

Review on Transdermal Drug Delivery System: Novel Approches

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Abstract: Transdermal drug delivery system (TDDS) is one of the novel drug delivery systems coming 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. Conventional dosage forms have significant drawbacks of poor bioavailability and repeated dosing due to hepatic first pass metabolism. Transdermal delivery has many advantages over conventional drug delivery. It avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance. This review gives the idea about anatomy physiology of skin, components of TDDS, advantages and disadvantages, and evaluation test for TDDS. The present drug delivery system is highly significant if compared to oral route for less side effect, better bioavailability, longer duration of action. Due to good nature of skin is the greatest challenge that has to be overcome for successful delivery of the drug molecules to the systemic circulation via transdermal route. This article gives the information of recent trends in the area of TDDS to increase the release pattern of drug and related things which is beneficial for patient.

Keywords: Transdermal Drug Delivery, NDDS, Drug delivery.

INTRODUCTION

Novel Drug delivery System (NDDS) refers to the approaches, formulation technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. NDDS is a system for delivery of drug other than conventional drug delivery system. The method by which a drug is delivered can have a significant effect on its efficacy.

Some drugs have an optimum concentration range within which maximum benefit is derived, and concentration above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of the severe diseases has suggested a growing need for multidisciplinary approach to the delivery of therapeutics to targets in tissues. From these new ideas on controlling the Pharmacokinetics, Pharmacodynamics, nonspecific toxicity, Immunogenicity, Biorecognition and efficacy of drug generated. These new strategies often called Novel Drug Delivery Systems [NDDS], are based on interdisciplinary approaches that combine polymer science, pharmaceuticals, bioconjugated chemistry and molecular biology[1].

Transdermal Drug Delivery Systems [TDDS]

TDDS is one of the systems lying under the category of controlled drug delivery in which the aim is to deliver the drugs through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices defined surface area that deliver a predetermined amount of drugs to the surface of intact skin at a programmed rate to reach the systemic circulation[1].

Anatomy and Physiology of Human Skin [2, 3]

The skin is the largest organ in the body and has a surface area about 1.5 to 2 sq. meter in adult and includes glands, hair and nails. There are two main layers: the epidermis and the dermis.

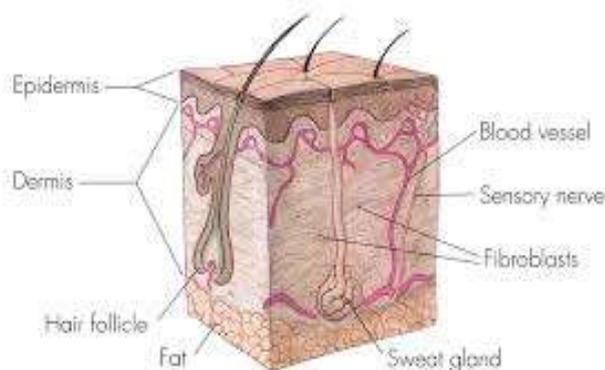


Fig-1: Sectional view of human skin

EPIDERMIS

The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on the palms of the hands and soles of the feet. There are blood vessels or nerve endings in the epidermis, but its deeper layers are bathed in interstitial fluid from the dermis which provides oxygen and nutrients, and drains away as lymph. The maintenance of healthy epidermis depends upon three processes:

- Desquamation of the keratinized cell from the surface
- Effective keratinisation of the cell approaching surface
- Continual cell division in the deeper layers with newly formed cells being pushed to the surface.

Dermis

The dermis is tough and elastic. It is formed from connective tissue and the matrix contains collagen fibers interlaced with elastic fibers. Rupture of elastic fibers occurs when the skin is overstretched, resulting in permanent striae, or stretch marks, that may be found in pregnancy and obesity. Collagen binds water and gives the skin its tensile strength, but as this ability declines with age, wrinkles develop. Fibroblasts, macrophages, and mast cells are found in the dermis. Underlying its deepest layer is areolar tissue and varying amounts of adipose tissue. The structures in the dermis are blood vessels, lymph vessels, sensory nerve endings, sweat glands and their ducts, hair follicles, arrector pili muscles, and sebaceous glands.

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support, and mechanical protection. It carries principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation, while in case of topical drug delivery, only penetration

through the stratum corneum is essential, and then retention of drug in skin layers is desired.

