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Transdermal Drug Delivery Systems with major emphasis on Transdermal patches : A Review

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ABSTRACT

Due to the recent advances in this technology and as the incorporation of the drug to the site of action is done without rupturing the skin membrane, the transdermal route is becoming very widely accepted route of drug administration. When transdermal formulations are applied to the intact skin , they deliver the drug through the skin at a controlled rate to the systemic circulation. Any formulation like ointments , creams , gels can be used as transdermal formulations for a particular drug, after careful selection of the base and addition of the penetration enhancers . Transdermal patches are the best available TDDS systems which are applied on the surface of the skin to deliver a specific dose of medication through the skin to the blood stream, thus this review mostly revolves around TDDS patches. Various other methods used for drug transport to the blood through skin are Intophoresis, Electroporation, Ultrasound, Reverse electrporation, Photochemical wave etc which also come under TDDS. This review is an attempt to compile the relevant information and techniques under Transdermal Drug Delivery Systems (TDDS) along with the evaluation (in vitro and in vivo) of these. This review also includes recent advances in the field of TDDS. Authors have also made a comment on the limitations of TDDS, comparision of topical and TDDS and toxicity considerations of topical preparations.

Key words: Transdermal Drug Delivery Systems (TDDS), Intophoresis, Electroporation, Ultrasound, Reverse electrporation, Photochemical wave , in vitro and in vivo, topical formulations,

INTRODUCTION

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders .Before the transdermal drug delivery was invented it was noticed that babies to whom baby powders containing Boric acid was applied, produced toxic reactions as Boric acid penetrated through the skin into systemic circulation .

The occurrence of systemic side-effects with some of these formulations is indicative of absorption of the drugs through the skin, which lead to the idea of TDDS. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation.[1]

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to administer it by mouth and by parenteral routes, patients often forget to take their medication and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable over the blood level spikes and troughs produced by oral dosage forms . This pattern of drug release makes TDDS to be used as effective SRDFs (Sustained release dosage forms)

These advantages are offered by the currently marketed transdermal products. One of the most successful, the nicotine patch, releases nicotine over sixteen hours, continuously suppressing the smoker's craving for a cigarette. The scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically. The fentanyl patch acts for seventy-two hours, providing long-lasting pain relief. and an estrogen–progestin contraceptive patch needs to be applied only once a week, a boon for women who find it onerous to take one pill every day.

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Historical Perspective
Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. The mustard plaster, applied as a home remedy for severe chest congestion, may be considered an example. Powdered mustard seeds were mixed with warm water, and the resulting paste was spread on a strip of flannel, which was applied to the patient's chest with a cloth binding wrapped around the body to hold the plaster in place. The history of plasters has been traced back to antiquity. In addition to mustard plasters, several other plasters were recognized in early 20th century editions of the United States Pharmacopeia (USP) and National Formulary (NF). At one time, Belladonna Plaster, containing 0.25 – 0.30% of belladonna root alkaloids, was believed to act transdermally as an analgesic.

Perhaps the most remarkable forerunner of modern transdermal medication was Stronger Mercurial Ointment, used as a treatment for syphilis when Salvarsan and other arsenicals were in use, before the discovery of penicillin. For the first time use of transdermal drug delivery system was done by the U .S F & D in December 1979, which administered scopolamine for motion sickness.[2]

Novelty of Application Of Transdermal Drug Delivery [9]
Efficient treatment of diseases is expected when the timing of drug delivery is taken into account and adjusted in a proper way. This implies an easy to use, noninteractive and user independent drug delivery system that allows delivery at anytime.

Transdermal delivery systems allow drug delivery from an extracorporeal device without using intravenous pathways and offer possibilities for self-administrated drug delivery.

The skin is essentially a multilayer configuration with an outer protective layer, the stratum corneum, followed by the epidermis, basal membrane, dermis and fatty tissue. The drug has to be transported to the dermis, where the subpapillary network is located and drugs can diffuse into the vascular system and apply therapy. The biggest barrier in this delivery is Stratum corneum.There are a number of ways in which the main barrier, the stratum corneum, can be penetrated to deliver the therapy, as follows.

