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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
A Transdermal 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. Transdermal delivery provides a advantage over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal patches deliver the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enter the bloodstream directly though the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood, for a long period of time, maintain the constant concentration of drug in the blood flow. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, penetration enhancers, various components of Transdermal patches, types of Transdermal patches.

KEYWORDS: Transdermal Drug Delivery, Patches, Types, Drug In Adhesive.

INTRODUCTION[1,2,3]
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. At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has some drawbacks -namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise, spatial and temporal placement within the body thereby reducing both the size and number of doses. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. Theprimary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing.

Advantage[4,5,6]
1. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first- pass" effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc.
2. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.
3. Topical patches are a painless, non-invasive way to deliver substances directly into the body.
4. Topical patches are cost-effective.
5. Self administration is possible with these systems.
6. More uniform plasma levels and maintain plasma concentration of potent drugs.
7. Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
8. Flexibility of terminating the drug
9. Administration by simply removing patch from the skin.
10. Improved patient compliance and comfort via non-invasive, painless and simple application.
11. Avoid inter and intra patient variation and enhance therapeutic efficacy.

Disadvantage[7,8,9]
1. Coefficient fail to reach systemic circulation.
2. Difficult to administer the large dose, i.e. more than 10 mg/day.
3. Ionic drugs create problems

4. Drugs having size more than 500 Dalton are not suitable for TDDS.
5. Drugs in high concentration may cause skin irritation.
6. Difficult to achieve high plasma drug concentration.
7. Long-term adherence creates discomfort to patients.

Structure of skin[8,9]

Skin is the major organ of the human body. It contain of largest surface area with through connection to the atmosphere. The human skin is consist of two layers, epidermis and dermis which is shown (Fig.1).

Skin is not only protects the body from microbes, it also control and cover the muscles which indirectly maintains the temperature body. Skin protects to us beside microbes, and of furthermore gives the sensations about touch and temperature changes. The epidermis layer is the outer layer of the skin that comprises of keratinized, stratified squamous epithelium cells as five layers contingent upon its area in the body. From profound toshallow, these layers named as stratum basale, stratumspinosum, stratum granulosum, and stratum lucidum and stratum corneum. The outermost layer, stratum corneum acts as a barrier which allows only lipophilicdrug moieties of molecular weight less than 500 Da tocross the skin. Several techniques have designed to overcome this barrier and enhance the transdermal drug delivery of molecules with high molecular mass. Therefore, permeation enhancers have been used to alter the lipid content of stratum corneum and increase the permeability of drug molecules across the skin. The dermis layer contain vascular, connective tissue, nerves,and hair follicles and sweat ducts. The epidermis layer is a vascular and called outermost layer of the skin. Stratum corneum, is the important barrier of skin especially to hydrophilic compounds, which is containsof keratin, dead epidermal cells named corneocytes fixed inside a fat rich matrix .Skin also serves numerouscritical abilities, including securing the body againstinjury, managing body temperature, balance the waterand electrolyte level and contributes for vitamin Dproduction. Topical or transdermal route of drugdelivery has many advantages than other routes becauseof patient compliance, preventing the first passmetabolism, and few side effects.

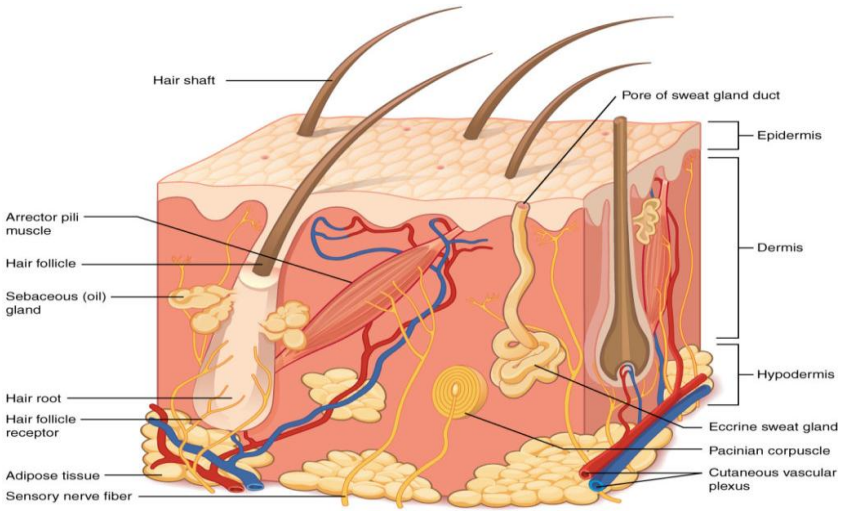

Fig. no. 1: Structure of skin.

