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Transdermal Drug Delivery Systems: An Overview

***Latheeshjlal.L, P. Phanitejaswini, Y.Soujanya, U.Swapna, V.Sarika, G.Moulika,**

Department of Pharmacy, Maheshwara Institute of Pharmacy-Hyderabad,India.

****Corres.author: latheesh18@yahoo.co.in***

INTRODUCTION[1-3]

The most common form of drug delivery is the oral route. In this route of administration has notable advantages and also have significant drawbacks like first pass metabolism, drug degradation in gastrointestinal tract due to enzymes, pH etc. To overcome these difficulties a Novel drug delivery system was developed.

In recent years it has been shown that the skin is a useful route for drug delivery to the systemic circulation. Transdermal drug delivery system includes all topically administered drug formulations intended to deliver the active ingredients into the circulation. They provide controlled continuous delivery of drugs through the skin to the systemic circulation. The drug is mainly delivered through the skin with the aid of transdermal patch. A Transdermal patch is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. A drug is applied in a relatively high dose to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration in the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

Advantages of Transdermal drug delivery over the conventional dosage forms:[1,3,4]

1. The Transdermal drug delivery system (TDDS) can be defined as a delivery device, which upon application on a suitable skin surface will be able to deliver the drug into the systemic circulation at sufficient concentration to ensure therapeutic efficacy, an additional limitation to oral drug delivery, can be avoided with transdermal administration.
2. Steady permeation of drug across the skin, allowing consistent serum drug level, often a goal of therapy.
3. Similar to intravenous infusion, it also achieves consistent plasma levels, but noninvasive in nature.
4. In addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch.
5. Transdermal drug delivery can be used as an alternative delivery system for patients who cannot tolerate oral dosage forms.
6. It is of great advantage in patients who are nauseated or unconscious.
7. Drugs that cause gastrointestinal upsets can be good candidates for transdermal delivery because this method avoids direct effects on stomach and intestine.
8. Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing

regimen can aid in patient adherence to drug therapy.

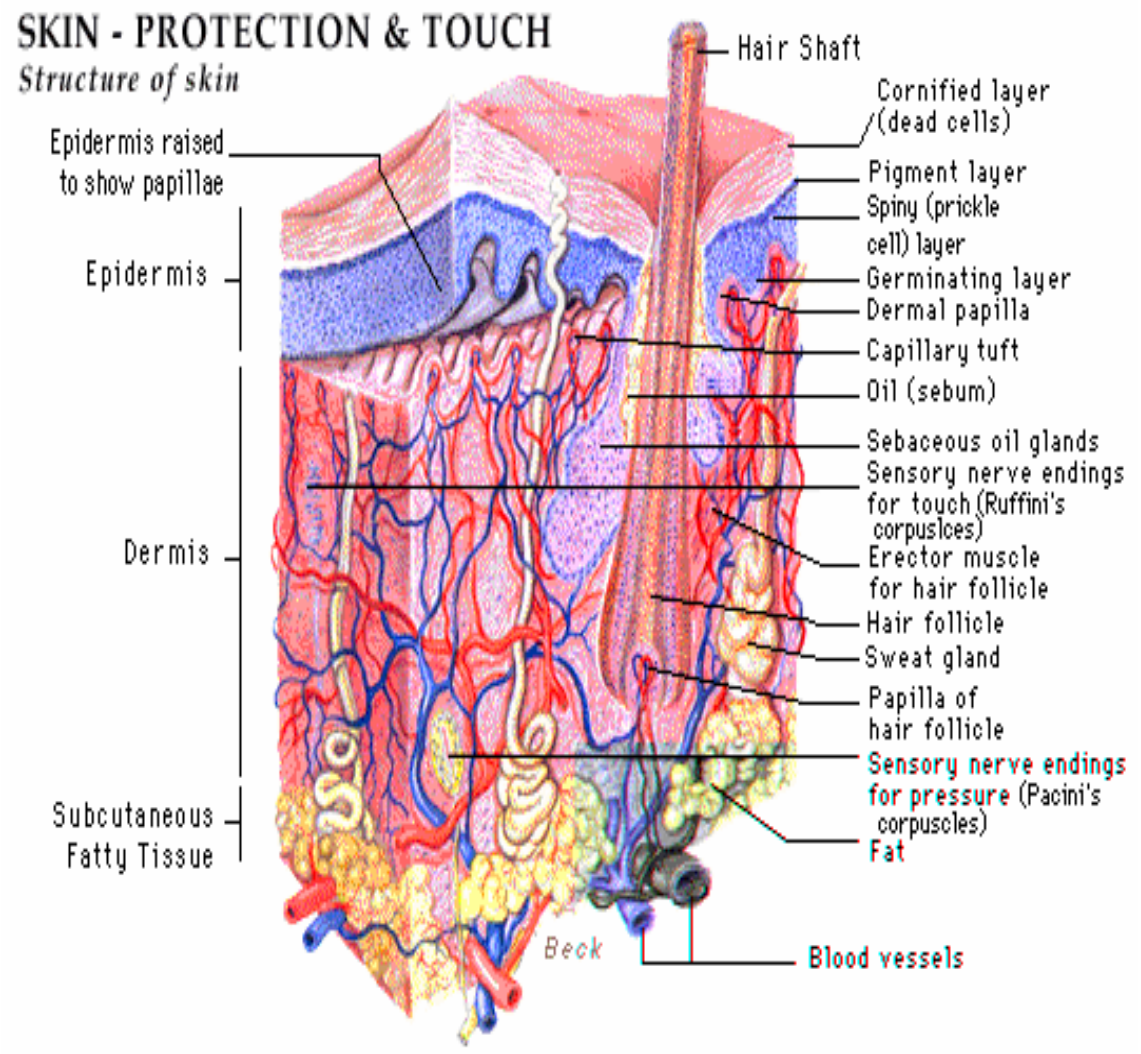
9. Peaks and troughs in plasma level can be avoided, which reduce the risk of side effects. Thus, drugs that require consistent plasma levels are very good candidates for transdermal drug delivery.
10. Allows continued drug administration permitting the use of a drug with short biological half-life.

