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A REVIEW: TRANSDERMAL DRUG DELIVERY SYSTEM – BASIC UNDERSTANDING FOR DEVELOPMENT

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ABSTRACT

Transdermal drugs are self-contained, discrete dosage form. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. This system generated tremendous excitement and interest amongst the major pharmaceutical companies in the 1980s and 90s. The advantages of avoidance of first-pass liver metabolism, avoidance of exposure to chemical and biological conditions of the gastrointestinal tract, reduction or avoidance of adverse events, improved patient compliance, and the ability to provide a controlled delivery of drugs with short half-lives and/or narrow therapeutic windows were all attractive features that the pharmaceutical industry was looking for. TDDS is such a mode of delivery which has been explored extensively over the last 25 years, with therapeutic success. TDDS is ideally suited for diseases that demand chronic treatment. 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 in this method. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation. This review article describes the components and the methods of preparation of different types of transdermal patches such as matrix patches, reservoir type, membrane matrix and micro reservoir patches. In addition, the various methods of evaluation of transdermal dosage form have also been reviewed.

INTRODUCTION

Drug is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment or cure of disease. WHO (1966) has given a more comprehensive definition - 'Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient'[1]. Drug substances are seldom administered alone; rather they are given as a part of formulation in combination with one or more non medicinal agents that serve varied and specialized pharmaceutical function. Selective use of these non medicinal agents, referred to as excipients, produces dosage form of various types like tablets, capsules, syrups, suspensions etc[2]. The most common form of delivery of drugs is the oral route. It has the notable advantage of easy administration, but also have significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and / or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there was a need for the development of new drug delivery system; which can improve the therapeutic efficacy and safety of drugs by more precise spatial and temporal placement within the body thereby reducing both the size and number of doses[3].

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin[4]. Transdermal Drug Delivery Systems are defined as 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[5]. Transdermal drug delivery is the delivery of drugs across epidermis to achieve systemic effects. The success of transdermal patches lies in their commercialization. Transdermal patches control the delivery of drugs at controlled rates by employing an appropriate combination of hydrophilic and lipophilic polymers[6].

HUMAN SKIN

For the delivery of a drug into the body through transdermal layer of skin, it is necessary to understand about the skin. Skin is described as protective, sensitive, reparative, and capable of maintaining an individual's homeostasis. The skin covers 1.2 to 2.3 m^2 of area and is the heaviest organ of the body. The three layers of the skin are the outer epidermis, middle

dermis, and the underlying hypodermis or subcutaneous tissue. The appendages include the hair, nail, eccrine and apocrine sweat glands, and the sebaceous glands. The functions of the skin include protection, sensation, water balance, temperature regulation, and vitamin production[7]