- A variety of drugs are capable of penetrating through the stratum corneum.
- Current research is focusing on so-called penetration enhancers such as molecules attached to the drug, which open up the transdermal pathway.
- Electric fields can be used to support the transport of ionic drugs into the epidermis, a process known as iontophoresis.

•Hollow microneedle arrays penetrating the upper layer of the skin (epidermis and basal membrane if necessary) can access the subpapillary network with liquid drugs in a pain free manner. In contrast to enhancer technology and iontophoresis, the use of this microinvasive method is independent of the properties of the drug, thus obviating the need for an additional modification of the drug molecule. This is, therefore, considered to be a universal and suitable interface for chronotherapeutic drug delivery systems.

Transdermal Drug Delivery- Technology [11,12,13,14]
Many drugs which can be trasported directly into the blood stream via skin have been formulated.The formulations are of many kinds like TDD patches and semisolids including gels, creams, ointments etc.

Understanding How TDS Works

A) Anatomy and Physiology Of Skin [15]
The human skin comprises three tissue layer epidermis (stratified,), underline dermis of connective tissue & subcutaneous tissue. Hairy skin contains hairfolicle and sebaceous gland.

B) Pathways Of Absorption [15.]
A drug can penetrate the skin by transcellular (across the cell) intracellular (between the cell) transappendageal(through hair follicles, sebaceousglandd.etc) Majority of drug transport occurs through the transcellular pathway .since exstracellular space is concentrated with lipids ,the lipid solubility of molecule is very important for its transdermal delivery.

C) Drug Transport Through Skin

Diffusion Process
In passive diffusion ,matter moves from one region of a system that is from more concentrated form to the lower part of the system .diffusion process is explained by Fick's Law of diffusion

$$J = -D \frac{C}{x} .$$

Where J = rate of transfer per unit area of surface ,(the flux)
C = is concentration of diffusing substance
x = space coordinate measured normal to the section,
D = is diffusion coefficient.
And –ve sign indicates that the flux is in direction of decreasing order

Skin is very effective as it is selectively permeable ,and epidermis plays important role as barrier as most small water soluble materials ie non electrolytes diffuses into the capilary system thousand times more rapidly when the epidermis is absent.

When we apply any preparation on the surface of skin the process is carried in to 3 steps

1 Release of medicament from vehicle .
2 Penetration through the skin barrier .
3 Activation of the pharmacological response

Factors Affecting Transdermal Drug Delivery [15,16 ,17]

1. Skin Condition
The intact skin itself acts as barrier but many agents like acids ,alkali cross the barrier cells andpenetrates through the skin ,many solvents open the complex dense structure of horny layer Solvents like methanol, chloroform remove lipid fraction, forming artificial shunts through which drug molecules can pass easily.

2. Skin Age
It is seen that the skin of adults and young ones are more permeable than the older ones but there is no dramatic difference .Children shows toxic effects because of the greater surface area per unit body weight .thus potent steroids, boric acid, hexachlorophene have produced severe side effects.

3. Physicochemical Factors [15,18]

a) Hydration Of Skin
Generally water when saturates the skin -- swells tissues, softens wrinkles on the skin and its permeability increases for the drug molecules which penetrates through the skin .

b)Temperature and pH of the Skin
Penetration rate varies if temperature varies**,** as diffusion coefficient decreases as temperature falls down, however adequate clothing on body prevents wide fluctuations in temperature and penetration rates .According to pH only unionized molecules pass readily across the lipid membrane, now weak acids and dissociate to different degrees according to pH and their pKa or pKb values .Thus the concentration of un ionized drug in applies phase will determine the effective membrane gradient which directly related to its pH.

