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TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT:

Transdermal drug delivery systems have become an intriguing research topic in pharmaceutical technology area and one of the most frequently developed pharmaceutical products in global market. The use of these systems can overcome associated drawbacks of other delivery routes, such as oral and parenteral. This transdermal delivery system consist of various methods like drug/vehicle interactions, vesicles and particles, stratum corneum modification, energy-driven methods and stratum corneum bypassing techniques. Through suitable design and implementation of active stratum corneum bypassing methods, notably microneedle technology, transdermal delivery systems have been shown to deliver both low and high molecular weight drugs. Microneedle technology platforms have proven themselves to be more versatile than other transdermal systems with opportunities for intradermal delivery of drugs/ biotherapeutics and therapeutic drug monitoring. These have shown that microneedles have been a prospective strategy for improving transdermal delivery systems.

KEYWORDS: Transdermal Drug Delivery, Classification, Mechanism, Advantages, Dis-advantages, Limitation.

INTRODUCTION:

Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. 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. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system.

Transdermal SCOPE was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.2 The common ingredients which are used for the preparation of TDDS are as follows.

a) Drug: Drug is in direct contact with release liner. Ex: Nicotine, Methotrexate and Estrogen

b) Liners: Protects the patch during storage. Ex: polyester film.

c) Adhesive: Serves to adhere the patch to the skin for systemic delivery of drug. Ex: Acrylates, Polyisobutylene, Silicones.

d) Permeation enhancers: Controls the Release of the drug. Ex: Terpenes, Terpenoids, Pyrrolidones Solvents like alcohol, Ethanol, Methanol Surfactants like Sodium Lauryl sulphate, Pluronic F127, Pluronic F68. (1)

LITERATURE SURVEY:

a. Rastogi Vaibhav, Yadav Pragya:
Transdermal drug delivery system (TDDS) is one of the systems lying 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. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therpay.

b. Patel Anjali V. and Shah Biren N:

The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the non-invasive nature of drug delivery.

c.Delly Ramadon, Maeliosa T. C. McCrudden, Aaron J. Courtenay, Ryan F. Donnelly:

Transdermal drug delivery systems have become an intriguing research topic in pharmaceutical technology area and one of the most frequently developed pharmaceutical products in global market. The use of these systems can overcome associated drawbacks of other delivery routes, such as oral and parenteral.

d. Shingade GM, Aamer Quazi, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad DD:

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. [(2)(3)]

Transdermal Drug Delivery System:

- **Defination:**

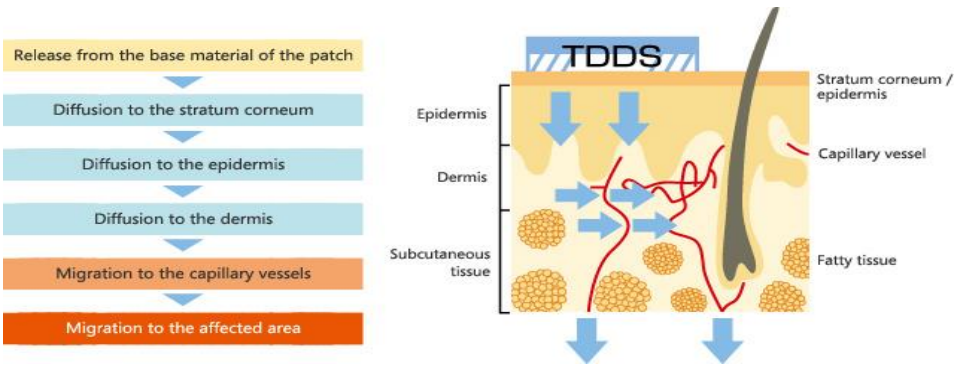
Transdermal drug delivery systems (TDDS), also known. as "patches". Transdermal delivery refers to the direct drug delivery through the skin. The most commonly used technique is via hypodermic needles, which bring discomfort to patients, such as pain, needle phobia, and potential transmission of infectious diseases through the needle.

