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TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT
Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. The stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules. There are three main routes of drug penetration, which include the appendageal, transcellular and intercellular routes. Skin age, condition, physicochemical factors and environmental factors are some factors that are to be considered while delivering drug through this route. Basic components of TDDS include polymer matrix, membrane, drug, penetration enhancers, pressuresensitive adhesives, backing laminates, release liner, etc. Transdermal patches can be divided into various systems like reservoir system, matrix system and micro-reservoir system, which are used to incorporate the active ingredients into the circulatory system via the skin. After preparation of transdermal patches, consistent methodology are adopted to test the adhesion properties, physicochemical properties, in vitro drug release studies, in vitro skin permeation studies, skin irritation studies and stability studies. According to the duration of therapy, various drugs are commercially available in the form of transdermal patches.

KEYWORDS: Matrix system, microreservoir system, penetration enhancer, pressure-sensitive adhesives, reservoir system, stratum corneum, Transdermal drug delivery system.

INTRODUCTION
Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches" when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.

The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application.

That will improve 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 delivery not only provides controlled, constant administration of drugs, 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. Several important advantages of transdermal drug delivery are limitations of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady plasma level of drug. The developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy.

The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a

zero order rate for a period of several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions.[9] 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.

Advantages of transdermal drug delivery

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls olf 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 candidate for transdermal drug delivery.
- 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, such a simple dosing regimen can aid in patient adherence to drug therapy.
- 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.
- The activity of drugs having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- It is of great advantages in patients who are nauseated or unconscious.
- Transdermal patches are better way to deliver substances that are broken down by the stomach aids, not well absorbed from the gut, or extensively degraded by the liver.
- 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 (octanol/ water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
- Long-time adherence is difficult.

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY

Skin condition

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

Skin age

It is seen that the skin of adults and young ones is more permeable than that of the older ones. but there is no dramatic difference. Children show toxic effects because of the greater surface area per unit body weight. Thus, potent steroids, boric acid and hexachlorophene have produced severe side-effects.

Physicochemical factors

Hydration of skin: Generally, when water saturates the skin, it swells tissues, softens wrinkles on the skin and its permeability increases for the drug molecules that penetrate through the skin.

Temperature and pH of the skin: The penetration rate varies if the temperature varies and the diffusion coefficient decreases as the temperature falls;, however adequate clothing on the body prevents wide fluctuations in temperature and penetration rates. According to pH, only unionized molecules pass readily across the lipid membrane, and weak acids and bases dissociate to different degrees according to their pH and pKa or pKb values. Thus, the concentration of unionized drug in applied phase will determine the effective membrane gradient, which is directly related to its pH.

Environmental factors

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

Cold season: The cold season often results in itchy and dry skin. The skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

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

Major transdermal systems

Drug in adhesive system

1.1 Single layer drug in adhesive

The adhesive layer of this system contains the drug. In this type of patch, the adhesive layer not only serves to adhere the entire the various layers together, along with system to the skin, but is also responsible for releasing of the drug. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The adhesive layer is surrounded by a temporary linear and a backing layer.

Fig. 01: Single Layer Adhesive Transdermal Delivery System.

1.2 Multi-layer drug in adhesion

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. One of the layer is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer patch also has a temporary linear layer and a permanent backing.

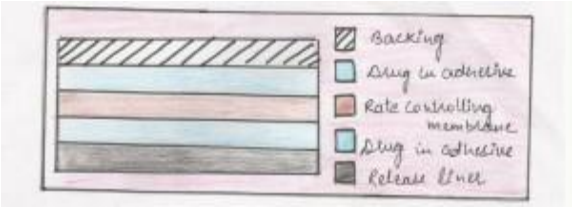

Fig. 02: Multilayered Drug in Adhesive Transdermal System.

1.3 Reservoir

Unlike the single layer and multilayer drug in adhesive 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.

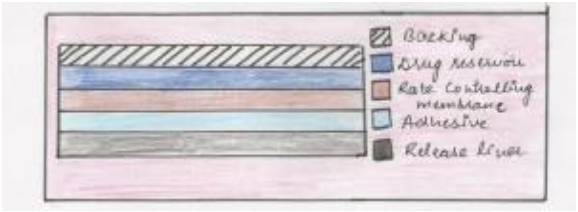

Fig.03: Schematic Representation of Reservoir Transdermal Delivery System.

