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Review Article

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Transdermal Patches as a tool for permeation of drug through skin

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ABSTRACT

For many decades for the treatment of disease many of the dosage form are using which are including tablets, capsules, pills, creams, ointments, liquids, injectables. To maintain the concentration of drug it is necessary to take these types of dosage form several times of day. A novel drug delivery system thus aim at releasing one or more drug continuously at a predetermined pattern for a fixed period of time, either systematically or to a specific target organ. Transdermal drug delivery system includes all topically administered drug formulations intended to deliver the active ingredients into the circulation. A patch contained high dose of drug which is retained on the skin for prolonged period of time. Drug from patch enters into blood flow via diffusion process. Skin contains 10-70 hair follicles and 200-250 sweat ducts per cm^2 of the skin so it is easily accessible by drugs. Drug can penetrate through skin via three pathways- through hair follicles, sebaceous gland, and sweat ducts. Its main advantages includes controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. There are factors such as physiochemical as well as biological which affect the bioavailability of transdermal medicament. Due to technological advancement, many new techniques which have attained attention are Iontophoresis, phonophoresis, Electroporation and micro needles etc. This review covers general aspects regarding transdermal patches like advantages, basic components of transdermal drug delivery system, methods of preparation of transdermal patches and evaluation.

Keywords: TDDS, Transdermal patch, Skin, Diffusion process, Hepatic first pass metabolism.

INTRODUCTION

The goal of pharmaceutical research is to reduce the side effects, and get the desirable therapeutic effects [1]. To achieve this goal many of the routes of administration are developed such as oral, sublingual, rectum, intramuscular, intravascular, subcutaneous, inhalation etc. The route of administration is the way through which the dosage form is administered into the body for treatment of various diseases and disorders. Various routes of administrations play a marked role in the bioavailability of the active drug in the body. A route of administration in pharmacy is the path by which a drug is taken into the body [2].

The most common form of drug delivery is the oral route. All conventional oral doses forms are required to be administered in multiple doses at a particular time interval in a particular amount for effective therapy [3]. This route has advantages but also has the significant drawbacks like poor bioavability due to hepatic first pass metabolism, drug degradation in to GIT due to enzymes, pH etc. To overcome these difficulties a Novel drug delivery system was developed and for improving such characters the transdermal route is one of the best route of drug administration [4].

Transdermal Drug Delivery System

The word Transdermal has been derived from the root ‘trans’ meaning through, across or beyond and ‘derma’ meaning skin [5]. Transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. Transdermal systems are a desirable form of drug delivery because of the obvious advantages

over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients [6]. Transdermal drug delivery system is self-contained, discrete dosage form which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation [7]. 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. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism [8].

Skin as a site for transdermal drug administration:

Skin [9, 10]

Skin is the largest human organ of our body. The skin ordinarily receives very little respect from its inhabitants, but architecturally it is a marvel. It covers the entire body has a surface area of 1.2-2.2 m^2, weigh 4-5 kg = 9-11 pounds, and account about 7% of total body weight in the average adult. The skin varies in thickness from 1.5-4.0 mm. The skin functions as a sensory organ, as an organ of metabolism that has synthesizing, excretory, and absorptive function. It acts as a protective barrier against the external environment and as an important factor in temperature regulation Fig. 1.

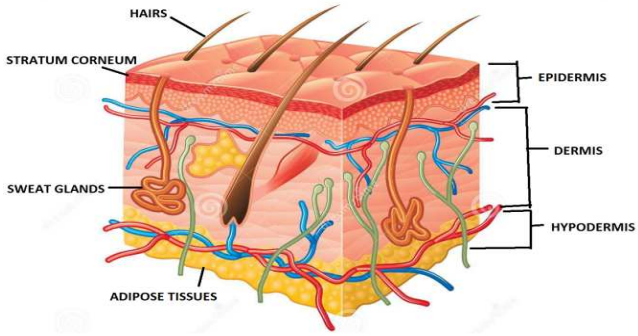


Fig.1. -Diagram of human skin

Epidermis: [11, 12]

Most superficial layer and is composed stratified keratinized squamous epithelium. The cells populating the epidermis include Keratinocytes, melanocytes, Markel cells, and Langerhans cells. There are no blood vessels or nerve ending in the epidermis. Epidermal cells originate in the germinative layer and under gradual changes as they progress towards the skin surface. The cells on the surface are flat, thin, non-nucleated, dead cell or squamous in which the cytoplasm has been replaced by fibrous protein keratin. The epidermis is thickest in palms, soles and thinner over the ventral surface of the trunk. The stratum corneum is responsible for the barrier function of skin. It also behaves as the primary barrier to percutaneous absorption [4, 6].

