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TRANSDERMAL DRUG DELIVERY: A NOVEL APPROACH - A REVIEW

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ABSTRACT

Conventional indefinite quantity forms that need multidose medical aid have several issues and complications. Today regarding seventy four of medicine are taken orally and are found to not be as effective as desired. To improve such characters percutaneous drug delivery system was emerged. Drug delivery through the skin to attain a general result of a drug is usually referred to as percutaneous drug delivery and differs from ancient topical drug delivery. Transdermal drug delivery systems (TDDS) are indefinite quantity forms involves drug transport to viable stratum and or dermal tissues of the skin for native therapeutic result whereas an awfully major fraction of drug is transported into the general blood circulation. The adhesive of the percutaneous drug delivery system is essential to the security, efficaciousness and quality of the merchandise. Topical administration of therapeutic agents offers several benefits over standard oral and invasive ways of drug delivery. Several vital benefits of percutaneous drug delivery limitation of viscous initial pass metabolism, sweetening of therapeutic potency and maintenance of steady plasma level of the drug. This article provides an outline of sorts of percutaneous patches, ways of preparation and its chemistry ways of analysis.

KEYWORDS

TDDS, Topical drug delivery and Systemic blood circulation.

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INTRODUCTION

The transdermic route has become one in every of the foremost booming and innovative drug delivery system for analysis in pharmaceutical sciences. Transdermic drug delivery provides a number one edge over inject able and oral routes by increasing patient compliance and avoiding 1st pass metabolism respectively[1]. Transdermic drug delivery isn't solely provides controlled, constant administration of the drug, but additionally permits continuous input of medicine with short biological

half-lives and eliminates periodical entry into circulation. The success of medical specialty drug to be used for general drug delivery depends on ability of the drug to penetrate through skin in adequate quantities to realize the specified therapeutic effect[2]. Oral route is that the in style route of drug delivery. Though it's some disadvantages together with 1st pass metabolism, drug degradation in alimentary canal thanks to enzymes, pH etc. To cross these issues, a completely unique drug delivery system was developed. During this transdermic delivery system medicated adhesive patches area unit ready that deliver therapeutically effective quantity of drug across the skin once it placed on skin. Medicated adhesive patches or transdermic patches area unit of various sizes, having quite one ingredient. Once they apply on unbroken skin they deliver active ingredients into circulation passing via skin barriers. A patch containing high dose of drug within that is maintained on the skin for prolonged amount of your time, that get enters into blood flow via diffusion method. Drug will penetrate through skin via 3 pathways-through hair follicles through sebaceous glands, through ductule. Transdermic drug delivery systems area unit utilized in numerous skin disorders, additionally within the management of heart condition, pains, smoking surcease disorders like Parkinson's illness[3,4]. Nowadays, the foremost common kind of delivery of medicine is that the oral route. whereas this has the notable advantage of straightforward administration, it additionally has vital drawbacks - specifically poor bioavailability thanks to viscous metabolism (first pass) and therefore the tendency to supply speedy blood level spikes (both high and low), resulting in a necessity for top and/or frequent dosing, which might be each price prohibitory and inconvenient[5]. To beat these difficulties there's a necessity for the event of recent drug delivery system; which can improve the therapeutic effectualness and safety of medicine by a lot of precise (i.e. website specific), special and temporal placement inside the body thereby reducing each the scale and variety of doses. New drug delivery system are essential for the delivery of novel, genetically built prescription drugs (i.e. peptides, proteins) to their website of action, while not acquisition vital immunogenicity or biological inactivation. Transdermic drug delivery is outlined as self-contained, separate dose forms that, once applied to the intact skin, deliver the drug, through the skin at controlled rate to the circulation. Transdermic drug delivery system and #40; TDDS and #41; established itself as associate degree integral a part of novel drug delivery systems[6]. These days regarding seventy four of medicine area unit taken orally and area unit found to not be as valuable as darling. To advance such characters transdermic drug delivery system was emerged. With the creation of current time of pharmaceutical dose forms, transdermic drug delivery system and #40; TDDS and #41; recognized itself as a crucial a part of novel drug delivery systems. Transdermic dose forms, still an expensive different to traditional formulations, have become in style attributable to their exclusive blessings. Improved bioavailability, Controlled absorption, additional uniform plasma levels, painless and reduced facet effects straightforward application and suppleness of terminating drug administration by merely removing the patch to the skin area unit a number of the potential blessings of transdermic drug delivery[7]. Oral standard dose forms like tablets and capsules area unit most generally used drug delivery system however each dose forms face downside of stomach drug/enzyme instability 1st pass metabolism. Oral route has several more issues like unpleasant style, odor and color. Numerous extra issues area unit arising throughout taking pills; thence issues area unit being visage throughout treatment. Generally Patients become non-compliant. TDDS patches medication area unit utilized by continuous unleash in order that they show their impact for actual period and skin patch is nonirritating and noninvasive technique. It's enticing different techniques over conservative techniques for general administration of drug[8].

