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Review Article

TDDS – A Review

Recent Advancements in Transdermal Drug Delivery System: A Review

Rajesh Jain[1], Dr.Manish Goswami*, Dr.Sanjeev Kumar Mittal[2] and Simran[3]

[1]Department of Pharmaceutical Sciences, RIMT University, Gobindgarh, Punjab

**Department of Pharmaceutical Sciences, Saraswati Group of Colleges, Gharuan, Mohali*

[2]Department of Pharmaceutical Sciences, RIMT University, Gobindgarh, Punjab

[3]Department of R and D-Pharmaceutics, Ananta Medicare Limited (Collaborating Affiliation: Department of Pharmaceutics, Saraswati Group of Colleges, Gharuan, and Mohali)

Abstract: Other non-invasive administration methods have recently become an alternative to the more conventional method of ingesting medications, which involves using a needle. The Transdermal Drug Delivery System (TDDS) is the most attractive method among them because of its low rejection rate, appreciable simplicity of administration, and superior convenience for patients. TDDS may find applications not only in the pharmaceutical industry but also in the sectors of skincare and cosmetics. This technique focuses mainly on delivering the medication in a particular area. As a result, it could reduce the formation of a local concentration of the drug and nonspecific transport to tissues that the agent does not precisely target. However, because the physicochemical characteristics of the skin translate to several obstacles and restrictions in transdermal distribution, a significant number of research is required to overcome these bottlenecks. In this study, the many different kinds of available TDDS approaches have been addressed, as well as a critical assessment of their benefits and limits, characterization methods, newly added drugs, and potential. In addition, the present study analyzes the potential of these techniques. The advancement of research into these other technologies has shown the TDDS's high level of efficiency, which has the potential to find applications in a diverse variety of industries.

Keywords: Transdermal Delivery System, Skin, Transdermal Patch, Methods, Penetration enhancers, Market growth of TDDS.

***Corresponding Author**

Dr.Manish Goswami , Department of Pharmaceutical Sciences, Saraswati Group of Colleges, Gharuan, Mohali

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1. INTRODUCTION

There has been a significant increase in interest over the last few years in the research and development of novel drug delivery structures for already existing therapeutic particles. The story of an innovative transport structure for existing drug atoms not only enhances the drug's efficacy in terms of its viability and safety but also makes a substantial contribution to the total recovery benefit and considerably improves the constant sequence. When applied to the skin, the distinct and separate dose structures of the transdermal drug delivery system, sometimes referred to as patches, transport the medicine through the skin at a regulated pace and in a mainstream manner. TDDS, or transdermal delivery systems, are dosage structures that provide treatment to the patient's calming skin and convincing[1-3]. The transmission of medications through the skin at a predetermined pace with minimal burial and untraversable variety is the fundamental objective of the transdermal drug administration system. Transdermal drug delivery is one medication delivery method showing the most significant promise. Because of this, the quantity generally injected into the digestive system and liver by oral course is reduced. Both short-term and long-term adherence is improved as a result, as is health. As a consequence of the temporary overstock of the drug, the effects of the drug are improved, and it is handy for transdermal drugs that need the correct application. The vast majority of transdermal patches are designed for dynamic fixation at a zero-application rate over a time ranging from seven hours to several days after the patch has been applied to the skin. This is very helpful as a prophylactic medication for many ailments. Indicators of percutaneous drug retention include the patient's clinical response to treatment with controlled medications, measurable quantities of the drug in the patient's blood, detectable levels of the drug and its metabolites in the patient's urine, and the patient's blood levels of the drug [4,5]. The Delivery of drugs via the skin, also known as transdermal drug delivery, is an attractive option for administering medications orally and is also designed to provide an alternative to the practice of subcutaneous infusion[6,7]. Since the beginning, people have been applying various substances to their skin to produce a healing effect. In more recent times, different theme techniques for the treatment of acute symptoms have been devised. In 1979, the FDA in the United States gave its approval to a solution that could carry scopolamine into the body for three days at a time. This solution was intended to be used in the treatment of stroke. After ten years, nicotine patches were introduced as the first [8, 9]

