Review Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Yadav *et al.*, 13(2):10-16, 2022

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Transdermal Drug Delivery Patches: Overview of Systemic Review

Manoj Kumar Yadav*, Mahima Pandey and Keshav Lodhi

Department of Pharmacy, Barkatullah University, Bhopal, (M.P.) - India

Article info

Received: 07/01/2022

Revised: 18/02/2022

Accepted: 25/02/2022

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Abstract

Transdermal patches are now widely used as cosmetic, topical and trans dermal delivery system. A transdermal patches is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. This promotes healing to an injured area of the body. An advantage of a trans dermal drug delivery route over the types of medication delivery such as topical, intravenous, intramuscular, etc. that the patch provide a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layer of medication embedded in the adhesive. Transdermal drug deliver offers controlled release of the drug into the patient, it enables a steady blood level profile resulting in reduced systemic side effect and sometime, improved efficacy over other dosage forms. The main objective of trans dermal drug delivery system is to deliver drug into systemic circulation through skin at predetermined rate with minimal inter and intra patient variations.

Key-words: Patches, Transdermal, Blood

Introduction

In water bodies, phytoplankton communities are The skin is the largest organ in the human body by mass, with an area of between 1.5 and 2.0m^2 in adult. Drug have been applied to the skin to treat superficial disorder, for the trans dermal administration of therapeutics to manage systemic ailments and as cosmetic, dating back to the oldest existing medical records of man. The use of salves, ointment, potions and even patches, consisting of plant animal or mineral extracts, was already popular in ancient Egypt and in Babylonian medicine.

The goal of this review is to detail the rich history of topical and trans dermal delivery that has evolved over thousands of years, focusing particularly on the evolution and current use of trans dermal patches. The potential efficacy and suitability of this technology for systemic therapy is normally determined by drug blood level-time profile which can be compared to or predicted from parenteral administration. [1]

Trans dermal delivery is also used to produce clinical effect such as local anesthesia and anti inflammatory activity deep within or beneath the skin. In contrast, topical delivery seeks to treat superficial, although at time very serious, skin problem through a relatively local action.[1]

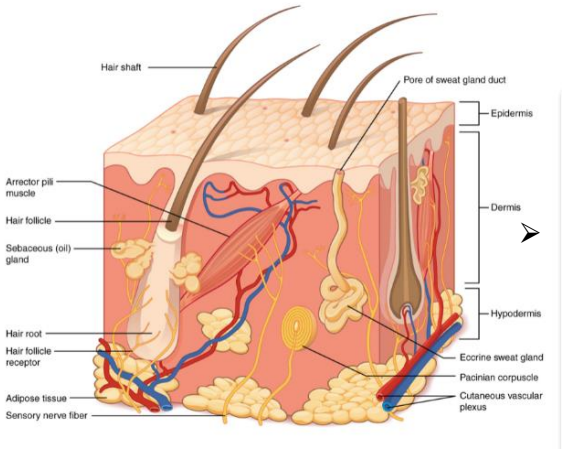
***Corresponding Author**
E.mail: yadavmanoj2k@gmail.com

Human skin:

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

Structure of skin:

Anatomically the skin has many histological layers, but it is divided into three layers.[3]



Epidermis layer:

The stratum conium forms the outer most layer of the epidermis and consists many layers of compacted , flattened in the stratified layer. Water content of stratum conium is around 20%. The moisture required for stratum conium is around 10%(w/w) to maintain flexibility and softness.

Dermis layer:

It contains blood and lymphatic vessels, nerve ending and sweet gland. It is typically 3-5 mm thick and is the major component of human skin. It provides a minimal barrier to the delivery of most polar drug, although the barrier may be significant when delivering highly lipophilic molecules.

Subcutaneous layer:

It bridges between the overlying dermis and the underlying body constituent. The layer of adipose tissue serves to insulate the body and to provide mechanical protection against physical shock. It also provides supply of high energy molecules .principle blood vessels and nerves are carried to the skin in this layer.

Basic Components of Transdermal Drug Delivery Systems:

Polymer Matrix:

Release of drug from trans dermal drug delivery system is essentially controlled by polymer. As the concentration of polymer is increased, a denser matrix is formed there by giving slow drug release rate. Conversely on decreasing the polymer concentration a lesser dense matrix is formed ensuring a higher release rate. The mechanism of drug release is usually diffusion across the polymeric matrix and rate of drug release depends upon the physicochemical properties and concentration of the drug and polymer used in the preparation of device.