Transdermal patch (Skin patch) uses a special membrane to manage the speed at that the liquid drug contained within the reservoir inside the patch

will experience the skin and into the Bloodstream. Some medication should be combined with substances, like alcohol, that increase their ability to penetrate the skin so as to be employed in a pad. Drugs administered through skin patches embrace hyoscine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and Lidocaine to relieve the pain of shingles (herpes zoster). Molecules of hormone and plenty of alternative substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the necessity for tube-shaped structure access by syringe or the employment of pumps. Transdermal patches were developed within the Seventies and also the initial was approved by the government agency in 1979 for the treatment of ailment[9,10]. It was a three-day patch that delivered scopolamine. In 1981, patches for vasodilator were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, Lidocaine, nicotine, nitroglycerin, estradiol, oxybutynin, scopolamine, and testosterone. There are combination patches for family planning, as well as hormone replacement[11,12]. Depending on the drug, the patches generally last from one to seven days. The major blessings provided by transdermic drug delivery embrace the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved medical care thanks to maintenance of plasma levels up to the top of the dosing interval compared to a decline in plasma levels with standard oral indefinite quantity forms. Transdermal patches are helpful in developing new applications for existing medicine and for reducing first-pass drug-degradation effects. Patches also can cut back aspect effects; as an example, oestrogen patches area unit utilized by over 1,000,000 patients annually and, in distinction to oral formulations, don't cause liver injury. of two major sub-categories - therapeutic and cosmetic), aroma patches, weight loss patches, and Non medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure[13,14]. Transdermal drug delivery system and #40, TDDS and #41; provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy[15]. The principal of transdermal drug transport is to deliver drug across epidermis to achieve systemic effect over a prolonged period of time[16]. The human skin is a readily accessible surface for drug delivery. Skin of a median material body covers a surface of roughly two money supply and receives concerning common fraction of the blood current through the body. Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The human skin surface is thought to contain a median, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one in all the foremost pronto accessible organs of the chassis. There is right smart interest within the skin as a website of drug application each for native and systemic impact[17]. A perfect indefinite quantity type would be maintaining the drug concentration within the blood at a relentless level nearly coinciding with the minimum effective concentration (MEC) of drug throughout the treatment period. This ends up in the conception of the controlled drug delivery. The primary objective of controlled drug delivery is to confirm safety and effectivity of the medication still as patients compliance. TDDS is one in all the systems lying below the class of controlled drug delivery, in which the aim is to deliver the drug through skin in a predetermined and controlled rate[18]. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders and these show local action but occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin this idea cause the birth of TDDS. Moreover, it over comes numerous aspect effects like painful delivery of the medication and also the initial pass metabolism of the drug occurred by alternative suggests that of

drug delivery systems. TDDS has been an excellent field of interest in recent times. Many drugs which can be injected directly into the blood stream via skin have been formulated by TDDS[19]. Transdermal drug delivery system is convenient route for the delivery of drugs having short biological half-life. Transdermal drug delivery is based on absorption of drugs into the skin after topical application. Transdermal patches are pharmaceutical preparation of varying sizes containing one or more active ingredients that when applied to skin deliver drug directly into systemic circulation after passing through skin barrier[20]. Transdermal drug delivery is a viable administration route for potent, low molecular weight therapeutic agents which cannot withstand the hostile environment of the gastro-intestinal tract and /or are subject to considerable first pass metabolism by the liver. It uses the skin as an alternate route for the delivery of systemically acting medication. Dermal drug delivery is that the topical application of medicine to the skin within the treatment of skin diseases, wherein high concentrations of drugs can be localized at the site of action, thereby reducing the systemic drug levels and side effects[21-23]. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is that the vital website of drug application for each the native and general effects. For effective transdermic drug delivery system, the medication area unit simply ready to penetrate the skin and simply reach the target website. TDDS increase the patient compliance and reduces the load as compared to oral route[24]. Transdermal drug delivery systems have evolved as a successful alternative to systemic drug delivery[25]. It is a new approach to provide prolonged action of the drug with low toxicity and better patient compliances and thus reduces the side effects caused by oral route[26].

Advantages of transdermal drug delivery system

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivering drug across skin to achieve systemic effect are,

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. Predictable and extended duration of activity.
4. Minimizing undesirable side effect.
5. Provides utilization of drug with short biological half-life, narrow therapeutic window.
6. Avoiding the fluctuation in drug level.
7. Maintain plasma concentration of potent drug.
8. Termination of therapy is easy at any point of time.
9. Greater patient compliances due to elimination of multiple dosing profile.
10. Ability to deliver the drug more selectively to a specific site.
11. Provide suitability for self-administration.
12. Enhance therapeutic efficacy.

Disadvantages of transdermal drug delivery system

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age[27].

Anatomy and physiology of skin

The skin is one in all the foremost in depth organs of the shape covering a region of regarding 2m2 in a

median human adult. This multilayered organ receives approximately one third of all blood circulating through the body[18]. Human skin comprises of three distinct but mutually dependent tissues.

A. The stratified, vascular, cellular epidermis
B. Underlying dermis of connective tissues
C. Subcutaneous layer or hypodermis

Each layer has its own function and own importance in maintaining the integrity of skin and thereby the whole body structure[19].

The more common pathway through the skin is via the intercellular route[28].

The stratified, vascular, cellular epidermis

The multilayered epidermis varies in thickness depending on the cell size and number of cell layers of epidermis, ranging from 0.8mm on palms and soles down to 0.06mm on the eyelids. Table No.1 gives thickness, water permeability and diffusivity of water through epidermis. It consists of outer stratum corneum and viable epidermis[17]. Epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards the skin surface. Below this layer are the other layers of the epidermis-the stratumlucidum, stratum granulosum, stratumspinosum and stratumgerminativum. Together, these other layers constitute the viable epidermis[18].

Stratum corneum[17]

This is the outermost layer of skin also called as horney layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called ascorneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of Horney layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar”.

Viable epidermis[17]

This is situated beneath the stratumcorneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface.

Dermis[17]

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It conjointly provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to among zero. 2millimetre of skin surface and supply sink conditions for most molecules penetrating the skin barrier.

Hypodermis[17]

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 mechanical protection. It carries principal blood vessels and nerves to skin and will contain sensory pressure organs. For transdermal drug delivery, drug needs to penetrate through of these 3 layers and reach into circulation whereas just in case of topical drug delivery solely penetration through horny layer is crucial and then retention of drug in skin layers is desired.

