances from entering the body from the environment.

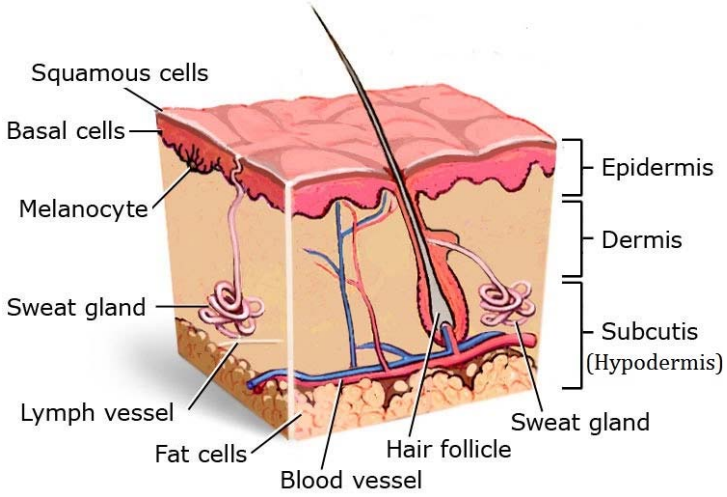


Figure 1 represents a cross-sectional view of the skin.

The major divisions of the skin, from top to bottom, are the epidermis, dermis, and the hypodermis. The hypodermis portion is where fat is stored, as shown by the ovals in the figure representing adipocytes. Larger blood and lymph vessels are also found here.

The dermis is where structures such as sweat glands, hair follicles, and the smaller blood vessels are located. Therefore, in order to have drug delivery via the skin, the drug must pass through the epidermis into the dermis where it can be absorbed by capillaries into the circulatory system.

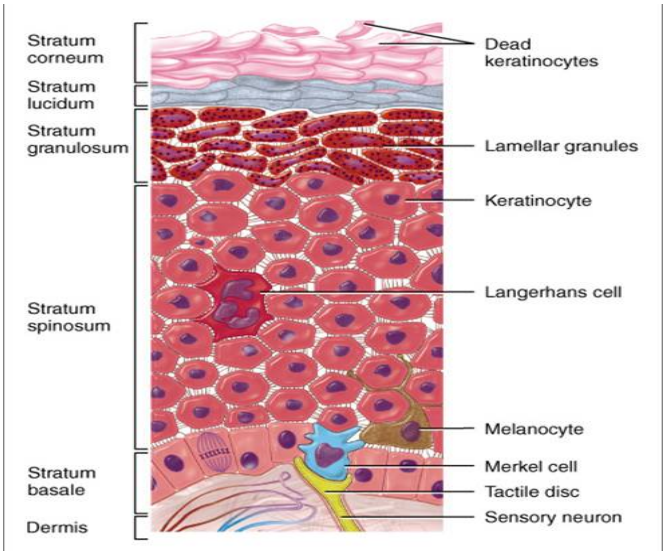


Figure 2 shows a cross-sectional view of the epidermis.

Of the five layers of the epidermis, the most important barrier layer is the outer layer, or stratum corneum. The stratum corneum is made up of dead, keratinized cells called keratinocytes, or sometimes corneocytes. Although it represents the major barrier to drug absorption, the stratum corneum accounts for only about 0.1mm of the skin's 1.5mm thickness.

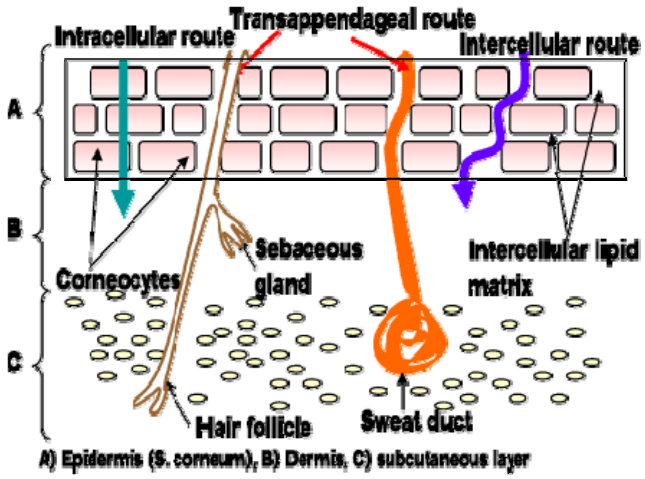


Figure 3- Different routes of permeation.