1.4 Matrix

The Matrix system design 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 overlying it. These type of patches are also known as monolithic device.

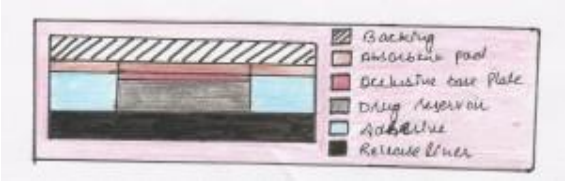

Fig. 04: Schematic Representation of Matrix Transdermal Delivery System.

1.5 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 controlled vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigrate that one smokes in a mouth are also available on the market.

Various methods for preparation of transdermal drug delivery system

1) 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.

1.1 Asymmetric TPX membrane preparation

These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardener knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

2) 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 to be stirred for 12 h and then poured into a circular teflon mould. The moulds are placed on a levelled surface and covered with an inverted funnel to control solvent vaporization in a laminar flow hood model with speed of air 1/2 m /sec. The solvent is allowed to evaporate for 24 h. Before evaluation the dried films are to be stored for another 24 h at 25±0.5 °C in a desiccators containing silica gel before to eliminate aging effects. These types of films are to be evaluated within one week of their preparation.

3) 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 homogeneous dispersion and poured in to a levelled mercury surface. Then the solution is covered with inverted funnel to control solvent evaporation.

4) By using "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940polymer 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.

5) 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 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 will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

6) 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 custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

7) 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 1:2 can be used as an optimized ratio. The proliposomes are prepared by taking 5mg of mannitol powder in a 100ml 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. Aliquot of 0.5 ml of the organic solution is introduced into the round bottomed flask at 37 °C containing mannitol after complete drying second aliquots (0.5ml) 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 desiccators over night and then sieved through 100 mesh. The collected powder is transferred in to a glass bottle and stored at the freeze temperature until characterization.

8) By using free film method

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is prepared by using chloroform. Plasticizers are incorporated at a concentration of 40% w/w 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 petridish. 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 desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

Desirable features for transdermal patches

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is zero order.
- Delivery is efficient.

Conditions in which patches are used

- When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.

- It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which patches are not used

- Cure for acute pain is required.
- Where rapid dose titration is required.
- Where requirement of dose is equal to or less than 30 mg/24 hrs.

Evaluation of transdermal patches

The transdermal patches can be characterized in terms of following parameters

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

Physicochemical evaluation

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

- **Thickness**

The thickness of transdermal film is determined by travelling 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.

- **Content uniformity test**

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

- **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 X 100

- **Moisture Uptake**

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

% moisture uptake = Final weight – Initial weight X 100

- **Flatness**

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. 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 to 100 percent flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

- **Folding Endurance**

Evaluation of folding endurance 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 is folding endurance value.

- **Tensile Strength**

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

- **Tack properties**

It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

- **Thumb tack test**

The force required to remove thumb from adhesive is a measure of tack.

- **Rolling ball test**

This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

- **Quick stick (Peel tack) test**

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inch/min.\

- **Probe tack test**

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

***In vitro* release studies**

Transdermal patches can be *in vitro* evaluated in terms of Franz diffusion cell the cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds th**e** receptor compartment. The drug content is analyzed using suitable method, maintenance of sink condition is essential.

***In vivo* Studies**

Transdermal patches can be *in vivo* evaluated in terms of *In vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using animal models 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, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted leads 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 model

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

CONCLUSION

TDDS is a newer approach in the area of dosage forms for many injected and orally delivered drugs having appropriate physicochemical and pharmacological properties. The TDD ensures that a pharmacologically active substance arrives at a relevant in vivo location with minimal side-effects. Because of the several advantages of the TDDS, many new researches are going on to incorporate newer drugs in the system. Various devices that help in increasing the rate of absorption and penetration of the drug are also being studied. TDDSs are heavily based on polymers, penetration enhancers, backing laminates, plasticizers, liners to ensure good adhesion and controlled release of drug to systemic circulation via skin over a period of several hours or days. Transdermal patches can be divided into various systems, like reservoir system, matrix system and microreservoir system. After preparation of transdermal patches, consistent methodologies are adopted to test the various parameters. Because of the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane, the transdermal route is becoming the most widely accepted route of drug administration. This drug delivery overcomes the challenges associated with current popular drug delivery; thus, it shows a promising future. According to the duration of therapy, various drugs are commercially available in the form of transdermal patches.

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