

Review Article

A REVIEW ON TRANSDERMAL DRUG DELIVERY

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ABSTRACT

This article deals with the study of transdermal drug delivery system. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs through the skin. A transdermal patch is defined as medicated adhesive patch which is placed on the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. This article includes the study of transdermal drug delivery system regarding its advantages, disadvantages, mechanism of action, types, developments, components, methods, factors affecting transdermal delivery, and its evaluation.

Keywords: Transdermal, patch, reservoir

INTRODUCTION

Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs through the skin. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is the important site of drug application for both the local and systemic effects. [1-3] A Transdermal patch is defined as medicated adhesive patch which is placed on the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream.[4-11]. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is the important site of drug application for both the local and systemic effects. For effective Transdermal drug delivery system, the drugs are easily able to penetrate the skin and easily reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. FDA approved the first Transdermal system Transdermal -SCOP in 1979. FDA approved this for the prevention of nausea and vomiting associated with ravel, particularly by sea. Transdermal therapeutic systems are also defined as a self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintains drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. The simplicity of the drug administration is become popular with the demonstration of the percutaneous absorption. In addition, transdermal films are convenient, painless, and it is generally accepted for their improved patient compliance[12]. Delivery of drugs into systemic circulation via skin has generated a lot of interest during the last decade as transdermal drug delivery systems (TDDS) offer many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, decrease in frequency of administration, reduction in gastrointestinal side effects and improves patient compliance.[13,14] Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine, and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation [15,16]

Advantages of TDDS

1. Avoid the first pass metabolism of drugs.
2. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
3. The simplified medication regimen leads to improved patient compliance and reduced the side effects.

4. It increases the therapeutic value of many drugs via avoiding GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
5. This route is suitable for the administration of drugs having very short half-life, narrow therapeutic window and poor oral availability.
6. Improved patient compliance and comfort via the non-invasive, painless and simple application.

Disadvantages of Transdermal drug delivery system

1. Local irritation may develop at the site of application.
2. A drug has large molecular size makes absorption difficulty. So drug molecule should ideally be below 800-1000 daltons.
3. Many drugs with a hydrophilic structure having a low penetration through the skin and slowly to be of therapeutic benefit.
4. Transdermal drug delivery system cannot achieve high drug levels in the blood.[17,18]

Mechanism of Action of Transdermal Patch

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

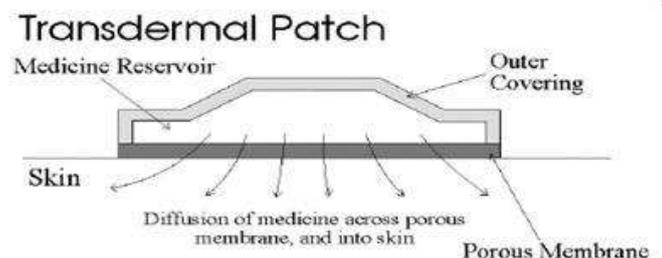


Fig 1: Mechanism of drug release from transdermal patch.

Iontophoresis

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used for pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

Electroporation

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the

skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

Application by ultrasound

Application of ultrasound, particularly low-frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz *et al.* reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

Use of microscopic projection

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in the development of cutaneous vaccines for tetanus and influenza. Various other methods are also used for the application of the transdermal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stage of development and required further detail studying.[19]

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. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi-layer drug in adhesive: This type is also similar to the single layer but it contains an immediate drug release layer and another 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 serves to adhere the various layers together but also serves as release vapor. The vapor 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 is used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. The hypoallergenic adhesive polymer can be applied as an outer surface polymeric membrane which is compatible with the drug.

e) Matrix system

i. 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 (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system: In this type the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed onto an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive

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 polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross-linking agents.[20,21,22]

FACTORS THAT INFLUENCE TRANSDERMAL DELIVERY

Biological parameters

Physicochemical parameters

Biological parameters

a) Skin Condition: The skin is a tough barrier to penetration, but only if it is intact. Vesicants such as acid, alkalis injure barrier cells and thereby promoting penetration. In disease characterized by defective stratum corneum, percutaneous absorption increases.

b) Blood flow: Theoretically, changes in peripheral circulation, or blood flow through the dermis, could affect percutaneous absorption. Thus an increased blood flow could reduce the time for which a penetrate remain in the dermis and also raise the concentration gradient across the skin.

c) Regional skin sites: Variation in cutaneous permeability around the body depends on the thickness and the nature of stratum corneum and the density of skin appendages. However, the rate of absorption at identical skin sites in different healthy volunteers varies.

d) Skin metabolism: It has been recently reviewed the role which the skin plays in the metabolism of drugs and steroidal hormones. The topical bioavailability should account for not only skin permeation but also cutaneous drug metabolism. [16]

e) Species differences: Mammalian skin differs widely in characteristics such as horny layer thickness, sweat gland, and hair follicle densities, and pelt condition, the capillary blood supply, and the sweating ability from species to species, so affect the permeation

Physicochemical parameters

a) Hydration of skin: When water saturates the skin; tissue swells, softens and wrinkles and its permeability increases markedly. In fact, hydration of stratum corneum is one of an important factor in increasing the penetration rate of most substances that permeate the skin.

b) Temperature: The penetration rate of material through the human skin can change tenfold for large temperature variation, as the diffusion coefficient decreases as the temperature falls.