Functions of the Skin [2]

1. Protection
2. Regulation of the body temperature
3. Heat production
4. Heat loss
5. Formation of vitamin
6. Controlled body temperature
7. Absorption
8. Excretion

Types of TDDS [1]

Matrix system

Drug in adhesive system

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

Matrix dispersion system

In this type, the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug-containing polymer disc is fixed on to an occlusion 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 rim.

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 drug in an aqueous solution of water-soluble polymer and when dispersed in the solution homogeneously in a lipophilic polymer to form thousands of unreachably microscopic spheres of drug reservoir. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using a cross-linking agent.

Physicochemical and biological properties of drug

Table-1: Physicochemical, Biological properties of Drug:[4-6]

Physicochemical Properties of drug	Biological properties of drug
The drug should have a molecular weight less than 1000 Daltons	Drug should be very potent ,i.e. it should be effective in few mg/day
The drug should have affinity for both lipophilic and Hydrophilic	The drug should have short biological half-life.
Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.	Tolerance to the drug must not develop under near zero order release profile of transdermal delivery.
Along with these properties the drug should be potent, having short half-life and be non-irritating.	The drug should not be irritant and non-allergic to human skin.
The drug should have low melting point.	The drug should be stable when contact with the skin
Dose is less than 50 mg per day, and ideally less than 10 mg per day.	They should not stimulate an immune reaction to the skin.

Advantages and disadvantages of tdds

Table-2: Advantages and Disadvantages of Drug:[8-12]

Advantages of Drug	Disadvantages of Drug
Avoid GIT absorption.	Large daily dose is not possible.
Avoid FP hepatic metabolism of drugs.	Local irritation is major problem.
More improved and convenient patient compliance	Drug with long half-life cannot be formulated in TDDS.
Self-medication is possible.	Uncomfortable to apply.
Reduces frequency of doses.	May not be economical.
Possible for sustained or controlled release drugs.	Barrier of the physiological differ in the functions.
Minimizing undesirable side effects.	Transdermal drug delivery system cannot deliver ionic drugs.
Provide utilization of drug with short biological half-lives, narrow therapeutic window	It cannot achieve high drug levels in blood.
Inter and intra patient variation.	It cannot achieve high drug levels in blood.
Termination of therapy is easy at any point of time.	It cannot deliver drugs in a pulsatile fashion.
Provide suitability for self-administration.	It cannot develop if drug or formulation causes irritation to skin.
They are noninvasive, avoiding the inconvenience of parental therapy.	Possibility of local irritation at site of application.

Basic components of tdds: [1]

Drug

The drug is in direct contact with release liner. Example: Nicotine, Methotrexate and Oestrogen. Some of the desirable properties of a drug for transdermal delivery are as follows:

- The drug molecule should possess an adequate solubility in oil and water.
- The drug should have molecular weight less than approximately 1000 Daltons.
- The drug should have low melting point.
- The drug molecule would require a balanced partition coefficient to penetrate the stratum corneum.

Polymer matrix

- These polymers control the release of the drug from the drug reservoir.

- Natural polymer: Shellac, gelatin, waxes, gums, starch etc.
- Synthetic polymer: Polyvinyl alcohol, polyamide, polyethylene, polypropylene, polyurea, polymethylmethacrylate etc.

Permeation enhancer

Substances exist which temporarily diminish impermeability of the skin are known as accelerants or sorption promoters or penetration enhancers. This include water, pyrrolidones, fatty acids and alcohol, ozone and its derivatives, alcohol and glycols, essential oils, terpenes and derivatives, sulfoxides like dimethylsulfoximide and their derivatives urea and surfactants.

Adhesive

Serves to add to the skin for systemic delivery of drug Examples: silicones, polysobutylene

Backing layer

Backing layer protect patch from outer environment. Example: cellulose derivatives, polypropylene silicon rubber.

Transdermal patch

The system for passive transdermal delivery, two areas of formulation research is focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

FACTORS AFFECTING TDDS [13-16]

- Not all drug substance 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. 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.
- 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, increasing skin hydration.
- Percutaneous absorption appears to be greater when the TDDS is applied to a site with a thin horny layer than with a thick one.
- Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption.

