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A Comprehensive Review: Transdermal Drug Delivery System: A Tool For Novel Drug Delivery System

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Abstract

In the recent decade, skin delivery (topical and transdermal) has gained an unprecedented popularity, especially due to increased incidences of chronic skin diseases, demand for targeted and patient compliant delivery and interest in life cycle management strategies among pharmaceutical companies. Transdermal drug delivery system was presented to overcome the difficulties of drug delivery especially oral route. Transdermal drug delivery refers to a means of delivering drugs through the surface of the skin for local or systemic treatment. The drug functions after absorption through the skin into the systemic circulation *via* capillary action at a certain rate. Transdermal patches are now widely used as cosmetic, topical and transdermal delivery systems. These patches represent a key outcome from the growth in skin science, technology and expertise developed through trial and error, clinical observation and evidence-based studies that date back to the first existing human records. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of delivery system such as oral, topical, intravenous (i.v.), intramuscular (i.m.), etc. is that the patch provides a controlled release of the medication into the patient, 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 stems from the fact that the skin composition offers very effective barrier that allow only small molecule based drugs to penetrate the skin and pass through the barrier. Sildenafil citrate (SLD) is a selective cyclic guanosine monophosphate-specific phosphodiesterase type 5 inhibitor used for the oral treatment of erectile dysfunction and more recently, it has been used for the treatment of pulmonary arterial hypertension and the enhancement of uteroplacental perfusion in case of fetal growth retardation. The challenges facing the oral administration of the drug include poor bioavailability and short duration of action that requires frequent administration. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variations.

Keyword: Skin delivery, Transdermal drug delivery, Oral rout, Sildenafil citrate, Pulmonary arterial hypertension

Introduction

Oral route is the most popular route of drug delivery system but it has some disadvantages including first pass metabolism, drug degradation in gastrointestinal tract due to enzymes, pH etc. To overcome these problems, a novel drug delivery system was developed by Chien in 1992, Banker in 1990, Guy in 1996 based on transdermal patches meant for transdermal delivery[1]. Transdermal drug delivery system (TDDS) refers to a route of drug delivery through the skin to achieve local or systemic therapeutic action. It is one of the focus areas of research for the third-generation pharmaceutical preparations, next only to oral medication and injection[2]. The reasons lie in the administration route of the drug, which is convenient, easy to use, non-invasive, and also improves patient compliance[3]. It also reduces the fluctuation of the drug concentration in the blood, provides steady plasma levels and fewer chances of overdose and easy detection of the drug[4,5]. At the same time, it evades problems associated with oral delivery such as the effect of the gastrointestinal environment (pH, enzymatic activity, drug and food interaction) on the drug efficacy and the 'first pass effect' (the rapid uptake and metabolism of an agent into inactive compounds by the liver, immediately after enteric absorption and before it reaches the systemic circulation). They are available in different sizes & having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barrier. A transdermal patch containing high dose of drug inside is retained on the skin for prolonged period of time and enters into blood circulation via diffusion process. 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[6,7]. Transdermal drugs will continue to gain popularity along with further improvements to improve safety and efficacy. A further major step forward will be the production of patches delivering peptide and even protein substances including insulin, growth

hormone, and vaccines[8]. Transdermal patches can be categorized into three categories - first generation, second generation, and third generation.

First generation transdermal patches

They are the first set of patches and have been used much in clinics. The transdermal patch design consists of a drug in a reservoir that is enclosed on one side with impermeable backing and an adhesive, which contacts the skin[8]. However, due to certain limitations, not all drugs with suitable properties can be delivered. The first generation transdermal patches are limited primarily to the outermost skin barrier that is stratum corneum. Hence, the drugs should be of low molecular weight, lipophilic, and efficient at low doses.