Common disadvantages of TDDS: [1,3-5]

1. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.
2. The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.
3. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

SKIN[1,6-9]

The Site of Percutaneous Absorption:



The skin of an average adult human covers a surface area of nearly $2m^2$ and receives about one-third of the blood circulating through the body. Microscopically skin is composed of three main histological layers: epidermis, dermis and subcutaneous tissues. The epidermis is further divided into two parts- the non-viable epidermis (stratum corneum) and the viable epidermis. The viable epidermis is divided into four layers, viz., stratum lucidium, stratum granulosum, and stratum spinosum and stratum germinativum.

Stratum corneum & Epidermis: The main barrier to percutaneous absorption:

The SC consists of multiple layers of horny dead cells, which are compacted, flattened, dehydrated and keratinized. The horny cells are stacked in highly interdigitated columns with 15-25 cells in the stack over most of the body. It has a density of 1.55g/cc. The SC has a water content of only 20% as compared to 70% present in physiologically active stratum germinativum. It exhibits regional differences over most of the body and is approximately 10-15µm in thickness. However, the thickness may be several hundred micrometers (300-400µm) on friction surfaces such as the palms of the hand and soles of the feet. Keratin present in the cells of the SC is a fibrous protein, which is poor in sulphur and forms a filamentous network to assure cohesion, flexibility and recovery. The unique properties of stability, insolubility and resistance observed in the SC are due to the thick cell membrane and cell matrix, which consists of amorphous proteins rich in sulphur content and lipids with many disulphide linkages. The SC is described as the only rate-limiting barrier of the skin with regard to the viable epidermis and dermis. The SC is a heterogeneous membrane consisting of alternating lipophillic and hydrophilic layers. The pH of the skin surface is between 3 and 4, which is about the isoeletric point of keratin in the SC layer. Below the SC remains the viable epidermis, which is more accommodative of permeant molecules. The viable epidermis is an aqueous solution of protein encapsulated into cellular compartments by thin cell membranes, which are fused together by tonofibrils. The viable epidermis has a density near that of water. The germinal (proliferative) layer above dermis undergoes cell divisions producing an outward displacement of the cell towards the surface. As the germinal layer moves upwards, it changes shape into a more rounded form with spiny projections and appears as a stratum spinosum. After the germinal layer has raised 12-15 layers above its point of origin, it becomes flattened and the basophilic nuclear material is dispersed throughout the cells as granules. The layer is referred to as stratum granulosum.

The stratum lucidium layer, which lies just below the SC, is the site where nuclei disintegrate and keratinization and sulphahydryl-rich matrix formation takes place. Eventually it moves upwards to form the SC. It should be pointed out that the epidermis contains no vascular elements. The cells receive their nourishment from the capillary beds located in the papillary layers of the dermis by diffusion of plasma and serum components.