Stratum Corneum as Skin permeation Barrier

The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per sq. centimetre. Especially water soluble substances pass quicker through these ducts; still these ducts do not contribute abundant for skin permeation. Therefore most neutral molecules pass through horny layer by passive diffusion. Regional variation in water permeability of stratum corneum showed in Table No.1 and permeation of drug molecule through skin showed in Figure No.2.

Series of steps in sequence

1. Sorption of a penetrant molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis and finally reaches to dermis and then
3. The molecule is taken up into the microcirculation for systemic distribution. Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum[17].

Drug Penetration Pathways[19]

There are a unit critically 3 ways within which a drug molecule will cross the intact stratum corneum: via skin appendages (shunt routes); through the animate thing lipoid domains; or by a transcellular route (Figure No.3). A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

The appendageal route

Skin appendages offer a continual of things. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skin's surface area), therefore limiting the area available for direct contact of the applied drug formulation.

Transcellular route

Drugs coming into the skin via the transcellular route withstand corneocytes. Corneocytes containing extremely hydrate certain offer associate degree liquid setting from that hydrophilic medication can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps.

Intercellular route

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons:

Recalling the 'bricks and mortar' model of the stratum corneum, the inter-digitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route.

The intercellular domain is a region of alternating structured bilayers. Consequently, a drug should consecutive partition into and diffuse through recurrent liquid and lipide domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

Limitations of TDDS[31]

1. Limited skin permeability.
2. Restricted to potent drug.
3. Cannot use for large molecule (>500 Dalton)
4. Significant lag time.
5. Difficulty for adhesion.
6. The drug undergoes degradation in the skin.
7. Variation in absorption efficiency at different sites of skin.

FACTORS INFLUENCE TRANSDERMAL DRUG DELIVERY SYSTEM[32,33]

Physiochemical properties of drug

Size of drug molecule and molecular weight
Partition coefficient and solubility
Drug concentration
pH condition.

Formulation characteristics

Release rate of drug
Ingredients of formulation
Presence of permeation enhancer.

Physiological factors

Skin hydration
Temperature and pH
Diffusion coefficient
Drug concentration
Partition coefficient
Molecular size and shape.

Biological factors

Skin hydration
Skin age
Blood flow
Regional skin site.
Skin metabolism
Species difference.

Basic components of TDDS

Transdermal drug delivery systems square measure designed to support the passage of drug substance

from the surface of skin through its varied layers and into the circulation. There are two basic types of transdermal dosing system; those that control the rate of drug delivery to the skin and those that allow the skin to control the rate of drug absorption.

Polymer matrix[20,23,24]

The polymers play a serious role in transcutaneous drug delivery systems of medicine. The release of drug to the skin is controlled by drug free film called rate dominant membrane. Polymers are utilized in the matrix devices that during which within which} the drug is embedded in compound matrix which management the length of unleash of medicine. The polymers used for transdermal drug delivery system are categorising based on their sources as follows;

a) Natural and semi synthetic polymers: Carboxymethyl cellulose, cellulose acetate phthalate, ethyl cellulose, gelatin, methyl cellulose, starch, shellac, waxes natural rubber etc.
b) Synthetic elastomers: Polybutadiene, polysiloxane, acrylonitrile, butyl rubber, Neoprene, polyisoprene, ethylene-propylene-diene-terpolymer etc.
c) Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polystyrene polyester, polyacrylate, polymethylmethacrylate, polypropylene etc. The polymers should fulfil the following requirements;
d) Molecular weight, physical characteristics and chemical functionality of the polymer must allow the diffusion of the drug substances at desirable rate.
e) The polymer and its decomposed product should be nontoxic.
f) The polymer should be chemically non-toxic, nonreactive and it should be an inert drug carrier.
g) The polymer must be easy to manufacture and fabricate into the desired product. It ought to enable incorporation of enormous quantity of chemical agent.
h) The cost of the polymer should not be excessively high[34-36].

Drug

Judicious alternative of drug is vital within the undefeated development of a transcutaneous product. The vital drug properties that have an effect on its diffusion from device yet as across the skin embody mass, solubility, physical properties and melting point. The structure of the drug additionally affects the skin penetration. Diffusion of the drug in adequate quantity to supply a satisfactory therapeutic result is of prime importance. The following square measure a number of the fascinating properties of a drug for transcutaneous delivery. The drug should have molecular weight less than 1000 Daltons.

The drug should have affinity for both lipophilic and hydrophilic phases.

The drug should have a low melting point.

The half-life of drug should be short.

The drug must not induce a cutaneous or allergic response.

The drugs, which degrade in gastrointestinal tract or inactivated by hepatic first pass effect are suitable candidates for transdermal drug delivery system[34-36].

Adhesives

The adhesion of all transdermal devices to the skin in an essential requirement and it has so far been accomplished using a pressure sensitive polymeric adhesive. The types of adhesives commonly used in transdermal drug delivery system are

Rubber based adhesives: Natural gum (Karaya gum), olylisoprene, polybutene, and polyisobutelene.

Polyacrylic based adhesives: Ethyl acrylate, 2-ethylhexylacrylate, iso-octyl acrylate.

Polysiloxane based adhesives: Polydimethylsiloxane, polysilicate resins, sufloxane blends.

An adhesive system should fulfil the following requirements;

a) It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with skin.

b) It should adhere to the skin aggressively.
c) It should be easily removable without leaving a un washable residue.
d) It should be physically and chemically compatible with the drug, the excipients and enhancers.
e) It should not affect the permeation of the drug.
f) The adhesive property should not deteriorate as the drug, enhancers and excipients permeate into the adhesive[34-37].

Backing membrane

It provides protection from external factors during application period. The backing layer must be flexible and provide good bond to the drug reservoir-thereby preventing the drug from leaving the dosage form from the top and accept printing. They are usually impermeable to water vapours. The most commonly used backing materials are polyethylene terephthalate, metalized polypropylene, metallized plastic, pigmented polyester film etc[34-36].