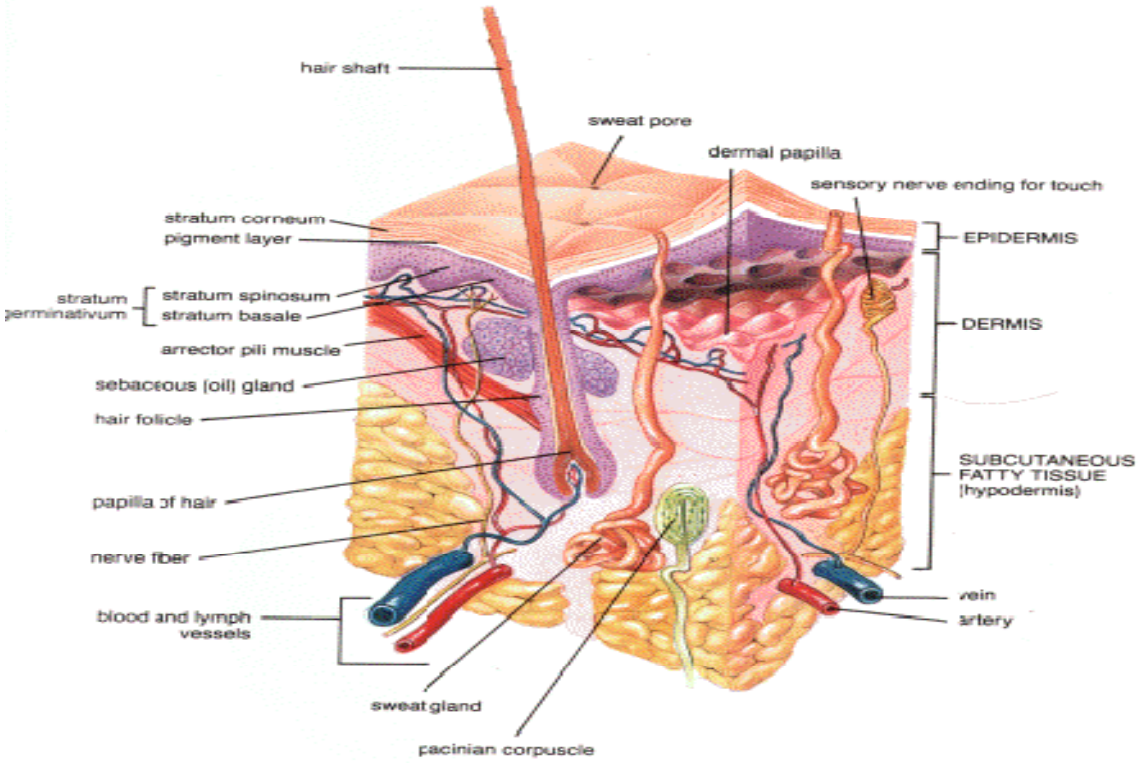

Figure 1: Structure of skin

Human skin comprises of three distinct but mutually dependent tissues :

A) The stratified, vascular, cellular epidermis,

B) Underlying dermis of connective tissues and

C) Hypodermis[8].

Epidermis

This outer layer of the skin serves to protect underlying structures from invasion by microbes and other foreign substances. The cornified, external layer of the epidermis helps in the body's regulation of water loss. The innermost sublayer bends into the dermis and serves as the basis for the glands, nails, and hair roots. The epidermis does not have vascular supply; it depends on the dermal level for its nourishment[9]. The epidermis is further divided into five sublayers. From the bottom (innermost), these sublayers are stratum basale (basal cell layer), stratum spinosum (prickle cell layer), stratum granulosum (granular cell layer), stratum lucidum (clear layer) and stratum corneum (horny cell layer)[9].

Stratum Basale (Basal Cell Layer)

It is the deepest sublayer of the epidermis and is composed of a single layer of basal cells. This sublayer forms the boundary to the dermis. Keratinocytes are produced in this sublayer. It holds approximately 8% of the water in the epidermis. With aging, this layer becomes thinner and loses the ability to retain water. Melanocytes, which were mentioned in the previous section, also lie in this layer[9].

Stratum Spinosum (Prickle Cell Layer)

It refers to the 10 to 20 layers that lie on top of the basal cell layer. Basal cells, through the process of turn-over, make their shape somewhat flatter (multi-sided) and form these layers. These cells are called prickle cells and have little spines on the outside of their membrane. The thickness of this sublayer is typically from 50 to 150 μm[9].

Stratum Granulosum (Granular Cell Layer)

It is composed of 2 to 4 granular cell layers. The typical thickness is 3 μm. In this sublayer, cornification called keratinization of keratinocytes begins. In this process, organelles such as nuclei and mitochondria start to resolve. Cells are increasingly filled with keratin fibers and contain less moisture than basal and prickle cell layers. The shape of these cells becomes much flatter during this process[9].

Stratum Lucidum (Clear Layer)

It can only be found in soles and palms. It is a highly refractive sublayer. Its cells become flatter and more densely packed during turn-over[9].

Stratum Corneum (Horny Cell Layer)

It is the exterior sublayer of the epidermis. Its thickness ranges from 8 to 15 μm. This sublayer is composed of several layers of hexagonal-shaped flat and hard cells named horny cells or corneocytes. These are dry dead cells without organelles and filled with keratin fibers. This sublayer prevents excessive dehydration of the skin tissue and usually contains 10 to 15% of the mass of water in the epidermis, depending on the skin condition. Horny cells are surrounded by intercellular lipids. A principal constituent is *ceramide*, which plays a crucial role in water retention. Horny cells also contain special chemical compounds called natural moisturizingfactor (NMF) that also plays an important role in retaining skin moisture. NMF is composed of sodium PCA, sphinolipids and ceramides, phospholipids, fatty acids, glycerol, squalane and cholesterol. Skin that lacks NMF and ceramide tends to be very dry[9].