Second generation transdermal patches

The second generation transdermal patches consists of advanced system that allows increased the skin permeability, reduced damage to the deeper tissues and better transport into the skin. However, enhancement methods developed in this generation, such as chemical enhancers, non-cavitation ultrasound and iontophoresis experienced difficulty in balancing between increased permeation through stratum corneum and at the same time protection of tissues at the deeper level. Chemical enhancers disrupt the highly ordered bilayer of the stratum corneum by inserting amphiphilic molecules to help in better permeation. This leads to skin irritation. Similarly, Iontophoresis involves administration of drugs into the stratum corneum under low voltage current. It mainly provides an electrical driving force for transport across stratum corneum. It does not disturb the skin barrier, thus, can be used for delivery of small molecules that carry a charge and some macromolecules up to a few Daltons. Rate of drug delivery can be controlled using a microprocessor. In Non-cavitation ultrasound, the pressure gradients and oscillation associated with ultrasound emerges to be responsible for passage of drug through the skin by disrupting stratum corneum and thereby increasing the permeability. The effects of ultrasound have been limited to small lipophilic molecules. It has been limited due to its associated tissue heating, which can damage the deeper tissue[9].

Third generation transdermal patches

The third generation of transdermal delivery system involves targeted approach of disruption of stratum corneum while protecting deeper tissues intact. Novel chemical enhancers, electroporation, cavitational ultrasound, microneedles, thermal ablation and microdermabrasion are few newer techniques that deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials[10].

Skin

The skin is the largest and most visible organ of the body. The skin covers a total surface area of approximately 1.5-2 m2 and is the barrier between human body and the external environment[11]. Many of its functions include temperature regulation, immunity from microorganisms, maintaining electrolyte balance, as well as protection from physical injuries, chemical agents, and ultraviolet radiation[12,13]. In addition, skin is also an important avenue for absorption of drugs and exerting their efficacy. The skin is composed of epidermis, dermis, and subcutaneous tissue, and contains appendages (such as hair follicles, sebaceous glands, sweat glands), blood vessels, lymphatic vessels, nerves, etc. The epidermis can be divided into five layers from the inside to the outside, namely the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (SC) (Figure 1) [13,14]. The properties of SC are quite different from those of the other layers, with the overall structure composed of inactive keratinocytes and intercellular lipids that form a 'brick and mortar' model, in which, the protein-rich keratinocytes serve as the bricks and the intercellular lipids serve as the mortar[15,16]. SC is the main factor determining the skin barrier, and also the major obstacle limiting the rate of percutaneous absorption even though the thickness is only 10-20 μm[17,18]. There are two routes of transdermal permeation of drugs. One is through the natural channel of skin appendages. These channels are hydrophilic and have a diameter of few microns. Owning to the fact that the average follicular orifice area on the human skin surface is only about 0.1% of the total surface area[19], it is not the primary pathway of percutaneous absorption. The second route is through the penetration of the epidermis, to enter the dermis through the SC and the deeper epidermis, being absorbed in the body circulation by the capillaries. As for the penetration of drugs and passing through the SC, two pathways exist,namely, the transcellular route, through which substances infiltrate the keratinocytes and intercellular lipids, and subsequently pass through and are transported. The drug needs to diffuse through hydrophilic and hydrophobic areas, and therefore, it may not be applicable to most drugs. The second and most likely route taken by drugs when penetrating the SC is via a tortuous pathway through the lipids surrounding the keratinocytes, known as the intercellular route[20].

Mechanism of action of transdermal patch

A typical transdermal patch consists of an adhesive layer which sticks on to the skin, a semi solid to liquid drug is smeared between the layers of drug releasing membranes which are exclusively semipermeable in nature. An outermost clear backing protects overall patch during application. A transdermal patch when applied to skin, establishes a good connection between the skin and semi permeable membrane Figure 2. A slow and a sustained flow of drug occurs from drug reservoir of the patch to the skin via drug release membrane by simple diffusion/ osmosis process through percutaneous drug delivery system[21].

Advantages of transdermal drug delivery

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.
- Avoidance of first pass metabolism.
- The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
- As a substitute for oral route.
- The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
- Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
- Avoidance of gastro intestinal incompatibility.
- Convenience especially notable in patches that require only once weekly application, such a simple dosing regimen can aid in patient adherence to drug therapy.
- Minimizing undesirable side effects.