Table-1: Examples of Transdermal drug Delivery system:[17-20]

Therapeutic agent	TDDS	Design, content
Clonidine	Catapres-TTS(Boehringer Ingelheim)	Four layer patch(a) backing of pigment polyester film; (b)reservoir of clonidine , mineral oil, polyisobutylene, colloidal silicon dioxide;(c) microporous polypropylene membrane controlling rate of delivery (d)adhesive formulation of agents.
Estradiol	Estraderm(novartis)	Four layer patch; (a)transparent polyester film;(b) reservoir of estradiol alcohol gelled with hydropropyl cellulose (c) ethylene vinyl acetate copolymer membrane ; (d)adhesive formulation of light mineral oil, polyisobutylene
Nicotine	Habritrol (Novartis consumer)	Multilayer round patch (a) aluminize backing film (b) pressure sensitive acrylate adhesive ;(c) methacrylic acid copolymer solution of nicotine disperse in pad of nonwoven viscous, cotton (d) protective aluminize release liner that overlies adhesive layer, remove prior to use.
Nitroglycerin	Depoint (Schwarz Pharma)	Three layer system (a) covering foil (b) nitroglycerin matrix with polyisobutylene adhesive, plasticizer, release membrane (c) protective foil remove, before use.
Scopolamine	Transdermscop (Novartis consumer)	Four layer patch (a) backing layer of aluminize polyester film reservoir of scopolamine, mineral oil, polyisobutylene (c) microporous polypropylene membrane for rate delivery of scopolamine (d) adhesive of polyisobutylene, mineral oil, scopolamine
Testosterone	Testoderm(alza)	Three layer patch (a) backing layer of ethylene – vinyl acetate copolymer, polyester laminate (b) reservoir of testosterone, alcohol, glycerin, glycerylmonooleate, methylaurate gelled with acrylic acid copolymer (c) adhesive strips of polyisobutylene, colloidal silicon dioxide .

Evaluation parameter [20, 28]

Physical Appearance

All the formulated patches were visually inspected for color, clarity, opaque, transparency, flexibility & smoothness.

Interaction Studies

Not only in TDDS almost all the dosage forms contain the excipients. These excipients must be compatible with the drug to avoid a loss of stability and reduce in bioavailability. The interaction studies are commonly carried out in thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical properties of drug excipients.

Thickness of Patch

The thickness of patch is measured in different points of the formulated patches by different points of formulated patches by using digital micrometer/micrometer screw gauge/ travelling microscope/venire calipers. Determine the average thickness and standard deviation for the same ensure the thickness of the formulated patch.

Weight Uniformity

Before done the weight uniformity test the formulated patches were dried at 60^oc for 4 hours. A specified area of the patch is to be cut in different parts of patch and it is weighed in digital balance. The average weight and standard deviation values are to be calculated from individual weights.

Folding Endurance

A specific area of the patch is cut evenly and folds it repeatedly at the same place till it broke. The number of folding is noted before the breaking of patch. It will give 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. After the 24 hours the patches are weighed at a specific time interval until the constant weight is obtained. The percentage moisture loss is calculated by using following formulae Percentage moisture loss = (Initial wt - final wt)/initial wt) X 100

Percentage Moisture Uptake

Formulated patches are weighed individually and kept in a desiccators containing saturated potassium chloride or ammonium chloride. The RH is maintained as 84%. After 24 hours the patches are reweighed at a specific time intervals till the constant weight is attained. Percentage moisture uptake = (final wt - initial wt)/initial wt) X 100.

Water Vapour Permeability Evaluation (WVP)

It is determined by natural air circulation over. It can be determined by following formulae; $WVP = W/A$ WVP is expressed in g/m² per 24 hours. Where, W = amount of vapour permeated through the patch (gm/24 hour) A = surface area of the exposure samples (m²).

Drug Content Analysis

An accurately weighed portion of formulated patches is dissolved in a suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 hours by using shaker incubator. Then the solution is sonicated and it is filtered. Then the filtrate is analyzed by using suitable techniques such as UV (or) HPLC etc., with proper dilution.

Uniformity of Dosage Unit

An accurately weighed portion of formulated patches are cut in small pieces which are transferred in to a specific volume in volumetric flask. Dissolve it in a suitable solvent and sonicate for complete extraction of drug from patch and volume make up with solvent. The solution is allowed to settle down for an hour and the supernatant liquid was collected and performs a proper dilution to give desired concentration. It is filtered using 0.2 μm membrane filter and analyzed by using suitable analytical techniques like UV, HPLC etc.

