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APPROACHES AND EVALUATIONS OF TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. The success of Transdermal therapeutic system has created much interest in the pharmaceutical industry and has activated research activities related to it. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance. Drug delivery with Transdermal patch systems exhibit slow, controlled drug release and absorption. The plasma drug concentration does not vary significantly over time. Transdermal delivery system is a growing market that is expected to expand in the near future with the discovery of new drug treatment applications and technologies. The biomaterials research field has broadened in the last 3 decades including drug delivery systems, immunological kits and biosensors. Extensive efforts have been focused on placing a drug delivery system in a particular region of the body for maximizing drug availability and minimizing the dose dependent side effects. Apart from the development of oral controlled release formulations, Transdermal drug delivery systems using thin polymeric membranes have been widely studied. Treatment of chronic diseases such as asthma and rheumatoid arthritis by Transdermal route of drug administration might prove to have several advantages over other routes of drug administration. Plasticization of the membranes can be achieved by blending the polymer with another polymer, by crosslinking or by both crosslinking and blending. The advantages of such polymers are not only to create additional free space to accommodate the drug, but also that these systems are biocompatible.

KEYWORDS: Transdermal Drug Delivery System (TDDS), Skin barriers, predetermined rate.

INTRODUCTION

Transdermal therapeutic system are defined as self contained, discrete dosage form which when applied to intact skin deliver the drug through the intact skin at a control rate to the systemic circulation and maintain the drug concentration within the therapeutic window for prolonged period of time. Recently, the use of transdermal patches for pharmaceuticals is limited because only a few drugs has proven to be effectively delivered through skin. in order to achieve the objective of systemic medication through topical application to the intact skin surface. They were exemplifies first with the development of a scopolamine-releasing TDD system (Transderm-scop) for 72 hrs for prophylaxis or treatment of motion-induced nausea, then by the successful marketing of nitroglycrine-releasing TDD system (Deponit, Nitrodisc, nitro-dur, transderm-nitro). Transdermal patch uses a special membrane to control the release rate at which the liquid drug contained patch reservoir can pass through the skin and itno the blood stream. Transdermal delivery not only provide controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half lives, and eliminates pulsed delivery into systemic circulation which is responsible for undesirable side effects.[1]

Advantages[2,3]

- Transdermal medication delivers a steady infusion of the drug over prolonged period of time therefore avoiding adverse side effects and therapeutic failure frequently associated with intermittent dosing can also be avoided.
- Alternative route of administration for the patients who cannot tolerate oral dosage forms such as vomiting patient.
- Increases therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption and drug interaction with food, drink and other administered drugs.
- Avoidance of first pass metabolism because it by passes the liver.

- Simplified regimen leads to improved patient compliance and reduced inter and intra-patient variability.
- Self administration is possible and they are non invasive, avoiding the inconvenience of Parenteral therapy.
- Drug input can be terminated at any point of time by removing the transdermal patch.
- They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings. At the same time transdermal drug delivery has few disadvantages that are limiting the use transdermal delivery.

Disadvantages[2,3]

- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels
- The use of transdermal delivery may be un economical.

For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

Anatomy and physiology of skin[1]

Skin is one of the most extensive organ of the body covering an area of about $2m^2$ on in an average human adult. This multilayerd organ receives approximately one third of all blood circulating through the body. With thickness of only a millimeter, the skin separates the underlying blood circulation network from outside environment. 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.

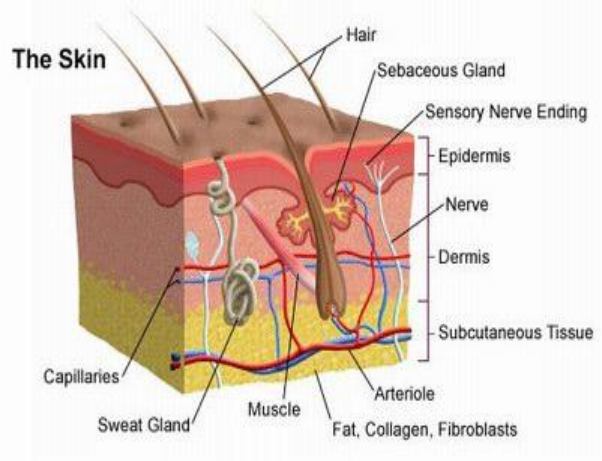


Fig. 1: Anatomy of the Skin.