Dermis: The site of systemic absorption:

The dermis is 0.2-0.3 cm thick and is made of a fibrous protein matrix, mainly collagen, elastin and reticulum embedded in an amorphous colloidal ground substance. It is divided into two distinct zones: a superficial finely structured thin papillary layer adjacent to the epidermis and a deeper coarse reticular layer (the main structural layer of skin). The dermis is also the locus of the blood vessels, sensory nerves segments of the sweat glands and pilosebaceous units. The blood vessels supply blood to the hair

Subcutaneous fatty tissue:

Cushioning the epidermis and dermis is the subcutaneous tissue or fat layer where fat is manufactured and stored. It acts as a heat insulator and a shock absorber. It essentially has no effect on the percutaneous absorption of drugs because it lies below the vascular system.

Transdermal Permeation:[3,10-13]

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and really accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows.

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary later.
5. Effect on target organ.

Care taken while applying Transdermal patch:[4,5]

1. The part of the skin where the patch is to applied should be properly cleaned.
2. Patch should not be cut because cutting the patch destroys the drug delivery system.
3. Before applying a new patch it should be sure that the old patch is removed from the site.
4. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.
5. The patch should be applied accurate to the site of administration.

Properties that influence Transdermal delivery of the drug: [13-15]

a. Release of the medicament from the vehicle.
b. Penetration through the skin barrier.
c. Activation of the pharmacological response.

FACTORS THAT INFLUENCE TRANSDERMAL DRUG DELIVERY:[15-22]

Biological factors include:

1. Skin condition
2. Skin age
3. Blood flow
4. Regional skin sites
5. Skin metabolism
6. Species differences

Physiological factors include:

1. Skin hydration
2. Temperature and pH
3. Diffusion coefficient
4. Drug concentration
5. Partition coefficient
6. Molecular size and shape

BASIC COMPONENTS OF TDDS:[15-23]

1. The drug
2. Polymer matrix
3. Permeation enhancers
4. Adhesive
5. Backing layer.

1. DRUG

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

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

2. POLYMER MATRIX

These polymers control the release of the drug from the drug reservoir.
Natural polymers: shellac, gelatin, waxes, gums, starch etc.,
Synthetic polymers: polyvinyl alcohol, polyamide, polyethylene, polypropylene, Polyurea, polymethyl-methacrylate etc.

3. PERMEATION ENHANCERS:

Substances exist which temporarily diminish the impermeability of the skin are known as accelarants or sorption promoters or penetration enhancers. These include water, pyrolidones, fatty acids and alcohols, azone and its derivatives, alcohols and glycols, essential oils, terpenes and derivatives, sulfoxides like dimethyl sulfoximide and their derivatives, urea and surfactants.
Surfactants are proposed to enhance polar pathway transport especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.
Anionic surfactants: sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.,
Nonionic surfactants: Pluronic F 127, Pluronio F68, etc.,
Enhancer actions can be classified by lipid-protein-partitioning concept. This hypothesis suggests that enhancers act by one or more ways selected from three main possibilities.
Lipid action The enhancer interacts with the organized intracellular lipid structure of the stratum corneum so as to disrupt it and make it more permeable to drug molecules. Very many enhancers operate in this way. Some solvents act by extracting the lipid Components and thus make the horny layer more permeable.
Protein modification Ionic surface active molecules in particular tend to interact well with the keratin in the corneocytes, to open up the dense keratin structure and make it more permeable. The intracellular route is not usually prominent in drug permeation, although drastic reductions to this routes resistance could open up an alternative path for drug penetration.
Partitioning promotion Many solvents can enter the stratum corneum, change its solvent properties and thus increase the partitioning of a second molecule into the horny layer. This molecule may be a drug, a coenhancer or a cosolvent.
For example ethanol has been used to increase the penetration of the drug molecules

nitroglycerin and estradiol.

4. ADHESIVE

Serves to adhere the patch to the skin for systemic delivery of drug.

Ex: Silicones, Polyisobutylene.

5. BACKING LAYER

Backing layer protects patch from outer environment.

Ex: Cellulose derivatives, Polypropylene silicon rubber.

TYPES OF TRANSDERMAL PATCHES: [7,9,21-25]

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 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 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 the 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 vapour 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 porous or nonporous. 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 the drug.

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 pn an impervious backing layer. On top of the reservoir, unmediated adhesive polymer adhesive polymer layers are applied for protection purpose.

ii) Matrix-dispersion system

In this type the drug is dispersed homogenously in a hydrophilic or lipophillic 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) Micro reservoir system

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophillic 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.

FACTORS AFFECTING TRANSDERMAL BIOAVAILABILITY:[23-26]

Two major factors affect the bioavailability of the drug through transdermal routes:

(1)Physiological factors (2) Formulation factors

Physiological factors include:

i. Stratum corneum layer of the skin
ii. Anatomic site of application on the body
iii. Skin condition and disease
iv. Skin metabolism
v. Skin irritation and sensitization

Formulation factors include:

(i) Penetration enhancers used
(ii) Vehicles and membrane used
(iii) Physical chemistry of transport
(iv) Method of application
(v) Device used

ABSORPTION ENHANCEMENT BY ENERGY INPUT:[2,14-17,23]

Transfer of drugs through the skin by the action of electrical or other forms of energy is done by Phonophoresis, Iontophoresis, Electroporation and Radiofrequency waves.