Occlusive vehicles increase skin temperature by few degrees, but any consequent increased permeability is small compared to the effect of hydration.

c) Diffusion coefficient: The diffusional speed of molecule depends mainly on the state of matter in the medium. In gasses and air, diffusion coefficients are large because the void space available to the molecules is large as compared to their size.

d) Drug concentration: The drug permeation usually follows the ficks law. The flux of solute is proportional to the concentration gradient across the entire barrier phase.

e) Partition Coefficient: Partition coefficiently is important in establishing the flux of the drug through the stratum corneum. The balanced partition coefficient is required for drug permeation.

f) Molecular size: Absorption is apparently inversely related to molecular weight. Small molecule penetrates faster than large once.[23-25]

Components of transdermal drug delivery system

1. Drug
2. Matrix
3. Reservoir
4. Semi-permeable membrane
5. Adhesive
6. Backing layer
7. Release liner
8. Solvents, penetration enhancers
9. Plasticizers

Drug: The drug, of which transdermal system will be designed, should possess some physicochemical characteristics. Drug should have relatively low molecular weight, medium level lipophilic character and water solubility. Also, the drug should be a potent compound, which is effective at a low dose.

Matrix: In the formulation of matrix type transdermal systems, the drug is dispersed or dissolved in a polymer matrix. This matrix with polymer structure controls the release rate of the drug, synthetic and semisynthetic polymers (e.g. cellulose derivatives) are used as the polymer.

Reservoir: In this type of transdermal patches, a semi-permeable membrane controlling the drug release rate is used. The drug presents in a reservoir as liquid or solid

Semipermeable (release) membrane: It takes place in reservoir type transdermal systems and multi-layer adhesive systems. Ethylene-vinyl acetate copolymer, silicones, high-density polyethylene, polyester elastomers, cellulose nitrate and cellulose acetate are used as a membrane. These membranes control the release rate of drugs.

Adhesive: Adhesive should enable the transdermal system to easily adhere to the skin and should not be irritant/allergen for skin. Generally, pressure-sensitive adhesives are used in transdermal systems.

Backing layer: It protects the system from external effects during administration and ensures the integrity of the system in the storage period. For this purpose, the materials impermeable for drug molecule are used as backing layer. The backing layer must be inert and not compatible with the drug and other substances used in the formulation. Generally, ethylene vinyl acetate, polyethylene, polypropylene, polyvinylidene chloride and polyurethane are used as backing layer.

Release liner: This is the part which protects the formulation from the external environment and which is removed before the system adheres to the skin. Ethylene vinyl acetate, aluminum foil or paper can be used. Ideally, it should be easily peeled from the adhesive layer and should not damage the structure of adhesive layer. Also, silicone, fluorosilicone, perfluorocarbon polymers can be used

Solvents, penetration enhancers: Various solvents are used to solve or disperse the polymer and adhesive or drug used in the preparation of the transdermal systems. Among those, chloroform, methanol, acetone, isopropanol, and dichloromethane are used frequently. Also, various penetration enhancer substances are added to the formulations to increase permeation from the skin of the drug.

Plasticizers: Plasticizers are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material.[26]

6. Polymers used in Transdermal system

Natural Polymers: e.g. zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes, and chitosan etc.

Synthetic Elastomers: e.g., hydrin rubber, polyisobutylene, polybutadiene, silicon rubber, nitrile, neoprene, butyl rubber, acrylonitrile etc.

Synthetic Polymers: e.g. polyvinylchloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.[4-11]

Preparation of Different Types of Transdermal Patches

Matrix type

Reservoir type

Membrane matrix hybrid

Micro reservoir type

Drug in adhesive type

Matrix Type Transdermal Patches: Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogeneously dispersed in the hydrophilic or lipophilic polymer. The required quantity of plasticizers like dibutyl phthalate, triethyl citrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and

controlled thickness over the mercury on the horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film. Commonly used polymers for the matrix are cross-linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone, and hydroxypropylmethylcellulose. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross-linking of polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature.