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery (such as oral, topical, intravenous, or intramuscular) is that the patch provides 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 layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this method. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979. These patches administered scopolamine for motion sickness. [(4)]

- **COMMON TRANSDERMAL PATCH DRUGS:-**

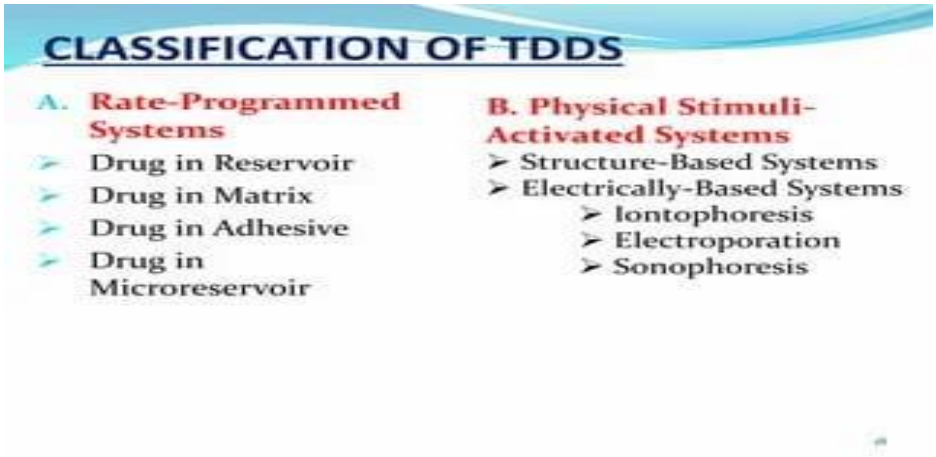
  - Nicotine.
  - Fentanyl and Buprenorphine.
  - Nitroglycerine.
  - Selegiline.
  - Methylphenidate.
  - Scopolamine.
  - Hormones.
  - Clonidine. [(5)]

Mechanism of Transdermal Drug Delivery System: Once a TDDS product is applied, the active pharmaceutical ingredients permeate the skin. They then pass through the stratum corneum, go into the epidermis, penetrate into the dermis, and finally are absorbed into peripheral capillary vessels to be distributed into the rest of the body. [(6)]



Classification:

- **TDDS classified into three types:-**
  1. Reservoir system
  2. Matrix system
  3. Microresevior system [7]

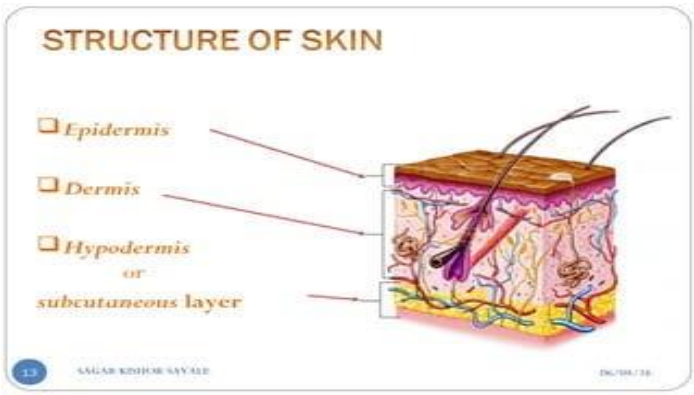


1.Reservoir System: Drug reservoir (homogenous dispersion of drug with polymeric matrix. or suspension of drug in un leachable viscous liquid medium such as. silicone fluid) is encapsulated within drug impermeable metallic plastic. laminate and a rate controlling polymeric membrane (ethylene vinyl. acetate co polymer).

2.Matrix System: In a matrix or monolithic delivery system the drug is either molecular dissolved or dispersed inside a matrix. Compared to a reservoir system, a matrix system is not enveloped within a rate limiting membrane. As such the release rate of the drug from the matrix system is normally not constant and decreases in time.

3.Microreservoir 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. [8]

7.Skin and drug permeation:



1.Epidermis Layer: The epidermis is the top layer of skin in your body. It has many important functions, including protecting your body from the outside world, keeping your skin hydrated, producing new skin cells and determining your skin color.

2.Dermis Layer: The dermis is a connective tissue layer sandwiched between the epidermis and subcutaneous tissue. The dermis is a fibrous structure composed of collagen, elastic tissue, and other extracellular components that includes vasculature, nerve endings, hair follicles, and glands.