Epidermis: it results from an active epithelial basal cell population and is approximately 150 micrometer thick. It is the outermost layer of skin and process of differentiation results in migrationof cells from basal layer towards the skin surface. The end result of this process is the formation of a thin, stratified and extremely resilient layer (the stratum corneum) at the skin surface.

Stratum corneum: This is the outermost layer of skin, also called horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

Viable epidermis: This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms.

Dermis: electron microscopic examination shows that the dermis is made up of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross striations. It is about 3 to 5 mm and contains the blood vessels, lymph vessels, and nerves. It also provide oxygen and nutrients to the skin while removing toxins and waste products.

Hypodermis: The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layersis desired.

Route of Permeation of Skin[2,3]

The diffusant (drug) has two potential entry routes to the blood vasculature; through the epidermis itself or diffusion through shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts. Therefore, there are two major routes of penetration.

Transcorneal penetration

Intra cellular penetration[4]: Drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

Intercellular penetration[5]

Non-polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

Transappendegeal penetration

This is also called as the shunt pathway. In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands. The transappendegeal pathway is considered to be of minor importance because of it's relatively. Smaller area (less than 0.1% of total surface). However this route may be of some importance for large polar compounds. The route through which permeation occurs is largely dependent on physico-chemical characteristics of penetrant, most importantantly being the relative ability to partition into each skin phase.

The transdermal permeation can be visualized as composite of a series in sequence as

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, the various skin tissue layers can be represented by a simple multilayer model.

Kinetics of transdermal permeation[2]

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic system. Transdermal permeation involves following steps

- Sorption by stratum corneum.
- Penetration of drug through viable epidermis.
- Uptake of the drug by capillary network in dermal papillary layer.

This permeation is possible only if drug posses certain physicochemical properties. The rate of permeation across the skin (dQ/dt) is given by

$$\frac{dQ}{dt} = P2\ (\text{Cd-Cr}) \rightarrow \qquad (1)$$

Where Cd and Cr are the concentrations of the skin penetrant in the donor compartment (e.g, on the surface of stratum corneum) and in the receptor compartment (e.g, body) respectively Ps is the overall permeability coefficient of the skin tissue to the penetrant and is given by

$$P_{SS} = \frac{ks}{ks} \times Dss$$

Where K_{ss} the partition coefficient for the interfacial partitioning of the penetrant molecule form a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady state diffusion of the molecule through a thickness hs of the skin tissue. As the ks, Dss, hs are constant under given condition, the permeability coefficient (ps) for a skin penetrant can be considered to be a constant. Now it is clear that a constant rate of drug permeation can be obtained only when Cd>>Cr i.e, the drug concentration at the stratum corneum (Cd) is consistently greater than the concentration in the body (Cr), then equation one becomes.

The rate of skin permeation (dQ/dt) is constant provided the magnitude of Cd remains fairly constant throughout the course of skin permeation. the drug should be released from the device at a rate (Rr) that is either constant or greater than the rate of skin uptake (Ra) i.e., Rr>> Ra Since, Rris greater than Ra, the drug concentration on the skin surface (Cd) is maintained at a level equal to or greater than the equilibrium (or saturation) solubility of the drug in stratum corneum (Cs) i.e., Cd>> Cs. therefore maximum rate of skin permeation[(dQ/dt)m] is given by equation dQ/dt)m=Ps×Cs

From the above equation, it can be seen that the maximum rate of skin permeation depends on the skin permeability coefficient (Ps) and its equilibrium solubility in the stratum corneum (Cs). Thus skin permeation appears to be stratum corneum limited.

Basic Components of Transdermal Drug Delivery Systems[2]

- Polymer matrix or matrices.
- The Drug.
- Permeation enhancers.
- Other excipients.