There are three possible ways that drug molecules can pass through stratum corneum. The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes. [7,8]

Transfollicular route

Transfollicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs. Skin has various sweat glands, oil glands, hair follicles and pores opening to the outer surface of the skin via their ducts. These ducts offer a continuous channel across the stratum corneum for

drug transport but various factors like secretion from glands, content and amount of secretion etc., affect the transport of drugs through this route. However transappendageal route occupies only 0.1% of total skin surface and therefore contributes a little. [3,9]

Transcellular route

Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. Corneocytes are surrounded by lipids connecting these cells. So a drug requires a number of partitioning and diffusion steps. It is the most widely used route by various types of drugs. In transcellular route drug passes through the matrix (cytoplasm) of the cells. This route is suitable for hydrophilic drugs. The drug
passes through the corneocytes of stratum corneum. The highly hydrated keratin provide aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix. [9,10]

Intercelluar route- As the name indicates intercellular the drug diffuses through the lipid bilayer between the cells. In this route, the molecule stays in the lipid bilayer and winds around the keratinocytes on its way to the dermis.

Although both paths are possible, the most common route of drug penetration is the intercellular route because most drug molecules are more soluble in the lipid environment of the bilayer than in the protein environment of the keratinocytes. [10,11]

FACTORS AFFECTING TRANSDERMAL PERMEABILITY [26-30]

The principal transport mechanism across mammalian skin is by passive diffusion through primarily, the trans-epidermal route at steady state or through transappendageal route at initial non-steady state. The factors controlling transdermal permeability can be broadly placed in the following classes.

1. Physicochemical properties of the penetrant molecule
2. Physicochemical properties of drug delivery system
3. Physiological and pathological conditions of the skin

1. Physicochemical properties of the penetrant molecule

a. pH conditions

Application of solutions whose pH values are very high or very low can be destructive to the skin. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

b. Partition coefficient

A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.

c. Penetrant concentration

Concentrations higher than the solubility, excess solid drug functions as a reservoir and helps to maintain a constant drug concentration for a prolonged period of time.

2. Physicochemical properties of drug delivery system

Generally, the drug delivery system vehicles do not increase the rate of penetration of a drug into the skin but serve as carriers for the drug.

a. Composition of drug delivery systems

The composition of the drug delivery system not only affects the rate of drug release, but also the permeability through stratum corneum by means of hydration, mixing with skin lipids or other sorption promoting effects.

b. Release characteristics

Solubility of the drug in the vehicle determines the release rate. The mechanisms of drug release depend on the following factors;

- pH of the vehicle.
- Whether the drug molecules are dissolved or suspended in the delivery systems.

- The interfacial partition coefficient of the drug from the delivery systems to the skin tissue.

c. Enhancement of transdermal permeation

Majority of drugs will not penetrate the skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs, the permeation can be improved by the addition of sorption or permeation promoter into drug delivery systems. Such promoters can be of following types;

- **Organic solvents:** These agents cause an enhancement in the absorption of Oil soluble drugs, due to the partial leaching of the epidermal liquids, resulting in the improvement of the skin conditions for wetting and for transepidermal and transfollicular penetration. e.g. dimethyl acetamide, dimethyl formamide, dimethyl sulphoxide, cineole, propylene glycol, cyclohexane, acetone etc.
- **Surface active agents:** The permeation promoting activity of surfactants is assumed to be due to action to decrease the surface tension, to improve the wetting of the skin, and to enhance the distribution of the drugs. Anionic surfactants are the most effective. Their action may be due to their modification of the stratum germinativum and/or to their denaturation of the epidermal proteins. Ex. Sodium lauryl sulfate and sodium dioctyl sulfo-succinate.

