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A BRIEF STUDY ON TRANSDERMAL PATCHES: AN OVERVIEW

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ABSTRACT
Transdermal drug delivery system was presented to overcome the difficulties of drug delivery mainly oral route. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a particular specific dose of medication through the skin and into the bloodstream. It initiated to promote healing to an injured area of the any part of body. An advantage of a transdermal drug delivery route over other types of delivery system such as oral, topical, i.v., i.m., etc. is that the patch provides a controlled release of the medication into the affected individual, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems from the fact that the skin is a very effective barrier, as a result, only medications whose molecules are small can easily penetrate the skin, so it can be delivered by this method.

KEYWORDS: Transdermal Patch, Matrix Patches, Reservoir Type, Membrane Matrix, Drug-In-Adhesive Patches, Micro Reservoir Patches.

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. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. 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.

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

Advantages
1. Avoidance of first pass metabolism of drugs.
2. Reduced plasma concentration levels of drugs, with decreased side effects.
3. Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half- life and low therapeutic index.
4. Reduction of dosing frequency an enhancement of patient compliance.
5. Transdermal medications deliver a steady infusion of a drug over an extended period of time.

Disadvantages
1. Possibility of local irritation such as erythmea, itching, and local edema at the site of application.
2. The number of drugs that can be delivered in this manner is limited because of low permeability of the skin.

Conditions in which the transdermal patches are not used

- The transdermal patch is not suitable when, treatment of acute pain.
- Where rapid dose irritation is required.
- Where the required dose is equal to or less than 30 mg/24 hours.

Care taken while applying transdermal patch

- The part of the skin where the patch is to be applied should be properly cleaned.
- The patch should not be cut, because it destroys the drug delivery.
- The old patch should be removed before applying new patch.
- Don't touch the adhesive layer before application by hand itself or by other things it may produce changes in releas rate & bioavailability.
- Then the patch is placed accurately to the site of application.

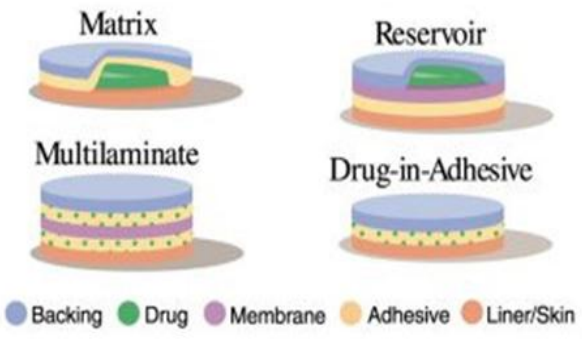
Drug can penetrate through skin via three pathways-

a) Through hair follicals.
b) Through sebaceous glands.
c) Through sweat duct.

Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.[2]

Types of Transdermal Drug Delivery System

Single-layer Drug-in-Adhesive System: In this type of patch the adhesive layer of this system contains the drug. The adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but it is also responsible for the releasing the drug. The adhesive layer is surrounded by a temporary liner and a backing (Figure 1).



Reservoir System: In this System the drug reservoir is kept in between backing layer and a rate controlling membrane. And drug releases through microporous rate controlled membrane. Drug can be in the form of a solution, suspension, and compartment.

Matrix System: This system is of two types:

a) Drug-in-Adhesive System: For the formation of drug reservoir, the drug dispersed in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) on to an impervious backing layer.

b) Matrix-Dispersion System: In this system the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. And this containing polymer along with drug is fixed onto an occlusive base plate in a compartment fabricated from a drug- impermeable backing layer. In this system the adhesive is spread along the circumference instead of applying on the face of drug reservoir to form a strip of adhesive rim.[3]

Micro-Reservoir System: This system is a combination of reservoir and matrix- dispersion systems. In which drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.[4]

The main components to a transdermal patch are

• Polymer matrix– backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate.
• Drug- The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life.eg fenatyl, nitroglyceriene etc.
• Permeation enhancers- increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvent, surface active agents and two component systems. E.g. DMSO
• Adhesive- increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug.
• Backing laminates- should have low modulus or high flexibility. E.g.vinyl, polyethylene.
• Release liner- Protects the patch during storage. The liner is removed prior to use.
• Other excipients like plasticizers and solvents

Drug Delivery Routes across Human Skin.