1.1. Drug absorption through the skin

Due to the enormous surface area of the skin, it is a place that has the potential to be used for the absorption of drugs. For pharmaceuticals to be absorbed into the bloodstream, it is necessary for them to first travel through the skin, and it is molecular structures[11]. As seen in Figure 1, the process of medicine absorption from the skin through the stratum corneum may be broken down into two distinct pathways: the transappendageal and the transepidermal pathways [12]. Transepidermal absorption is considered to be the significant and essential route of absorption. Because the stratum corneum has a larger surface area, it is easier for medications to disseminate over the skin's surface and penetrate the transcellular cells or the interspaces between the cells intercellular when they are delivered via a transdermal patch. The transepidermal pathways may further be broken into two subcategories: the transcellular and the intercellular routes[13,14]. The transcellular route allows for the passage of pharmaceuticals via the stratum corneum cells as part of absorption. As a consequence of this, drugs are required to traverse the lipid bilayer membranes[15,16]. The transepidermal pathways may further be broken down into two subcategories: the transcellular and the intercellular routes. Medications can pass through the stratum corneum cells through the transcellular route as part of the absorption process. As a consequence of this, drugs are required to traverse the lipid bilayer membranes. Because of the hydrophobic properties of the lipid complex found in the stratum corneum cell membranes, hydrophobic drugs prefer to be administered by this route. The second route, the intercellular pathway, requires the drug to diffuse through resident keratinocytes' lipid matrix in the stratum corneum's intercellular region. The trans-appendageal route of drug absorption from the skin is defined as drug transport through sweat glands or hair follicles in the skin[17,18]. This pathway accounts for about 10% of all drug absorption from the skin. This pathway is necessary for the transport of ionizable or polar substances. It is advantageous for transporting large macromolecules that have trouble moving through epidermal cells because of their molecule size and different partition characteristics. However, compared to the transepidermal route, the transdermal route has a much smaller absorption region (only 0.1 per cent of the entire skin surface), as shown in Figure 1. This means that the Transdermal route has a very restricted use[20].

