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TRANSDERMAL PATCHES: PRINCIPLES, EVALUATION AND PERSPECTIVES

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ABSTRACT

The skin is considered to be one of the most accessible and convenient site for the administration of various medications. Transdermal drug delivery systems are formulated with the intent of developing safe and efficacious means of delivering medications across the skin. After being discovered in 1981, it has gained a lot of interest and continues to garner much time and investment with the continuous advancement of new and innovative approaches. 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. There are various types of transdermal patches which are further modified to increase the potential of the drug delivery. New transdermal drug delivery system technologies now have been developed that is considered to be helpful in rate controlled delivery of drugs that are difficult to administer. Various types of Transdermal patches are used that delivered the specific dose of medication directly into the blood stream. This review article covers a brief outline of the transdermal drug delivery system, with special emphasis on principle, advantages and formulation criterion for drug-in-adhesive patches meant for transdermal delivery.

KEYWORDS: Transdermal patches, controlled delivery, drug-in-adhesive patches, specific dose, transdermal delivery.

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 meno pause), 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]

During the past 20 years, advances in drug formulations and innovative routes of administration have made. Our understanding of drug transport across tissues has increased. While topical products or drug delivery systems have been used for centuries for the treatment of local skin disorders, the use of the skin as a route for

systemic drug delivery is of relatively recent origin.[7] The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness.[8,9]

Transdermal Drug Delivery (TDD)

TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin.[10,11] The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.[12,13] TDD has many advantages over other conventional routes of drug delivery mainly because it can be used for wide spectrum of active molecules.[14,15]

Advantages

1. They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
2. They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
3. To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Tradermal clonidine day.
6. 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.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.[16,17,18]

Disadvantages

1. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
2. Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.
3. Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
4. Long time adhere is difficult.[19,20]

Anatomy of Human skin

The skin plays an important role in the transdermal drug delivery system. The skin of an average adult body covers a surface area of approximately 2 m^2 and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. The main three layers of skin play an important role in transdermal drug delivery system.[21,22]

Subcutaneous fat layer

- It bridges between the overlying dermis and the underlying body constituents.
- It is relatively thick in order of several millimeters.
- The layer of adipose tissue serves to insulate the body and to provide mechanical protection against physical shock.
- It also provide supply of high energy molecules
- Principal blood vessels and nerves are carried to the skin in this layer.

Dermis

- It contains blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands (eccrine and apocrine).
- It provides physiological support for the epidermis.
- It is typically 3-5 mm thick and is the major component of human skin.
- It is composed of a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility, embedded in a mucopolysaccharide gel.
- It provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

Epidermis

- It is 100 µm thick.
- It contains various layers. The stratum germinativum is the basal layer. Above the basal layer are the stratum spinosum, the stratum granulosum, the stratum lucidum, and finally, the stratum corneum (SC).
- SC is the rate limiting barrier that restricts the inward and outward movement of chemical substances consists of flattened keratin-filled cells (e.g., corneocytes). Upon reaching the SC, these cells are cornified and flatten. The corneocytes are then sloughed off the skin at a rate of about one cell layer per day, a process called desquamation.
- The main source of resistance to penetration and permeation through the skin is the SC.[23]

Theory of transdermal permeation

Transdermal permeation is based on passive diffusion. Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum-the

skin permeation barrier. In the initial transient diffusion stage drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium through the intact stratum corneum becomes the primary pathway for transdermal permeation. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process (Fig.1), which involves:-

- Process of dissolution and release from the formulation
- Partitioning into the skin's outermost layer, the stratum corneum
- Diffusion through the SC, principally via a lipidic intercellular pathway
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake into the papillary dermis and into the microcirculation.[24]