- Provide utilization of drug with short biological half lives, narrow therapeutic window.
- Avoiding in drug fluctuation drug levels.
- Inter and intra patient variation.
- Termination of therapy is easy at any point of time.
- Provide suitability for self administration.
- They are non invasive, avoiding the inconvenience of parentral therapy.
- The activity of drugs having a short half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- It is of great advantages in patients who are nauseated or unconscious.
- Transdermal patches are better way to deliver substances that are broken down by the stomach aids, not well absorbed from the gut, or extensively degraded by the liver.
- Transdermal patches are cost effective.

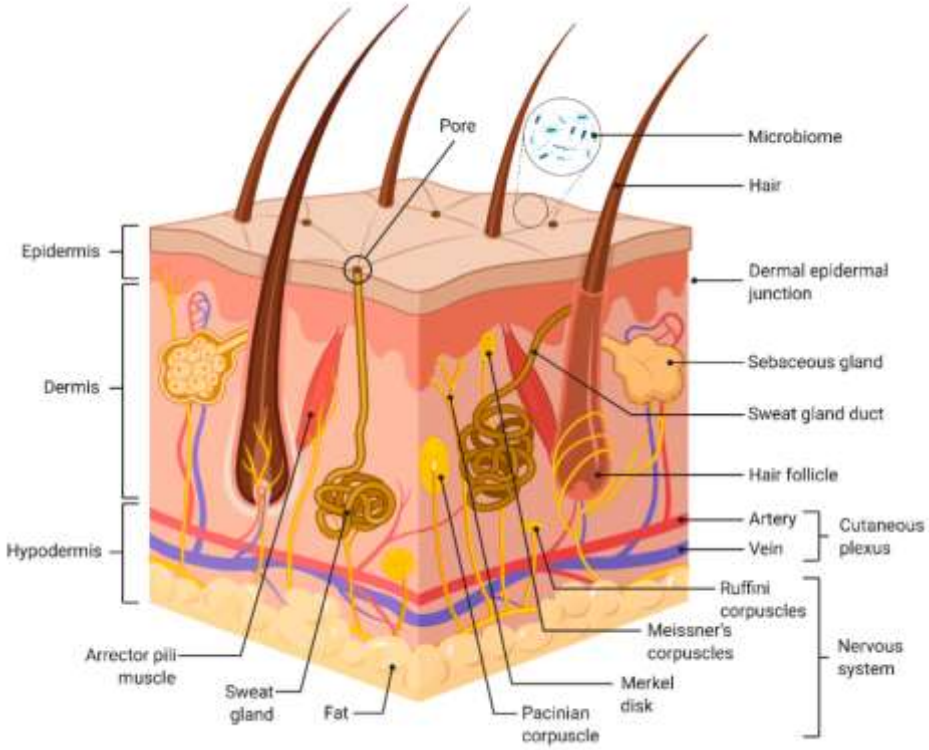

Figure 1: Schematic representation of the different skin layers

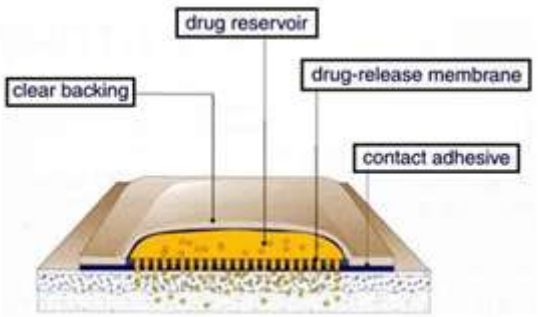

Figure 2: Different layers of transdermal patch with mechanism of action[22]

Disadvantages of transdermal drug delivery

- Transdermal drug delivery system cannot deliver ionic drugs.
- It cannot achieve high drug levels in blood.
- It cannot develop for drugs of large molecular size.
- It cannot deliver drugs in a pulsatile fashion.
- It cannot develop if drug or formulation causes irritation to skin.
- Possibility of local irritation at site of application.
- May cause allergic reaction.
- Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.