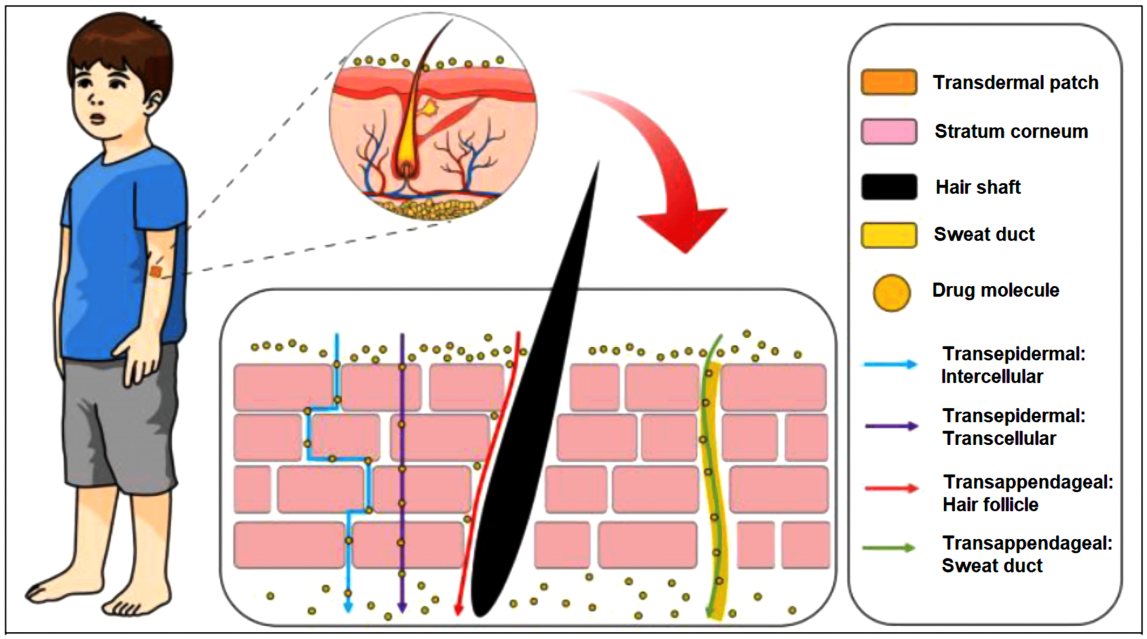

Fig 1: Schematic representations of transdermal drug delivery mechanisms[21].

This figure explains the entire mechanism of the transdermal drug delivery system. Also, it shows the schematic representation of how a patch works by applying it on the topical layer and how it goes to different layers of the skin.

1.2. Advantages of TDDS

When compared to more conventional administration techniques, transdermal medicine delivery systems provide several significant benefits, including the following:

1. A longer duration of action leads to a reduced need for dosing on a regular basis[22].
2. An increase in the convenience of administering drugs that, under other circumstances, would need consistent dosing
3. Increased availability in the body
4. The capacity to halt medication delivery by just removing the patch from the patient's skin
5. Increased patient comfort and compliance thanks to a method of administration that is non-invasive, painless and straight forward[2324].

1.3. Disadvantages

1. A large dose of the drug does not penetrate via the TDDS because the drug moiety must exhibit particular physicochemical features for penetration by the skin and if the dose of the drug is large, which is defined as being greater than 10–25 mg per day.
2. If the drug moiety does exhibit these particular physicochemical features for penetration by the skin, then a small dose of the drug can penetrate via the TDDS.
3. The medication or the excipients included in the formulations of TDDS may produce local irritation at the administration site, manifesting as itching and oedema in the affected area.
4. Clinical necessity is another essential consideration that must be given before creating a product that may be applied transdermally.
5. Due to the components of the system, some patients get contact dermatitis at the site where the medication is applied.
6. Adjustments to the dose regimen and calculations of compartment kinetics take a considerable amount of time when dealing with TDDS.[27]
7. It usually is quite difficult for large medication molecules (those with a size greater than 500 Da) to get through the stratum cornea.
8. Substances with either very low or very high partition coefficients do not enter the circulation.
9. Because they have a low solubility in water and fat, medications with a high melting point may be delivered using this method because it does not need refrigeration[25,26].

2. CLASSIFICATION OF TDDS BASED ON CONSTRUCTION

2.1 Transdermal patches

A transdermal patch, also known as a skin adhesive patch, is a device loaded with a drug candidate and often attached to the skin to transport a specific amount of medication through the skin and into the bloodstream[28-30]. The adhesive serves two functions: It is the glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug[31]. The drawbacks with this are that the concentration of the medicine within the adhesive directly influences the "stickiness" of the adhesive. Therefore, if large amounts of the drug are to be supplied, either the patch size must be raised or the patch must be reapplied repeatedly. Several medications are typically mixed with chemicals such as alcohol within the patch to increase skin penetration and absorption[32]. As shown in Table 1, The US Food and Drug Administration has authorized transdermal patches and delivery methods on this list.Only the first authorized product for a particular medicine or drug combination is displayed via a specific administration mode. No topical creams, ointments, gels, or sprays are included.