Reservoir Type Transdermal Patches: The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unextractable viscous liquid medium (e.g. silicon fluids) to form a paste-like suspension or gel or a clear solution of drug in a releasable solvent (e.g. ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate. The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid-filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of the nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness of the membrane. Hence, the choice of membrane material is dependent on the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per unit area of the device can be controlled. Mostly EVA, ethyl cellulose, silicon rubber, and polyurethanes are used to prepare rate controlling membranes. EVA is used most frequently to prepare rate controlling membrane in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting vinyl acetate content of the polymer. Polyurethane membranes are suitable especially for hydrophobic polar compounds having low permeability through hydrophobic polymers such as silicon rubber or EVA membrane studied controlled release of scopolamine through EVA membrane in transdermal patch formulations and release rates compared with uncontrolled reservoirs. It was found that an EVA membrane patch released scopolamine at a constant rate for more than 72 hours. Krishna and Pandit (1994) prepared three transdermal formulations containing propranolol hydrochloride in a hydrophilic polymer matrix, one without rate controlling membrane and other two with EVA rate controlling membranes of different thickness. It was found that increased thickness of EVA led to greater retention of the drug in device and zero order profile was observed with EVA. The rate controlling membrane may be prepared by a solvent evaporation method or compression method. In the case of a solvent evaporation method, the polymer is dissolved in a solvent with or without plasticizer. Then the solution is poured on the horizontal surface and left for evaporation of the solvent in order to obtain a thin film. In the case of compression method, the polymer is compressed with required force at high temperature for a specific period of time. Drugs that require relatively high doses or greater permeation enhancement, such as testosterone, use liquid reservoir systems. But the application of enhancers and adhesive technologies has allowed many drugs that were initially administered in liquid reservoirs to be used as matrix type systems e.g. estradiol, nicotine, nitroglycerine. The main advantage of reservoir type patches is that this patch design can provide a true zero order release pattern to achieve a constant serum drug level.

Membrane matrix hybrid type patches: This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate.

Micro reservoir types transdermal patch: The drug reservoir is formed by suspending the drug solids in an aqueous solution of water-miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogeneously dispersed by a high shear mechanical force in the lipophilic polymer, forming thousands of unextractable microscopic drug reservoirs (micro-reservoirs). The dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ which produce a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane.

The drug in the adhesive type transdermal patch: The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in the adhesive matrix is sandwiched between the release liner and the backing layer. Drug -in the -adhesive patch may be single layer or multi layer. The multi-layer system is different from the single layer in that it adds another layer of drug-in- adhesive, usually separated by a membrane. Some examples of suitable pressure sensitive adhesives are polysiloxanes, polyacrylates, and polyisobutylene. These pressure sensitive adhesives are hydrophobic in nature and are prepared as solutions of polymer dissolved in organic solvents. Hence, this type of system is preferred for hydrophobic drugs as it is to be incorporated into organic solvent based hydrophobic adhesive. prepared drug in adhesive patches of green tea extract and it was observed that major catechins and caffeine extracted from green tea were successfully delivered transdermally from drug-in-adhesive patches prepared and evaluated monolithic drug in adhesive type transdermal patches of melatonin and used eudragit E100 as adhesive polymer 60. Lake and Pinnock (2000) proved that once a week drug in adhesive patch of estrogen is more patient compliant as compared to twice a week reservoir patch. Characteristics of the drug in the adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion.[27-29]

Evaluation methods for transdermal dosage form

Physicochemical evaluation

In vitro evaluation

In vivo evaluation

Physicochemical Evaluation

(a) Interaction studies: The drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, FTIR, UV and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, absorption maxima.

(b) Thickness of the patch: The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

(c) Weight uniformity: The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

(d) Folding endurance: A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.

(e) Percentage moisture content: The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 hrs the films are to be reweighed and determine the percentage moisture content by below formula 40.

Percentage moisture content = $[\text{Initial weight} - \text{Final weight} / \text{Final weight}] \times 100$.

(f) Percentage moisture uptake: The prepared patches are to be weighed individually and to be kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake by below formula.

Percentage moisture uptake = $[\text{Final weight} - \text{Initial weight} / \text{initial weight}] \times 100$

(g) Drug content: A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyses the drug contain with the suitable

method (UV or HPLC technique). Then take the average of three different samples.

(h) 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.

(i) Uniformity of dosage unit test: An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analyses by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated [29,30]

CONCLUSION

This article provides a valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. There are several considerations in the optimization of a transdermal drug delivery system. The choice and design of polymers, adhesives, penetration enhancers and plasticizers in transdermal systems are crucial for drug release characteristics as well as mechanical properties of the formulation. Beside the other components of transdermal patches, plasticizers also significantly change the viscoelastic properties of the polymers. The reasons for the use of plasticizers in transdermal drug delivery systems are the improvement of film forming properties and the appearance of the film, preventing film cracking, increasing film flexibility and obtaining desirable mechanical properties.

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