Penetration enhancers

Penetration enhancers are molecules, which reversibly alter the barrier properties of the stratum corneum. They aid in the systemic delivery of drugs by allowing the drug to penetrate more readily to viable tissues. Penetration enhancer should have the following properties;

a) The material should be pharmacologically inert and should spread well on skin.
b) It should be non-toxic, non-irritant and have a low index of sensitization.
c) It should be odourless, tasteless and colourless. Its penetration enhancing action should be immediate and should have suitable duration of effect.
d) The enhancer should be chemically and physically compatible with a wide range of drugs and pharmaceutical adjuncts[34-36].

Release liner

Release liner is the part of primary packaging and prevents the loss of drug from the polymer matrix and prevents contamination of the patch from outside environment during storage and transport. It is peeled off at the time of use. Release liner may be occlusive (e.g. polyethylene, PVC) or non-occlusive (paper fabric). Polyester foil and metallic foil are also used for release liner[34-36].

Types of Transdermal Patches[30,39,11-13]

Single layer drug in adhesive

In this kind the adhesive layer contains the drug. The adhesive layer not solely serves to stick the varied layers along and conjointly liable for the cathartic the drug to the skin. The adhesive layer is encircled by a short lived liner and a backing.

Multi -layer drug in adhesive

This type is additionally almost like the one layer however it contains an immediate drug unharness layer and alternative layer are going to be a controlled unharness alongside the adhesive layer. The adhesive layer is liable for the cathartic of the drug. This patch conjointly encompasses a temporary liner-layer and a permanent backing.

Vapour patch

In this kind of patch the role of adhesive layer not solely serves to stick the varied layers along however conjointly is unharness vapour. The vapour patches square measure new the market, ordinarily used for cathartic of essential oils in decongestion. Various alternative varieties of vapor patches {are also square measure are offered within the market that are accustomed improve the standard of sleep and reduces the fag smoking conditions.

Reservoir system

In this system the drug reservoir is embedded between colorfast backing layer and a rate dominant membrane. The drug releases solely 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, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive compound is applied as outer surface chemical compound membrane that is compatible with drug.

Matrix system

Drug-in-adhesive system

In this kind the drug reservoir is made by dispersing the drug in AN adhesive compound and so spreading the medicated adhesive compound by

solvent casting or melting (in the case of hot-melt adhesives) on AN colorfast backing layer. On high of the reservoir, immediate adhesive compound layers square measure applied for cover purpose.

Matrix-dispersion system

In this kind the drug is distributed homogenously during a deliquescent or lipotropic compound matrix. This drug containing compound disk is mounted on to AN occlusive base plate during a compartment fancied from a drug rubber backing layer. Instead of applying the adhesive on the face of the drug reservoir, it's unfold alongside the circumference to create a strip of adhesive rim.

Micro reservoir system

In this kind the drug delivery system could be a combination of reservoir and matrix-dispersion system. The drug reservoir is made by 1st suspending the drug during and solution of water soluble compound and so dispersing the answer homogeneously in a lipotropic compound to form thousands of unapproachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilised quickly by right away cross-linking the compound in place by exploitation cross linking agents.

Various Methods for Preparation TDDS

Asymmetric TPX membrane method[14]

An epitome patch may be fictional for this a heat sealable polyester film (type 1009, 3m) with a cupulate of 1cm diameter are going to be used because the backing membrane. Drug sample is distributed into the cupulate membrane, lined by a TPX asymmetric membrane, associate degreed sealed by an adhesive.

Asymmetric TPX membrane preparation

These area unit fictional by exploitation the dry/wet inversion method. TPX is dissolved during a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to create a chemical compound resolution. The chemical compound resolution is unbroken at 40°C for twenty-four hrs and sew together a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is gaseous at 50°C for thirty sec, then the glass plate is to be immersed immediately in coagulation bath maintained the temperature at 25°C. After ten minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.

Circular teflonmould method[40]

Solutions containing polymers in numerous ratios area unit employed in associate degree organic solvent. Calculated quantity of drug is dissolved in 0.5 the amount of same organic solvent. Enhancers in numerous concentrations area unit dissolved within the partner of the organic solvent so side. Di-N-butyl phthalate is side as a plasticiser into drug chemical compound resolution. The total contents area unit to be stirred for twelve hrs so poured into a circular teflonmould. The moulds are to be placed on a leveled surface associate degreed lined with inverted funnel to regulate solvent vaporization during a streamline flow hood model with an air speed of zero.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films area unit to be hold on for an additional twenty four hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films area unit to be evaluated inside one week of their preparation.

Mercury substrate method[41]

In this methodology drug is dissolved in chemical compound resolution in conjunction with plasticiser. The higher than resolution is to be stirred for 10- quarter-hour to supply a uniform dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

By using "IPM membranes" method[42]

In this methodology drug is spread during a mixture of water and antifreeze containing carbomer 940 chemical compound and stirred for twelve hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer hydrogen ion concentration seven.4 may be employed in order to get resolution gel, if the drug solubility in solution is incredibly poor. The shaped gel are going to be incorporated within the IPM membrane.

By using "EVAC membranes" method[43]

In order to arrange the target transdermic therapeutic system, 1 Chronicles carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug isn't soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in antifreeze, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the required space. A rate dominant membrane are going to be placed over the gel and also the edges are going to be sealed by heat to get a leak proof device.