3. Physiological and pathological conditions of the skin

a. Lipid Film

The lipid film on the skin surface acts as protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of the stratum corneum.

b. Skin Hydration

Hydration of the SC can enhance transdermal permeability, although the degree of penetration enhancement varies from drug to drug. Simply covering or occluding the skin with plastic sheeting, leading to the accumulation of sweat and condensed water vapour can achieve skin hydration. Increased hydration appears to open up the dense, closely packed cells of the skin and increase its porosity.

c. Reservoir effect of the horny layer

The horny layer is deeper layers, can sometimes act as a depot and modify the transdermal permeation characteristics of some drugs. The reservoir effect is due to the irreversible binding of part of the applied drug with the skin. This binding can be reduced by the pre-treatment of the skin surface with anionic surfactants.

d. Skin Temperature

Raising skin temperature results in an increase in the rate of skin permeation. This may be due to

- Thermal energy required for diffusivity.
- Solubility of drug in skin tissues and increased vasodilatation of skin vessels.

e. Regional Variation

Differences in the nature and thickness of the barrier layer of the skin causes variation in permeability.

e. Traumatic / Pathological injuries to the skin

Injuries that disrupt the continuity of the stratum corneum increase permeability due to increased vasodilatation caused by removal of the barrier.

f. Cutaneous drug metabolism

Catabolic enzymes present in the viable epidermis may render a drug inactive by metabolism and thus affect the topical bioavailability of the drug.

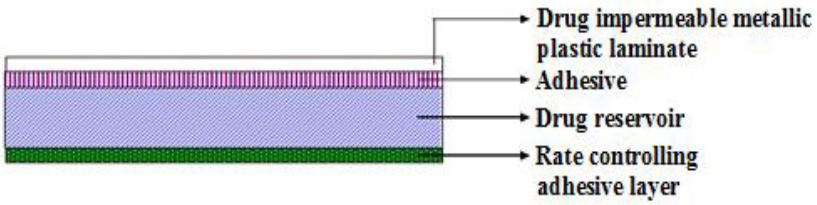
TYPES OF TDDS

1. Drug in adhesive TDDS

In this system drug is dispersed in the adhesive layer of the patch (figure 4). The adhesive layer not only serves to adhere the components of the patch with the skin but also controls the rate of drug delivery to the skin. The adhesive layer is surrounded by the liner. It is of two type:

a. Single–layer adhesive

In this system drug is dispersed in the adhesive layer of the patch. In this type patches the adhesive layer serves to adhere the various layer together and also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing. [19,20]

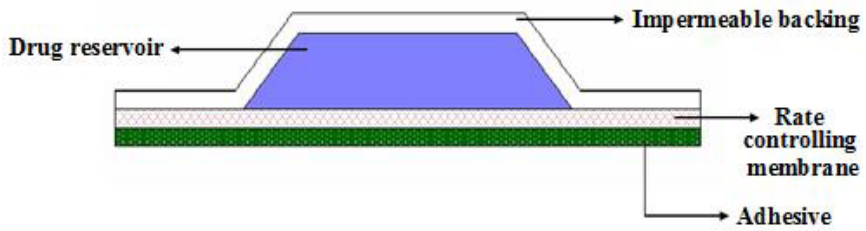


Adhesive Dispersion Type transdermal delivery

b. Multi-layer adhesive TDDS

In this system drug is dispersed in the adhesive layers of the patch same as in single layer drug in adhesive. But the only difference is that it contain multiple layers of drug in adhesive separated by a membrane. This patch also has a temporary liner – layer and a permanent backing. [19,20]