Example of few polymers used:

Hydroxyl propylmethyl cellulose (HPMC), Polyvinyl alcohol (PVA), starch, etc.[4]

Drug or Active Pharmaceutical Ingredient (API):

Trans dermal drug delivery system to be a success drug should be chosen with great care. Drug reservoir if usually in direct contact with the adhesive layer or release liner. Drug candidate for trans dermal drug delivery system depends on the physicochemical properties and biological properties of the drug.

EXAMPLES:

Nicotine, fentanyl, testerone, estradiol, etc. are some of the marketed trans dermal drug delivery systems.[5]

Penetration enhancers:

Penetration enhancers are those compounds which enhance the skin permeability by altering the barrier properties of the skin to the flux of a drug . these are essential in most of the trans dermal formulation.[6]

Flux of drug across skin can be define as:

$$J = D[dc/dx]$$

Where,

D= Diffusion coefficient

C= concentration of drug

X= Spatial co-ordinate

Plasticizer:

Plasticizer are the agent responsible for reducing the brittleness of the polymer film. They also

provide flexibility or elasticity to the polymeric film. Above mentioned uses are observed at lesser concentration of plasticizer.

Polyethylene glycol, glycerol, di butyl phthalate is some of the example of agent used as plasticizer in Trans dermal drug delivery system.[7][8]

Drug reservoir components:

This mainly includes polymers either as a single polymer or in combination with other polymer in different concentration ratios depending on the density of matrix desire.

It should be able to incorporate the required amount of drug to be formulated into final product.

It must not alter or affect the physicochemical, biological or pharmacological properties of the drug.

Viscosity is an important parameter for semisolid trans dermal drug delivery system.[9]

Backing laminates:

The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage from through top. They must be impermeable to drug and permeation enhancers. They must have optimal elasticity, flexibility and tensile strength. They must be chemically compatible with the drug, enhancers adhesive and other excipients. They must be relatively inexpensive and must allow printing and adhesive lamination. Type of packing membranes are composed of a pigmented layer an aluminum vapor coated layer, a plastic film and heat seal layer.[4]

Rate controlling membrane:

Rate controlling membrane regulate the rate at which drug is released from the product and presented to the skin for penetration. This rate is dependent upon:[4]

- The pore size of the rate controlling membrane.
- Molecular weight of the drug.
- Molecular size of the drug.
- Solubility of the drug under local condition of product usage.
- Thickness of the rate controlling membrane.

Adhesive layer:

Adhesive layer fasten the trans dermal device on the surface of the skin ensuring its position on it under various mechanical stresses experienced during the period of usage.[4]

The three major classes of polymers used in trans dermal drug delivery system are:

- poltisobutylene type
- Acrylic type pressure
- Silicone type pressure

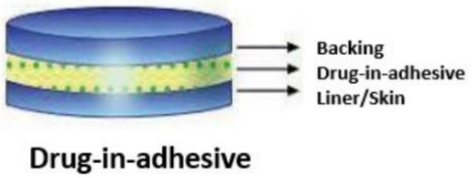
Release liners:

The release liner has to be removed before the application of trans dermal system and it prevent the loss of the drug that has migrated into the adhesive layer during storage. It also help to prevent contamination. It is composed of a base layer which may be non occlusive or occlusive and a release coating layer made of silicon or Teflon.[4]

Type of trans dermal patches:

Single layer drug in adhesive:

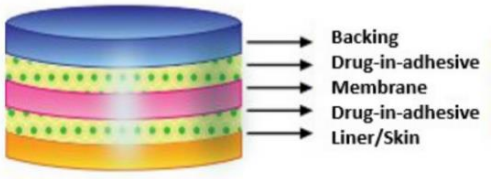
The adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layer together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary line and a backing.[10]



Drug-in-adhesive

Multi-layer drug in adhesive:

This system is similar to the layer but it contains an immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the release of the drug .[11]



Multilaminate

Reservoir:

The reservoir trans dermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi permeable membrane and adhesive . the adhesive component of the product responsible for skin adhesive can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.[12][13]

Reservoir

Matrix:

The matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct con tact with the release liner. The component responsible for skin adhesive is incorporated in an overlay and from a concentric configuration around the semisolid matrix.[12]

Matrix

Various methods for preparation trans dermal drug delivery system:

Circular Teflon mould method:

Polymers were dissolved in various ratios in an organic solvent .calculated amount of drug is dissolves in half the quantity of same organic solvent. Di-n-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The mould are to be placed on a leveled surface sand covered with inverted funnel to control solvent vaporization.[4]

Mercury substrate method:

Drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minute to produce a homogenous dispersion and poured in to a leveled mercury surface covered with funnel solvent evaporation.[12]

- **Aluminum backed adhesive film method:**

TDDS may produce unstable matrices if the loading dose is greater than 10mg. aluminium backed adhesive film method is a suitable one. The drug is dissolvent in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.[12]