Types of transdermal drug delivery system[10,11]

a) Single layer drug in adhesive

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

b) Multi -layer drug in adhesive

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

c) Vapour patch

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

d) Reservoir system

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

adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system

i. Drug-in-adhesive system

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

ii. Matrix-dispersion system

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

f) Micro reservoir system

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

Components of transdermal patches[12,13]

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
b) Diffuses properly and gets released through it.
c) The polymer should be stable.
d) The polymer should be nontoxic
e) The polymer should be easily of manufactured
f) The polymer should be inexpensive
g) The polymer and its deagration product must be non toxic or non-antagonistic to the host.
h) 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.

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.

Biological properties

a. The drug should be potent with a daily dose of the order of a few mg/day.
b. The half life (t½) of the drug should be short.
c. The drug must not produce allergic response.
d. Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

3. Permeation enhancer: - The flux J. of drug across the skin can be write As

J = D dc/dx
J = the Flux
D = diffusion coefficient
C = Concentration of the diffusing spectes
X = Spatial coordinate

a) Solvent: - These compounds increase penetration possibly by swelling the polar pathway. e.g.: Water alcohols–Methanol & ethanol, / Dimethyl acetemide Propylene glycol and Glycerol.
b) 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 Diacetyl sulphosuccinate
ii. Nonionic Surfactant:- Pluronic F127, Pluronic F68
iii. Bile Salt: - Sodium taurocholate, Sodium deoxycholate.
c) 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 sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein
d) Enhance the permeation:- eg. Urea, calcium thioglycolate.

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.
v. Physical & chemical compatibility with the drug
vi. Permeation of drug should not effected.

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

7.6 Backing: - Protect the patch from the outer environment.

Preparation of transdermal patches[4,5]

Transdermal drug delivery patches can be prepared by various methods

a. Mercury substrate method

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is keep aside until air bobbles removed completely and then poured in to 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 dried films are to be stored in a desiccator1.

b. 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. Plasticizeradded into drug polymer solution. The total contents are to be stirred and then poured into a circular teflonmould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflonmould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccator.

c. Glass substrate method

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry anumbrapetriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After over night, the dried films are taken out and stored in a desiccator2

d. By using "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 hrs 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.

e. By using "EVAC membranes" method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (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 us+ed 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 will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. 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 adhesive 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 aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.

g. Asymmetric TPX membrane method

A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive

Evaluation of transdermal patches[

Physicochemical evaluation

1. Thickness

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

2. 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.

3. Drug content determination

It can be determined by completely dissolving a small area (1 cm 2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.

4. Content uniformity test

The test is carried out by performing assay to find out the content of drug material contained in polymeric film of

the patch. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity.

5. 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.

The percent moisture content is calculated using following formula, % moisture content = (Initial weight – final weight)/Final weight*100FlatnessA transdermal patch should possess a smooth surface and should not constrict with time. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent 100flatness.

6. Folding endurance

It involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking gives the folding endurance value.

In-vitro drug release studies

The paddle over disc method (USP apparatus V) can beemployed for assessment of the release of the drug from the prepared patches.

In-vitro skin permeation studies

An In vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male wistar rats weighing 200 to 250 g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before starting the experiment pared patches.

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: Animal models and Human volunteers.

A. 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 systems are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Based on the experiments conducted so far it is concluded 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 invivo evaluation of transdermal drug delivery.

B. 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 are conducted to assess the transdermal systems including the efficacy, risk involved, side effects, and patient compliance.

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. Though human studies require considerable resources but they are the best to assess the performance of the drug.

CONCLUSION

Nowdays the TDDS becoming a most widely used routes of administration directly into bloodstream without any pain. We can overcome the challenges associated with current popular drug delivery by formulating the drug as Transdermal patches.

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