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Approaches of Transdermal Drug Delivery System Review

K. Sravanthi*, D. Rama Brahma Reddy, A. Sirisha, A. Pavani, B. Kanaka mahaLakshmi, B. Sowjanya

Department of Pharmacology, Nalanda institute of Pharmaceutical sciences, Kantepudi, Guntur.

ABSTRACT: Transdermal drug delivery system has become a proven technology that offer significant clinical benefit over the dosage forms. Drugs with very short half-life, narrow therapeutic window, and poor bioavailability-transdermal drug system are convenient. Skin serves as site of drug application for local as well as systemic effects. There are wide varieties of drugs for which topical or transdermal is viable options. Skin penetration enhancement technique have been developed for such drugs, there are number of physical methods to increase drug delivery through the skin, many of which requires the usage of devices. This delivery has to full-fill some parameters such as high potency, better permeability through the skin and non-irritation for better compliance. Fick's-law of diffusion is the principle of drug kinetics. This review article provides the valuable information regarding the transdermal drug delivery system and highlights the detailed role of physical penetration and describes the kinetics of transdermal drug system and recent advance techniques in transdermal drug delivery system such as iontophoresis, sonophoresis, microneedles, electroporation.

KEYWORDS: Transdermal Drug Deliverypredetermined rate, Transdermal therapeutic system, biosensors.

I. INTRODUCTION

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981 by FDA. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation. Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once weekly application. Such a simple dosing regimen aids in patient adherence to drug therapy[1].

POLYMER MATRIX:

Backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be nontoxic, cost should not be high. Eg: cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinyl lchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate[2].

DRUG:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window or drugs with short halflife. Eg:fenatyl, nitroglyceriene etc.

PERMEATION ENHANCERS:

Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvent, surface active agents and two component systems[3]. Eg: DMSO

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ADHESIVE:

Increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. Drug Delivery Routes across Human Skin. Drug molecules can penetrate by three pathways: 1. Sweat ducts 2. Hair follicles 3. Sebaceous glands Or Directly across the stratum corneum. The stratum corneum is the outermost layer of the epidermis, composed of large, flat, polyhedral, plate-like envelopes filled with keratin that is made up of dead cells that have migrated up from the stratum granulosum[4]. This skin layer is composed mainly of dead cells that lack nuclei. As these dead cells slough off on the surface in the thin air-filled stratum disjunctum, they are continuously replaced by new cells from the stratum germinativum (basale). The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15µm in the dry state to 40µm when they are hydrated. It is comprised mainly of a multi-layered "brick and mortar" like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) that is composed of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters. The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulosum discharging their lamellar contents into the intercellular space[5]. The initial layers of the stratum corneum rearrange to form broad intercellular lipid lamellae which then associate into lipid bilayers. As a result of the stratum corneum lipid composition, the lipid phase behavior is different from that of other biological membranes. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor which helps to maintain suppleness. To understand the physicochemical properties of the diffusing drug and vehicle influence across stratum corneum, it is essential to determine the predominant route of drug permeation within the stratum corneum. A molecule travelling via the transcellular route partition into and diffuse through the keratinocyte, but in order to move to the next keratinocyte, the molecule must partition into and diffuse through the estimated 4-20 lipid lamellae between each keratinocyte. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavorable for most drugs. Therefore the intercellular route is now considered to be the major pathway for permeation of most drugs across the stratum corneum[6].