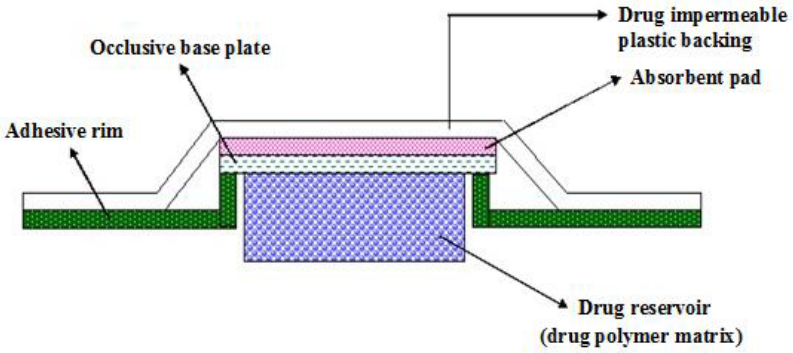
2. Reservoir controlled TDDS: Reservoir transdermal system has a separate drug layer enclosed in a rate controlling microporous or nonporous membrane and an impermeable backing laminate. The drug layer is a liquid compartment containing a drug solution or suspension separated by the backing layer. The release rate of the drug is determined by the abrasion rate, permeability, diffusion and thickness of the membrane. In this type of system the rate of release is zero order. [20,21]



Reservoir controlled transdermal delivery system

3. Matrix controlled TDDS

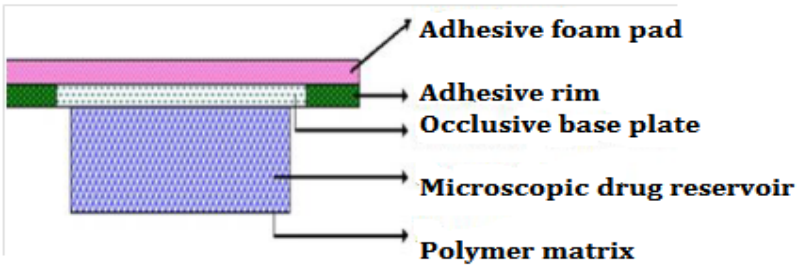
In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The adhesive layer in this patch surrounds the drug layer partially overlaying it. It also have occlusive baseplate, absorbant pad and backing laminate on the back. [20,21]



Matrix controlled transdermal delivery system

4. Microeservoir TDDS

This System is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents. [20,21]



Microreservoir type transdermal delivery system

BASIC COMPONENTS OF TDDS

Transdermal drug delivery systems are designed to support the passage of drug substance from the surface of skin through its various layers and into the systemic circulation. There are two basic types of transdermal dosing system; those that control the rate of drug delivery to the skin and those that allow the skin to control the rate of drug absorption.

1. Polymer matrix [20,23,24]

The polymers play a major role in transdermal drug delivery systems of drugs. The release of drug to the skin is controlled by drug free film known as rate controlling membrane. Polymers are also used in the matrix devices in which the drug is embedded in polymer matrix which control the duration of release of drugs. The polymers used for transdermal drug delivery system are categorising based on their sources as follows;

a. Natural and semisynthetic polymers: Carboxymethyl cellulose, cellulose acetate phthalate, ethyl cellulose, gelatin, methyl cellulose, starch, shellac, waxes natural rubber etc.

b. Synthetic elastomers: Polybutadiene, polysiloxane, acrylonitrile, butyl rubber, Neoprene, polyisoprene, ethylene-propylene-diene-terpolymer etc.

c. Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polystyrene polyester, polyacrylate, polymethylmethacrylate, polypropylene etc. The polymers should fulfill the following requirements;

d. Molecular weight, physical characteristics and chemical functionality of the polymer must allow the diffusion of the drug substances at desirable rate.

e. The polymer and its decomposed product should be nontoxic.
f. The polymer should be chemically non-toxic, non reactive and it should be an inert drug carrier.
g. The polymer must be easy to manufacture and fabricate into the desired product. It should allow incorporation of large amount of active agent.
h. The cost of the polymer should not be excessively high.

