An updated review on transdermal drug delivery systems

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Abstract
Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver 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. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. With the advancement in technology Pharma industries have trendified all its resources. Earlier we use conventional dosage form but now we use novel drug delivery system. One of greatest innovation of novel drug delivery is transdermal patch. The advantage of transdermal drug delivery system is that it is painless technique of administration of drugs.

Keywords: Transdermal drug delivery systems (TDDS), Diffusion, First-generation TDS, Second-generation TDS, Polymer Matrix, Permeation enhancers, Iontophoresis, Microneedles

1. Introduction
Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the Bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness.[1,2] It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement.[3,4] Depending on the drug, the patches generally last from one to seven days. The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestradiol patches are used by more than a million patients
annually and, in contrast to oral formulations, do not cause liver damage. Of two major sub-categories - therapeutic and cosmetic), aroma patches, weight loss patches, and Non medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure. [5,6]

1.1 Definition:
A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. [7]

2. Advantage and Disadvantage

2.1 Advantages
i) They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
ii) They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
iii) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.
iv) They are noninvasive, avoiding the inconvenience of parenteral therapy.
v) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Tradermal clonidine day.
vi) The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
vii) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.[8,9]

2.2 Disadvantages
i) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
ii) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.
iii) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
iv) Long time adhere is difficult. [10,11]

3. Care taken while applying transdermal patch
The part of the skin should be properly cleaned before application of patch. Cutting the patch destroys the drug delivery system therefore patch should not be cut. It should be made sure that the old patch is removed from the site before applying a new patch. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch. The patch should be applied accurately to the site of administration.

4. First-generation transdermal delivery systems
The first generation of transdermal delivery systems is responsible for most of the transdermal patches that have thus far been in clinical use. Significant advances in patch technology, and public acceptance, have enabled the recent surge in first-generation transdermal patches reaching the market. However, this surge will taper off as drugs with suitable properties for such systems are depleted. First-generation delivery candidates must be low-molecular weight, lipophilic and efficacious at low doses. Usually, their transdermal delivery should be more attractive than oral delivery due to low oral bioavailability, the need or desire for less frequent dosing or steady delivery profiles, or other factors.

5. Second-generation transdermal delivery systems
The second generation of transdermal delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should (i) increase skin permeability by reversibly disrupting stratum corneum structure, (ii) provide an added driving force for transport into the skin and (iii) avoid injury to deeper, living tissues. However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-avitational ultrasound, have struggled with the balance between achieving increased delivery across stratum corneum, while protecting deeper tissues from damage. As a result, this second generation of delivery systems has advanced clinical practice primarily by improving small molecule delivery for localized, dermatological, cosmetic and some systemic applications, but has made little impact on delivery of macromolecules. [12, 13, 14]
6. Anatomy and physiology of skin

Human skin comprises of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as “epidermis”. Underlying dermis of connective tissues, Hypodermis (Figure 1).

6.1 Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum. This is the outermost layer of skin also called as horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” The lipids are arranged in multiple bilayers.

There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form. Viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

6.2 Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

6.3 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 mechanically protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired. [16]

7. Components of transdermal patches

7.1 Polymer Matrix

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
b) The polymer should be stable.
c) The polymer should be nontoxic
d) The polymer should be easily of manufactured

e) The polymer should be inexpensive

f) The polymer and its degradation product must be non-toxic or non-antagonistic to the host.
g) Large amounts of the active agent are incorporated into it.

Types of polymer:

- a) Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.
- b) Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.
- c) Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

7.2 Drug: - Drug solution in direct contact with release liner.

Physiochemical properties:

a) The drug should have a 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.
**7.3 Permeation Enhancer:** - The flux $J$ of drug across the skin can be written as $J = D \frac{dc}{dx}$

- **Solvent:** - These compounds increase penetration possibly by swelling the polar pathway.
  e.g.: Water alcohols - Methanol & ethanol, / Dimethyl acetamide Propylene glycol and Glycerol.