Table 1: Transdermal drugs approved by US FDA

Approved year	Drug/product name	Indications	Company
2001	Ortho Evra	Contraception	Ortho-McNeil Pharmaceutical (USA)
2003	Estradiol with Levanorgestrel	Menopausal Symptoms	BayerHeathcare Pharmaceuticals(USA)
2005	Lidocaine with tetracaine/ Synera	Local dermal analgesia	Endo pharmaceuticals
2006	Fentanyl HCL	Acute postoperative pain	Alza
2006	Methylphenidate	Attention deficit hyperactivity disorder	Shire (Wayne, PA, USA)
2007	Rotigotine	Parkinson's disorder	Schwarz Pharma (USA)
2007	Rivastigmine	Dementia	Novartis

2.2 Components of transdermal patch

1. Drug: The drug is in direct contact with the liner that contains the medication.
2.The liner safeguards the patch while it is being stored. Therefore, it is necessary to take out the liner before utilizing the product.
3.Adhesive: This not only helps to adhere the patch to the skin but also helps to bond the various components of the patch together. For example, acrylics, polyisobutylene, and silicone are all examples of adhesives that have several uses in the pharmaceutical industry. When an adhesive, medicine, and maybe boosters are combined in a single application, choosing a PSA can be more complex and time-consuming.
4. The membrane is responsible for regulating the release of drugs from reservoirs and multi-layer patches.
5. Backing: The film acts as a barrier between the patch and protects the drug from the outside environment.

2.3 First-generation transdermal drug delivery system

The first generation of transdermal delivery technologies is responsible for the majority of transdermal patches now in clinical use. Candidates for first-generation Delivery must be low-molecular-weight, lipophilic, and effective at low dosages. Because of inadequate oral bioavailability, the requirement or desire for less frequent dosing, constant delivery patterns, or other causes, transdermal administration should be more appealing than oral Delivery.The barrier created by the stratum corneum, the skin's outermost layer, which is 10 to 20 µm thick, is the primary limitation of the first-generation technique to transdermal distribution.

2.4 Second-generation transdermal drug delivery system

The second generation of transdermal delivery systems acknowledges the need to improve skin permeability to broaden the scope of transdermal medications. The optimal enhancer should

- Increase skin permeability by reversibly altering stratum corneum structure
- Provides an increase in skin permeability.
- Prevent harm to deeper, live tissues by providing additional pushing power for passage into the skin.

However, this generation's enhancement technologies, such as
1. Conventional chemical enhancers
2. Iontophoresis
3. Nonactivational ultrasound has failed to strike a compromise between increasing distribution over the stratum corneum and sparing deeper tissues from damage.

2.5 Third-generation transdermal drug delivery system

Because it targets its effects on the stratum corneum, the third generation of transdermal delivery devices is set to influence medication delivery significantly. This targeting allows for more effective transdermal distribution while safeguarding deeper tissues by disrupting the stratum corneum barrier. In human clinical trials, we discovered that new chemical enhancers, electroporation, cavitational ultrasound, and, more recently, microneedles, thermal ablation, and microdermabrasion could transfer macromolecules through the skin, including therapeutic proteins and vaccinations. Active and passive transdermal patches are the two categories available for purchase. When an external force is applied, it helps the medicine penetrate the skin more effectively in an active patient.Regarding the passive form, the medication is often distributed using a gradient mechanism depending on its solubility or concentration. This sort of dispersion is considered to be the most common. The effective delivery rate of a drug is typically influenced by several parameters, including the molecular structure of the medication, its solubility, and its potency. Permeation enhancers might be used in passive systems to hasten the drug diffusion process. There are four distinct options to choose from while shopping for transdermal patches, as shown in Figure 2.

1. **Drug-in-adhesive: In this drug-in-adhesive** coating with a single layer, the drug is kept in direct touch with the adhesive that is adhered to the skin. The adhesive layer binds the various layers together and the skin and contributes to releasing the medication.
2. **Multi-layer:** Drug-in-adhesive with many layers because the medication is included directly into the adhesive, the Single-layer drug-in-adhesive operates like that of the multi-layer drug-in-adhesive. Multiple drug-in-adhesive layers are inside the system, each separated by a membrane. In addition, this repair patch comes with a removable liner layer and a permanent backing layer.
3. **Reservoir:** A liquid compartment that contains a medicinal solution or suspension is kept separate from the liner by a semipermeable membrane and an adhesive layer.
4. **Matrix:** A semisolid matrix medicament layer that contains a medication as a solution or suspension and is in direct contact with the liner is included in this system as one of its components. The sticky layer covers some of the drug

layers within this apparatus before completely covering it. This treatment strategy may help patients whose Alzheimer's disease is mild to moderate in severity. In a large, multinational, 24-week, double-blind, randomized clinical trial and subsequent 28-week open-label extension study, the potency, safety, and tolerability features of the rivastigmine patch were compared to those of a placebo. This demonstrates the point.