Electroporation: Electroporation is the creation of aqueous pores in the lipid bilayers by the application of short electrical pulses. Electroporation may combine with iontophoresis to enhance the permeation of peptides such as vasopressin, calcitonin and neurotensin.

Phonophoresis: In this process ultrasonic energy is used. The medicine is placed on the skin over the area to be treated and massaging the site with an ultrasound source. The ultrasonic energy disturbs the lipid packing in the intercellular spaces of the stratum

corneum by heating and cavitations effects, and thus enhances drug penetration into the tissue.

Iontophoresis: Iontophoresis is a method of transferring substances across the skin by applying an electrical potential difference. It promotes the transfer of charged ionic drugs and possibly high molecular weight substances such as peptides. Electric current is applied through two electrodes, placed in the patient's skin. The first, or donor, electrode (cathode) delivers the negatively charged therapeutic agent (e.g., an organic acid), whereas the second or receptor, electrode (anode) serves to close the circuit. This setup is named cathodal iontophoresis. For positively charged drugs (e.g., amines or peptides), the cell arrangement is reversed called anodal iontophoresis. The silver (anode) and silver chloride (cathode) electrode system utilized in both types of iontophoresis.

Radiofrequency waves: In this the energy of radiofrequency waves are used to form microchannels through the stratum corneum. A densely spaced array of microelectrodes takes microseconds to form holes through which an applied drug passes easily into the skin.

EVALUATION PARAMETERS:[16-26]

Interaction studies:

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physiochemical characters such as assay, melting endotherms, characters wave numbers, absorption maxima etc.,

Thickness of the patch:

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Drug content determination:

An accurately weighed portion of film is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 hrs in shaker incubator. Then the whole solution is sonicated. After incubation and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Percentage Moisture content:

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. The films are weighed again after a specific interval until they show a constant weight. The percent moisture content is calculated using formula.

Percentage moisture content

$$= \frac{\text{Initial weight- Final weight}}{\text{Final weight}} \times 100$$

Percentage Moisture uptake:

Weighed films are to be taken in a desicator at room temperature for 24 hrs. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desicator until a constant weight is achieved. Percentage moisture uptake is calculated as given below.

Percentage moisture uptake=

$$\frac{\text{Final weight- Initial weight}}{\text{Initial weight}} \times 100$$

Water vapour permeability evaluation (WVP):

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula.

$WVP = W/A$

Where, WVP is expressed in gm^2 per 24 hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m^2.

Folding Endurance:

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folded endurance.

Flatness test:

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by

determining percent constriction. Zero constriction is equivalent to 100% flatness.

Percent constriction =

Initial length - Final length X 100
of each strip of each strip
Initial length of each strip

Weight uniformity:
The prepared patches are to be dried at 60^0c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Uniformity of dosage unit test:
An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume in volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2um membrane filter and analysed by suitable analytical technique and the drug content per piece will be calculated.

Percentage elongation break test:
It is determined by noting the length just before the break point, the percentage elongation can be determined from below formula.
Elongation percentage=

Final length - initial length X 100
of each strip of each strip
Initial length of each strip

Thumb tack test:
The force required to remove thumb from adhesive is a measure of tack.

Rolling ball tack test:
This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (peel tack) test:
The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90^0 at the speed of 12 inch/min.

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 adhesive 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.

Polariscope examination:
This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

Sheer adhesion test:
This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackfier added. An adhesive coated tape is applied into a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

Peel adhesion test:
In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing , membrane of choice and then tape is pulled from the substrate at a 180^0 angle, and the force required for tape removed is measured.

In vitro drug release studies:
The paddle over disc method can be employed for assessement 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 500ml of the dissolution medium or

phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5^{0}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 can be withdrawn at appropriate time intervals upto 24hrs and analysed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

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 weighing 200-250 gm. 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^{0}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. Flux can be determined directly as the slope of the curve between the steady state values of the amount of drug permeated vs. time in hrs and permeability coefficients were deduced by dividing the flux by the initial drug load.

Skin irritation study:

Skin permeation and sensitization testing can be performed on healthy rabbits. The dorsal surface of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24hrs and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

Stability studies:

Stability studies are to be conducted according to ICH guidelines by storing the TDDS samples at 40±0.50c 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.

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