Dermis: [11, 13]

The dermis is a strong stretch envelops that helps to hold the body together. The dermis is a 3-5 mm thick layer and is composed of a matrix of connective tissue which contains lymph vessels, blood vessels, and nerves. To regulate the body temperature the continuous blood supply is essential. To remove toxins and waste products it provides nutrients and oxygen to the skin. While capillaries reach to within 0.2mm of skin surface they provide sink condition for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeates very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation.

Hypodermis: [14, 15]

The hypodermis layer is composed of loose connective tissues and its thickness varies according to the body surface. The reticular region is attached to underlying organ such as bone and muscle by subcutaneous Layer called the hypodermis or superficial fascia. Nerve ending which are sensitive to cold is found deep into the dermis, while those sensitive to heat .are located in the intermediate and superficial dermis. The hypodermis and subcutaneous fat tissue supports the dermis and epidermis. The hypodermis serves as a fat storage area. This layer provide the nutritional support and mechanical protection by regulate the temperature. It carries principal blood vessels and nerves to skin and may contain sensory pressure organ.

Routes of Penetration [16, 17]

For a long term treatment and for a multidose treatment the most suitable system is transdermal drug delivery system because different patches are prepared for long period of time in a suitable dose providing treatment. There are two diffusion pathways to penetrate a molecule in normal human skin: the appendageal and the transepidermal pathway. For the ions and large polar molecules the appendageal route is best and for the unionized molecule which can cross the intact layer the skin follow the transepidermal pathway. A molecule should have adequate lipophillicty and optimum molecular weight to penetrate in to the skin. Hydrophilic drugs partitioned preferentially via intercellular domains and the lipophilic permeants partitioned the subcutaneous via intercellular route. Most of the molecule traverses the stratum corneum by both routes. The transport of various drug molecules through the skin, promptly restricted by the barrier properties of the epidermis. To avoid these difficulties in permeation through SC, penetration enhancers are used.

General features of skin: [10]

Color: Skin color represent an aggregate of the remitted and reflected light, the wavelength of which depends largely on the presence of 4 biochromes.

Two biochromes are present in epidermis

1) Melanin: This is brown in color and absorbs UV and visible light.
2) Carotenoids: This is yellow.

Other two are present in dermis.

1) Oxyhemoglobin: this is bright red found in arterioles and capillaries of papillary layer.
2) Reduced hemoglobin: this is bluish red and is found in the sub-papillary venous plexus.

Functions of skin: [9, 13, 18]

It is also called the integumentary system, which simply means “covering” the skin’s function go well beyond serving as a large, opaque bag for the body contents.

1) It is absolutely essential because it keeps water and other precious molecule in the body. It also keeps water out structurally the skin is marvel.
2) It insulates and cushions the deeper body organs and protects the entire body from mechanical damage (bumps & cuts), chemical damage (from acid & base), UV radiation, sunlight & bacteria.
3) Sensation: The skin contains abundant nerve ending and receptors that detect stimuli related to temperature, touch, pressure and pain.
4) Regulation of body temperature: In response to high temperature or strenuous exercise the evaporation of sweat from the skin surface helps lower an elevated body temperature to normal body temperature. Changes in the flow of blood to the skin also help regulate body temperature.
5) Immunity: It provides immunologic information obtained during antigen processing to the appropriate effector cells in the lymphatic tissue.
6) Excretion: Excretion is carried out by exocrine secretions of sweat, sebaceous and apocrine gland. These excretory secretions are being utilized now to detect certain diseases of the blood.
7) Drug Delivery Route: Certain lipid soluble substances and low molecular weight drugs have been successfully absorbed systemically, across the skin by transdermal patches, for example, nitroglycerin, hormones, nicotine, scopolamine etc.

TRANSDERMAL PATCHES: [19, 20]

A transdermal patch is medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. In this system the drug therapy can be stopped instently in situation where drug input is no longer desirable. The system allows reduce frequency of dosing which is particular favorable for compound with short biological half life. The transdermal drug delivery is affected by limitations as well that are due to the primary function of human skin. A number of drugs can be administered transdermally**.** For example, scopolamine patches to check motion sickness and fentanyl patches to treat cancer pain or chronic pain syndromes are being used currently by the transdermal route.