Dermis The middle layer of the skin, the dermis, provides support for the outer epidermal layer. It is a very vascular connective tissue and the blood vessels are integral to regulation of

body temperature and blood pressure. The arteriovenous anastomoses, under control of the sympathetic nervous system and found in the dermal layer, are able to dilate or constrict in response to environmental conditions of heat and cold and to internal stimulation from anxiety or blood volume loss. The sensory function of the skin includes receptors for heat, cold, touch, pressure, and pain; these are located in the dermal layer. There is a great variety in the function of the nerve endings; multiple stimuli are mediated centrally and result in patterned responses[9].

Hypodermis

The hypodermis or subcutaneous skin layer consists of connective tissue interspersed with fat. The fat of the hypodermis has the protective functions of heat retention and cushioning the underlying structures. In addition, the fat of the subcutaneous skin layer serves as storage for calories[9].

PRINCIPLES OF TRANSDERMAL PERMEATION

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 readily 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 layer.
5. Effect on target organ[10].

BASIC COMPONENTS OF TDDS

- Polymer matrix/ Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Rate controlling membrane
- Release liner
- Other excipients like plasticizers and solvents[11].

Polymer Matrix

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion–cohesion balance, physicochemical properties, and compatibility and stability with other components of the system as well as with skin [12].

The polymers utilized for TDDS can be classified as

• Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*.

• Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*.

• Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane[12].

Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery[13].

Physicochemical Properties

- The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml)
- The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree

absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible.

- Substances having a molecular weight of less than 1000 units are suitable.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.
- Hydrogen bonding groups should be less than 2[14].

Biological Properties

- Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day)
- The drug should have short biological half life.
- The drug should be non irritant and non allergic to human skin.
- The drug should be stable when in contact with the skin.
- The drug should not stimulate an immune reaction to the skin.
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery.
- The drug should not get irreversibly bound in the subcutaneous tissue.
- The should not get extensively metabolized in the skin[14].

Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids.

Examples

Water alcohols : methanol and ethanol;

Alkyl methyl sulfoxides : dimethyl sulfoxide,

Alkyl homologs : methyl sulfoxide dimethyl acetamide

Pyrrolidones : 2 pyrrolidone,

b) Surfactants

These compounds 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: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate

Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.

Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

c) Miscellaneous Chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein[15].

Pressure Sensitive Adhesive

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both types of adhesive system should fulfill the following criteria -

- Should adhere to the skin aggressively, should be easily removed.
- Should not leave any unwashable residue on the skin.
- Should not irritate or sensitize the skin.

  The face adhesive system should also fulfill the following criteria.
- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- The delivery of simple or blended permeation enhancers should not be affected[16].

Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films[17].

Rate Controlling Membrane Rate controlling membranes in transdermal devices govern drug release from the dosage form. Membranes made from natural polymeric material such as

chitosan show great promise for use as rate controlling membranes. Recently composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application[18].

Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to the skin. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form delivering the active principle. However, because the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding the chemical inertness and permeation to the drug, penetration enhancer, and water. In case cross-linking is induced between the adhesive and the release liner, the force required to remove the liner will be unacceptably high[19].

Other Excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch[20].

METHODS OF PREPARATION OF TDDS

Polymer Membrane Permeation-Controlled TDDS:

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, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied (Figure-1). The rate of drug release from this type of Transdermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate controlling membrane[21].

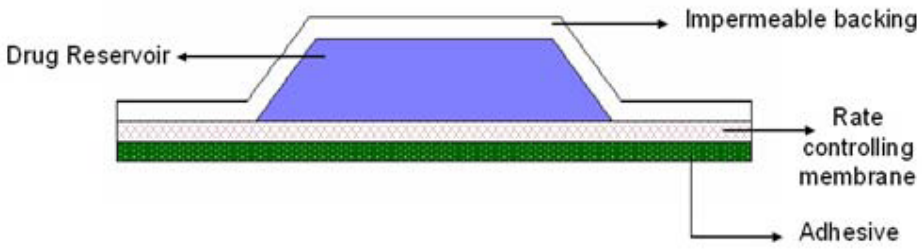

Figure: 2 Polymer membrane permeation-controlled TDDS

TransdermScop (Scopolamine) for 3 days protection of motion sickness and TransdermNitro (Nitroglycerine) for once a day medication of angina pectoris.

Adhesive Diffusion Controlled TDDS:

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer (Figure-2). The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery system[21].