2. Drug

Judicious choice of drug is critical in the successful development of a transdermal product. The important drug properties that affect its diffusion from device as well as across the skin include molecular weight, solubility, physical properties and melting point. The structure of the drug also affects the skin penetration. Diffusion of the drug in adequate amount to produce a satisfactory therapeutic effect is of prime importance. The following are some of the desirable properties of a drug for transdermal delivery;
a. The drug should have molecular weight less than 1000 Daltons.
b. The drug should have affinity for both lipophilic and hydrophilic phases.
c. The drug should have a low melting point.
d. The half-life of drug should be short.
e. The drug must not induce a cutaneous or allergic response.
f. The drugs, which degrade in gastrointestinal tract or inactivated by hepatic first pass effect are suitable candidates for transdermal drug delivery system. [20,23,24]

3. Adhesives [20,23,24]

The adhesion of all transdermal devices to the skin in an essential requirement and it has so far been accomplished using a pressure sensitive polymeric adhesive. The types of adhesives commonly used in transdermal drug delivery system are;

- Rubber based adhesives: Natural gum (Karaya gum), olylisoprene, polybutene, and polyisobutelene.
- Polyacrylic based adhesives: Ethyl acrylate, 2-ethylhexylacrylate, iso-octyl acrylate.
- Polysiloxane based adhesives: Polydimethyl siloxane, polysilicate resins, sufloxane blends.

An adhesive system should fulfil the following requirements;
a. It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with skin.
b. It should adhere to the skin aggressively.
c. It should be easily removable without leaving an unwashable residue.
d. It should be physically and chemically compatible with the drug, the excipients and enhancers.
e. It should not affect the permeation of the drug.
f. The adhesive property should not deteriorate as the drug, enhancers and excipients permeate into the adhesive. [20,23,24,25]

4. Backing membrane

It provides protection from external factors during application period. The backing layer must be flexible and provide good bond to the drug reservoir-thereby preventing the drug from leaving the dosage form from the top and accept printing. They are usually impermeable to water vapours. The most commonly used backing materials are polyethylene terephthalate, metalized polypropylene, metallized plastic, pigmented polyester film etc. [20,23,24]

5. Penetration enhancers

Penetration enhancers are molecules, which reversibly alter the barrier properties of the stratum corneum. They aid in the systemic delivery of drugs by allowing the drug to penetrate more readily to viable tissues. Penetration enhancer should have the following properties;

a. The material should be pharmacologically inert and should spread well on skin.

b. It should be non-toxic, non-irritant and have a low index of sensitization.

c. It should be odourless, tasteless and colourless. Its penetration enhancing action should be immediate and should have suitable duration of effect.

d. The enhancer should be chemically and physically compatible with a wide range of drugs and pharmaceutical adjuncts. **(20,23,24)**

Table:1- Different class of enhancers and their mechanism of action(34)

CLASS	EXAMPLES	MECHANISM OF ACTION
Hydrating substances	Water Occlusive preparations	Hydrates the SC
Keratolytics	Urea	Increase fluidity and hydrates the SC
Organic solvents	Alcohols Poly ethylene glycol DMSO	Partially extracts lipids Replace bound water in the intercellular spaces Increase lipid fluidity
Fatty acids	Oleic acid	Increase fluidity of intercellular lipids
Terpenes	1,8-Cineole , Menthol	Opens up polar pathway
Surfactants	Polysorbates Sodium lauryl sufate	Penetrates into skin, micellar solubilisation of SC
Azone	1-Dodecylhexahydro-2HAzepine-2on2	Disrupts the skin lipids in both the head group and tail region

6. Release liner

Release liner is the part of primary packaging and prevents the loss of drug from the polymer matrix and prevents contamination of the patch from outside environment during storage and transport. It is peeled off at the time of use. Release liner may be occlusive (e.g. polyethylene, PVC) or non-occlusive (paper fabric). Polyester foil and metallic foil are also used for release liner. **(20,23,24)**