Benefits of transdermal patches: [8, 19, 21, 22]

- Improve systemic bioavailability resulting from bypassing the first hepatic metabolism.
- Deliver a constant infusion of drug for a longer duration.
- No interference with gastric and intestinal fluids.
- The simplified medication regimen leads to improve patient compliance and comfort via non-invasive, painless and simple application.
- Duration of action gets extended & predictable.
- Ease of handling and application.
- Topical patch are painless.

- It is great advantage in patients who are nauseated or unconscious.
- Steady permeation of drug across the skin, allowing consistent plasma levels, but non-invasive in nature.
- Drug therapy may be terminated rapidly by removal of its application from the surface of the skin.
- Allowed continued drug administration permitting the use of a drug with short biological half-life.
- They are easily and rapidly identified in emergencies because of their physical presence, features, and identifying markings.
- Self administration is possible in this system.
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on stomach and intestine.
- It can avoid inter-individual & intra-individual variation and hence increase therapeutic efficacy.
- In case of poisoning transdermal patches can easily be removed from skin.
- Less dosing frequency due to prolong action.
- This route is alternative for those people who cannot prefer the oral route to take medication.
- These patches are cost-effective, convenient.
- The transdermal patches have been useful in developing new application for existing therapeutic.

Drawbacks of transdermal patches: [4, 6, 21, 22, 23]

There is a chance of allergic reactions due to drug, adhesive, or other excipients like-itching, rashes, local edema at site of patch application, needs discontinuous of therapy.

- The use of transdermal delivery may uneconomical.
- It cannot achieve high drug levels in blood/plasma.
- Skin's impermeability creates hindrance against drug entry, so only potent API can be administered via this route.
- Large molecular size of drug creates difficulty in absorption.
- Ionic drugs create problems.
- Difficult to administer large dose i.e. more than 10 mg/day.
- Drugs with very low or high partition coefficient fail to reach systemic circulation.
- The delivery system cannot be used for drugs requiring high blood levels.
- Drug with hydrophilic character is less suitable as compare to drug with lipophilic character because of their low permeability.
- Only small lipophilic drug can be administered through the skin.
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.
- In this system drug cannot be used in a pulsatile fashion.
- Not suitable for high drug dose.
- Adhesion may vary with patch type and environmental condition.

FACTORS INFLUENCE TRANSDERMAL DRUG DELIVERY SYSTEM [3, 4]:

1) Physiochemical properties of drug

a) Size of drug molecule and molecular weight
b) Partition coefficient and solubility
c) Drug concentration
d) pH condition.

2) Formulation characteristics

a) Release rate of drug
b) Ingredients of formulation
c) Presence of permeation enhancer.

3) Physiological factors

a) Skin hydration
b) Temperature and pH
c) Diffusion coefficient
d) Drug concentration
e) Partition coefficient
f) Molecular size and shape.

4) Biological factors

a) Skin hydration
b) Skin age
c) Blood flow
d) Regional skin site.
e) Skin metabolism
f) Species difference

Types of transdermal patches: [24, 25, 26]

➢ **Single layer drug in adhesive:**

In this type of patches the adhesive layer contains drugs. Here the property of adhesive layer is not only adhere the various layer together although this type of layer is responsible for the releasing the drug to the skin. The backing and the temporary liner is surrounded on the adhesive layer.

➢ **Multi-layer drug in adhesive:**

The multi-layer drug in adhesive is similar to the single layer but it contains an immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. For releasing of the drug the adhesive layer is responsible. This patch also has a temporary liner-layer and a permanent backing.

➢ **Vapour patch:**

The adhesive layer in this patch not only serve as adhere the various layer together but also serves market, commonly used for releasing of essential oils in decongestion. Other marketed vapour patches are used to improve the quality of sleep and reduces cigarette smoking conditions.

➢ **Reservoir system:**

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

➢ **Microreservoir system:**

This system is the combination of the reservoir and matrix – dispersion system. By suspending the drug in an aqueous solution of water soluble polymer the drug reservoir is formed and then dispersing the solution homogeneously in a lipophilic polymer to form thousand of unreachable, microscopic spheres of drug reservoirs. By immediately cross-linking the polymer in situ b using cross linking agent this thermodynamically unstable dispersion is stabilized.