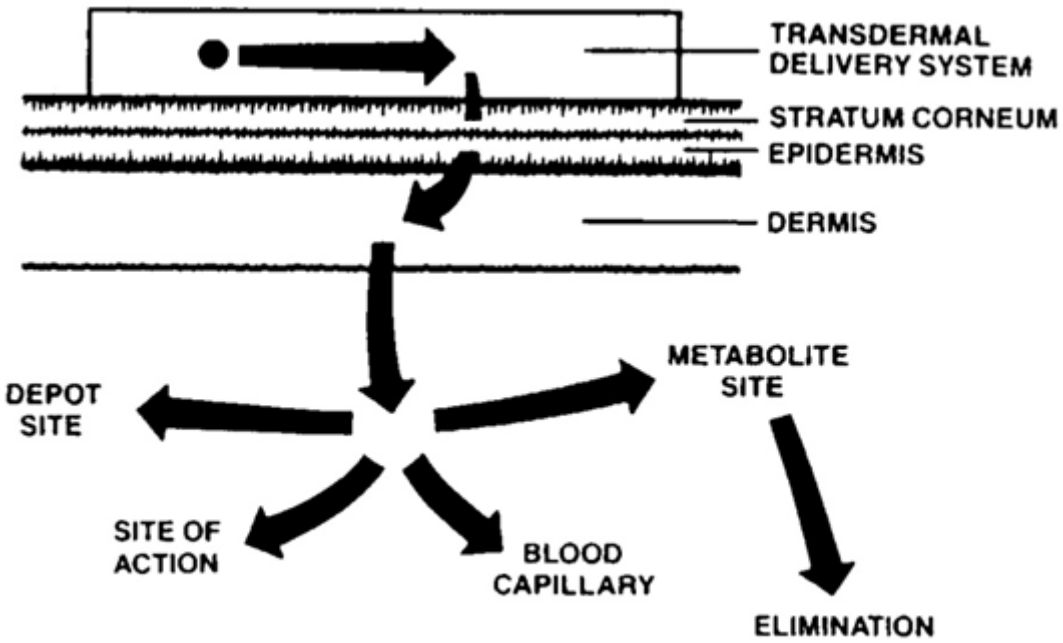

Fig. 1: Process of Transdermal Permeation.

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.[25,26]

(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 ipid 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.[25]

(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' sdryingeffects. Agoodmoisturizerwill 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 downthenaturalskin' soilsthatnormally trap moisture in skin and keep it supple.[27]

Conditions in which patches are used

1. 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.
2. 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.
3. It can be used in combination with other enhancement strategies to produce synergistic effects.[28,29,30]

Conditions in which patches are not used

1. Cure for acute pain is required.
2. Where rapid dose titration is required.
3. Where requirement of dose is equal to or less than 30 mg/24 hrs.[28,29,30,31]

Evaluation of Transdermal Patches

The transdermal patches can be characterized in terms of following parameters;

a) Physicochemical evaluation
b) In vitro evaluation
c) In vivo evaluation

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

i) Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.[32]

ii) 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.[33,34]

iii) 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.[35,36]

iv) 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% to 125% 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.[37]

v) 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

vi) 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.[38]

% Moisture uptake = Final weight – Initial weight X 100

vii) 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.[37]

viii) **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.[39,40]

% constriction = $I^1 - I^2$ X 100

Where I^1 = Initial length of each strip

I^2 = Final length of each strip

ix) **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.[33]

x) **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.[41]

xi) **Thumb tack test**: The force required to remove thumb from adhesive is a measure of tack.[39]

xii) **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.[41]

xiii) **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.[42]

xiv) **Probe tack test**: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.[33]

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.(Fig.2) The receptor compartment has a volume of 5-12 ml and effective surface area of 1-5 cm^2. The diffusion buffer is continuously stirred at 600 rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment. The drug content is analyzed using suitable method, maintenance of sink condition is essential.[43]

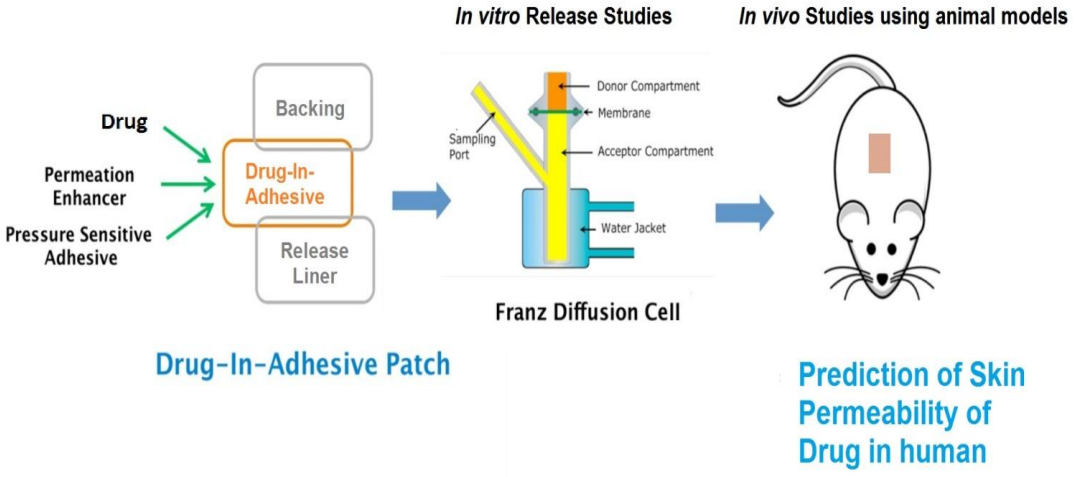

Fig. 2: Representation of flow of evaluation procedures of transdermal patch.

In vivo Studies: Transdermal patches can be evaluated in vivo as these 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.[33]

Animal models: Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale.(Fig.2) 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.[44]

CONCLUSION

The potential of Transdermal formulation for drug delivery was first demonstrated around 1980s and since then several transdermal drug delivery systems (TDDS) have been developed with the aim of accomplishing the objective of systemic medication through the transdermally controlled delivery of pharmaceuticals. This technology is applicable to various active

pharmaceutical ingredients and in conditions, such as hypertension, angina pectoris, asthma, arrhythmias, diabetes, rheumatoid arthritis, cancer, depression, menopausal syndrome etc. with the aim of transdermal delivery of a newly synthesized or even already existing active moiety. However, there is good number of significant publications and successfully marketed products in this field but it is still devoid of rational and scientific backdrop to support preformulation and formulation considerations of transdermal preparations.

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