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A REVIEW ON NOVEL DRUG DELIVERY SYSTEM: TRANSDERMAL PATCH

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ABSTRACT

In the last two decades, the transdermal drug delivery system has become a well-known technology that offers significant clinical benefits over other conventional dosage forms. 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. Delivery of drugs through the skin has always been a challenging area for research due to barrier properties exhibited by stratum corneum the outermost layer of skin. Transdermal patches have made an important contribution to medical practice, but have yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections and the market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. This review article gives brief information regarding benefits of transdermal patches over other conventional dosage forms, types of transdermal patches, components of transdermal patch and evaluation of transdermal patches.

KEYWORDS: Transdermal patch, Skin, Transdermal permeation.

INTRODUCTION

Transdermal drug delivery system (TDDS) is one of the most effective, appealing as well as reliable drug delivery system under the category of controlled drug delivery with the aim of delivering the drugs through the skin at a predetermined and controlled rate. A transdermal patch is a medicated adhesive patch designed to deliver a specific amount (dose) of the drug at a predetermined rate of release into the blood stream via skin, when they are directly

applied on the intact skin. Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimizes and avoids the limitations associated with conventional as well as parenteral route of administration such as fluctuation in plasma drug concentration, pain and inconvenience of injections, and the limited controlled release options of both.[1-4]

The first transdermal system, Transderm SCOP, for the prevention of nausea and vomiting associated with travel was approved by the FDA in 1979. 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.[5] The challenges for patch development such as attaining sufficient skin permeability to match dose requirements, attaining optimal adhesive performance, and avoiding skin irritation upon patch application to the site must be overcome for the development of an efficacious transdermal delivery system.[6]

Basic principles of transdermal permeation[7]

Transdermal permeation is based on passive diffusion. Before a topically applied drug can act either locally or systemically, it must penetrate the skin permeation barrier-stratum corneum. 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 which becomes the primary pathway for transdermal permeation. The release of a drug from a transdermal patch applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves the following steps.

- Dissolution within and release of the drug 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.

Advantages of transdermal drug delivery[8]

1. Reduction of dosing frequency, due to longer duration of action.
2. Convenient in administration of the drugs.

3. Improved bioavailability.

4. Provides more uniform plasma levels.

5. Significant reduction of side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.

6. Drug administration can be easily terminated by simply removing the patch from the skin.

7. Improved patient compliance and comfort through non-invasive, painless and simple application.

8. Avoidance of first pass metabolism.

9. 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.

10. Transdermal patch is of great advantages in patients who are nauseated or unconscious.

11. 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.

Disadvantages of transdermal drug delivery

1. Possibility of local irritation at the site of application.

2. There may be problem of Erythema, itching, and local edema due to the drug, the adhesive, or other excipients in the formulation of a patch.[9]

Factors affecting transdermal drug delivery system[10-13]

- Not all drug candidates are suitable for transdermal delivery. Among the factors playing a part in percutaneous absorption are the physical and chemical properties of the drug, including its molecular weight solubility partitioning coefficient and dissociation constant (pka), the nature of the carrier vehicle, condition of skin.
- Drug concentration is an important factor in TDDS. Generally, the amount of drug percutaneously absorbed per unit of surface area per time interval increases with increase in the concentration of drug in the TDDS.
- The larger the area of application (the larger the TDDS), the more drug is absorbed.
- The drug should have greater physicochemical attraction to the skin than to the vehicle so that the drug will leave the vehicle in favor of skin.
- Percutaneous absorption appears to be greater when the TDDS is applied to a site with a thin horny layer than with a thick one.

- Drug with molecular weight of 100 to 800 and adequate lipid and aqueous solubility can permeate lipid and aqueous solubility can permit the skin. The ideal molecular weight of a drug for transdermal drug delivery is believed to be 400 or less.
- Hydration of skin generally favors percutaneous absorption. The TDDS acts as an occlusive moisture barrier through which sweat cannot pass thus increasing skin hydration.
- Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption.

Components of a transdermal patch[14]

Transdermal patch consists of the following components.

1. Liner: During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Since the liner is in intimate contact with the TDDS, the liner should be chemically inert**.**

2. Drug: Drug solution is in direct contact with release liner.

3. Adhesive: It has dual function of adhering the components of the patch together as well as adhering the patch to the skin.