Polymer matrix[1,2,20]

Advances in transdermal drug delivery technology have been rapid because of the sophistication of polymer science that now allows incorporation of polymers in transdermal system (TDS) in adequate quantity. The release rate from TDS can be tailored by varying polymer composition. Selection of polymeric membrane is very important in designing a variety of membrane permeation controlled TDS. The following criteria should be satisfied for a polymer to be used in a transdermal system.

• Molecular weight, glass transition temperature and chemical functionality of polymer should be such that the specific drug diffuses properly and gets released through it.
• Polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product and inexpensive.
• Polymer and its degradation product must be non-toxic or non-antagonistic to the host.
The mechanical properties of the drug the polymer should not deteriorate excessively when large amount of active agents are incorporated into it.

Polymer useful for transdermal devices.

S. No	Polymer	Category	Role
1	Gelatin	Natural	Base, adhesive
2	Na-alginate	Natural	Base, adhesive
3	Gum Arabic	Natural	Base, adhesive
4	Gum tragacanth	Natural	Base, adhesive
5	Carmellose	Semi synthetic	Base, adhesive
6	Methyl and ethyl cellulose	Semi synthetic	Base, adhesive
7	Hydroxy propyl cellulose	Semi synthetic	Base, adhesive
8	Polyvinyl alcohol	synthetic	Base, adhesive
9	Polyethylene	synthetic	Liner, backing
10	Polypropylene	synthetic	Membrane,backing
11	Polyvinyl chloride	synthetic	Base, adhesive
12	Ethylene vinyl acetate	synthetic	membrane
13	Polystyrene	synthetic	Co-adhesive

Drug[1]: For successfully developing the transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of drug for transdermal drug delivery.

Physicochemical properties
1. The drug should have a molecular weight less than approximately 1000 Daltons.
2. The drug should have affinity for both- lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin.
3. The drug should have a low melting point usually below 200 ^{0}c.
4. Since the skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin. However for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.

Biological properties
1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half life t½ of the drug should be short.
3. The drug should be non-irritating and non allergic.
4. Drugs which degrade in the gastro intestinal (GI) tract or inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.

Permeation enhancers[2]: These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

$$I = D \times \frac{dc}{dx}$$

Where D is the diffusion coefficient and is a function of size, shape and flixibilty of the diffusing molecule as well as the membrane resistance, c is the concentration of the diffusing molecule and x is the spatial coordinate.
- Thus enhancement of flux across membranes reduces to considerations of.
- Thermodynamics(lattice energies, distribution coefficient)
- Molecular size and shape.
- Reducing the energy required to make a molecular hole in the membrane

Permeation enhancer are hypothesized to affect structure of proteins and lipids therefore altering the barrier energy to hole formation.

Chemical approach[3,6]
This includes
(a) Synthesis of lipophilic analogs.
(b) Delipidization of stratum corneum.
(c) Co-administration of skin permeation enhancers.

This chemical approach can further be classified according to their chemical class.
(i) Sulfoxides: Dimethyl sulfoxide, decylmethal sufoxide.
(ii) Alcohols: Ethanol.
(iii) Polyols: Propylene glycol.
(iv) Alkenes: Long chain alkanes (C7-C16).
(v) Fatty acids: oleic acid.
(vi) Esters: Isopropyl myristate.
(vii) Amines and amides: Urea, dimethyl acetamide, dimethyl formamide.
(viii) Pyrrilidones: N-methylpyrrilidone, azones.
(ix) Terpenes: Eugenol.
(x) Surface active agents: Cationic surfactants.
(xi) Cyclodextrines.

Biochemical approach
This includes
(a) Synthesis of bio-convertible pro-drugs and.
(b) Co-administration of skin metabolism inhibitors.

Physical approach
This includes
(a) Iontophoresis.
(b) Sonophoresis: Ultrasonic energy.
(c) Thermal energy.
(d) Stripping of stratum corneum and.
(e) Hydration of stratum corneum.