➢ **Matrix system**

- **Drug-in-adhesive system:** 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. For protection purpose the unmediated adhesive polymer layers are applied on top of the reservoir.
- **Matrix-dispersion system:** In hydrophilic or lipophilic polymer matrix the drug is homogenously dispersed. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. To form a strip of adhesive film, applying the adhesive on the face of the drug reservoir, it is spread along with the circumference.

COMPONENTES OF TRANSDERMAL PATCHS [4, 27, 28, 29]

1. **DRUG:** Drug should have desirable physicochemical properties .Drug should have low molecular weight (up to 1000 Dalton), low melting point, short half life, affinity for lipophilic and hydrophilic, potent, and non-irritant as showed in table 1

TABLE 1: IDEAL PROPERTIES OF DRUGS

S.No.	Parameter	Properties
1.	Dose	Should be low
2.	Half life in hr	Should be 10 or less
3.	Molecular weight	Should be less than 500
4.	Partition coefficient	Log P (octanol-water between –1 and 3)
5.	Skin permeability coefficient	Should be less than 0.5 $x10^{-3}$cm/h
6.	Skin reaction	Should be non-irritating
7.	Oral bioavailability	Should be low
8.	Therapeutic index	Should be low
9.	Concentration	Minute
10.	pH of saturated aqueous solubility	5-9
11.	Dose deliverable	<20mg/day

2. BACKING LAYER: It protects the patch from the external environment, provides support to it and accepts printing.

3. POLYMER: Polymer is the main part of the system which determines and controls the drug loading, rate of drug release and adhesion of the patch to the skin properly.

Characteristics of polymers:

- Stable
- Non-toxic

- Inexpensive
- Inert
- Biocompatible
- Allow large amount of drug to be incorporated

Types of polymers:

i. **Natural:** gelatin, protein, shellac.
ii. **Synthetic elastomers:** neoprene, silicon rubber, acrylonitrile.
iii. **Synthetic polymers:** PVC (poly vinyl chloride), PVA (poly vinyl alcohol), polyurea.

4. **ADHESIVE:** Adhesive maintains the patch in continuous contact with the skin. It should be non irritant, compatible with the other ingredient of the formulation and skin easily removable.
5. **PLASTICIZERS:** Plasticizers provide flexibility and improve the brittleness of the polymer. These changes the physical and mechanical parameters of the polymer when added.
6. **MEMBRANE:** Membrane controls the release of drug from the reservoir and multilayer patches.
7. **RELEASE LINER:** Release liner is the part of primary packaging and prevents the loss of drug from the polymer matrix. It can protect the patch which will remove during application of patch to the skin.
8. **OTHER EXCIPIENTS LIKE PLASTICIZERS AND SOLVENTS:** Various solvents such as methanol, chloroform, acetone, isopropanol, and dichloromethane. Plasticizers used triethylcitrate, polyethylene glycol, propylene glycol, dibutylpthalate. Fig. 2.