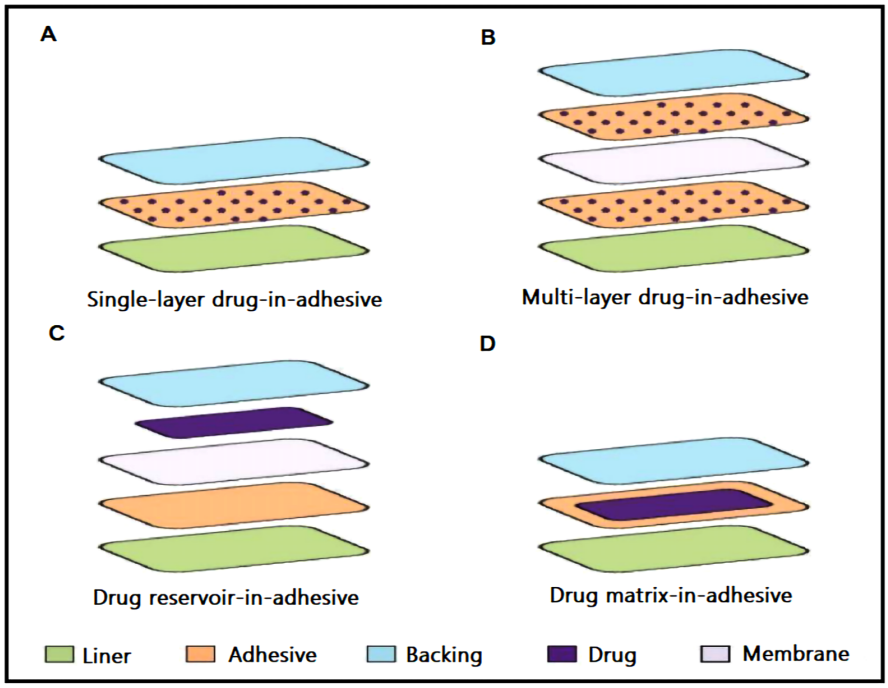

Fig 2: Representation of different types of patches

As shown in Figure 2 represents the different types of patches available in transdermal drug delivery systems. In addition, other types of patches have further use of components.

3. MICROFABRICATED MICRONEEDLES

A combination of a hypodermic needle and the transdermal patch is used to administer and transfer the medicament across a membrane. An epidermis- and stratum corneum-penetrating drug reservoir and projections extending from the pool make up the system.

