Review Article

Transdermal Drug Delivery System: A Review

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ABSTRACT

Transdermal drug delivery system (TDDS) is the administration of therapeutic agents through intact skin for systematic effect. It has emerged as a potential novel drug delivery system by improving the therapeutic efficacy and safety, maintain steady state plasma level of drugs and overcome significant drawbacks of the conventional oral dosage forms and parenteral preparations. TDDS is ideally suited for diseases that demand chronic treatment with frequent dosing. This review deals with a brief insight on the formulation aspects, the physical and chemical enhancers being explored to enhance the transdermal delivery of drugs across the stratum corneum, the evaluation parameters (physicochemical, *in vitro*, *in vivo* studies) and therapeutic applications of TDDS.

Keywords: Transdermal drug delivery system (TDDS), Transdermal patch, Penetration enhancers.

INTRODUCTION

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver the drug via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. For effective Transdermal drug delivery system, the drug 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 Transderm-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 maintain 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.[1,2]

Advantages of Transdermal drug delivery system[3,4,5,20]

1. Avoidance of first pass metabolism of drugs
2. Transdermal medication delivers a steady infusion of a drug over a prolonged period of time. 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, inter and intra-patient variability.
4. No interference with gastric and intestinal fluids.
5. Maintains stable or constant and controlled blood levels for longer period of time.
6. Comparable characteristics with intravenous infusion.
7. It increases the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
8. This route is suitable for the administration of drugs having very short half life, narrow therapeutic window and poor oral availability.
9. Improved patient compliance and comfort via non-invasive, painless and simple application.

10. Flexibility of terminating the drug administration by simply removing the patch from the skin.
11. Self administration is possible in these system.

Disadvantages of Transdermal drug delivery system

1. The possibility of local irritation may develop at the site of application. Many problems like Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.
2. Drugs 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 peneteration through the skin and slowly to be of therapeutic benefit. Drugs with a lipophillic character, however, are better suited for transdermal delivery.
4. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
5. Transdermal drug delivery system cannot achieve high drug levels in blood/plasma.

Structure of Skin [4, 6, 7,8,20]

The human skin is a multilayered organ composed of many histological layers. Skin is most accessible organ in body. Its major functions are; protection of major or vital internal organs from the external influences, temperature regulations, control of water output and sensation. The skin of an average adult body covers approximately surface area of two square meters and receives about one-third of the blood circulating through the body. Skin is the complex organ and allows the passage of various chemicals into and across the skin. Skin serves as the point of administration for systemically active drugs, the drug applied topically will be absorbed, first into the systemic circulation and then transported to target tissues.

Layers of skin

Three major layers of the skin are Epidermis, Dermis and Hypodermis.

Epidermis

The epidermis is a stratified, squamous, keratinizing epithelium. The keratinocytes comprisethe major cellular component (> 90%)

and the responsible for the evolution of barrier function. Keratinocytes change their shape, size and physical properties when migrating to the skin surface. Other cells present which are present in this layer include Melanocytes, Langerhans cells and Markel cells, none of which appears to contribute to the physical aspects of the barrier. Microscopically, the epidermis further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. Stratum corneum is the outermost layer of epidermis approximately 100-150 micrometers thick, has no blood flow. This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, then it can enter the blood stream. A process known as passive diffusion, which occurs too slowly, is the only means to transfer normal drug across the layer.

Dermis

The dermis is the inner and larger (90%) skin layer, comprises primarily of connective tissue and provides supports to the epidermis layer of the skin. The boundary between dermis and epidermis layer is called Dermal- Epidermal junction which provides a physical barrier for the large molecules of drug and cells. The dermis incorporates blood and lymphatic vesicles and nerve endings. The extensive microvasculature network which is found in the dermis represents the site of resorption for drugs absorbed across the epidermis. The dermis can be divided into two anatomical region; papillary dermis and reticular dermis. Papillary is the thinner outermost portion of the dermis. Collagen and elastin fibres are mostly vertically oriented in the papillary region and connected with the dermal-epidermal junction. In reticular dermis, fibres are horizontally oriented. As skin is major factor for the determination of various drug delivery aspects like permeation and absorption of drug across the dermis.

Hypodermis

The hypodermis is the adipose tissue layer which is found in between of dermis and aponeurosis and fasciae of the muscles. The subcutaneous adipose tissue is structurally and functionally are well integrated with the dermis through the nerve and vascular networks. The hypodermis layer is composed of loose connective tissues and its thickness

varies according to the surface of body.

ENHANCERS OF TDDS[3, 6, 20]

Enhancers increase the penetration of permeants by disrupting the structure of skin's outer layer i.e stratum corneum and increasing penetrant solubility. Disruption either by the means of chemical which may affect both the intracellular and extracellular structure. Disruption may be due to protein denaturation, fluidization and randomization of intercellular lipids or intercellular delamination and expansion. Enhancers of Transdermal drug delivery system are
1. Physical enhancers.
2. Particulate systems.
3. Chemical enhancers.

Physical enhancers

The enhancers of Transdermal drug delivery system are the iontophoresis, electroporation, magnetophoresis, microneedle and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various types of therapeutic agents.

Particulate system

The enhancers of Transdermal drug delivery system are liposomes, microemulsion, transfersome, niosomes and nanoparticles are the examples of particulate means of enhancement.