3.Hypodermis OR Subcutaneous Layer: The hypodermis is the bottom layer of skin in your body. It has many important functions, including storing energy, connecting the dermis layer of your skin to your muscles and bones, insulating your body and protecting your body from harm. [9]

ADVANTAGES:

a) Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.

b) Ease of usage makes it possible for patients to self-administer these systems.

c) In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.

d) Since the composition of skin structurally and biologically is the same in almost all humans, there is minimal inter and intra patient variation.

e) Drugs showing gastrointestinal irritation and absorption can be suitably administered through skin.

f) Continuous, non-invasive infusion can be achieved for drugs with short biological half-life which would otherwise require frequent dosing. (10)

g) Due to reduced frequency of dosing there is better patient compliance.

h) Therapeutic failures associated with irregularities in dosing with conventional therapies can be avoided.

i) Adverse effects are minimized due to a steady and optimum blood concentration time profile.

j) Risks, pain and inconvenience associated with parenteral therapy are evaded.

k) At times the maintenance of the drug concentration within the BioPhase is not desired; therefore, transdermal systems are suitable in this case.

l) Daily dose of drug required is lower than that with conventional therapies.

m) Drug release is such that there is a predictable and extended duration of activity.

n) Avoidance of first pass metabolism of drugs. (11)

DISADVANAGES:

a) application may vary from dermatitis to death resulting from secondary reasons.
b) Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.
c) The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.
d) There is possibility of skin irritation due to the one or many of formulation components.

e) Binding of drug to skin may result in dose dumping.

f) It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina and diabetes.(12)

g) Lag time is variable and can vary from several hours to days for different drug candidates.

h) Cutaneous metabolism will affect therapeutic performance of the system. Transdermal therapy is feasible for certain potent drugs only.

i) Transdermal therapy is not feasible for ionic drugs. (13)

Limitation of TDDS: The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dosage required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult if not impossible. Skin irritation or contact dermatitis due to the drug, excipients and enhacers of the drug used to increase percutaneous absorption is another limitation. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product The barrier function of the skin changes from one site to another on the same person, from person to person and with age. (14)

- **Limitations for a drug substance to be incorporated into a transdermal delivery system are: -**

a) Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.

b) Drugs with very low or high partition coefficient fail to reach blood circulation.

c) Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.

d) Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy. (15)

The major considerations for enhancing transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle), vesicles, particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers (sulphoxides, azones, glycols, alkanols, terpenes, etc.

a) Medicament application site.
b) Thickness and integrity of the stratum cornea epidermidis. (16)

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 a immediate drug release layer and other 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 various layers together but also serves as release vapour. The vapour 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 are 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 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. [17]

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 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.

f) 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. [18]

VARIOUS METHODS FOR PREPARATION TDDS:

a) Asymmetric TPX membrane method:
A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly(4-methyl-1-pentene)}asymmetric membrane, and sealed by an adhesive.

b) Circular Teflon mould method:
Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate 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 moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c) Mercury substrate method:
In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a levelled mercury surface, covered with inverted funnel to control solvent evaporation. [19]

d) By using IPM membranes" method:
In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

e) By using EVAC membranes" method:
In order to prepare the target transdermal therapeutic system, 1% Carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; Carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f) Aluminium backed adhesive film method:

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved 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. [20]

EVALUATION PARAMETERS:

a) Skin Irritation study:

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

b) Stability studies: [21]

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 analyse suitably for the drug content.

c) Percentage Elongation break test:

The percentage elongation break is to be determined by noting the length just before the reak point, the percentage elongation can be determined from the below mentioned formula. Elongation percentage = L1-L2 ×100 L2 .Where, L1is the final length of each strip and L2 is the initial length of each strip.

d) Rolling ball tack test:

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

e) Quick Stick (peel-tack) test: [22]

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

f) Probe Tack test:

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

g) In vitro drug release studies: [23]

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500- mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analysed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

h) In vitro skin permeation studies:

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats of weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analysed spectrophotometrically or HPLC. [24]

CONCLUSION:

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effect and sometimes, and improved efficacy over other dosage form. It offer the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. Transdermal patches have become a proven technology that offers variety of significant clinical benefits over other dosage form.

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