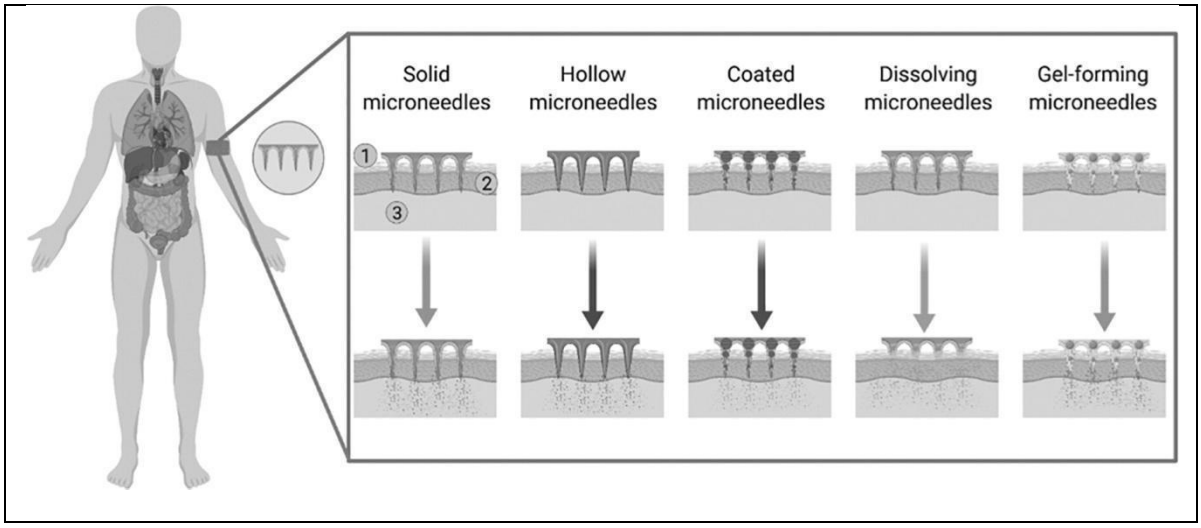

Fig 3: Delivery site for microneedle technology[3435].

This figure explained the sites for the microneedle technology. Also, this figure shows different types of microneedles and their mechanism. For example, the hollow needles have an applied formulation, while the solid needles are manufactured using silicon etching technology and micromechanical system manufacturing. Because the hollow needles don't go deep enough into the skin to reach nerve endings, as shown in Figure 3, the patient feels no pain when the solid needles are inserted. For TDDS, there have been some techniques for delivering microneedles. The following are among them:

Poke with patch method: A small hole is poked into the skin, and the medication patch is applied.
Coat and poke method: After the needles are coated with the medication, the medications are injected into the skin, disintegrating and becoming available to the body.

Biodegradable microneedles: Polymeric microneedles, biodegradable, are used to administer medication.
Hollow microneedles: A hollow bore needle is used to give the medication[36].

This table enlists the drugs and nutraceuticals successfully incorporated into the novel drug delivery systems. In addition, this table shows which pharmaceuticals and nutraceuticals have already been used in which kind of delivery system, as shown in Table 2 below.

Table 2: Pharmaceuticals (drugs and nutraceuticals) successfully incorporated into NDDS.

Delivery Approach	Nutraceuticals	Intended Effect	References
Nano Complex	Folic acid, β-carotene, ergocalcifer ol and curcumin	Nutraceuticals delivery	[37]
Phytosome	Silymarin	Oral Delivery	[38]
Nutraceuticals conjugated gold nanoparticles	Quercetin, Andrographolide	Leishmaniasis	[39]
Nanospheres and nanocapsules	Curcumin	Oral Delivery	[40]
Metal and Nanoparticles	Garlic cayenne Pepper	Antibacterial activities	[41]
Colloidal Nanoparticle	Curcumin	Anticancer Oral Delivery	[42]
	Caffeine, Curcumin	Oral Delivery	[43]
Liposomes	Ginseng extract, Curcumin	Oral Delivery	[44]
Solid lipid nanoparticles	α- Lipoic acid	Topical Delivery	[45]
nanostructure lipid carriers	Resveratrol	Oral Delivery	[38]
Dendrimers	Green tea extract, ginseng	Oral Delivery, nasal Delivery	[46]
Biopolymer nanoparticles	Casein, Zein Zein-quercetin	Oral Delivery	
Gold Nanoparticles	Quercetin	Antileishmanial efficiency	[47] [48]

4. ADVANCEMENTS IN PENETRATION ENHANCEMENT TECHNIQUES

4.1. Skin Penetration Physicochemical Aspects

The drug diffusion through the skin is a passive kinetic process that takes place down the concentration gradient from a high concentration to a lower concentration. Fick's first law of diffusion49 can describe the steady-state equation. The equation describes the transfer rate (flux, J) of a diffusing substance through the unit area A of the membrane and diffusion coefficient D to the concentration gradient across the membrane (dc/dx).

$$J = -AD\frac{dc}{dx} \quad (1)$$

The negative sign in eq. (1) is because the diffusion process occurs in the opposite direction to increased concentration. Fick's second law of diffusion, Eq. (2), can be derived from eq. (1) to describe membrane transport under no steady-state conditions.