- **Surfactants:** - The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.
  i) Anionic surfactant:- Sodium lauryl sulphate
  ii) Nonionic Surfactant:- Pluronic F127, Pluronic F68
  iii) Bile Salt: - Sodium taurocholate, Sodium deoxycholate.

- **Miscellaneous Chemicals:** - These include urea, a hydrating and keratolytic agent; N, N dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness is sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.

- **Enhance the permeation** eg. Urea, calcium thioglycolate.

**7.4 Other excipients:** - (a) **Adhesives:** - The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.
  i) It should not be irritant
  ii) It should be easily removed
  iii) It should not leave an un washable residue on the skin
  iv) It should have excellent contact with the skin.

- **Physical & chemical compatibility with the drug**
  - Permeation of drug should not be affected.

**7.5 Linear:** - Protect the patch during storage. The linear is removed prior to use.

**8. Factors affecting transdermal bioavailability**

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

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

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

- **Drug concentration:** The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of 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 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.

**8.2 Biological Factors**

- **Skin condition:** Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

- **Skin age:** The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting the bioavailability of drug in TDDS.

- **Blood flow:** Changes in peripheral circulation can affect transdermal absorption.

Regional skin sites 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 efficacy of drug permeated through the skin.
Species differences: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration. [24-29]

9. Types of transdermal patches

Single-layer Drug-in-Adhesive: The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing. [30]

Multi-layer Drug-in-Adhesive: The multi-layer drug-in-adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing. [31]

Reservoir: Unlike the Single-layer and Multi-layer Drug-inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order. [32]

Matrix: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. [33]

Vapour Patch: In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market. [34]

10. Various methods for preparation of TDDS

Asymmetric TPX membrane method: - A prototype patch can be fabricated using a heat sealable polyester film with a concave of 1 cm diameter will be used as the backing membrane. Drug sample is dispensed into concave membrane, covered by TPX [poly- (4- methyl-1-pentene)] asymmetric membrane, and sealed by an adhesive.

Circular Teflon mould method: - Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are stirred for 12 h and poured into circular Teflon mould. The moulds are placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

Mercury substrate method: - In this method, drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 min to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

“IPM membranes” method: - In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

“EVAC membranes” method: - In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by
using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane is placed over the gel and the edges are sealed by heat to obtain a leak proof device.

Aluminium backed adhesive film method: Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesives are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

Preparation of TDDS by using proliposomes: - The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 min. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture; a 0.5 ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquot (0.5 ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freezing temperature until characterization.

Free film method: - Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/v is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/v of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish.

The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution. [35-41]

11. Approaches in the development of transdermal Therapeutic System: - Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies are as follows:

Adhesive dispersion type system: - The system consists of drug-impermeable backing membrane, the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On top of this, a layer of rate-controlling adhesive polymer (non-medicated) of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system with detachable release liner which in an ideal situation is removed and the patch is applied to the skin for a required period of time. Illustration of this type of system is exemplified by development and marketing of transdermal therapeutic system of angina pectoris and Valsartan as angiotensin II type 1 selective blocker for one day medication.

Membrane permeation controlled system: - In this system the drug reservoir is totally embedded in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane The drug molecules are permitted to release across the rate controlling membrane simply by diffusion process through the pores. In the reservoir compartments the drug solids are dispersed homogeneously in a solid polymeric matrix (e.g. polyisobutylene) suspended in the unseachable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution. The rate controlling membrane, can be either a microporous or non-porous polymeric membrane e.g. ethylene–vinyl acetate copolymer, having specific drug permeability.

On the top surface of the polymeric membrane a thin layer of drug compatible adhesive polymer, e.g., silicone adhesives, can be applied, to provide intimate contact of the transdermal system with the skin surface. The release rate from this transdermal system can be tailored by varying the polymer composition, thickness of the rate controlling membrane, permeability coefficient and adhesive. Examples of this system are TransdermScop (Scopolamine- 3 days protection) of motion sickness and TransdermNitro (Nitroglycerine-for once a day) medication of angina pectoris.