EVALUATION PARAMETERS FOR TDDS PATCH

1. Physical appearance

The prepared patches were physically examined for colour, clarity and surface texture. (11)

2. Thickness of the patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. Patch will have an equal thickness at every point. The variation of thickness within the patch and patch to patch can be calculated. [12, 13]

3. Weight uniformity

The patches are dried at 60°C before weighing. The weight uniformity of the patch is measured by cutting and weighing the 1 cm^2 piece of 3 patches and then calculating the weight variation. The mean of the 3 is taken as the weight of the patch. The individual weight should not deviate significantly from average weight. [13,14]

4. Folding endurance:

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.[14]

5. Percentage moisture content [12, 13]

Individually weighed patches are kept in the desiccators having fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches are to be reweighed and percentage moisture content is calculated by the formula:

$$\text{Percentage moisture content} = \frac{\text{(Initial weight - Final weight)}}{\text{Final weight}} \times 100$$

6. Percentage moisture uptake [12, 13]

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

$$\text{Percentage moisture uptake} = \frac{\text{(Final weight- Initial weight)}}{\text{Initial weight}} \times 100$$

7. Water vapour transmission rate (WVTR) [12, 14]

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 gm of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90% RH. The cells were taken out and weighed after 24 hrs. The amount and rate of water vapour transmitted was calculated by the difference in weight using the formula. Water vapour transmission rate is usually expressed as the number of grams of moisture gained/($hr.cm^2$).

$$\text{Transmission rate} = \frac{\text{Final weight – Initial weight}}{\text{Time X Area}} \times 100$$

8. Drug content [12, 13]

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 analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. Flatness test [12, 13]

Flatness test is performed to determine the smoothness of the film. Three strips of the film one from the center and two from the both sides of the film are to be cut and measured length wise. Variation in length is measured by finding out percent constriction. Zero percent constriction is considered equivalent to 100% flatness.

10. Thumb tack test

It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected. [12, 13]

11. Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength. [13-15]

12. Peel Adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at a 180° angle. No residue on the substrate indicates 'adhesive failure' which is desirable for transdermal devices. Remnants on the substrate indicate 'cohesive failure' signifying a deficit of cohesive strength in the coating. [12-15]

13. Rolling ball tack test

In this test a steel ball of 7/16 inch in diameter is rolled down an inclined having horizontally placed patch facing adhesive surface upward. The ball rolls down and runs horizontal distance on the patch. The distance run by the ball gives the tack property of the adhesive patch. [12]

14. Quick Stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width. [15,16]

15. Uniformity of dosage unit test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2m membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated. [15,16]

16. Polariscope examination

This test is performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is kept on the object slide and observed for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

17. Skin Irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface ($50cm^2$) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury. [15,16]

18. In vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated. [16-18]

19. Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content. [16]

20. In vivo study: The In vivo study involves:

a) Animal model

b) Human model

Most preferably In vivo study is conducted on animal models as compared to human models because of easy availability of animals, ease of experiment and toxicity and safety parameters associated with the experiment. Various species of mouse, rat, dogs, monkey, pig, cat, rabbit and squirrel are used for animal study. Mainly hairless animal are preferred over hairy animals for transdermal formulation evaluation. In final stage of formulation development human volunteers are studied to determine the pharmacokinetic and pharmakodynamic profile of the drug including safety and efficacy of the formulation. Clinical trials are conducted in IV phases. Phase I trials are conducted on small group of volunteers to determine the safety and toxicity profile. Phase II trials are conducted on a small group of patients for safety and toxicity for short term. Phase III study is conducted on a large group of patients and phase IV is the post marketing survey. [16-18]

ADVANCEMENTS IN TDDS

The drug delivery through the skin was recognized in 20th century. Due to some limitation in delivery of drug through skin, it cannot be used as a drug delivery route for all drug candidates. The continuous advancement in the science and technology is making the TDDS as the preferred and most convenient route for most of the drugs. The transdermal delivery is categorized into 3 generations according the advancements in TDDS.