Aluminium backed adhesive film method[44]

Transdermal drug delivery system could turn out unstable matrices if the loading dose is bigger than ten mg. Aluminium backed adhesive film methodology could be a appropriate one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and material are going to be side to the drug resolution and dissolved. Acustammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

Preparation of TDDS by using Proliposomes[45,46]

The proliposomes area unit ready by carrier methodology exploitation film deposition technique. From the sooner reference drug and emulsifier within the quantitative relation of zero.1:2.0 may be used as associate degree optimized one. The proliposomes area unit ready by taking 5mg of water pill powder during a one hundred mil spherical bottom flask that is unbroken at 60-70°C temperature and also the flask is turned at 80-90 revolutions per minute and dried the water pill at vacuum for half-hour. After drying, the temperature of the water bath is adjusted to 20-30°C. Organic solvent mixture is used for the dissolution of drug and lecithin, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the answer is to be added. A lyophilizer is used for drying of proliposomes. The drug loaded mannitol powders are placed in a desiccator for overnight then sieved through 100 mesh. The collected powder is transferred into a glass bottle and hold on at the freeze temperature till characterization.

By using free film method[47]

Free film of cellulose ester is ready by casting on mercury surface. A chemical compound answer a pair of w/w is to be ready by victimization chloroform. Plasticizers are to be incorporated at an amount of four-hundredth w/w of chemical compound weight. 5 milliliter of chemical compound answer was poured in an exceedingly glass ring that is placed over the mercury surface in an exceedingly glass Petri dish. The speed of evaporation of the solvent is controlled by putting Associate in nursing inverted funnel over the Petri dish. The film formation is noted by observant the mercury surface once complete evaporation of the solvent. The dry film are separated out and hold on between the sheets of paper in an exceedingly desiccator till use. Free films of various thickness are often ready by dynamic the quantity of the chemical compound answer.

Evaluation parameters

Interaction studies

Excipients are integral parts of virtually all pharmaceutical dose forms. The soundness of a formulation amongst alternative factors depends on the compatibility of the drug with the excipients. The drug and the excipients should be compatible with each other to supply a product that's stable, so it's necessary to find any potential physical or chemical interaction because it will have an effect on the bioavailability and stability of the drug. If the excipients are new and haven't been employed in formulations containing the active substance, the compatibility studies play a very important role in formulation development. Thermal analysis, FT-IR, UV and activity techniques by instrumental examination their chemical characters like assay, melting endotherms, characteristic wave numbers,

absorption maxima etc. are used for Interaction studies[48,49].

Thickness of the patch

The thickness of the drug loaded patch is measured in several points by employing a digital micrometer and determines the common thickness and variance for an equivalent to make sure the thickness of the ready patch[50].

Weight uniformity

The ready patches are to be dried at 60°c for 4hrs before testing. As such as space of patch is to be cut in several components of the patch and weigh in digital balance. The common weight and variance values ar to be calculated from the individual weights[50].

Folding endurance

A strip of specific are is to be cut equally and repeatedly collapsable at an equivalent place until it stony-broke. The amount of times the film might be collapsable at an equivalent place while not breaking gave the worth of the folding endurance[50].

Wet content

The ready films are to be weighed one by one and to be unbroken in an exceedingly desiccator containing consolidated salt at temperature for twenty-four hrs. Once twenty four hrs. The films are to be reweighed and confirm the share wet content from the below mentioned formula[50].

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

Wet uptake

The weighed films are to be unbroken in an exceedingly desiccator at temperature for twenty-four hrs containing saturated answer of K-lor so as to keep up eighty four RH. Once twenty four hrs. The films are to be reweighed and confirm the percentage wet uptake from the below mentioned formula[50].

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

Water vapour permeability (WVP) evaluation

Water vapour permeability are often determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The formula is,

$$WVP = W/A$$

Where, WVP is expressed in gm/m2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in $m2$[9].

Drug content

A suitable solvent in specific volume is use for dissolution of specified area of patch. Then the answer is to be filtered through a filter medium and analyse the drug contain with the acceptable method (UV or HPLC technique). Each value represents average of three different samples[9].

Uniformity of dosage unit test

For complete extraction of drug from the patch, an accurately weighed portion of the patch is to be dig small pieces and dissolved in selected volumetric flask with suitable solvent and sonicate, volume made up to mark with same. The resulting solution was allowed to accept about an hour, and therefore the supernatant was suitably diluted to offer the specified concentration with suitable solvent. The solution was filtered using 0.2μm membrane filter and analysed by suitable analytical technique (UV or HPLC) and therefore the drug content per piece are going to be calculated[10].

Polariscope examination

This test is to be performed to look at the drug crystals from patch by polariscope. A specific area of the piece is to be kept on the thing slide and observe for the drugs crystals to differentiate whether the drug is present as crystalline form or amorphous form in the patch[10].

Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and therefore the composition of polymer, type and therefore the amount of tackifier added. An adhesive coated tape is applied onto a chrome steel plate; a specified weight is hung from the tape, to affect it pulling during a direction parallel to the plate. Shear adhesion strength is decided by measuring the time it takes to tug the tape off the plate. For removal longer time take is required, then greater is the shear strength[10].

Peel Adhesion test

In this test, the force required to get rid of an adhesive coating form a test substrate is mentioned as peel adhesion. Molecular weight of adhesive polymer, the sort and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a chrome steel plate or a backing membrane of choice then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured[10].

Thumb tack test

It is a qualitative test which is applied for tack adhesive property determination. The thumb is just pressed on the adhesive and therefore the relative tack property is detected[10].

Flatness test

Three longitudinal strips are to be cut from each film at different portion like one from the middle, other one from the left side, and another one from the proper side. The length of every strip was measured and therefore the variation long due to non-uniformity in flatness was measured by determining percent constriction, with 0% constriction like 100% flatness[49].

