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A Review Article of Transdermal Drug Delivery System (TDDS)

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***Abstract*: Transdermal drug delivery system (TDDS) is topically administered dosage form in the form of patches which deliver drugs for systemic effects at a predetermined and controlled rate. This review focuses towards the basic facts about the transdermal drug delivery system. including the methods of their preparation and some of the recent advancements that have in achieved this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral topical, intravenous. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects.**

***Keywords*: Transdermal Drug Delivery System**

1. Introduction

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms which deliver a therapeutically effective amount of drug across a patient' 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.

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. various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism.

Maintenance of steady plasma level of the drug. The first Transdermal system, transdar -SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.

The common ingredients which are used for the preparation of TDDS are as follows.

Drug: Drug is in direct contact with release liner.

Ex: Nicotine, Methotrexate

Liners: protects the patch during ex: polyester film

Adhesive: Serves to adhere the patch to the skin for systemic delivery of drug.

Ex: Acrylates, Polyisobutylene, Silicones.

Permeation enhancers: Controls the Release of the drug. Ex: Terpenes, Terpenoid.

Backing layer: Protect patch from outer environment. Ex: Cellulose derivatives, poly vinyl alcohol.

A. Types of transdermal patches

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.

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:

In this type of patch the role of adhesive layer not only as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor 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.

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:

Drug-in-adhesive system:

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

Matrix-dispersion system:

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. 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.

f) Micro- reservoir system:

In this type the drug delivery 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.

2. Skin as site for transdermal drug administration

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin is a multi-layered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis (Fig. 1.). Microscopically, the epidermis is further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeters of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface. Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum.

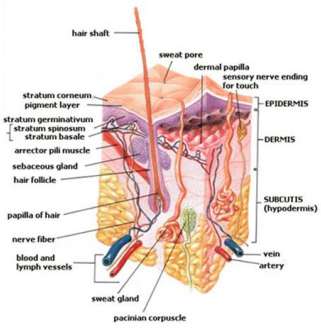

Fig. 1. Physiological skin structure

A. Components of TDDS

Polymer matrix / Drug reservoir:

- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other recipients like plasticizers and solvents

Polymer matrix / Drug reservoir:

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs.

Drug:

The Transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. the drugs for Transdermal delivery. In addition drugs like rivastigmine for Alzheimer's and Parkinson dementia, retightened for Parkinson, methylphenidate for attention deficit hyperactive disorder and elegizing for depression are recently approved as TDDS.

Permeation Enhancers:

These are the chemical compounds that increase permeability of stratum corneas so as to attain higher therapeutic levels of the drug candidate. Penetration structural components of stratum conium i.e., proteins, lipids. They alter the protein and lipid packaging of stratum conium, thus chemically modifying the barrier functions leading to increased permeability.

Pressure sensitive adhesives:

A PSA is a material that helps in maintaining an intimate contact between Transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in Todd's.

Release Liner:

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug.

Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition, plasticizers such as polyethylene glycol and propylene glycol are added to provide plasticity to the

transdermal patch.

B. 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 following types:

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

C. Physicochemical evaluation

Thickness: 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.

D. 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/ PhEur 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 / PhEur 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.

E. 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.

F. Animal models

Human volunteers:

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, 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. 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.

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.

3. Factors affecting transdermal permeation

A. Biological factor

1) Skin conditions

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

2) Skin age:

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

surface area per unit body weight. Thus potent steroids, boric acid, hexachlorophene have produced severe side effects.

3) Blood Supply:

Changes in peripheral circulation can affect transdermal absorption.

4) Regional skin site:

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

5) Skin metabolism:

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

6) Species differences:

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

B. Physicochemical factors

1) Skin hydration

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

2) Temperature and pH

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

3) 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.

4) Drug concentration

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

5) Partition coefficient

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

6) Molecular size and shape

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

C. Environmental factors

1) Sunlight

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

2) Cold Season

Often result in itchy, dry skin. Skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

3) Air Pollution:

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

4) Effect of Heat on Transdermal patch:

Heat induced high absorption of transdermal delivered drugs. Patient should be advised to avoid exposing the patch application site to external heat source like heated water bags, hot water bottles. Even high body temperature may also increase the trans dermally delivered drugs.

Advantages of transdermal drug delivery:

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.
- Avoidance of first pass metabolism.
- The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good.
- As a substitute for oral route.
- The patch also permits constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
- Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
- Avoidance of gastro intestinal incompatibility.
- Convenience especially notable in patches that require only once weekly application.
- Minimizing undesirable side effects.
- Provide utilization of drug with short biological half-lives, narrow therapeutic window.
- Avoiding in drug fluctuation drug levels.
- Inter and intra patient variation.
- Termination of therapy is easy at any point of time.
- Provide suitability for self-administration.
- They are non-invasive, avoiding the inconvenience of parentral therapy.
- It is of great advantages in patients who are nauseated or unconscious.
- Transdermal patches are cost effective.

Disadvantages of transdermal drug delivery:

- Transdermal drug delivery system cannot deliver ionic drugs.
- It cannot achieve high drug levels in blood.
- It cannot develop for drugs of large molecular size.
- It cannot deliver drugs in a pulsatile fashion.

- It cannot develop if drug or formulation causes irritation to skin.
- Possibility of local irritation at site of application.
- May cause allergic reaction.
- Sufficient aqueous and lipid solubility, a log P between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.

Physicochemical properties:

- The drug should have a molecular weight less than 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phasea. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
- The drug should have low melting point.
- Along with these properties the drug should be potent, having short half-life and be non-irritating.

Biological Properties:

- Drug should be very potent, i.e. it should be effective in few mg/day.
- The drug should have short biological half-life.
- The drug should not be irritant and non-allergic to human skin.
- The drug should be stable when contact with the skin.
- They should not stimulate an immune reaction to the skin.
- Tolerance to the drug must not develop under near zero order release profile of transdermal delivery.
- Dose is less than 50 mg per day, and ideally less than 10 mg per day.
- The drug should not get irreversibly bound in the subcutaneous tissue.
- The drug should not get extensively metabolized in the skin.

Table 1
Ideal properties of drug candidate for transdermal drug delivery

Parameter	Properties
Dose	Less than 20mg/day
Halflife	< 10 hrs
Molecular weight	<400 Dalton
Melting point	<200°C
Partition coefficient	1 to 4
Aqueous Solubility	>1mg/mL
pH of the aqueous saturated solution	5-9
Skin Permeability Coefficient	$>0.5\times10^{-3}$cm/h
Skin Reaction	Non irritating and non-sensitizing
Oral Bioavailability	Low

Ideal properties of a polymer to be used in a transdermal system:

- Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- The polymer should be stable.
- The polymer should be nontoxic
- The polymer should be easily of manufactured
- The polymer should be inexpensive
- The polymer and its deaggration product must be non-toxic or non-antagonistic to the host.
  Large amounts of the active agent are incorporated into it.

4. Conclusion

Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, membrane matrix hybrid, micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS.

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