4. Envirnomental Factors

a. Sunlight
Due to Sunlight the walls of blood vessels become thinner leading to bruising with only minor trauma in sun-exposed areas. Also pigmentation: The most noticeable sun-induced pigment change is a freckle or solar lentigo.

b. Cold Season
Often result in itchy, dry skin. Skin responds by Increasing oil production to compensate for the weather's drying effects . A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

c. Air Pollution
Dust can clog pores and increase bacteria on the face and surface of skin, both of which lead to acne or spots. Which affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with skin's natural protection system, breaking down the natural skin's oils that normally trap moisture in skin and keep it supple.

Transdermal Drug Delivery Methods

Transdermal Formulations [15]
Any formulation which is made to apply topically is not transdermal . But it can be made to act as transdermal drug formulation by addition of penetration enhancers and it also depends upon nature of drug .

a. Liqiud Preperations
Liquid preparations for external applications include simple soaks, liniments, lotions, tinctures and ear drops, simple soak provides active ingredient in aqueous solution or suspension, addition of gums and gelling agents may vary the consistency from mobile liquids to the rigid gels. Both additives such as oliatum emollient forms a layer of liquid paraffin on the stratum corneum and maintains its moisture contain by occlusion, parasiticides mainly used are diclophane, benzyl benzoate, gamma benzene hexaachloride, malathion. liniments used may have alcoholic or oily emulsions. and are not applied on broken skin .Lotions are aqueous solutions or suspensions form which water evaporates and leaves behind uniform coating of powders, these are useful in treating acutely inflamed areas .Alcohols increases the cooling effect and glycerol allows the powder to sticks to the skin. For ear drops alcohols and glycerol may be used .

b. Gels
It is mainly two component semisolid system which is rich in liquid. It has continuous structure which gives it solid like characteristics. In a gel, a natural or synthetic polymer builds a three dimensional matrix throughout a hydrophilic liquid. Polymers used are natural gums like tragacanth, carrageenan, pectin, agar, algiinic acid. Semisynthetic materials include methyl cellulose, carboxy methyl cellulose , hydroxyl propyl methyl cellulose and carbapol .Certain clays like bentonite, veegum and laponite may also be used along with the condition that the drug should not bind with the polymer.

c. Creams
Creams are semisolid emulsions for external use. Oil in water emulsions are used as water washable bases while water in oil emulsions are used as emollient and cleansing purpose. w/o type cream , spreads more easily, rapidly and is less greasy, and evaporating water soothes the inflamed tissue .o/w creams i.e. vanishing creams are rubbed into the skin ,the continuous phase evaporates and increase the concentration of water soluble drug in the adhering film .the concentration gradient for drug across the stratum corneum therefore increases, promoting percutaneous absorption. o/w cream is an non occlusive because it does not deposit continuous film of water –impervious liquid, but it can deposit lipids and other moisturizers on into the stratum corneum , restoring tissues hydration ability.

d. Pastes
Paste are the ointments containing as much as 50% powder dispersed in a fatty

base . They may be useful for absorbing noxious chemicals in babies such as the ammonia that bacteria release from urine. Because of their consistency, pastes, localize the action of an irritant or staining material such as dithranol or coal tar.They are less greasy than ointments because powder absorbs some of the fluid hydrocarbon . Pastes produces thick unbroken and impermeable film that can opaque and acts as efficient sun filter and block out the sunrays .

e. Aerosols

It functions as drug delivery systems for solutions, suspensions, powders, semi-solids and emulsion . Solution aerosols are simple products containing drug dissolved in propellant or propellant /solvent mixture. Typical agents incorporated are steroids, antibiotics and astringent Powder aerosols used for drugs which are difficult to dissolve for example steroids and antibiotics. Semisolid preparations such as ointments and creams may be prepared in flexible bag with compressed nitrogen used for expulsion. Medicinal stable foams that may be aqueous or non aqueous and stable or quick breaking can also be used for contraception.