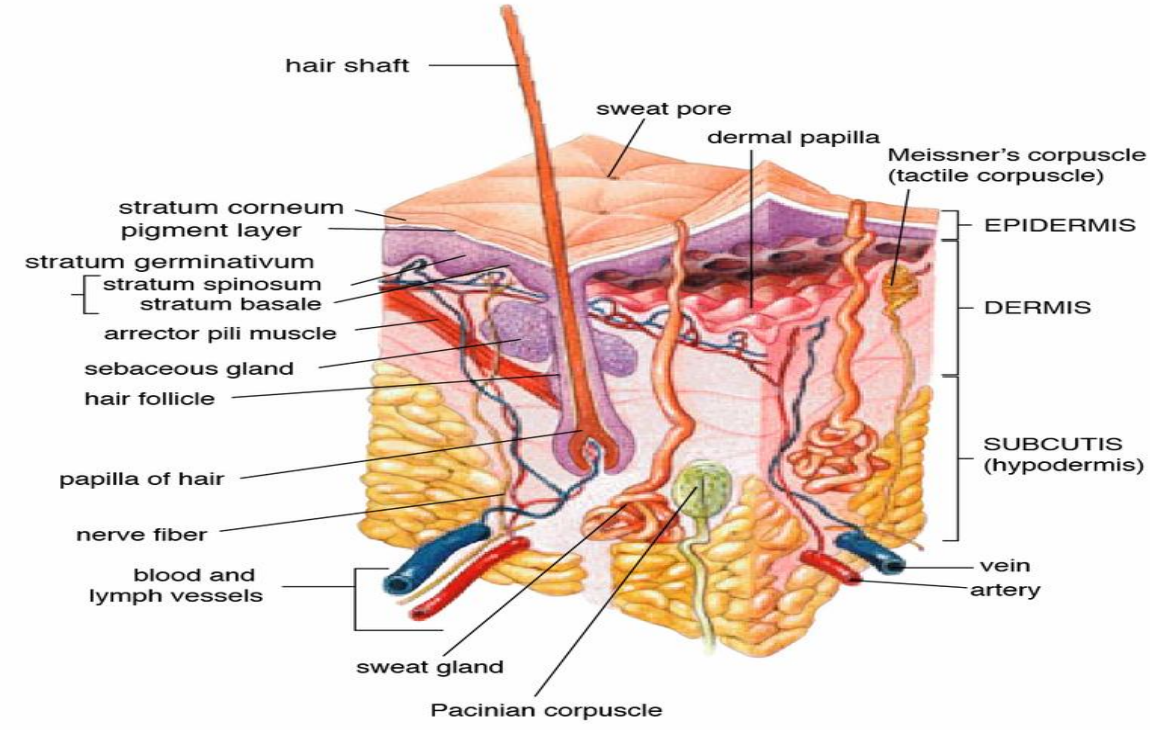

Figure1: Anatomy of Skin

ADVANTAGES:

- Stable and controlled blood level
- Long duration of action (ranging from few hours to one week)
- Suitable for administration of drugs having :

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1. Very short half life example : nitro-glycerine
2. Narrow therapeutic window
3. Poor oral availability

- Drug action can be terminated
- Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets.
- First pass metabolism, an additional limitation to oral drug delivery can be avoided with transdermal administration.

DISADVANTAGES:

- Possibility of local irritation at the site of application.
- Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the
- patch formulation.
- May cause allergic reactions.
- A molecular weight less than 500 Da is essential.
- Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeateto transverse SC and underlying aqueous layers.

II.TYPES OF TRANSDERMAL PATCHES

A). SINGLE-LAYER DRUG-IN-ADHESIVE:

The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

B). THE MULTI-LAYER DRUG-IN ADHESIVE

Patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir[7]. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane(but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

C). RESEVOIR

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

D). MATRIX

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it also known as a monolithic device[8].

E). VAPOUR PATCH

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and is used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market[9].

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III.METHOD OF PREPARATION OF TDDS

A). MEMBRANE MODERATED SYSTEMS

In this drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium e.g. silicon fluid[10]. The rate controlling membrane can be microporous or nonporous polymeric membrane e.g. ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with skin surface. Marketed systems: Transderm-Nitro system for once a day; Transderm-Scop system- 3 days medication; Catapres- TTS – for weekly treatment[11].

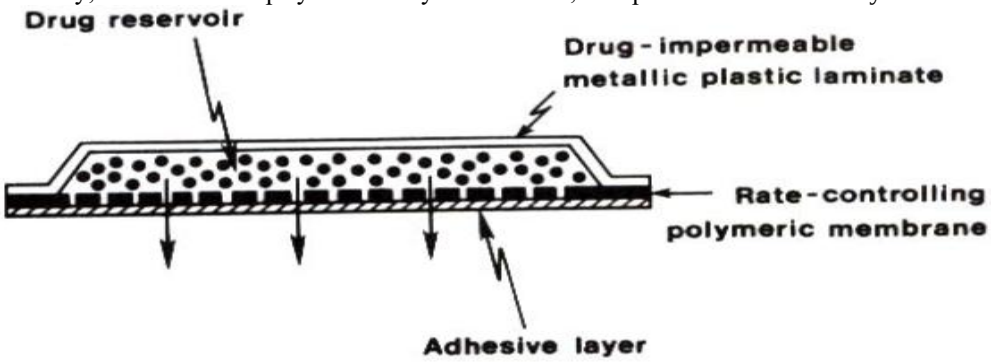

Figure2: Representation of membrane moderated system

B). ADHESIVE DIFFUSION CONTROLLED SYSTEM

It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer[12]. On the top of the reservoir layer, layers of non-medicated rate controlling adhesive polymer of constant thickness are applied. Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion [13].