Drug molecules can penetrate by three pathways:

1. Sweat ducts
2. Hair follicles
3. Sebaceous glands or directly across the stratum corneum.

The stratum corneum is the outermost layer of the epidermis, composed of large, flat, polyhedral, plate-like envelopes filled with keratin that is made up of dead

cells that have migrated up from the stratum granulosum. This skin layer is composed mainly of dead cells that lack nuclei. These dead cells slough off on the surface in the thin air-filled stratum disjunctum, they are continuously replaced by new cells from the stratum germinativum (basale). The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 µm in the dry state to 40 µm when they are hydrated. The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulose discharging their lamellar contents into the intercellular space. The initial layers of the stratum corneum rearrange to form broad intercellular lipid lamellae which then associate into lipid bilayers. As a result of the stratum corneum lipid composition, the lipid phase behavior is different from that of other biological membranes. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor which helps to maintain suppleness. To understand the physicochemical properties of the diffusing drug and vehicle influence across stratum corneum, it is essential to determine the predominant route of drug permeation within the stratum corneum. A molecule travelling via the transcellular route partition into and diffuse through the keratinocyte, but in order to move to the next keratinocyte, the molecule must partition into and diffuse through the estimated 4-20 lipid lamellae between each keratinocyte. In this series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavorable for most drugs. Therefore the intercellular route is now considered to be the major pathway for permeation of most drugs across the stratum corneum.[5]

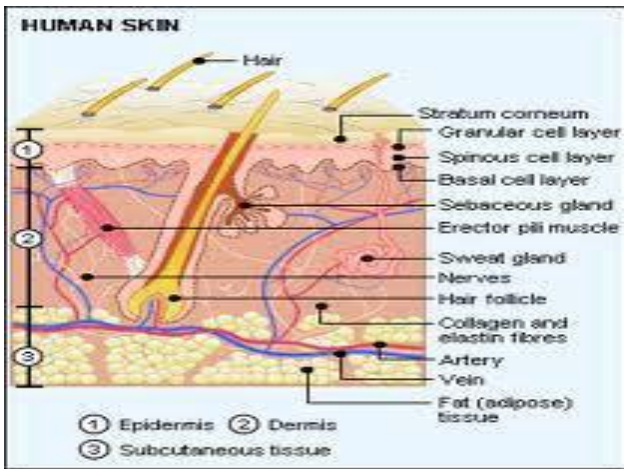


Fig. 2: Transverse section of skin showing routes of penetration.

1. Through the sweat ducts;
2. Directly across the stratum corneum;
3. Via the hair follicles.

Methods of Preparation of TDDS

a) Asymmetric TPX membrane method.
b) Circular Teflon mould method.
c) Mercury substrate method.
d) By using "IPM membranes" method.
e) By using "EVAC membranes" method.
f) Preparation of TDDS by using Proliposomes.
g) By using free film method.

Asymmetric TPX Membrane Method: This method was discovered by Berner and John in 1994. By this method prototype patch can be prepared by using heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter as the backing membrane. Drug dispersed on concave membrane, covered by a TPX [poly (4-methyl-1- pentene)] asymmetric membrane, and sealed by an adhesive.

a) *Preparation:* These are prepared by using the dry or wet inversion process. In this TPX is dissolved in a mixture of solvent (cyclohexane) and non- solvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate. Then casting film is evaporated at 50°C for 30 sec, and then the glass plate is to be immersed immediately in coagulation bath (temperature maintained at 25°C). After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.[6]

Circular Teflon Mould Method: It was discovered by Baker and Heller in 1989. Polymeric solution in various proportions is used as an organic solvent. Then that solution is divided in two parts. In one parts calculated amount of drug is dissolved & in another part enhancers in different concentration are dissolved, and then two parts mixed together. Then plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. After which a dried film formed & that is to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

Mercury Substrate Method: In this method drug & plasticizer get dissolved in polymeric solution. It stirred for 10- 15 min to produce homogenous dispersion then it is poured into leveled mercury surface, covered with inverted funnel to control solvent evaporation.

By Using "IPM Membranes" Method: In the mixture of water & polymer (propylene glycol containing Carbomer 940 polymer) drug get dispersed and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. If the drug solubility in aqueous solution is very poor then solution gel is obtained by using Buffer pH 7.4. The formed gel will be incorporated in the IPM membrane.

By Using "EVAC Membranes" Method: For the preparation of TDS, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membrane is needed as rate control membrane. If the drug is insoluble in water then use propylene glycol for gel preparation. Drug is dissolved in propylene glycol; 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 specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

Preparation of TDDS by Using Proliposomes: By carrier method using film deposition technique proliposomes are prepared. Drug and lecithin ratio should be 0.1:2.0 taken as an optimized one from previous references. For the preparation of proliosome in 100ml round bottom flask take 5mg of mannitol powder, then it is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20- 30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, 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 solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.[7]

By using Free Film Method: In this process firstly cellulose acetate free film is prepared by casting it on mercury surface. And 2% w/w polymer solution is prepared by using chloroform. Plasticizers are to be added at a concentration of 40% w/w of polymer weight. Then 5 ml of polymer solution is poured in a glass ring which is placed over the mercury surface in a glass petridish. The rate of evaporation of the solvent can be controlled by placing an inverted funnel over the petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in desiccators until use. By this process we can prepare free films of different thickness can be prepared by changing the volume of the polymer solution.[8]