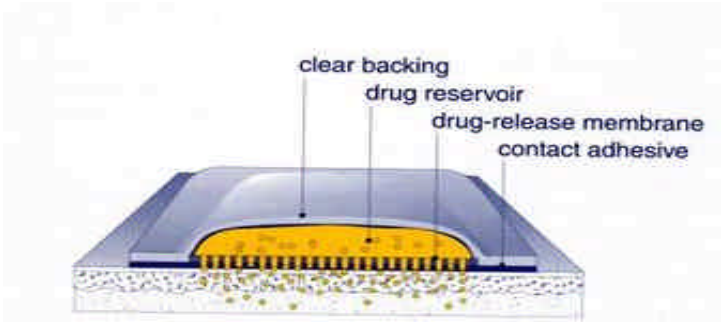
f. Ointments

Ointments are semisolid preparations ,often anhydrous and containing dissolved or dispersed medicaments .Hydrocarbon bases are consist of soft paraffin or mixture of hard and soft paraffin which forms greasy film on the surface of skin ,inhibiting moisture loss and improving hydration of the horny layer in dry scaly condition. Plastibases are a series of hydrocarbons containing polyethylene marix system .These are generally soft ,smooth ,non irritating and extremely stable vehicles.

Plastibases are compatible with most medicaments and maintain their consistency even at high temperature conditions silicones ,dimethyl polysiloxanes are similar to hydrocarbon bases. Absorption bases soak up water to form water in oil emulsions ingredients used are lanolin ,lanolin isolates ,cholesterol and other sterolsWhile emulsifying bases contain mainly oil in water emulsifying agents .Depending on the nature of emulsifying agent present in these bases ,the bases are of three types , anionic (emulsifying ointments) , cationic (cetrimide emulsifying ointment), and Non ionic (cetomacrogol emulsifying ointment) namely.Water soluble bases contains mixture of high and low molecular weight Polyethylene glycols, suitable combinations provide products with an ointment –like consistency ,which soften or melt on skin applications ,these are non occlusive ,mix readily with skin exudates easily washable.

g.. Transdermal Patch [11,19]

It is a patch which is applied on the surface of the skin to deliver a specific dose of medication through the skin to the blood stream.



Components of transdermal patch

1) Liner - Protects the patch during storage. The liner is removed prior to use. (2) Drug - Drug solution in direct contact with release liner. (3) Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin. (4) Membrane - Controls the release of the drug from the reservoir and multi-layer patches. (5) Backing - Protects the patch from the outer environment.

Mechanism Of Action of Transdermal Patch [11,15,]

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

Conditions in which Transdermal Patches are used [11,20]

1. When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
2. Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia
3. It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which transdermal patches are not used [21]

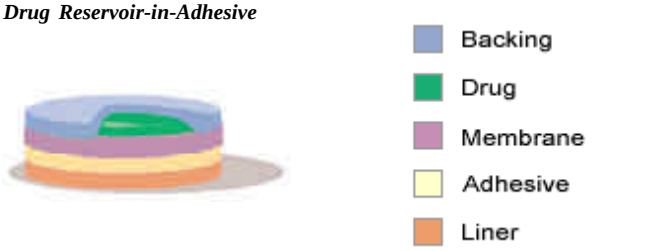
1 Cure for acute pain is required.
2 Where rapid dose titration is required.
3 Where requirement of dose is equal to or less then 30 mg/24 hrs.

Types Of Transdermal Patch [11,17.18]

1. Single-layer Drug-in-Adhesive

2. Multi-layer Drug-in-Adhesive

3. Drug Reservoir-in-Adhesive



4. Drug Matrix-in-Adhesive

5. Vapour patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep.

Marketed Formulations of TDDS Worldwide

1. Nicotine : to quit tobacco smoking.
2. Fentanyl: analgesic for severe pain.
3. Estrogen: menopause and osteoporosis.
4. Nitroglycerine :(glyceryl trinitrate) tratment of angina .and myocardial infarction ,congestive hrart failure .
5. Lidocaine : peripheral pain of shingles (*herpes zoster*).
6.Oestradiol it is mainly used to treat women for menopausal symptoms or other results of estarogen deficiency (hormone replacement therapy ,HRT)
7. Clonidine was originally introduced to treat hypertension .
8. Flector patch is used as NSAIDS for acute pain due to minor strains ,sprains and contusions also used in fibromyalgia .
9. Scopalmine can contol side effects of anticancer agents .controls vertigo.