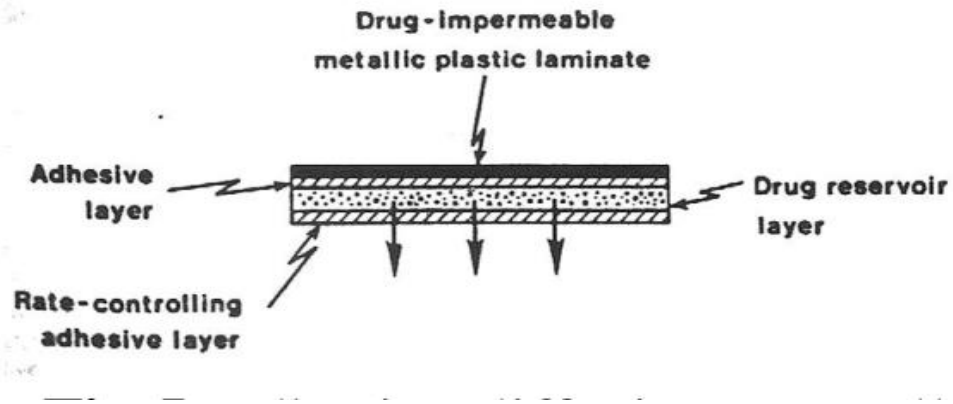

Figure3: Representation of adhesive diffusion control system

C). MATRIX DISPERSION

Here the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and medicated polymer is then molded into disc with defined area and thickness. This is glued on to an

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occlusive base plate on the surface of the disc, the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc [14].

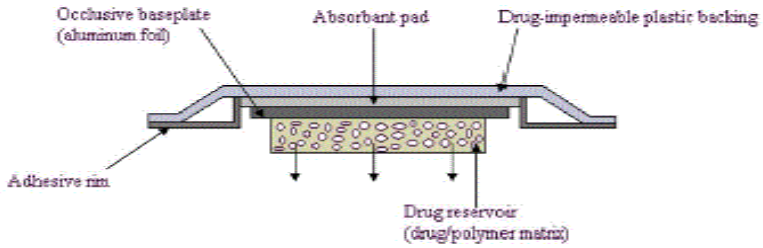

Figure4: Representation of matrix dispersion

D). MICRORESERVOIR SYSTEM

These are considered as combination of reservoir and matrix dispersion type. In this the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogenously in lipophilic polymer, by high shear mechanical force to form unleachable microscopic spheres of drug reservoir. This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness [15].

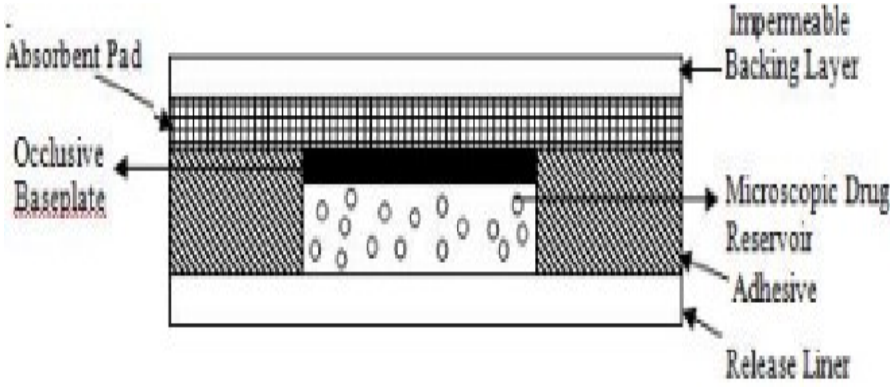

Figure5: Representation of microreservoir system

IV. EVALUATION PARAMETERS

A). THICKNESS OF THE PATCH

The thickness of the drug loaded patch is measured in different points by using digitalmicrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by travelingmicroscope dial gauge, screw gauge or Micrometer at different points of the film.

B). WEIGHT UNIFORMITY

The prepared patches are dried at 60°c 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 [16].

C). FOLDING ENDURANCE

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance [17].

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D).PERCENTAGE MOISTURE CONTENT

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to bereweighed and determine the percentage moisture content from the below mentioned formula as

% Moisture content = Initial weight – Final weight X 100 Final weight.

E). CONTENT UNIFORMITY TEST

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%.

F). MOISTURE UPTAKE

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as

% moisture uptake = Final weight – Initial weight X 100 Initial weight.

G). DRUG CONTENT

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples [18].

H). SHEAR ADHESION TEST VAPOUR PATCH

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by themolecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto 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.

I). PEEL ADHESION TEST

In this test, the force required to remove an adhesive coating form 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 180º angle, and the force required for tape removed is measured [19].

J). WATER VAPOR TRANSMISSION STUDIES (WVT)

For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated. WVT = W/ ST W is the increase in weight in 24 h; S is area of film exposed (cm2); T is exposure time.

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K). ROLLING BALL TACK TEST

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rollsdown and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch [20].

L). QUICK STICK (PEEL-TACK) TEST

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

M). PROBE TACK TEST

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams [21].

N). *IN VITRO* DRUG RELEASE STUDIES

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

O). *IN VITRO* SKIN PERMEATION STUDIES

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is 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 is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed 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 (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load [22].

P). SKIN IRRITATION STUDY

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

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Q). STABILITY STUDIES

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content [23].

V.CONCLUSION

Transdermal drug delivery systems have been used as safe and effective drug delivery devices since 1981. A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact wit h and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity. This article provides valuable information regarding the transdermal drug delivery systems and its evaluation process in details.

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