Adhesive layer[7,8,9]: The adhesive must posses' sufficient property so as to firmly secure the system to the skin surface and to maintain it in position for as long as desired, even in the presence of water. After removal of patch, any traces of adhesive left behind must be capable of being washed with water and soap. Pressure sensitive adhesives are used to achieve contact between the transdermal patch and the skin. Adhesion is understood to be the net effect of three phenomenon's namely.
1. Peel: The resistance against the breakage of the adhesive bond.
2. Track: The ability of a polymer to adhere to a substrate with little contact Pressure and.
3. Creep: The viscous relaxation of the adhesive bond upon shear.
The ideal characters of adhesive materials are (Qvist et al., 2002).
1. High biocompatibility (low irritancy, toxicity, allergic reaction etc.).
2. Good adhesive to oily, wet, wrinkled and hairy skin.
3. Good environment resistance against water and humidity.
4. Easy to remove from the skin.
5. High permeability of moisture to avoid excessive occlusion and for the drug itself and.
6. Non-reactive towards drug. There are three types of adhesive used mainly (Qvist et al., 2002; Govil et al., 1993).
1. Silicone type adhesive.
2. Polyisobutylene adhesive and.
3. Polyacrylate based adhesive.

Backing layer[8]: The backing layer must be impermeable to drug and permeation enhancers. The backing membrane serves the purpose of holding the entire system together and at the same time protects the drug reservoir from exposure to the atmosphere, which could result in the breakage or loss of the drug by volatilization. The most commonly used backing materials are polyester, aluminized polyethylene terapthalate, siliconised polyethylene.

Release liner: The peel strip prevents the loss of the drug that has migrated into the adhesive layer during storage and protects the finished device against contamination. Polyesters foils and other metalized laminates are typical materials which are commonly used.

Ideal properties of transdermal drug delivery system
• Shelf life should be up to 2.5 years
• Patch size should be less than 40 cm^2
• Dose frequency once a daily-once a week
• Should be clear or white color
• Should be non-irritating to the skin
• Release properties- should have consistent pharmacokinetic and pharmacodynamic profile over the Time.

Types of transdermal drug delivery system[1]
Polymer membrane permeation controlled TDD system: Drug reservoir sandwiched between drugs impermeable backing laminate and rate controlling polymeric membrane. In drug reservoir compartment drug is dispersed homogeneously in a solid polymeric matrix (e.g. poly isobutylene), suspended in a unleachable viscous liquid medium (e.g. silicon fluid) to form a paste like suspension. Rate controlling membrane is either a microporous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer.

Example of this type of patch are Estraderm (twice a week in treatment of postmenopausal syndrome) and Duragesic (management of chronic pain for 72 hrs).

Polymer Matrix Diffusion Controlled Systems[6]
The drug is prepared by homogeniously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded in to a medicated disc with a defined surface area and controlled thickness. The drug reservoir containing polymer disc is then pasted on to a occlusive base plate in a compartment fabricated from a drug impermeable plastic backing .Ex. Nitroglycerin TDDS for angina pectoris. Q/t1/2=[(2A-CP)Cp Dp] 1/2 A=initial drug loading dose dispersed in the polymer matrix Cp&Dp =solubility and diffusivity of the drug in the polymer respectively Advantage; absence of dose dumping due to polymer cannot rupture.

Drug reservoir gradient controlled TDD system
To overcome nonzero order drug release profile from polymer matrix TDD system can be modified to have drug loading level varied in incremental manner forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layer. e.g. Deponit system.

Microreservoir dissolution controlled TDD system
Considered as the hybrid system of reservoir and matrix dispersion type drug delivery. In this system **the** drug reservoir is formed by first suspending the drug solids in aqueous solution of water-miscible drug solubilser e.g. polyethylene glycol and then homogeneously dispersing the drug suspension with controlled aqueous soluble lipophillic polymer by high shear mechanical force to form thousands of unleachable microscopic drug reservoir.

Recent Technology Used in Transdermal Drug Delivery System
Iontophoresis: This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent19, 20. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro - repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro- pertubation (for both charged and uncharged). Several iontophoretic systems are currently under commercial development including the Phoresor device developed by Iomed Inc. and the Vyteris and E-TRANS devices developed by Alza Corp.

Electroporation[7]
This method involves the application of high voltage pulses to the skin which has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect permeation rate include pulse properties such as waveform, rate and number. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7kDA.[23]

Microneedle-based Devices
The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug. The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the drug on the microprojection array24, the latter being better for intracutaneous immunization.