4. Membrane: It is used to control the release of the drug from the reservoir and multi-layer patches. A membrane may be sealed to the backing to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin.

5. Backing: Backings are chosen for appearance, flexibility and need for occlusion. Examples of backings are polyester film, polyethylene film and polyolefin film. Other considerations are the backing additives leaching out and diffusion of excipients, drug or enhancer through the backing. An overemphasis on the chemical resistance often may lead to stiffness and high occlusivity to moisture vapor and air, which cause the TDDS to lift and possibly irritate the skin during long-term wear. It protects the patch from the outer environment.[15-17]

6. Enhancer and excipients: An enhancer (e.g. propylene glycol, methyl laurate, ethyl oleate, carvone, lauric acid, oleic acid, N-methyl-pyrrolidone, azone, isopropyl myristate, alcohol) may modulate the skin permeability in some fashion.[18-20]

7. Matrix Filler: It provides bulk to matrix as well as some of fillers acts as matrix stiffening agent.

Types of transdermal patches[21]

There are mainly five types of transdermal patches listed below.

1. Single-layer Drug-in-Adhesive: The adhesive layer of this system is also provided with the drug. The adhesive layer is responsible for adhering the various layers together, along with the release of drug. The adhesive layer is further surrounded by a temporary liner and a backing.

2. Multi-layer Drug-in-Adhesive: The multilayer drug-in adhesive patch has a close similarity with single-layer system in that, both adhesive layers are responsible for the release of the drug. The multi-layer system has additional layer of drug-in-adhesive, that is usually separated by a membrane (in many cases). This type of patch also has a permanent backing associated with the temporary liner layer.

3. Drug Reservoir-In-Adhesive: Unlike the Single-layer and Multi-layer Drug-in adhesive systems the drug reservoir–in-adhesive system has a separate drug layer. The drug layer is in the form of drug solution or suspension that has been separated by the adhesive layer. Backing layer is also provided with this patch. Zero order kinetics is followed in this type of system.

4. Drug Matrix-In-Adhesive: In this type of transdermal patch, the Matrix system is associated with a drug layer which is in the form of semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

5. Vapour Patch: Recently vapour patches have been introduced in the market containing essential oils which released essential oils upto 6 hours and due to this property, the vapour patches are used mainly in cases of decongestion. Controlled vapour patches are also present in the market that improves the quality of sleep. In the market there is also availability of Vapour patches that have been used to reduce the quantity of cigarettes.[22-24]

Table 1: Ideal properties of drug candidate for transdermal drug delivery.[25]

Parameter	Properties
Dose	Less than 20mg/day
Half-life	< 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

Evaluation of transdermal patches

Physical appearance

All the formulated patches are visually inspected for color, clarity, opaque, transparency, flexibility and smoothness.

Thickness

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

Folding endurance

A specific area of the patch is cut evenly and folded repeatedly at the same place till it breaks. The number of folding is noted before the breaking of patch, which gives the folding endurance.

Percentage moisture loss

The formulated patches are weighed individually and kept in a desiccators containing anhydrous calcium chloride at room temperature for 24 hours and the patches are weighed at a specific time interval until the constant weight is obtained. The percentage moisture loss is calculated by using following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight - final weight}}{\text{Initial weight}} \times 100.$$

Percentage moisture uptake

Formulated patches are weighed individually and kept in a desiccators containing saturated potassium chloride or ammonium chloride. The relative humidity is maintained as 84%. After 24 hours the patches are reweighed at a specific time intervals till the constant weight is attained. The percentage moisture uptake is calculated by using following formula.

$$\text{Percentage moisture uptake} = \frac{\text{final weight – Initial weight}}{\text{Initial weight}} \times 100.$$

Water vapour transmission rate[26]

Glass vials approx. 5 ml capacities of equal diameter are taken for transmission study. All vials are washed thoroughly and dried in an oven completely. Weigh about 1 gm of anhydrous/ fused calcium chloride and kept in respective vials. Fix the films on the brim of vials and weigh individually then kept in closed dessicator containing saturated solution of

potassium chloride to maintain humidity approx. 84%. The vials weighed in 6, 12, 24, 36, 48, and 72 hours respectively.