❖ Long time adherence is difficult[23-28].

Basic components of TDDS

✓ Polymer matrix/drug

✓ Reservoir Drug

✓ Permeation enhancer

✓ Adhesive

✓ Backing film

✓ Liner

✓ Plasticizer

Polymer matrix[29-38]

It is very important component in TDDS and control the release of drug from patch.

✓ They should not produce any toxic effect either alone (or) with other excipients in TDDS formulation.

✓ They shouldn't expensive one and it should be easily manufactured.

✓ They should have good stability and more compatibility with drugs and other components of system.

✓ The polymers used in TDDS should be stable.

The cross linked poly ethylene glycol, eudragit, ethyl cellulose, poly vinyl pyrolidine and hydroxyl propyl methyl cellulose are commonly used as matrix formers in TDDS. The polymers like EVA, poly urethane and silicone rubber are used as rate controlling membrane.

Table 1 List of polymers used in TDDS

Natural polymers	Synthetic elastomer	Synthetic polymer
Cellulose derivative, Gelatin, Shellac, Starch, Waxes, Gums, Natural rubber, Chitosan etc.	Poly butadiene, Hydrin rubber, Poly iso butylenes, Silicon rubber, Nitrile, Acronitryle, Neoprene, Butyl rubber etc	PVA, Poly vinyl chloride, Polyethylene, PVP, Poly acrylate etc.

Drug reservoir

The selection of drug is based on its properties like physiochemical as well as biological properties.

✓ Drug should have higher first pass metabolism.

✓ Drugs having narrow therapeutic window.

✓ Drugs with short half life.

✓ Drugs with frequent dosing.

✓ Low molecular weight moieties (<1000 Dalton)

✓ Drugs with low dose (mg/day).

✓ Low melting point substances (<200^{0}C)

✓ Drugs having affinity with both lipophilic and hydrophilic phases.

✓ Drugs without any dermatological effect are suitable for formulation as transdermal patch.

Permeation enhancers

These are the substances which are reversibly changes the structure of stratum corneum and increase the permeation of drug from skin to blood stream. They are two types

1) Chemical enhancers [accelerants, absorption promoters (or) permeation enhancers]

They act by increasing drug permeability by reversible damage to stratum corneum and to increase partition coefficient of drug.

Table 2 List of chemical enhancers used in TDDS

Chemical Enhancers	Examples
Solvents	Water, Methanol, Ethanol, Propylene Glycol, Di-Methyl Acetamide
Terpenes	Menthol, Cardamom Oil, Cinnamon Oil, 18-Cineol, Carvone
Pyrolidine	N-Methyl 2- Pyrolidine, Axone
Sulfoxides	DMS, Didecyl Sulfoxides
Fatty Acids & Esters	Oleic Acid, Linoleic Acid, Lauric Acid, Capric Acid
Surfactants	Anionic- SLS, Decodecyl Methyl, Sulfomide Non-Ionic- Pluronic F127, Pluronic F68, Bile Salts- Sodium Taurocholate, Sodium Deoxy Cholatte
Amides	Dimethyl Acetamide, Dimethyl Formamide
Miscellaneous	Phosphor Lipids, Amino Acid Derivatives, Enzymes, Urea

Physical enhancers

The following physical techniques have been used for enhancing the permeability of drug through skin.

- ✓ Ionotophoresis
- ✓ Electrophoresis
- ✓ Sonophoresis
- ✓ By using micro needles
- ✓ Magnetophoresis
- ✓ By using laser radiation

Adhesive

- ✓ It is used to affix the patch on the skin.
- ✓ It should be adhere onto the skin with light pressure applied by finger.
- ✓ It should be easily removed from the skin surface without leaving any residue. It should not produce any irritation.
- ✓ It should have excellent contact with the skin.
- ✓ It should be compatible with other components in formulation.
- ✓ It should allow permeation of drug freely from the patch E.g. polyacrylates, polyisobutylenes and silicone derivatives.