Abrasion: The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyper pigmentation and other skin blemishes.

Needle-less Injection[8]
This is reported to involve a pain-free method of administering drugs to the skin. Over the years, there have been numerous examples of both liquid (Ped-O-Jet, Iject, Biojector2000, Medi-jector and Intraject) and powder (PMED device formerly known as Powderject injector) systems. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin. of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. The SonoPrep device (Sontra Medical Corp.) uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability. This battery-operated, handheld device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrod.

Laser Radiation[9]
This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

Iontophoretic Drug Delivery System
"Iontophoresis can be defined as the permeation of ionized drug molecules across biological membranes under the influence of electrical current." Iontophoresis implies the use of small amount of physiologically acceptable electric current to drive ionic (charged) drugs into body by using an electrode of the same polarity as the charge on the drug; the drug is driven into the skin mainly by electrostatic repulsion. The technique has been observed to enhance the transdermal permeation of ionic drugs several folds and this proposed to expand the horizon of transdermal control drug delivery for systemic medication. Beside the usual benefit of transdermal drug delivery, iontophoresis present a unique opportunity to provide programmed drug delivery. This is because the permeation rate is proportional to the current density, which can be readily adjusted. Such dependence on current may also make drug absorption via iontophoresis less dependent on biological variables.

Microporation
Microporation involves the use of microneedles that are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. Microneedles

are needles that are 10 to 200 µm in height and 10 to 50 µm in width. Microneedles do not stimulate the nerves, so the patient does not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles.

Needleless injection: Needleless injection involves a pain-free method of administration of drugs to the skin. This **technique** involves firing the liquid or solid particles at supersonic speeds through the stratum **corneum**. Problems with this technique include the high developmental cost for both the device and dosage form and the inability to program or control drug delivery to compensate for intersubject differences in skin permeability. Needleless injection - Mechanism The mechanism involves forcing compressed gas such as helium or nitrogen through the nozzle with the resultant drug particles entrained within the jet flow, reportedly traveling at sufficient velocity for skin penetration.

Evaluation parameters

Thickness of the patch[4,11]: The thickness of the drug loaded patch is measured in different points by using a digital micrometer 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 travelling microscope dial gauge, screw gauge or micrometer at different points of the film.

Weight uniformity[11]: 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.

Folding endurance[12]: 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.

Percentage Moisture content[10,11]: 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 be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\%\ moisture\ content = \frac{initial\ weight - final\ weight}{final\ weight} \times 100$$

Content uniformity test[4,13]: 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%, then the transdermal patches pass the test.

Moisture Uptake[14]: 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 given below.

$$\%of\ moisture\ uptake = \frac{final\ weight - initial\ weight}{initial\ weight} \times 100$$

Drug content[4,15]: 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.

Shear Adhesion test[15]: 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 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.

Peel Adhesion test[16]: 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.

Water vapor transmission studies (WVT)[17]: 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.

$$WVT = \frac{W}{ST}$$

W is the increase in weight in 24 hr, S is area of film exposed (cm^2), T is the exposure time.

Rolling ball tack test[18]: This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

Quick Stick (peel-tack) test[19]: 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.

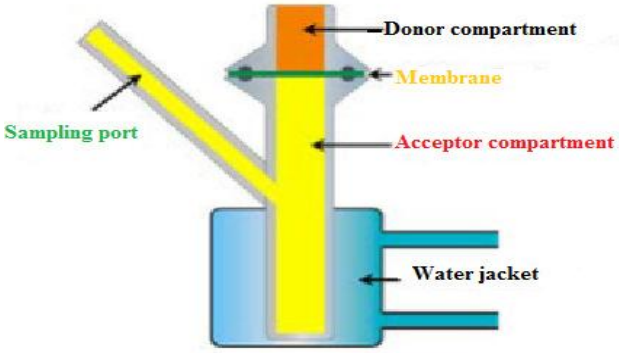
Probe Tack test5[20]: In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

In vitro drug release studies6[21]

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 500mL 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.

In vitro skin permeation studies[22]

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 (mg cm-2).



Tran's diffusion cell

Skin Irritation study[23]**:** Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

Stability studies[23]**:** 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.