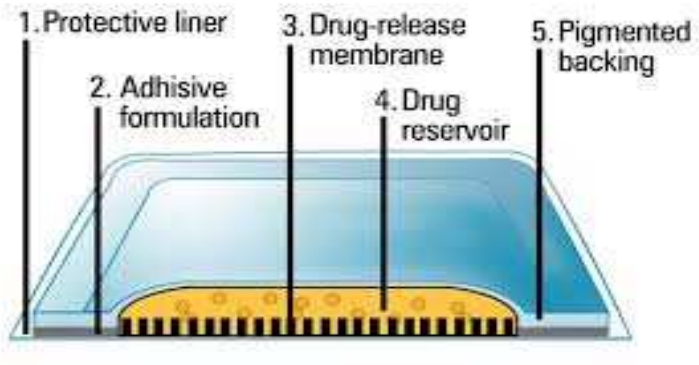
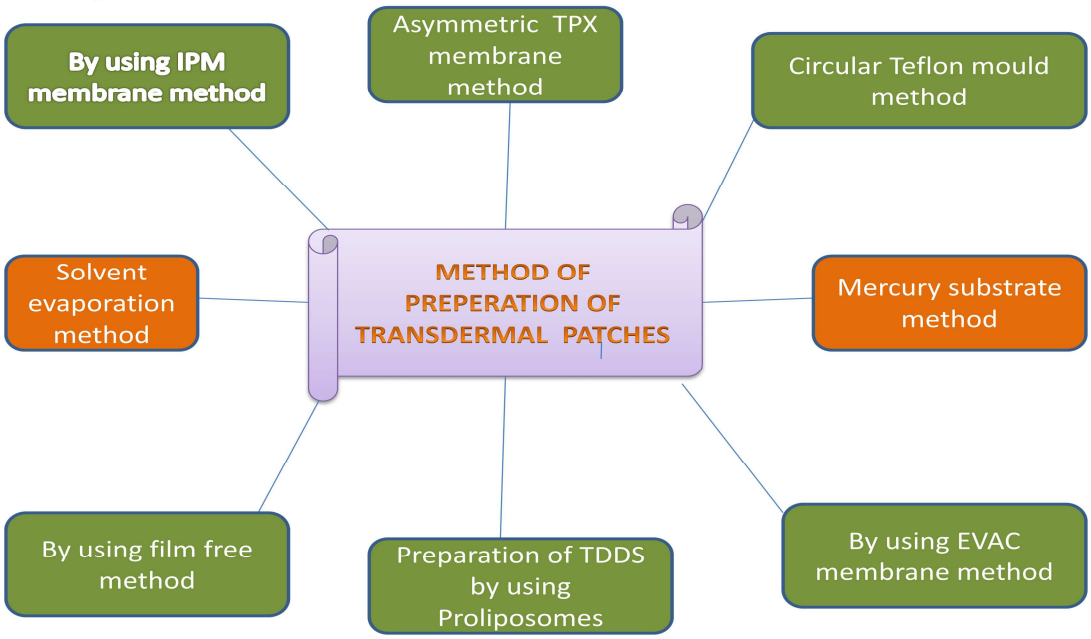


Fig.2. Components of transdermal Patches

Methods of Preparation:



PERMEATION ENHANCERS OF TRANSDERMAL [4, 24, 28, 30, 31]

Permeation enhancer increases the penetration of permeants by disrupting the structure of the skin's outer layer. Disruption either by the means of chemical which may affect both the intracellular and extracellular structure or it

may be due to protein denaturation, fluidization and randomization of intercellular lipids. Enhancers of Transdermal drug delivery system are:

1. Physical enhancers.
2. Chemical enhancers.
3. Particulate system.

Physical enhancers

Iontophoresis: In this ions transport the medication through the skin to bloodstream. It is loaded either be +ve or –ve by the manufacturer. Low mA or voltage is used. In this topically applied therapeutic agents by application of low level electric current either directly to skin or indirectly through dosage form.

Electroporation: Electroporation is done using high voltage pulses to the skin induce the formation of transit pores. High voltage (1000v) for millisecond is enough to cause Electroporation within stratum corneum i.e.- increase skin permeability of molecules with different lipophillicty and size (mol wt. >7K DA).

Microneedle: Percutaneous administration of drugs length 50-110 µm will penetrate stratum corneum and epidermis to deliver drug. Microneedle are of four different types have been developed include solid microneedle which coated with dry powder drugs or vaccines for dissolution in to skin.

Ultrasound (sonophoresis and phonophoresis): In this technique the ultrasonic energy is used to enhance the transdermal delivery of solute simultaneously or via pre-treatment. To enhance the skin permeability the low frequency ultrasound (55 kHz) is used for an average duration of 15 sec.

Magnetophoresis: The magnetic field exerts an external driving force to enhance the diffusion of a diamagnetic solute across the skin. The skin permeability is increases when it exposure to a magnetic field which induce structural alteration of the skin.

Needle-less injection: By using the suitable energy source the solid or liquid particles at supersonic speed introduced through the outer layer of the skin the transdermal delivery is achieved. The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration.

Skin Abrasion: In this technique there is a direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. The devices used in this technique employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of the acne, hyper pigmentation, scars and other skin blemishes.

Laser radiation: In this technique there is a removal of stratum corneum by the exposure of direct and controlled laser to the skin. This method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

Chemical enhancers

The chemical enhancers increase the partition coefficient of the drug to promote its release from the vehicle into the skin e.g. sulphoxide, glycols, alkanols, terpenes, azones etc. These are compounds which promote skin permeability by causing reversible damage to the stratum corneum or altering the skin as a barrier to the flux of a desired penetrant. The flux, J, of drugs across the skin can be written as

$$J=Ddc/dx$$

Where D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecule as well as the membrane resistance; C is the concentration of the diffusing species; X is the spatial coordinate.