Backing laminate

- ✓ It is used to protect the patch from outer environment.
- ✓ It should be chemically resistant.
- ✓ It should not allow permeation of components in the patch.
- ✓ It should have optimal elasticity, flexibility and tensile strength.
- ✓ It should have low water vapour transition rate.
- ✓ If a drug incorporated into a liquid (or) gel in the formulation, the backing material should be heat stable to allow fluid, the tight packing of drug reservoir (form-fill seal process). E.g. vinyl, poly ethylene and poly ester film

Liner

It is used to protect the patch during the storage.

- ✓ It is removed during application of patch on skin.
- ✓ It should be chemically inert.
- ✓ It consists of two layers, one is base layer and other is release coating layer. The base layer may be occlusive (E.g. poly ethylene, poly vinyl chloride). The release coat layer made up of silicon (or) Teflon.
- ✓ The polyester foil and metallized laminate are also used as release liner.

Plasticizer

- ✓ It is used to provide plasticity to transdermal patch.
- ✓ It is also chemically inert and compatible with all other ingredients in the formulation.
- ✓ Some of the plasticizer also acts as a permeation enhancer.

Major transdermal systems

Single-layer Drug-in-Adhesive: The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for releases of the drug. The adhesive layer is surrounded by a temporary liner and a backing[39].

Multi-layer Drug-in-Adhesive: The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for release of the drug. The multi-layer system is different however as it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing[40].

Reservoir: Unlike the Single-layer and Multi-layer Drug-inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order[41].

Matrix: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it[42].

Vapour Patch: In this type of patch the adhesive layernot only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and is used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep[43].

Various methods for preparation of TDDS

Asymmetric TPX membrane method: - A prototype patch can be fabricated using a heat sealable polyester film with a concave of 1 cm diameter will be used as the backing membrane. Drug sample is dispensed into concave membrane, covered by TPX {poly- (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

Circular Teflon mould method: - In this method, solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the

quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are stirred for 12 h and poured into circular Teflon mould. The moulds are 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. The dried films are 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 is dissolved in a polymer solution along with plasticizer. The above solution is stirred for 10-15 min to produce a homogenous dispersion and poured onto a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

"IPM membranes" method: - In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

"EVAC membranes" method: - In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 h in magnetic stirrer. The dispersion is neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

Aluminium backed adhesive film method: Aluminium backed adhesive film method is a suitable one when loading dose is greater than 10mg. For preparation of the same, chloroform is a solvent of choice because most of the drugs as well as adhesives are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked with tightly fitting cork blocks.

Preparation of TDDS by using proliposomes: - The proliposomes are prepared by carrier method using film deposition technique. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 min. 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 0.5 ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquot (0.5 ml) 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 over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freezing temperature until characterization.

Free film method: - In this method, free film of cellulose acetate isprepared by casting on mercury surface. A polymer solution (2% w/w) is prepared using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film is separated out and stored between the sheets of wax paper in desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution[44-50].

Future of transdermal drug delivery system

Future aspects in transdermal drug delivery system include administration of drugs meant for transdermal delivery through liposomes, niosomes and micro emulsions. Aim of this development 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 for transdermal delivery. The market for transdermal patches has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will increase 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 modesof '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 is 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 transdermal drug delivery systems have been designed as an alternative, safest and easy route for systemic drug delivery. The systemic drug administration through skin holds several advantages such as maintaining constant drug level in blood plasma, less number of side effects, and improvement of bio availability by circumventing hepatic firstpass metabolism and increase patient compliance with respect to drug regime used for treatment. In recent times, skin is considered as a safest port for drug administrationto provides continuous drug release into systemic circulation[51].

Conclusion

Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Wide range of drugs can be delivered improved drug uptake Minimal complications and side effects low cost and easy to use. Transdermal route of drug delivery system has been one of the advanced modes of drug delivery with

safety and good efficacy. There has been a lot of improvement in the process of transdermal route of drug delivery since its beginning years of 1981 to the current advancements till 2022. This TDDS review articles provide valuable information regarding the transdermal drug delivery systems and the process of preparation of transdermal patches as a ready reference for the research scientist who is involved in TDDS.

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