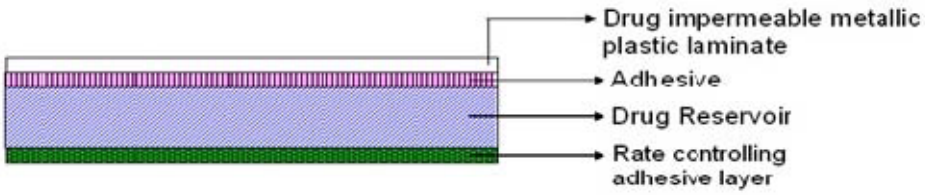

Figure: 3 Adhesive diffusion controlled TDDS

Deponit (Nitroglycerine) for once a day medication of angina pectoris.

Matrix Diffusion Controlled TDDS:

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer (Figure-3). Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim[22].

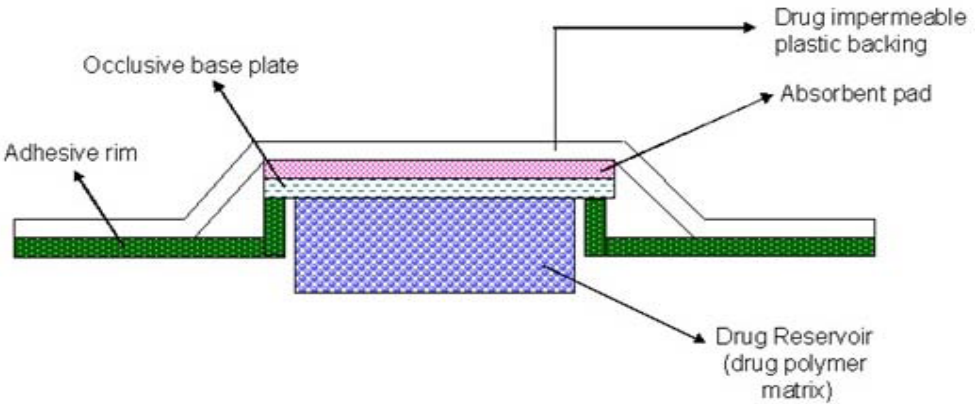

Figure: 4 Matrix diffusion controlled TDDS

Nitro Dur (Nitroglycerine) used for once a day medication of angina pectoris.

Microreservoir Controlled TDDS

This drug delivery system is a combination of reservoir and matrix-dispersion systems. 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 (Figure 4). The thermodynamically unstable dispersion is stabilized quickly by immediately crosslinking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc positioned at the center and surrounded by an adhesive rim[22].

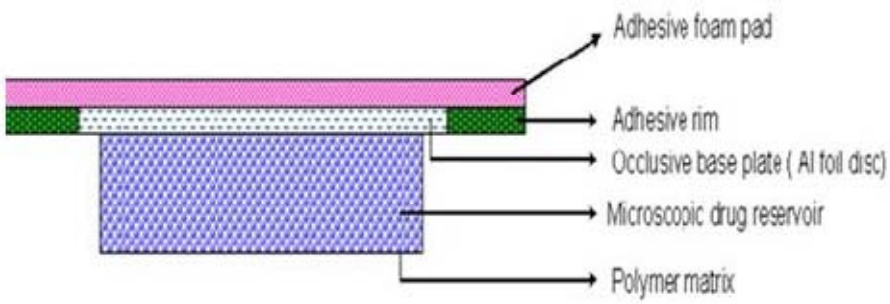

Figure 5: Microreservoir controlled TDDS

Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.

EVALUATION OF TRANSDERMAL PATCH

Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

• Physicochemical evaluation

• *In vitro* evaluation

• *In vivo* evaluation[23]

Physicochemical Evaluation

Thickness

The thickness of each film was measured using digital micrometer screw gauge at three different positions of the film and the mean value was calculated[24].

Uniformity of weight

10 randomly selected films were weighed individually and their average weight was calculated. Standard deviation for each film weight noted to check uniformity of weight[25].

Drug content determination

Drug content studies were conducted for all prepared batches of films. For this purpose the film was cut into 4cm^2 pieces from different places & was weighed accurately. The 4cm^2

films was then cut into small pieces & were taken in a 10ml volumetric flask. And then 5ml methanol was added. The films were dissolved completely by vigorous shaking. Required amount water was added to adjust the volume upto 10ml. After shaking, the mixture was filtered. Then 1ml of the filtrate was diluted 10 times by distilled water. A blank was prepared using a drug free patch treated similarly. Finally absorbance of the samples was measured by a Shimadzu UV spectrophotometer at 322nm[26].