Chemical enhancers

The enhancers of Transdermal drug delivery system by means of chemicals are sulphoxides, glycols, alkanols, terpenes, azones etc. Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers. Chemical enhancers act by increasing the drug permeability through the skin by causing reversible damage to the stratum corneum and by increasing the partition coefficient of the drug to promote its release from the vehicle into the skin.

IDEAL PROPERTIES OF TDDS[4,9]

The ideal properties of Transdermal drug delivery system are
1. Optimum partition coefficient required for the therapeutic action of drug.
2. Shelf life upto 2 years
3. Low melting point of the drug is desired which is less than 200oC
4. Patch size should be <40cm2

5. The pH of the saturated solution should be between 5-9.

TRANSDERMAL PATCHES

The transdermal route of drug delivery becoming the most popular route. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and directly into the bloodstream.

TYPES OF TRANSDERMAL PATCHES [10-14,21]

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 this type of layer is 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 a immediate drug release layer which is different from other layer which 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)   Reservoir system

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

d)   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 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 homogenously in a hydrophilic or lipophilic

polymer matrix. This drug containing polymer disk is fixed on to 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 rim.

e)   Microreservoir 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.

EVALUATION OF TRANSDERMAL PATCHES[15-18,20,21,22]
a.   Evaluation of adhesion
The measure of transdermal patch strength is evaluated for peel adhesion, tack properties (thumb tack test, rolling ball tack test, quick stick or peel tack test, probe tack test) and shear strength properties.

b.   Weight variation
Weight variation is studied by individually weighing 10 randomly selected patches. Such determination is performed for each formulation.

c.   Patch thickness
Patch thickness can be measured by using digital micrometer screw gauge at three different places and the mean value is calculated.

d.   Folding endurance
It can be determined by repeatedly folding a small strip of film (2x2 cm) at the same place till it breaks. The number of time the film could fold at the same place without breaking is the folding endurance value.

e.   Mechanical properties
The mechanical property is determined using plastic tensile test with Instron Instrument.

f.   Moisture content
Accurately weighed patches of specific area are kept in a desiccators using activated silica and reweighed individually until a constant weight is obtained. Percentage of moisture content is calculated based on the change in the weight with respect to the initial weight.

g.   Moisture uptake
Dry patches are exposed to higher relative humidity conditions and weight is taken periodically until a constant weight is obtained. The moisture uptake is calculated in terms of percentage increase in weight of patch over its initial weight.

h.   Interaction studies
Any interaction among drug, polymer, excipients and stratum corneum is analyzed by FTIR or DSC.

i.   Stability test
TDDS is analyzed for drug content and specific decomposition rate, color, consistency etc.

j.   Drug content and uniformity
Patches of specific area are cut and weighed accurately. Drug is extracted in suitable solvent and analyzed by spectrophotometer or HPLC.

k.   *In vitro* drug release studies
The paddle over disc method (USP apparatus V) is used to assess the release of the drug from the prepared patches. Dry films of definite shape is weighed, and fixed over a glass plate with an adhesive. The glass plate is then placed in a 500-mL of phosphate buffer pH 7.4 as the dissolution medium and the apparatus is equilibrated to 37±2 °C. The paddle is operated at a speed of 50 rpm. Samples (5- ml aliquots) is withdrawn at appropriate time intervals and analyzed by spectrophotometry or spectrofluorimetry.

l.   *In vitro* evaluation
The *in-vitro* permeation study of fabricated transdermal patches was carried out by using excised rat abdominal skin and franz diffusion cell. The skin was sandwiched between donor and receptor compartments of the diffusion cell. A 2.2 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 5°C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24 h, simultaneously replacing equal volume by

phosphate buffer pH 7.4 after each withdrawal. Then the samples were analyzed spectrophotometrically at 258 nm.

m. *In vivo* evaluation

The in vivo studies explore the pharmacokinetic and pharmacodynamic parameters which cannot be taken into account during in vitro studies. In vivo evaluation of TDDS can be carried out using animal models or healthy human volunteers. The most common animal species used are mouse, rat, dog and guinea pig. However, animal models are not very good predictive models for human because the penetration in these animals is higher than in human. Rhesus monkey is one of the most reliable models for in vivo evaluations but ethical consideration limits its use. Healthy human volunteers can be used for reliable results. The parameters studied are plasma concentration by GLC, *in* vivo absorption study, *in vivo* delivery and deposition by confocal laser scanning microscopy, in vivo permeation by GC-MS, ultra structure of skin by TEM and various pharmacodynamic studies.

n. Skin Irritation study

Skin irritation and sensitization testing is performed on hairless dorsal skin of healthy rats or rabbits. The patch is applied over the skin for 24 hours and removed and the skin is observed and classified into 4 grades (none, mild, moderate and severe) on the basis of the severity of erythema/edema and compared with the standard irritant, 0.8% formalin.

o. Histological examination

It is carried out to access the anatomical changes by enhancers.

p. Localized superficial infection

Bacteria, fungi may proliferate under occlusive dressing due to favorable conditions like increased temperature, hydration etc. It can be tested by quantitative bacteriological cultures of skin site before and after application of transdermal patches.

APPLICATIONS OF TRANSDERMAL PATCHES[1]

- Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Nitroglycerine patches are also sometimes prescribed for the treatment of Angina.
- Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflamatory drug are also available in the form of transdermal patches.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD)

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