Care Taken While Applying Trandermal Patch [11]

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

Recent Devlopments In Transdermal Patches

1. Pain-free diabetic monitoring using transdermal patches[33]

The first prototype patch measures about 1cm^2 and is made using polymers and thin metallic films. The 5×5 sampling array can be clearly seen, as well as their metallic interconnections. When the seal is compromised, the interstitial fluid, and the biomolecules contained therein, becomes accessible on the skin surface. Utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, a high-temperature heat pulse can be applied locally, breaking the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30ms duration. The temperature diminishes rapidly from the skin surface and neither the living tissue nor the nerve endings are affected. This painless and bloodless process results in disruption of a 40–50µm diameter region of the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.

2. Testosterone Transdermal Patch System in Young Women with Spontaneous Premature Ovarian Failure [34]

In premenopausal women, the daily testosterone production is approximately 300 µg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone. The addition of TTP to cyclic E2/MPA therapy in women with sPOF produced mean free testosterone levels that approximate the upper limit of normal.

3. Transdermal Patch of Oxybutynin used in overactive Bladder.[35]

The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe under the brand name of Kentera. OXYTROL is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval. OXYTROL offers OAB patient's continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with and oral formulation. In most patients these side effects however are not a troublesome

4. Rotigotine transdermal patch[36]

The rotigotine transdermal patch is used for symptom control in Parkinson's disease. The patchesare effective in reducing the symptoms of early Parkinson's disease, and in reducing "off" time in advanced Parkinson's disease. It is available in market under the brand name of NeuproR.

5.US FDA Approves Emsam (Selegiline)[37]

Selegiline consists of methamphetamine skeleton with proparygyl group attached to the nitrogen atom. The Food and Drug Administration (FDA) has approved selegiline, the first transdermal (skin) patch for use in the treatment of major depression in adults. The new patch, is sold under the brand name Emsam, was developed by Somerset Pharmaceuticals, Inc. In December 2004, Bristol-Myers Squibb (BMS) and Somerset entered into an agreement that gave BMS (the world™s 8th largest drug company) distribution rights to market Emsam in the United States. Selegiline was initially approved in capsule form for use in the treatment of Parkinson's disease.

The patch is only approved for adults, and will not be used to treat depression in children below 17yrs of age. Emsam interacts with three neurotransmitters in the brain that are believed to be involved with depression.

6. The *in vitro* percutaneous migration of chemical elements from a thermal mud for healing use[38]

In-vitro experiments have been developed to ascertain whether pelotherapy applications involve the transfer of chemical elements from the healing mud to the human body, across the skin. All the materials used for therapy (raw clay, mineral water and healing mud obtained after maturation) have been characterized from different points of view (mineralogy, chemistry, exchange properties, radioactivity, grain size and microbiology) in order to get an accurate knowledge of the natural media used for therapy and to follow the development of maturation in the spa centre.

A polymineralic silty clay with rather a common mineralogical and chemical composition is used; the mud is matured in a very saline mineral water, of marine origin, for 5 months. Under these conditions the maturation process increases the dispersion of clay particles and allows cation exchange between clays and water, whereas neither microbiological nor mineralogical changes are detectable. In absence of the biologic indicators of mud maturity, the equilibration of clay with mineral water represents an objective quantitative criterion.

In-vitro tests have been carried out by using the Franz-type diffusion cells, which show that the transfer of chemical elements across the skin is very well-developed, and also involving many essential or possibly essential elements. The amounts of chemical elements transferred were compared with toxicological guidelines and with world-wide daily requirement models.

Other advances in trans Dermal Delivery

1. Iontophoresis[15.18,22,23]

Iontophoresis it is the electrical driving of charged molecules into tissue. Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. It has application in dentistry, opthalmology, surgery and general medicine.