Evaluation of transdermal patches

Physicochemical evaluation

Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.[9]

Drug content determination

It can be determined by completely dissolving a small area (1 cm 2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.[10]

Content uniformity test

The test is carried out by performing assay to find out the content of drug material contained in polymeric film of the patch. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity.[11]

Moisture content

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight.[12] The percent moisture content is calculated using following formula,

% moisture content = (Initial weight – final weight)/Final weight*100

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.[13]

Folding Endurance

It involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking gives the folding endurance value.[14]

In-vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches.

In-vitro skin permeation studies

An In vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male

wistar rats weighing 200 to 250 g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before starting the experiment pared patches.[15, 16]

In-vivo studies

In-vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in-vitro studies can be fully explored during in-vivo studies. In-vivo evaluation of TDDS can be carried out using: Animal models and Human volunteers.[17]

A. Animal models

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery systems are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Based on the experiments conducted so far it is concluded that hairless animals are preferred over hairy animals in both in-vitro and in-vivo experiments. Rhesus monkey is one of the most reliable models for invivo evaluation of transdermal drug delivery.

B. Human models

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials are conducted to assess the transdermal systems including the efficacy, risk involved, side effects, and patient compliance. Phase-I clinical trials are conducted to determine mainly safety in volunteers and phase-II clinical trials determine short term safety and mainly effectiveness in patients. Phase-III trials indicate the safety and effectiveness in large number of patient population and phase-IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

Recent advances in the field of transdermal patches

Recently a number of therapeutically active substances are delivered transdermally including large proteins, testosterone, oxybutynin and patches for the relief of pain.

1. Patch technology for protein delivery

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printed patch technology for transdermal delivery of proteins thereby complementing its ViaDerm delivery technology. Such printed patches contain accurate doses of proteins in a dry state. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-Micro Channels, forming a highly concentrated protein solution in-situ. The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.[18]

2. Pain free diabetic monitoring using transdermal patches

The patch (about 1cm2) is made using polymers and thin metallic films. The metallic interconnections and sampling array can be clearly seen. 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, breaching the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30 ms 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 40–50 μm diameter region in the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.[19]

3. Testosterone transdermal patch system in young women with spontaneous premature ovarian failure

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 (sPOF) 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.[20]

4. Transdermal Patch of Oxybutynin used in overactive Bladder (OAB)

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.[21]

5. Pain relief

Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch. Several others are available in the market. Lidoderm, a lidocaine patch (5%), which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E-Trans fentanyl HCl patch. This credit card-size patch is an active delivery device that has a self-contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self-controlled analgesic systems that are very expensive, cumbersome, and require considerable nursing care.[22]

6. Molecular absorption enhancement technology

Absorption enhancers are the compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as well as certain phenols seem to improve transdermal absorption. For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to a therapeutic level. Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen. Phloretin, a polyphenol, enhanced the absorption of lignocaine. The enhancement in permeation of celecoxib through rat skin was estimated using transcutol and oleic acid as permeation enhancers. A comparative flux pattern of formulations containing these enhancers (oleic acid and transcutol) showed that transcutol was less effective as a permeation enhancer than oleic acid in increasing the flux of celecoxib.[23] In general, absorption enhancement research has been done with excised animal skin (rat, pig or rabbit) or human skin obtained from cadavers or plastic surgery procedures.

Future of Transdermal Drug Delivery System

Future novel formulation approaches and technologies include liposomes, niosomes and micro emulsion. Aim of this strategy is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal devices has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will rise in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low-frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetophoresis, has been investigated as a means to increase drug flux across the skin. The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase. In current scenario, transdermal route of drug delivery system in comparison with oral treatment as the most successful innovative research area in new drug delivery system, with around 40% of the drug delivery candidate products under clinical trials related to transdermal or dermal system. The systemic drug administration though skin holds several advantages such as maintenance constant drug level in blood plasma, less number of side effects, and improvement of bio availability by circumvention of hepatic first pass metabolism and increase patient compliance with respect to drug regime used for treatment. In recent times, skin considered as a safest port for drug administration, to provide continuous drug release into systemic circulation.

CONCLUSION

Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. TDDS are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy. It offers the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. This may be achieved by by-passing the hepatic first metabolism. Almost all major and minor pharmaceutical companies are developing TDDS. Potential development in drug delivery systems include the use of improved adhesive and/or enhancer technologies; and systems that exploit thermal, electrical, ultrasonic, or other forms of energy to "drive" molecules through the stratum corneum or microneedles to bypass the occlusive nature of the stratum corneum in a controlled fashion.

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