Percentage Elongation break test

The percentage elongation break is to be determined by noting the length just before the break point, the share elongation are often determined from the below mentioned formula.

$$\text{Elongation percentage} = L1\text{-}L2/\ L2 \times 100$$

Where, L1is the final length of each strip and L2 is the initial length of each strip[51].

Rolling ball tack test

This test measures the softness of a polymer that relates to speak. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so as 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[51].

Quick Stick (peel-tack) test

In this test, the tape is pulled far away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to interrupt the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width[21].

Probe Tack test

In this test, the tip of a clean probe with an outlined surface roughness is brought into contact with adhesive, and when a bond is made 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].

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***In vitro* drug release studies**

The paddle over disc method (USP apparatus V) are often employed for assessment of the discharge of the drug from the prepared patches. Dry films of known thickness is to be dig definite shape, weighed, and glued over a glass plate with an adhesive. The glass plate was then placed during a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and therefore the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of two.5 cm from the glass plate and operated at a speed of fifty rpm. Samples (5-mL aliquots) are often 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[48].

***In vitro* skin permeation studies**

An *in vitro* permeation study are often administered by using diffusion cell. 200 to 250g of male Wistar rats is weighing. Hair is removed from the abdominal region carefully; the dermal side of the skin was thoroughly cleaned with distilled water, equilibrated for an hour in dissolution medium (phosphate buffer pH 7.4) before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusion. The temperature of the cell was maintained at 32 ± 0.5°C employing a thermostatically controlled heater. The piece of isolated rat skin 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 far away from the receptor compartment at regular intervals, and an equal volume of fresh medium is to get replaced. Samples are to be filtered through filtering medium and may be analyzed spectrophotometrically or HPLC. Flux are often determined directly because the slope of the curve between the steady-state values of the quantity 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)[48].

Skin Irritation study

Skin irritation and sensitization testing are often performed on healthy rabbits (average weight 1.2 to 1.5kg). 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[10].

Stability studies

Stability studies are to be conducted consistent with the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for six months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content[48].

Applications of Transdermal Patches[5,6,52]

- The very best selling skin patch within the us is that the nicotine patch, which releases nicotine in controlled doses to assist with cessation of tobacco smoking.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (Marketed as Bu Trans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms also as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- The anti-hypertensive drug Clonidine is out there in skin patch form.
- Transdermal sort of the MAOI selegiline, became the primary transdermal delivery agent for an antidepressant.
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Advancements in TDDS

The drug delivery through the skin was recognized in 20th century. Due to some limitation in delivery of drug through skin, it cannot be used as a drug delivery route for all drug candidates. The continuous advancement in the science and technology is making the TDDS as the preferred and most convenient route for most of the drugs. The transdermal delivery is categorized into 3 generations according the advancements in TDDS.

First Generation Transdermal Drug Delivery Systems

Currently, there are two sorts of simple patch design. The original patch design may be a liquid reservoir system where the patch consists of a backing material that's both protective and adhesive, a liquid drug reservoir, a release membrane. A more recent design is the adhesive matrix system where

the adhesive and the drug are combined in the same layer leaving only three layers to the patch; the backing layer, the drug and adhesive layer, and the protective layer that would be removed before applying the patch to the skin[54].

Second Generation Transdermal Drug Delivery Systems

2nd Generation TDDS attempt to enhance the delivery of organic molecules through the stratum corneum by disrupting its barrier function and/or by providing some sort of driving force for the movement of molecules through the epidermis. This disruption should be reversible and avoid injury to the skin. However, it are often difficult to disrupt the barrier without causing damage or irritation, especially when using chemical enhancers. In addition, these 2nd generation enhancement techniques are limited to small, lipophilic molecules and still have little effect on larger or hydrophilic molecules. 2nd generation enhancement methods include chemical penetration enhancers, gentle heating, and iontophoresis[55].

Third Generation Transdermal Drug Delivery Systems

The third generation patches are developed to permeate large hydrophilic drug molecules. Hormonal delivery through the transdermal patch become possible only by using latest techniques like Iontophoresis, Sonophoresis, electrophoresis, Magnetophoresis and micro needle technique etc. These permeation enhancers forcefully allow the drug molecules to pass across the skin or physically damage the skin[56].

Advanced Techniques For Penetration Enhancement in Transdermal Drug Delivery System[34,57]

Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a particular area using the electrode remains in touch with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia.

Ultrasound

In this technique, there's a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism thanks to development of transient channels.

Electroporation

It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to make small pores within the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.

Electro-Osmosis

To the porous membrane which has some charge, a voltage difference is applied thereto, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

Micro-needle

Concept employs an array of micron-scale needles that is inserted into the skin sufficiently far that it can deliver drug into the body, but not so far that it hits nerves and thereby avoids causing pain. An array of micro-needles measuring tens to hundreds of microns in length should be long enough to deliver drug into the epidermis and dermis, which ultimately leads to uptake by capillaries for systemic delivery. This is similar to conventional transdermal patch delivery, except the rate limiting barrier of the stratum corneum is circumvented by the pathways created by microneedles. Small microneedles can also be painless if designed with an understanding of skin anatomy. Needles of micron dimensions can be made using micro-fabrication technology, which is the same

technology used to make integrated circuits. In this micro-fabrication approach, silicon, metal, polymer or other materials are exposed to masking steps, which define the shape of structures to be created, and chemical etching steps, which sculpt the material into the prescribed shapes.

Metered-Dose Transdermal Spray (MDTS)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come nonvolatile in nature, which consists the completely dissolved medicament in solution. The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential Advantages:

1. Improves delivery potential without skin irritation due to its non-occlusive nature.
2. Increased acceptability.
3. Dose flexibility
4. Simple manufacture

Powderject Device

High speed gas flow is used to propel the solid drug particles across the skin. This consists of a gas canister that permits helium gas at high to enter a chamber at the top of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that leads to the gas to expand quickly which forms a robust motion sort of a wave that travels down the nozzle. This takes place at the speed of 600-900m/s.