First Generation Transdermal Drug Delivery Systems

Currently, there are two types of simple patch design. The original patch design is a **liquid reservoir system** where the patch consists of a backing material that is both protective and adhesive, a liquid drug reservoir, a release membrane. A more recent design is the **adhesive matrix system** where the adhesive and the drug are combined in the same layer leaving only three layers to the patch; the backing layer, the drug and adhesive layer, and the protective layer that would be removed before applying the patch to the skin. [31]

Second Generation Transdermal Drug Delivery Systems

2nd Generation TDDS attempt to enhance the delivery of organic molecules through the stratum corneum by disrupting its barrier function and/or by providing some sort of driving force for the movement of molecules through the epidermis. This disruption should be reversible and avoid injury to the skin. However, it can be difficult to disrupt the barrier without causing damage or irritation, especially when using chemical enhancers. In addition, these 2nd generation enhancement techniques are limited to small, lipophilic molecules and still have little effect on larger or hydrophilic molecules. 2nd generation enhancement methods include chemical penetration enhancers, gentle heating, and iontophoresis.[32]

Third Generation Transdermal Drug Delivery Systems

The third generation patches are developed to permeate large hydrophilic drug molecules. Hormonal delivery through the skin patch become possible only by using latest techniques such as Iontophoresis, Sonophoresis, electrophoresis, Magnetophoresis and microneedle technique etc. These permeation enhancers forcefully allow the drug molecules to pass across the skin or physically damage the skin.[33]

ADVANCED TECHNIQUES FOR PENETRATION ENHANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEM [20,35]

Iontophoresis: It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia.

Ultrasound: In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

Photomechanical Waves: Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

Electroporation: It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.

Electro-Osmosis: To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

Microneedle concept employs an array of micron-scale needles that is inserted into the skin sufficiently far that it can deliver drug into the body, but not so far that it hits nerves and thereby avoids causing pain. An array of microneedles measuring tens to hundreds of microns in length should be long enough to deliver drug into the epidermis and dermis, which ultimately leads to uptake by capillaries for systemic delivery. This is similar to conventional transdermal patch delivery, except the rate limiting barrier of the stratum corneum is circumvented by the pathways created by microneedles. Small microneedles can also be painless if designed with an understanding of skin anatomy. Needles of micron dimensions can be made using microfabrication technology, which is the same technology used to make integrated circuits. In this microfabrication approach, silicon, metal, polymer or other materials are exposed to masking steps, which define the shape of structures to be created, and chemical etching steps, which sculpt the material into the prescribed shapes.

Metered-Dose Transdermal Spray (MDTS)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential Advantages:

1. Improves delivery potential without skin irritation due to its non-occlusive nature.
2. Increased acceptability.
3. Dose flexibility
4. Simple manufacture

Powderject Device

High speed gas flow is used to propel the solid drug particles across the skin. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

OTHER ENHANCEMENT TECHNIQUES:

1. Transfersomes: This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

2. Medicated Tattoos: Medical Tattoos is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

3. Skin Abrasion: This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules.

4. Laser Radiation: In this technique, exposure of the skin to the laser beams that result in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. This technique improves the delivery of lipophilic and hydrophilic drugs.

5. Controlled Heat Aided Drug Delivery (CHADD) System: heat is applied on the skin that increases the temperature which facilitates the transfer of drug substance to the blood circulation and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device.

CONCLUSION

This article provides valuable information regarding the transdermal drug delivery systems, different type of patches, components and its evaluation process. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. Many drugs have been formulated in TDDS form, such as hormonal therapy, wide range of analgesics, drugs of heart diseases, for avoiding GI effects and first pass metabolism. The better understanding of the skin physiology and anatomy helps us in further development in this field. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required.

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