A grounding electrode placed elsewhere on the body completes the electrical circuit .the port of the charged molecules is driven primarily by electrical repulsion from the driving electrode. However, polar neutral molecules can also be delivered by a current – induced connective flow of water (electro-osmosis) a problem with the method is that, although the apparent current density per unit area is low, nearely all the current penetrates via a low resistance route i.e the appendages, particularly the hair follicles, thus the actually current density in the follicle may be high enough to damaged growing hair. There is also concern about other possible irreversible changed to the skin.

2. Electroporation [15,18,24]

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude.

The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum

3. Ultrasound (Phonophoresis) [15,25]

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. Used primarily in physiotherapy and sports medicine, involves placing the topical preparation on the skin over the are to be treated and massaging the site with

an ultrasound source .The ultra sonic energy disturbs the lipid packaging in the intracellular spaces of the stratum corneum by heating and cavitations effects, and thus enhances drug penetration in to the tissue .This method is not readilly suitable for home use.

4. Photochemical Wave [15]

A drug solution is placed on the skin , covered by a black polystrene target,and irradiated with a laser pulse .the resultant photomechanical wave produces stesses in the horny layer that enhances drug delivery .the technique is likely to remain experimental.

5. Reverse Electroporation [26]

Reversible electroporation is the temporary permeabilization of the cell membrane through the formation of nano-scale pores that are transient defects in the membrane. These pores are caused by short electrical pulses . typically on the order of a few to several hundred microseconds that are delivered by electroporation electrodes inserted around the treated tissue. Reversible electroporation has become an important technique in molecular medicine. It is used to introduce macromolecules such as genes or anticancer drugs, to which the cell membrane is normally not permeable, into the cytosol

6. Use Of Microscopic Projection [15,22]

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in the development of cutaneous vaccines for tetanus and influenza.

7. Stratum Corneum Removal [15]

Laser ablation uses high – powered pulses to vaporizes pulses from laser to vaporize a section of horny layer so as to produce permeable skin regions .the apparatus is costly and requires expert handling to avoid damages like burns.

Use Of Penetration Enhancers To Increase The Permeability Of The Skin [27]

Skin acts as a huge barrier against foreign particles and prevent its entry into skin .Now if we want to allow the entry of drug particles to get entry through skin into systemic circulation then we use penetration enhancers.

These substances temporarily diminish the impermeability of the skin and also termed as accelerants or soption promoters if proves safe and non toxic these can be used as to enhance the penetration rate of drugs .

1. Enhancers

Solvents - Few solvents have shown to increase permeability of skin mainly by swelling polar pathway or by fluidizing lipids examples are

1. Water, alcohols like methanol and ethanol
2. Alkyl methyl sulfoxides –dimethyl sulfoxide
3. Alkyl homologs of methyl sulfoxides, dimethyl acetamide and dimethyl formamides

Surfactants - These compounds are proposed to enhance the polar pathway transport, especially of hydrophilic drugs. The ability of surfactants to alter penetration is a function of the polar head group and hydrocarbon chain length ,these are skin irritants, therefore a balance between penetration enhancement and irritation has to be considered.

Anionic surfactants –sodium laruryl sulphate ,dioctyl sulphosuccinate

Non ionic surfactants –pluronic F 127

Marketed Preperations of TDDS Used In India[42]

1. Arfur gel contains aceclofenac gel 1.5 %w/w (for painful inflammation)
2. Nobel gel contains diclofenac diethylamine 1.16%
3. NUPATCH 100 Diclofenac transdermal pach ,mfg by zydus cadila
4. Nicotine patches used for smoking cessation
5. Nitroglycerine patch – it is mainly used for treatment of angina, USA

Some of the Marketed Preperations In United States (U.S)[31,32]