Mechanism of chemical penetration enhancement: [32]

- They act on the stratum corneum intercellular keratin, denature it to or modify its conformation causing swelling and increased hydration.
- Effects demosomes that maintain cohesion between carenocytes.
- Modify the intercellular lipid domains to reduce the barrier resistance of the by layer lipids.
- Alter the solvent nature of the stratum corneum to modify partitioning of the drug or of co-solvent into the tissue.
- Modification of thermodynamic activity of the vehicle.

A large number of compounds have been investigated for their ability to enhance stratum corneum permeability example: Menthol, Limonene, Azone, Oleic acid, Linoleic acid, Lauric acid, Dimethyl sulphoxide(DMSO), Ethanol, Propylene glycol, Phospholipids, Enzymes, amino acid derivatives etc.

Ideal characteristics of chemical penetration enhancers [33]

Without damaging viable cells the penetration enhancers reversibly reduce the barrier resistance of the stratum corneum. Some desirable properties for penetration enhancers are given below:

- They should be non-toxic, non-irritating and non-allergenic
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- They should be cosmetically acceptable with an appropriate skin feel.
- They should have no pharmacological activity within the body.

Particulate system: The enhancers of transdermal drug delivery system are liposomes, micro emulsion, transferome, Niosomes, and Nanoparticles.

Marketed Products:

BRAND NAME	ACTIVE INGREDIENTS	INDICATION	MANUFACTURER
NICODERM	Nicotine	Smoking cessation	GlaxoSmithKline, Novartis Consumer Health
TESTODERM	Testosterone	Testosterone deficiency	Alza, Mountain View
LIDODERM	Lido cane	Post-herpetic neuralgia pain	Endo Pharmaceuticals
OXYTROL	Oxybutynin	Overactive bladder	Watson Pharma
EMSAN	Selegiline	Major depressive	Bristol-Myers Squibb
TRANSDERMSCOP	Scopolamine	Motion sickness	Novartis Consumer Health
TRANSDERMNITRO	Nitroglycerin	Angina pectoris	Novartis
CATAPRESS-TTS	Clonidine	Hypertension	Boehringer Ingelheim
ESTRADERM	Estradiol	Menopausal symptoms	Novartis
DURAGESIC	Fentanyl	Chronic pain	Janseen Pharmaceutical

Evaluation of transdermal patches

- **Physical appearance: [34]**

The patches were visually inspected for color, flexibility, smoothness and homogeneity.

- **Mass uniformity and Thickness: [35, 36]**
- The film of patches was dried at 60°C for 4 hours. Then the patches were weighed directly on the digital balance for the determination of mass and thickness of each patch at five different locations were done by using screw gauge.
- **Folding endurance: [37, 38]**

Folding endurance was determined by repeatedly folding the patch at the same place up to 200 times without breaking or until it breaks. The number of times the film could be folded at the same place without breaking was the folding endurance.

- **Drug content determination: [39, 40]**

For a drug content uniformity, patch was dissolved in a 100ml of isotonic phosphate buffer saline pH 7.4 for 12 hours under occasional stirring. The contents were filtered by whatman filter paper and then filtrate was analysed by U.V spectrophotometer at a specific ג $_{max}$.

- **Flexibility or Tensile strength:[41]**

The pulley system is used to determine the flexibility and tensile strength. With the help of two small catchers the patch was pulled in opposite direction by gradually increasing the force until the patch was broken. The tensile strength was noted from the scale of pulley in kg/cm^2.

- **Elongation break:[42]**

For elongation break study the longitudinal strips were cut from the transdermal patch. By using vernier calliper the flatness was determined at various points. By noting the length just before the break point the percentage elongation was determined and substituted in equation.

Elongation (%) = L1-L2/L2×100

Where L1 = final length of each strip
L2 = initial length of each strip

- **Percentage of moisture uptake: [43, 44]**

To check the physical stability of film in high humidity condition the film were placed in a desiccator containing a solution of aluminium chloride at room temperature for 24 hrs and exposed to 85% relative humidity until a constant weight of film was obtained. The film was reweighed and the percentage moisture uptake was determined by following formula.

Percentage moisture uptake = Final weight – Initial weight/Initial weight×100

- **Percentage moisture loss: [45, 46]**

To check the extent of moisture loss the films were weighed accurately and kept in the desiccators containing anhydrous calcium chloride. After 3 days the film were carried out and reweighed.