CONCLUSION

Due to recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin, membrane transdermal route is effective. The transdermal durg delivery system has been designed as an alternative, safest, and easy route for systemic drug delivery. It has been used as safe and effective drug delivery devices since 1981. 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. Transdermal drug therapy will revolutionalize the concept of "dose" of drug to be administered. No longer will physicians prescribe a certain "dose" of a drug, but

will prescribe drugs to be given at a certain "rate". Transdermal systems will be designed to give variable rates with variable areas thus TDDS may be very usefull in the treatment of chronic disorders such as hypertension, diabetes mellitus and many more.

REFERENCES

1. Novel drug Delivery system, Second Edition, Revised and Expanded, Yie W. Chien, 301-380.
2. Controlled and Novel Drug Delivery, N.K.JAIN, 100-129.
3. Barry B. Transdermal drug delivery, In edition: Aulton M.E, Pharmaceutics: the science of dosage form design, churhcill Livingston, 2002; 499-533.
4. Keleb E, Sharma Rk, Mosa EB,. Transdermal drug delivery system-design and evaluation. International journal of advances in pharmaceutical Sciences, 2010; 1: 201-211.
5. Baichwal MR. Polymer films as drug delivery system, advances in drug delivery system. Bombay, MSR foundation, 1985; 136-147.
6. Guy RH. Current status and future prospects of transdermal drug delivery, Pharm Res., 1996; 13: 1765-1769.
7. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism, Xonobiotica, 1987; 7: 325-343.
8. Chein YW. Transdermal controlled systemic Medication. New York and Basel, Marcel Dekkar Inc., 1987; 159-176.
9. Aulton.M.E, Pharmaceutics; The science of dosage form design, second edition, Churchill Livingston, Harcourt publishers, 2002.
10. Jain N.K., Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi, 1997.
11. Wester RC, Noonan PK. Relevance of animal models for percutaneous absorption. Int J Pharm, 1980; 7: 99-110.
12. Lin RY, Hsu CW, Chein YW. A method to predict the transdermal permeability of amino acids and dipeptides through porcine skin. J Cont Rel., 1996: 38: 229-34.
13. Willams AC, Barry BW. "Penetration Enhancers," Adv. Drug Del. Rev., 2004; 56: 603-618.
14. Pellet M, Raghavan S.L, Hadgraft J and DavisA.F. "The application of supersaturated systems to percutaneous drug delivery" In: Guy R.H and Dekker, Inc., New York, 2003; 305-326.
15. Loyd v. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, eighth edition, wolter kluwer publishers, New Delhi, 2005.
16. Brown MB, Jones SA. Hyaluronic acid: a unique topical vehicle for localized drug delivery of drugs to the skin. JEDV, 2000; 19: 308-318.21.
17. Williams A.C and barry B. w., Penetration Enhancers, Adv. Drug delivery ststems, Rev., 2004; 56: 603-618.
18. Aarti N, Louk A.R.M.P, Russel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement invivo in humans. Jour. control. Release, 1995; 37: 299-306.
19. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: an overview. International Journal of Pharmaceutical Sciences Review and Research, 2010; 3(2): 49-54.
20. Allen LV, Popovich NG, Ansel HC. Pharmaceutical dosage form and drug delivery systems, seventh edition, Lippincott Williams and Wilkins, 2002; 263-278.
21. Lec S.T, Yac S.H, Kim S.W and Berner B. One way membrane for Transdermal drug delivery system optimization. Int. J Pharm, 1991; 77: 231-237.
22. Bagyalakshmi J, Vamsikrishna RP, Manavalan R, Ravi TK, Manna PK. Formulation development and invitro and invivo evaluation of membrane moderated transdermal systems of ampicilline sodium in ethanol: pH 4.7 buffer solvent system AAPS Pharm Sci Tec. 2007; 8: 7.
23. Ubaidulla U, Reddy MV, Ruckmani K, Ahmed FJ, Khar RK. Transdermal therapeutic system of carvediol: effect of hydrophilic and hydrophobic matrix on invitro and invivo characteristics, AAPS Pharm Sci Tech, 2007; 8(1): 2.