Brand Name	Drug	Manufacturer	Indications
Nicotinell®	Nicotine	Novartis	Pharmacological smoking cessation
Matrifen®	Fentanyl	Nycomed	Pain relief patch
Ortho Evra™	Norelgostromin/ Ethinyl Estradiol	ORTHO-McNEIL	Postmenstrual syndrome
NuPatch 100	Diclofenac diethylamine	Zydus Cadila	Anti Inflammatory
Neupro®	Rigotine	UCB and Schwarz Pharma	early-stage idiopathic Parkinson's disease
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrualsyndrome
Nicoderm®	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/ Berlex Labs	Postmenstrual syndrome
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Transderm-Scop®	Scopolamine	Alza/Norvatis	Motion sickness
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Catapres TTS®	Clonidine	Alza/Boehinger Ingelheim	Hypertension
FemPatch	Estradiol	Parke-Davis	Postmenstrualsyndrome
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Climaderm	Estradiol	Ethical Holdings/ Wyeth-Ayerest	Postmenstrual syndrome
Duragesic®	Fentanyl	Alza/Janssen Pharmaceutical	Moderate/severePain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrualsyndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
Transderm-Nitro®	Nitroglycerin	Alza/Norvatis	Angina pectoris
Testoderm TTS®	Testosterone	Alza	Hypogonadism in Males
Oxytrol®	oxybutynin	Watson Pharma	Overactive bladder
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation

Evaluatuion of Transdermal Drug Delivery Systems

1. Determination of Drug partition coefficient[40]

The partition coefficient study can be performed using n-octanol as the oil phase and phosphate buffer pH 7.4 as the aqueous phase. The two phases can be mixed in equal quantities and then saturated with each other on a mechanical water bath shaker having 37 °C temperature for 24 h. The saturated phases can be separated by centrifugation at 2000 rpm. Standard plots of the drug can be prepared from both phosphate buffer pH 7.4 and n-octanol. Equal volumes (10 mL) of the two phases can be placed in hexaplicate in conical flasks and, to each, 100 mg of drug can be added. The flasks should be shaken at 37 °C for 6 h to achieve com-plete partitioning at 100 rpm. The two phases were separated by centrifugation at 1000rpm for 5 min and were then analyzed for respective drug contents

.

2. Transdermal Drug Delivery Kinetics [41]

Skin permeation kinetics of drug from these technology different TDDS systems can be evaluated using a two compartment diffusion cell assembly under identical conditions. This is carried out by individually mounting a skin specimen excised from either a human cadaver or a live animal on a vertical diffusion cell and its modification on a horizontal diffusion cell such as Franz diffusion cell and Valia –Chien skin permeation cell. Each unit of the TDD system is then applied with its drug releasing surface of the skin . The release profile of drug from these TDD system can also be investigated in the same diffusion cell assembly without a skin specimen .

3.*In Vitro* Methods [15]

These are valuable methods for screening and for measuring fluxes , partion coefficients and diffusion coefficients .Excised skin from rats, mice and guinea pigs (normal and hairless), rabbits, hamsters and pigs hairless dogs, monkeys etc are collected and mounted in diffusion cell but mammalian skin varies widely in stratum corneum so it is best to obtain the human skin from autopsies or cosmetic surgery. Investigator clamped the skin in diffusion cell and measure the compound passing from sratum corneum side through to a fluid bath

Three important quantities of drug vary with time viz

1 amount of drug entering the membrane .
2 amount of drug passing through diffusion cell.
3 amount that remains inside .the membrane .

As human skin is difficult to obtain variable investigator have used artificial membranesof material like cellulose acetate ,silicone rubber or isopropyl myristate or lamellar systems designed to mimic the intracellular lipid of the stratum corneum , however the these membranes are not as complex as human skin .

Released methods without a rate limiting membranes -
It mainly records the drug release to immiscible phase, it only measures drug/ vehicles interactions that affect the drug release characteristics and do not determine the skin absorption.Such procedures are important for Quality control protocol .

4.In Vivo Methods
In vivo methods animals are used, however most animals differ in features which affect precutaneous absorption .

5.Histology
These experiments are carried out to locate skin penetrations roots from microscopic sections. Problem associated with this method is that while handling, cutting and operating the skin tissue the secretions developed by skin may take away materials away from their original sites .

Histochemical techniques have been used for those few compounds that produce coloured end products after chemical reaction .