Percentage of moisture loss = Initial weight – Final weight/Initial weight×100

- **Water vapour transmission rate(WVT) studies: [47]**

It is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass vials of equal diameter were used as transmission cells. The film was placed on the vials, containing 3g of fused calcium chloride as desiccant, with an adhesive tape. The cell were accurately weighed and kept in a desiccator containing a saturated solution of potassium chloride to maintain RH of 84%. The vials was taken out and weighed at every 24 hours interval for a period of 72 hours.

WVT = Final weight –Initial weight/Area

The rate of water vapour transmission was calculated from the plot of amount of water vapour transmitted versus time.

- **Differential scanning calorimetry:[49]**

The DSC analysis of drug, cholesterol, span60, HPMC K4M, liposomal patch, niosomal patch and control patch were carried out. The analysis was conducted in the heating range of 54-260°C in nitrogen atmosphere at the rate of 150 ml/min using DSC.

- **Surface morphology Study: [50, 51]**

This study of formulated transdermal patches (both stable and unstable) were carried out by scanning electron microscope (SEM) at 15 kV under different magnification.. SEM was confirmed by direct deposition of film on double sided carbon tape and coated with gold. The sample was visualized using a SEM operated with a secondary detector at different acceleration voltage and at a different magnification.

- **Flatness:[52]**

The strips were cut out longitudinally from each film i.e. one from center and two from either side. The length of each strip was measured and the variation in the length because of nonuniformity in flatness was measured by determining percent constriction, considering 0% constriction is equivalent to 100% flatness:

% Constriction = L_1-L_2/L_2×100

Where L_1= initial length of each strip
L_2= final length of each strip

- **Stability study: [53]**

For stability study the prepared patch were sealed in polyethylene coated aluminum foils and kept at 25°C for few months. The samples were withdrawn at 0, 30, 60 and 90 days and the drug content was analyzed by a UV spectrophotometer method.

- ***In vitro* evaluation of TDDS**

a. ***In vitro* drug release study [54]:** For assessment of the release of the drug from the prepared patches the paddle over disc method (USP apparatus V) can be employed. A dried film cut in to defined shape having known thickness, weighed and fixed on a glass plate with an adhesive. The glass plate then placed in a prepared 500ml of dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32+ 0.5°C..The distance of the paddle from the glass plate is 2.5cm and operated at a speed of 50 rpm. After appropriate time interval about 24hrs the sample was withdrawn and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

b. ***In vitro* skin permeation studies [55]:** The *in vitro* permeation studies are carried out by using glass diffusion cell at 37˚C ± 0.2˚C.The abdominal skin of male Wistar rats having full thickness weighing 200-250 gm. By using the electric caliper the hairs are removed from the abdominal region. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels. The receptor compartment is filled with dissolution medium and phosphate buffer pH 7.4 and the hydrodynamics are maintained in the receptor compartment by stirring with magnetic bead at 50 rpm and for the uniform distribution of the diffusant. The temperature of the cell was maintained at 32+0.50c 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. Defined volume of sample is removed from the receptor compartment at regular intervals, and then equal volume of fresh medium is to be replaced. Then sample was taken then filter through filter medium and can be analyzed spectrophotometrically or HPLC.

c.

- **Skin irritancy studies: [56]**

The skin irritancy can be performed on healthy rabbits / mice albino / rats and potential of transdermal system can be evaluated by modified Draize test. The dorsal surface of given test animal is to be cleaned and remove the hair from the clean surface then applied rectified sprit. The transdermal formulation was applied over the clean surface for 24 hour. After the specific period of time, remove the formulation and observed the status of skin. The score are given from 0 to 4 depending the degree of erythema as follows : zero point given for no erythema , 1point for slight erythema-(barely perceptible-light pink), 2 point for moderate erythema(dark pink),3 points for moderate to severe erythema(dark pink) and 4 points for severe erythema.

- **Swelling property: [57]**

The patch is applied on a preweighed cover slip and weight is taken. Now it is place in a petridish containing 50 ml 7.4 pH phosphate buffer. At an interval of 5 minute the cover slip is removed from petridish, washed and weighed for 30 minutes. The change in the weight gives the swelling of the patch due to uptake of water.

Percentage swelling (S) is given by:

$$\% S = (Xt-X0/X0) \times 100 \quad (9)$$

Xt is weight at time‘t’ after swelling and X0is original weight of the patch.

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