Other Enhancement Techniques

Transfersomes

This device penetrates the skin barrier along the skin moisture gradient. Transfer some carriers can create a drug depot within the circulation that's having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus resulting in the deformable vesicles. Medicated Tattoos Medical Tattoos may be a modification of temporary tattoo which contains a lively drug substance for transdermal delivery. This technique is beneficial within the administration of drug in those children who aren't ready to take traditional dosage forms.

Skin Abrasion

This involves direct removal or disruption of the upper layers of the skin to supply better permeation of topically applied drug substance. In general, one approach is adopted to make micro channels within the skin by eroding the impermeable outer layers with sharp microscopic metal granules.

Laser Radiation

In this technique, exposure of the skin to the laser beams that result in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. This technique improves the delivery of lipophilic and hydrophilic drugs.

Controlled Heat Aided Drug Delivery (CHADD) System

Heat is applied on the skin that increases the temperature which facilitates the transfer of drug substance to the blood circulation and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device.

Table No.1: Regional variations in water permeability of stratum corneum

S.No	Skin region	Thickness (mm)	Permeation rate ($mg/cm^2/hr$)	Diffusivity ($cm^2/sec \times 10^{10}$)
1	Abdomen	15.00	0.34	6.00
2	Volar forearm	16.00	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13.00	0.85	12.9
5	Forehead	5.00	1.70	7.4
6	Back of hand	49.00	0.56	32.3
7	Palm	400.00	1.14	535.00
8	Plantar	600.00	3.90	930.00

Table No.2: Ideal properties of transdermal drug delivery system[29]

S.No	Properties	Range
1	Shelf life	Should be up to 2.5 years
2	Patch size	Should be less than 40 cm^2
3	Dose frequency	Once a daily-once a week
4	Appearance	Should be clear or white color
5	Packaging properties	Should be easily removable of release liner
6	Skin reaction	Should be non-irritating
7	Release properties	Should have consistent pharmacokinetic and pharmacodynamic profiles over time
8	Packaging properties	Should be easily removable of release liner

Table No.3: Ideal properties of drug for TDDS[29,30]

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

Table No.4: Different class of enhancers and their mechanism of action[38]

S.No	CLASS	EXAMPLES	MECHANISM OF ACTION
1	Hydrating substances	Water occlusive preparations	Hydrates the SC
2	Keratolytics	Urea	Increase fluidity and hydrates the SC
3	Organic solvents	Alcohols Poly ethylene glycol DMSO	Partially extracts lipids replace bound water in the intercellular spaces increase lipid fluidity
4	Fatty acids	Oleic acid	Increase fluidity of intercellular lipids
5	Terpenes	1,8-cineole,menthol	Opens up polar pathway
6	Surfactants	Polysorbates Sodium lauryl sulfate	Penetrates into skin, micellar solubilisation of SC
7	Azone	1-dodecylhexahydro-2Hazepine-2on2	Disrupts the skin lipids in both the head group and tail region

Table No.5: Marketed Products of Transdermal Drug Delivery System[29,53,21]

S.No	Product	Active drug	Type of transdermal patch	Purpose
1	Estraderm	Estradiol	Membrane	Postmenstrual syndrome
2	Duragesic	Fentanyl	Reservoir	Pain relief patch
3	Transderm-scop	(scopolamine)		Motion sickness
4	Alora	Estradiol	Matrix	Postmenstrual syndrome
5	Climara	Estradiol	Matrix	Postmenstrual syndrome
6	Androderm	Testosterone	Membrane	Hypogonadism in males
7	Captopress TTS	Clonidine	Membrane	Hypertension
8	Combipatch	Estradiol	Matrix	Postmenstrual syndrome
9	Esclim	Estradiol	Matrix	Hormone replacement therapy
10	Deponit	Nitroglycerine	Drug in adhesive	Angina pectoris
11	Fempatch	Estradio	Matrix	Postmenstrual syndrome
12	Lidoderm	Lidocaine	Drug in adhesive	Anesthetic
13	Ortho evra	Estradiol	Drug in adhesive	Postmenstrual syndrome
14	Testoderm TTS	Testosterone	Reservoir	Hypogonadism in males
15	Habitraol	Nicotine	Drug in adhesive	Smoking cessation
16	Prostep	Nicotine	Reservoir	Smoking cessation
17	Nicotrol	Nicotine	Drug in adhesive	Smoking cessation
18	Vivelle	Estradiol	Reservoir	Postmenstrual syndrome
19	Matrifen^{R}	Fentanyl	reservoir	Pain relief patch
20	Nupatch 100	Diclofenacdiethylamine	Drug in adhesive	Anti-inflammatory
21	Nicoderm CQ	Nicotine	Drug in adhesive	Smoking cessation
22	Vivelle-dot	Estradiol	Reservoir	Postmenstrual syndrome
23	Minitran	Nitroglycerine	Drug in adhesive	Angina pectoris
24	Nitrodisc	Nitroglycerine	Micro reservoir	Angina pectoris
25	Nitrodur	Nitroglycerine	Matrix	Angina pectoris
26	Transderm Nitro	Nitroglycerine	Reservoir	Angina pectoris
27	Oxytrol^{R}	Oxybutynin	Matrix	Overactive bladder
28	Nuvelle TS	Estradiol	Drug in adhesive	Harmone replacement therapy
29	Fematrix	Estrogen	Matrix	Postmenstrual syndrome
30	Climaderm	Estradiol	Matrix	Postmenstrual syndrome