Matrix diffusion controlled system: - In this approach, the drug reservoirs are prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix or combination of both. The resultant medicated polymer
is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature and/or under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is then spread to form a strip of rim along the medicated disc. This matrix type of transdermal system is best exampled by the nitroglycerin releasing transdermal therapeutic system. The advantage of matrix dispersion type transdermal system is the absence of the dose dumping since the polymer cannot rupture. 

**Micro reservoir type controlled system:** - This system is basically hybrid of reservoir and matrix dispersion type of drug delivery system. In this approach, drug reservoir is formed by suspending the drug in an aqueous solution of liquid polymer and then dispersing the drug suspension homogeneously in lipophilic polymer e.g. silicone elastomers by high energy dispersion technique by shear mechanical force to form thousands of unreachable and microscopic spheres of drug reservoirs. This technology has been utilized in the development of Nitro disc. Release of a drug from a micro reservoir-type system can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix. [42,43,44]

![Fig. (A): Showing the presence of microscopic spheres of drug reservoir](image)

![Fig. (B): Development of adhesive dispersion controlled therapeutic system](image)

![Fig. (C):Diagrammatic representation of membrane permeation controlled system](image)

![Fig. (D): Representation of matrix type transdermal system](image)

**12. Evaluation of transdermal patches**

Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

1. **Physicochemical evaluation**
2. **In vitro evaluation**
3. **In vivo evaluation**

Upon the success of physicochemical and in vitro studies, in vivo evaluations may be conducted.

**Physicochemical evaluation:**

- **Thickenss:** The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film. 

- **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 film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution. 

- **Moisture content:** The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight.

- **Adhesive studies:**

  - (a) **Shear adhesion test:** - The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch parallel to this plate. The time taken to pull off the patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength.

![Fig.10. Shear strength test](image)
(b) Peel adhesion test: - The measure of patch strength between an adhesive and a substrate is defined as adhesion. The force required removing adhesive coating from the steel used as test substrate. The type and amount of polymer molecular weight and the composition of polymers determine the adhesive properties. The single patch is adhering to test substrate (Steel) and it pulled from the substrate at 1800 angle. No residue on the test substrate indicates failure of adhesive.

![Fig.11. Peel adhesion test](image)

(c) Tack properties: - Tack is the ability of polymer to adhere to a substrate with little figure pressure it’s important in transdermal systems which are applied with little figure pressure. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer.

6. Tests for tack include: -

(a) Thumb tack test: - This is subjective test in which evaluation is done by pressing the thumb in to the adhesive. Experience is required for using the test.

(b) Rolling ball tack test: - This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is 7/16o inches and it released on inclined track having angle 22.50. More the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer.

![Fig.12. Rolling Ball Tack Test](image)

(c) Peel tack or quick stick test: - The peel force is the force required to break the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 90° with speed 12 inches/minute. The value of force is expressed in grams/inch or ounces/inch.

![Fig.13. Peel tack test](image)

(d) Probe tack test: - In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams.

![Fig.14. Probe tack test](image)

[2] IN VITRO RELEASE STUDIES: - Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system there are various methods available for determination of drug release rate of TDDS.

The Paddle over Disc: - ([USP apparatus 5/ Ph Eur 2.9.4.1]) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.

The Cylinder modified USP Basket: ([USP apparatus 6 / Ph Eur 2.9.4.3]) this method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C. The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages.

Preparation of skin for permeation studies: - An in vitro permeation study can be carried out by using...
diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

Fig. 12: Tran’s diffusion cell [50]

[3] IN VIVO STUDIES: - 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: [51]

Animal Models,

Human volunteers

1. Animal models: - Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man. [52]

Human models: - The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. [53-57]

Stability studies: - The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

13. Applications of transdermal patches: -

1) Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

2) Nitroglycerine patches are also sometimes prescribed for the treatment of Angina.

3) Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflammatory drug are also available in the form of transdermal patches.

4) Transdermal form of the MAOI selegiline became the first transdermal delivery agent for an antidepressant.

5) Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

14. Advance development in TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch polymer is required. TDDS realistic practical application as the next generation of drug delivery system. [58, 59]
15. Conclusion

This article provides valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

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