Transmission rate = Final weight - Initial weight X 100.

Area X Time

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 weighted 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 hrs in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug content in solution is estimated spectrophotometrically.

Swelling index

Weighed pieces 1x1 cm2of film were immersed in distilled water; at 5, 10, 30, 60min. Soaked films were removed from the medium at predetermined time, blotted to remove excess liquid and weighed immediately. The swelling index was calculated from the weight increase, as follows.

Swelling index = (W2-W1)/ W1

Where, W1 and W2 are the weight of the film before and after immersion in the medium, respectively.

Percentage elongation break test

It is determined by calculating the length of the patch just before the break point.

Percentage elongation= Final length-initial length x100.

Initial length

Interaction Studies

The interaction studies between drug and excipients in transdermal patches are commonly carried out by thermal analysis, FTIR, UV and chromatographic techniques.

In- vitro drug release studies[27]

In-Vitro drug release studies are performed by using a Franz diffusion cell with a receptor compartment having capacity of 60 ml. The cellulose acetate membrane is used for the determination of drug from the prepared transdermal matrix-type patches. The cellulose acetate membrane having a pore size 0.45 μ is mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal film is placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell is filled with phosphate buffer pH 7.4. The whole assembly is fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment is constantly and continuously stirred using magnetic beads, and the temperature is maintained at $32 \pm 0.5°C$, because the normal skin temperature of human is 32°C. The samples are withdrawn at different intervals of time and analyzed for drug content spectrophotometrically. The receptor phase is replenished with an equal volume of phosphate buffer at each sample withdrawal.

Evaluation of adhesiveness of transdermal patches[28]

The adhesiveness of the transdermal patch is evaluated by.

Peel Adhesion Properties

Peel adhesion is the force required to remove an adhesive coating form a test substrate. These properties are affected by the molecular weight of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at an angle of 180^0.

Tack Properties

Tack is ability of the polymer to adhere to substrate with little contact pressure. It is dependent on the molecular weight and composition of polymer as well as the use of tackifying resin in the polymer. Tests for tack include the following.

i. Rolling ball test

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

ii. Quick-Stick (Or Peel-Tack) test

The peel force requires breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 900 at a speed at 12 inch/min. The force is

recorded as the tack value and is expressed in ounce or grams per inch width with higher values indicating increasing tack.

iii. Probe tack test

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

Shear strength properties

Shear strength is the measurement of the cohesive strength of an adhesive polymer. It is affected by molecular weight as well as the type and amount of tackifier added. Shear strength or creep resistance is determined by measuring the time it takes to pull an adhesive coated tape off a stainless steel plate when a specified weight is hung from the tape which pulls the tape in a direction parallel to the plate.

Table 2: Marketed Products of Transdermal Patches.

Brand Name	Active Drug	Manufacturer
Nupatch 100	Diclofenac diethylamine	Zydus Cadilla
Habitrol	Nicotine	Novartis
Nicoderm	Nicotine	Glaxosmithkine
Transderm	Nitroglycerine	Novartis
Alora	Estradiol	Thera Tech/ Protocol & Gamble
Androderm	Testosterone	Thera Tech/ Glaxosmithkine
Femtech	Estradiol	Parke-Davis
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica
Estraderm	Estradiol	Alza/ Norvatis
Deponit	Nitroglycerine	Schwarz-Pharma
Climara	Estradiol	3M Pharmaceuticals/ Bertex Labs
Catapress TTS	Clonidine	Alza/ Boehinger Ingelheim
Nitrodur	Nitroglycerine	Key Pharmaceuticals
TransdermSCOP	Scopolamine	Alza/ Norvatis

CONCLUSION

The Transdermal patches have enormous advantages over conventional medications of avoiding hepatic first pass metabolism, maintain the constant therapeutic level for longer period of time, resulting in decreasing repeated dosing, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance. Due to the recent advances in technology and the incorporation of the

drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. Transdermal drug delivery systems have great potentials, being able to use for both hydrophilic and hydrophobic active substance into promising deliverable drugs. This review article can be beneficial to the research scientist who is involved in formulation designing of Transdermal patches.

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