- **By using free film method:**

Free film of cellulose acetate are prepared by casting on mercury. A polymer solution 3% w/w is to be prepared by using chloroform. Plasticizer are to be incorporated at concentration of 40%w/w of polymer weight. Polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri-dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri-dish. The dry film will be separated andin a desiccators until use. Free film of different thickness can be prepared by changing the volume of the polymer solution.[4]

Factor affecting trans dermal permeation:

- **Penetrate concentration:**

Increasing concentration of dissolved drug causes a proportional increases in flux. At concentration higher than the solubility, excess solid drug function as a reservoir and helps to maintain a constant drug concentration for a long period of time.[13]

- **pH Condition :**

Application of solution whose ph value are either in high or low extremities can be destructive to the skin. With moderate ph value the flux of ionizable drug is affected by change in ph that alter the ratio of charged and uncharged special and their trans dermal permeability.[14]

Release characteristics:

Solubility of the drug in the vehicle affected the rate. The mechanism of drug release depend on the following factors:

- Whether the drug molecules are dissolved or suspended in the delivery system.
- pH of the vehicle.
- The interfacial partition coefficient of the drug from the delivery system to the skin.[4][5]

Composition of the drug delivery system:

The composition of the drug delivery system which include boundary layer thickness polymer and vehicle which not only affect the rate of drug release but also the permeability of the stratum corneum by means of hydration making with skin lipids, or other sorption promoting effects.[13]

Evaluation parameters:

Interaction studies:

Excipients are an essential part of any formulation. Interaction studies are performed to confirm the absence of any chemical reaction between drug and excipients of the formulation during various stages of manufacturing process.[12] Studies are performed by various techniques:

- UV spectroscopy
- Thermal analysis
- FT-IR spectroscopy
- Chromatographic techniques

Weight uniformity:

The prepared patch are dried for 4 hours at 60c before performing the test. A specific part of a definite dimension is cut from various part of the patch and weight on a balance. The average weight and standard values are then calculated.[15]

Thickness of the patch:

The thickness of the drug loaded patch is determined at different points by using a digital micrometer. The average thickness and standard deviation are the calculate from individual values.[16]

Percentage of moisture content:

The drug loaded patches are weight individually and kept in a desiccotor containing fused calcium chloride at a room temperature for 24 hrs. After 24 hrs the film are reweighted. Determine the percentage moisture content from the below mentioned formula.[16]

Drug content:

A specified areas of patch is to be dissolved in a suitable solvent in volumetric flask. The solution is them filtered through a filter medium and using suitable method.[17]

Thumb tack test:

It is a qualitative test to evaluated tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.[18]

Skin irritation study:

This test is performed on animal and human volunteer. Relevant approvals and permission from various regulatory board are a must to proceed with the test. Pre–treatment of the animal to remove the hair is necessary. The patch is to be remove after 24hr and the skin is to be observed and classification into 5 grate on the basis of the severity of the skin injury.[19]

Stability studies:

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content. [19]

***In vitro* drug release studies:**

This test was performed using franz diffusion cell. The dissolution medium used was phosphate buffer (pH 7.4). Samples were withdrawn maintaining sink conditions and were evaluated for drug content using suitable analytical techniques.[12].

Limitations:

Drugs with high molecular weight (> 500 Da) are difficult to penetrate the stratum corneum.
Drug dose is a limiting factor.
Drugs with partition coefficients in either of the extremities (low or high) fail to reach the systemic circulation.
Bioavailability of a drug through transdermal

route is greatly reduced for the drugs which get metabolized in liver.
Skin permeability is also a limiting factor.
Drugs requiring higher blood levels are difficult to formulate as transdermal drug delivery systems.
May lead to skin irritation and allergic response.[20, 21]

ADVANTAGES

Increased patient compliance due to reduced dosing frequency.
Transdermal route bypasses first pass metabolism.
Minimizes fluctuations in physiological and pharmacological response.
Decreased side effects due to reduced plasma concentration.
Ease in self administration.
Reduces fluctuations in plasma concentration.
Drug candidates with short biological half life and low therapeutic index can be effectively utilized.
Avoids fluctuations in drug level.
Effect of inter and intra patient variations are minimized.
Low melting drugs can be given by this route due to low solubility both in water and fat.
Termination of therapy is easy and possible at any time[22]

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Cite this article as:
Yadav M.K., Pandey M. and Lodhi K. (2022). Transdermal Drug Delivery Patches: Overview of Systemic Review. *Int. J. of Pharm. & Life Sci.,* 13(2): 10-16.

Source of Support: Nil
Conflict of Interest: Not declared
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