Few compounds flurosce, revealing their behavior by microscopy eg vit A,tetracyclines , benzpyrene .

6.Microdialysis
In this technique micro dialysis probes are inserted in the dermis and perfused with buffer.

Drug molecule pass from the extracellular fluid into the buffer through pores in the membrane. .Which excludes large molecules, particularly proteins .The resulting drug solution is collected and analyzed .

7.Surface loss
In theory we able to explain the flux of material into skin from the loss rate from the vehicle however because of skin impermeability, the concentration decrease in vehicle would be generally be small and analytical techniques would be sensitive and accurate. Differences in vehicles concentration arises due to evaporation or dilution with sweat or transepidermal water and simply drug partitioning in to the skin

8.Other physical methods of evaluation of Transderrmal patches [39]
a. Thickness. – The thickness of patches can be measured at three different places using amicrometer (Mitutoyo Co., Japan) and mean values were calculated (6).

b. Mass variation. – The patches can be subjected to mass variation by individually weighing 10 randomly selected patches. Such determinations can be possibly carried out for each formulation.

c. Folding endurance. – This can be determined by repeatedly folding one film at the sameplace till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance .

d. Moisture vapour transmission *(MVT)*. – MVT is defined as the quantity of moisturetransmitted through unit area of film in unit time . Glass cells can be filled with 2 g ofanhydrous calcium chloride and a film of specified area can be affixed onto the cell rim.The assembly should be accurately weighed and placed in a humidity chamber (80 ± 5% RH)at 27 ± 2 °C for 24 h.

e. Drug content uniformity. – Patches of specified area (3.14 cm)were dissolved in 5 mLof Dichloromethane and the volume can be made up to 10 mL with phosphate buffer Dichloromethane should be evaporated using a rotary vacuum evaporator at 45 °C. A blankcan be prepared using a drug-free patch treated similarly. The solutions can be filtered througha 0.45-µm membrane, diluted suitably and absorbances can be read at 242 nm in a doublebeam UV-Vis spectrophotometer also adherence of the patch to the surface of the skin is also evaluated ie to check the required contact time for release of drug from patches and its absorption into the skin .

Conclusion And Authors Views-
Indications for Alternate Route aremany, like patients unwilling or unable to swallow medications , cancers of the mouth,throat and GI tract ,compromise of the GI tract ,bowel obstruction ,intolerable side effects during administration ,treating localized pain ,avoiding systemic side effects, neonatal/paediatric populations etc.TDDS can be an answer to few of above if not for all of above.

Transdermal drug delivery is not only defines about patch and its application but it is a system containing other formulations like ointments,creams ,gels which are made for use as transdermal drug delivery with the help of penetration enhancers but the dose concept can not be effectively controlled with these semisolid formulations as can be done in a patch.

Also a lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new research are going on in the present day to incorporate newer drugs via this system. Various devices which help in increasing the rate of absorption and penetration of the drug are also being studied. With the invention of the new devices and new drugs which can be incorporated via this system, it used is increasing rapidly in the present time.

At the same time the research in this area is not easy as there are various other limitations for TDDS to be used very common route of administration and with 100% success.Like – Skin is very complex and tough barrier for drugs to go through and reach blood. Not all drugs can go through skin easily. Occlusion of skin and penetration enhancers can not always ensure big success in development of TDDS for a drug candidate. Its very difficult to develop TDDS for a drug having high therapeutic dose, as its difficult to achieve the blood levels of the drug by passing through skin that is why so far TDDS is a success story for “potent” drugs. Large dose cannot be given as well large drug molecules cannot be delivered by TDDS .Some drugs can give rise skin irritationand therefore their the use in the Transdermal Drug Delivery System has been limited.

All formulations based on TDDS concept need to submit the in vivo, invitro data of drug concentration reaching the systemic circulation for their approval but at the same time consideration must be given to the systemic toxicity of the drug from topical formulations. Evidence of drug not reaching the systemic circulation can be one of the quality parameter for the topical formulations.

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