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)/initial length x 100.

Flatness

A transdermal patch should possess a smooth surface which not constrict with time. It can be studied by flatness test. In this test, one strip is cut from centre and two strips are cutted from right and left sides. The length of each strip is measured. The variation in length is measured by percentage constriction. If the percentage constriction is 0%, it indicates 100% flatness. % construction = (initial length -final length)/initial length x 100.

Thumb Tack Test

It is one of the qualitative test applied for the determination of tack property of adhesives. Simply the thumb is pressed over the adhesive layer and the relative tack property is determined.

Rolling Ball Tack Test

In this evaluation, the distance that stainless steel ball travels along an upward facing adhesive is measured. If the further travelling of ball, it indicates the adhesive is less tacky.

Quick Stick (Or) Peel Tack Test

It is used for the measurement of the peel force required to break the bond between the adhesive and the substrate by pulling the tape (adhesive layer) away from

substrate (stainless steel plate) at the speed of 12 inch/minute.

Probe Tack Test

The measurement of the force which is required to pull the probe away from the adhesive lower at fixed rate. It is expressed in grams.

Polariscope Examination

The specific surface area of pieces from the patch is cutted and placed on the objective slide to observe the drugs crystals. It is used to find out the drug whether in crystal form (or) amorphous form in the patch.

Shear Adhesion Test

It is used to measure the cohesive strength of the adhesive polymer. Adhesive film is placed over a stainless steel and a specified amount is hung from the tape to affect it pulling in direction parallel to the plate. Shear adhesion strength is measured by calculating the it takes to pull the tape of the plate. If the longer time take for removed, the shear strength is greater.

Peel Adhesion Properties

The peel adhesion is known the force required to remove the adhesive film from the substrate. The force required to pull a single coated tape is measured in this test. The coat is must applied to a substrate at 180°C.

In-vitro Drug Release Studies

The paddle over disc method (USP apparatus-V) can be utilised for the assessment of the drug release from the prepared patches. The dry film is cutted with specific size and the shape and it is weighed accurately. Then the piece of cutted patch is affixed in a glass plate by using adhesive. Then the plates are immersed in a 500ml of dissolution medium placed in the cylindrical vessel. The temperature is maintained at 30° + 5° C and the paddle was set at a distance of 2.5cm from the glass plate at the bottom. RPM is fixed as 50. The samples are withdrawn at appropriate time intervals up to 24 hours; fresh medium is replaced during each sampling. Then the samples are analysed by UV (or) HPLC to detect the drug release.

In-Vitro Drug Permeation Studies

It is done by using Franz diffusion cell. Abdominal skin with full thickness of male wistar rats (200-250 gm weight) is act as a semi permeable membrane. The membrane (abdominal skin) was isolated from rat abdomen and it is cleared properly, the tissues and the blood vessels present over the skin also removed. Then the skin is equilibrated in medium for 1 hour before starting the experiments and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of diffustant. The temperature of the cell was maintained at 32° + 5° C using thermostatically controlled heater. The isolated rate spin

is mounted between the donor receptor compartments of the cell, with the epidermis facing upward in to the compartment. The specified volume is taken out from the receptor compartment and it is repeated with fresh medium. Then the samples are filtered and analysed by UV (or) HPLC.

Skin Irritation Test

Skin permeation and sensitization testing is performed by using healthy rabbits. The formulated patches are applied on the dorsal surface of the skin rabbits. Before affixing the patch the hair is removed from the skin of the rabbits. After 24 hours the skin is to be observed.

Stability Studies

It is carried out according to ICH guidelines. The formulated transdermal patches are stored at 40° + 0.5° C and 75 + 5% RH for six months. The samples were withdrawn at 0,30, 60, 90 and 180 days and it analyse suitably for drug content.

Advance Development in TDDS [29,30]

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called "active" transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

CONCLUSION

The Transdermal drug delivery system has great advantages 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[31].

Due to recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin, membrane trasdermal route is effective. The transdermal durg delivery system has been designed as an alternative, safest, and easy route for systemic drug delivery.

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