Moisture content

The prepared films are to be weighed individually and to be kept in a desicator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films were weighed and the percentage of moisture content was determined from the below mentioned formula[27].

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

Water vapour transmission rate

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccators containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hrs of storage. The amount of water vapour transmitted was found using the formula[28].

$$\text{Water vapour transmission rate} = \frac{\text{Final weight - Initial weight}}{\text{Time}} \times \text{Area}$$

Water vapor transmission rate is usually expressed as the number of grams of moisture gained/h/cm2.

Flatness

Three longitudinal strips are to be cut from each film at different portion like one from he center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured; determining % constriction, with 0% constriction equivalent to 100% flatness[29].

Folding endurance

Folding endurance of film was determined by repeatedly folding a small strip of film (2 cm× 2cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value[30].

Tensile strength

Tensile strength was measured using modified analytical two-pan balance method. The patch of 20 mm width and 50 mm length were cut and clamped between two clamps on one side; weights were added to the pan on other side until the patch breaks. The weight required for breaking the patch was taken as a measure of tensile strength of the patch[31].

Tack properties

Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It is depends on the molecular weight andcomposition of polymer[32].

Test of tack includes.

(a) Thumb tack test

This is a subjective test in which evaluation is done by pressing the thumb briefly into the adhesive.

(b) Rolling ball tack test

This test involves measurement of the distance that a stainless steel ball travels along an upward – facing adhesive. The less tacky the adhesive the for they will travel.

(c) Quick stick (Peel tack) test

The peel force required for breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90^{o} at the speed of 12 inch/min.

(d) Probe tack test

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

***In Vitro* Release Studies**

A Paddle over disc assembly (USP 23, Apparatus 2) was used for the assessment of release of drug. The TDDS patch was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml phosphate buffer of pH 7.4. The apparatus was equilibrated to 37 ± 0.5oC and operated at 50 rpm. The samples (5 ml aliquots) were withdrawn at appropriate time intervals up to 8 hours and analyzed on a UV spectrophotometer at 258 nm[33].

***In Vitro* Permeation Studies**

In vitro evaluation of transdermal patches was carried out in Franz diffusion cell. The skin with the patch attached was mounted and clamped carefully between the receiver and donor compartment of diffusion cells with the patch facing the donor side. The receiver was maintained at 37^{0}C by thermostatically controlled water, which was circulated through a jacket surrounding each cell body, and the contents were stirred continuously at controlled

speed. Normal saline containing 0.02 M sodium azide was used as receiver solution to optimize drug solubility and to arrest fungal growth, so that sink condition was maintained. At predetermined time, samples were withdrawn from the receiver and assayed for Metformin HCl spectrophotometrically at 233 nm after proper dilution with the elution medium[34].

***In Vivo* Studies**

In vivo evaluation of trandermal patch can becarried out using –

i) Animal models

ii) Human Volunteers

Animal models

In *Vivo* animals models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species are used : mouse, rat, guinea pig, rabbit, rat, cat, dog, pig, house, monkey small hairy animals (e.g. rat, rabbit) or rhesus monkey is most reliable or in vivo evaluation of transdermal patches standard radiotracer methodology used. The application site is generally the abdomen which are the least hairy site on the animals body. The compound is applied after light clipper showing of the site[35].

Human models

Human subjects should give pertinent information with minimum risk to the subjects within responsible period. It is first described by Fieldman and Maibach. They includes determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labeled drug. 14C is generally used for radio labeling. Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body or excreted by routes. The percentage of dose absorbed transdermally is then calculated as.

$$\% \text{ Close absorbed} = \frac{\text{Total radioactivity exerted after topical Administration}}{\text{Total radioactivity exerted intervenes was Administration}}$$

The procedure takes 5-7 days for completion[35].

CONCLUSION

Transdermal system is an important route for drug delivery due to its several advantages when compared to other modes. It is particularly useful for the delivery of drugs that are prone to be destroyed by the liver when taken orally. Skin, however, acts as a major barrier to this process. Several physicochemical and biological factors influence assimilation through this route, and these are known to affect the efficacy of drugs penetrating the skin. Due to the

recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. These review work conclude that, older drugs by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

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