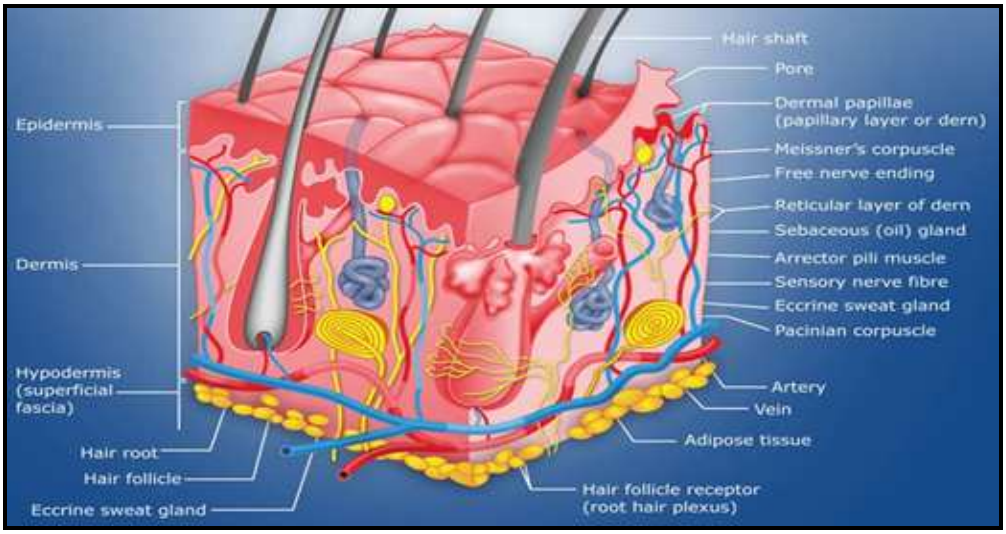

Figure No.1: Structure of human skin (copied from google.com)

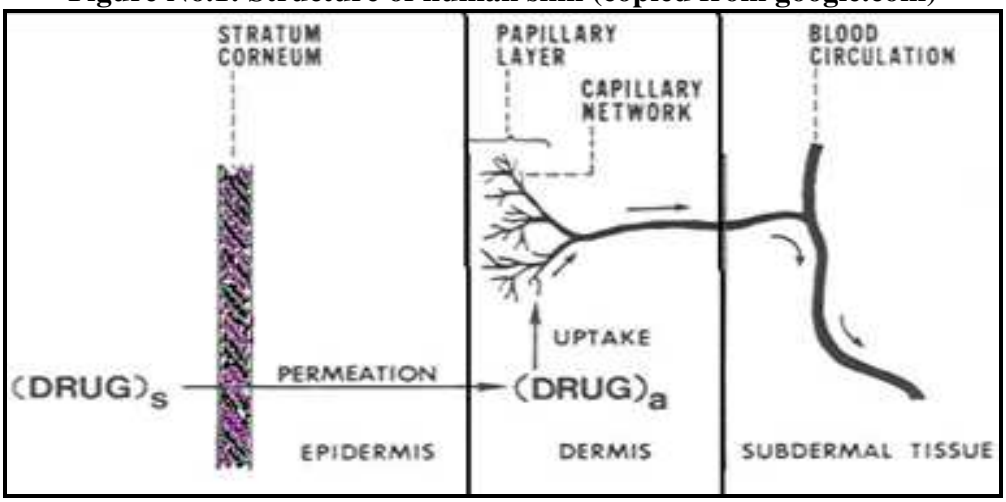

Figure No.2: A multilayer skin model showing sequence of transdermal permeation

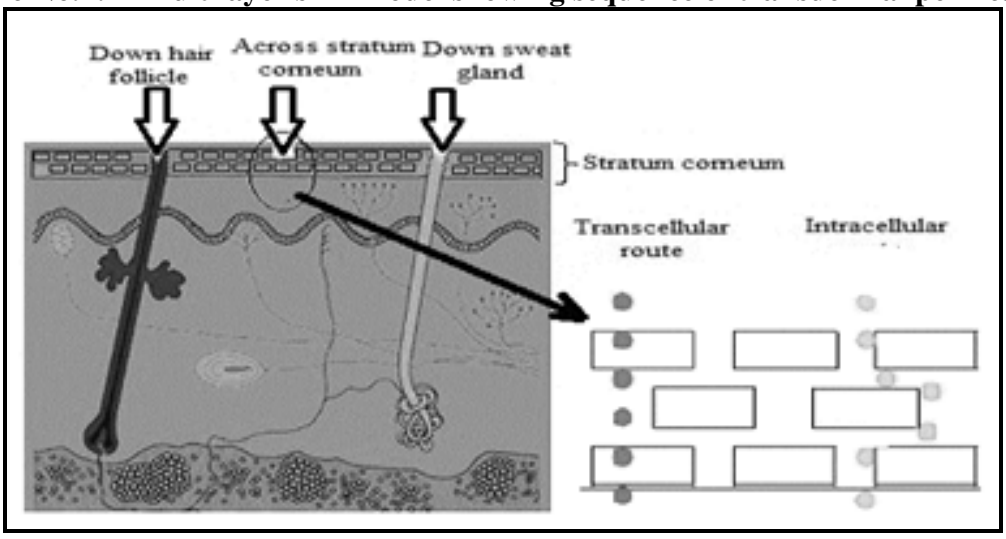

Figure No.3: Permeation pathways through the skin

CONCLUSION

This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, having the ability to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the various mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system. The transdermal drug delivery has capable advantage of avoiding hepatic first pass metabolism, improve to bioavailability, decrees gastro intestinal irritation due to local contact with gastric mucosa, maintaining constant blood level for a longer period of time resulting in decrees of dosing frequency and improved patient compliance. In recent years it's proved that benefits of intravenous drug infusion are often closely duplicated without harmful effects by using skin as a part of drug administration to supply continuous transdermal drug infusion through intact skin.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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