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c \partial c}{\partial x^2 \partial t} = D\frac{\partial^2 c}{\partial x^2} \quad (2)$$

By maintaining the sink conditions in the receptor compartment and maximum fixed concentration in the donor compartment, the eq. (2) can be written as

$$J = AD\left(-\right)\left(\frac{cm}{h}\right) \quad (3)$$

Cm is the concentration in the donor membrane interphase, and h is the effective diffusional path length. The Cm in the eq. (3) can be used to replace vehicle membrane partition coefficient (K) as the ratio between the concentration of permeant in the membrane at the donor-membrane interface and the vehicle in which applied (Cv)[50]. Modified Fick's first law of diffusion describes the steady-state flux across the membrane eq. (4)

$$Jss = \frac{ADK\,Cv}{h} \quad (4)$$

A change in D, K, and C can increase drug flux. The compounds which are skin penetration enhancers should potentially change the solubility or partition behaviour of the drug into stratum corneum or its diffusion properties or both[51]. Sometimes changes in the thermodynamic activity of the drug in the formulation manipulate the flux".

4.2. Electrically Mediated Skin Penetration Enhancement

4.2.1. Iontophoresis

Even before the 18th-century discovery of electricity, the ancient Greeks used electricity for medicinal purposes. A transdermal augmentation method for significant and charged compounds, Iontophoresis, was first developed in the 20th century[52]. Drugs with large molecular weights like polypeptides and proteins, which cannot be given at therapeutically effective rates by passive transdermal delivery methods, may be supplied at therapeutically effective rates using an active approach to improving transdermal administration. A direct electric current flows through an electrolyte solution containing the ionic medication to deliver ionic compounds into bodily tissue (for example, via the skin). An electro-osmosis mechanism may transport the uncharged medicines into the body. The donating electrode across the skin causes the movement of the uncharged medication in the liquid solvent. Electric field-induced electroporation is another kind of Iontophoresis that involves the transfer of material via transiently existing holes in a biological membrane. Thus, "iontophoresis" results in

1. Distribution of charged medications by electromigration/electro-repulsion.Administration of uncharged medicines via electro-osmosis[5556].
2. It charged drug distribution by electromigration and electro-osmosis processes that are linked.
3. Electropertubation combines electromigration and electro-osmosis to administer a mixture of charged and uncharged medications[5354].

4.2.2 Electroporation

Electroporation also called the "electropermeabilization" of a membrane, makes the membrane more permeable and can sometimes cause it to break. It is done by sending a short, high-voltage pulse (50–500V) through lipid bilayer membranes, which makes temporary channels for water to pass through[5758]. When electroporation is used with Iontophoresis, it can deliver larger molecules like therapeutic proteins and oligonucleotides through the skin. Iontophoresis mainly affects the drug, while electroporation affects the skin and some of the drug during a pulse [60, 61]. Under "electrophoretically equivalent" conditions, calcein flux is three orders of magnitude smaller when a low voltage current is used continuously than when a high voltage is pulsed[62,64]. It seemed to show that the changes in the skin's structure caused by pulsing were more critical than the electrophoretic force directly acting on the drug. In addition to the model compounds calcein, sulforhodamine, and caffeine, other drugs like fentanyl, metoprolol, flurbiprofen, cyclosporine heparin oligonucleotides, and genes have also been looked at for transdermal Delivery by electroporation[66].

4.2.3 Ultrasound (Sonophoresis / Phonophoresis)

Ultrasound-assisted medicine delivery was initially described by Fellinger and Schmid in 1954 when they used hydrocortisone and an ultrasound to treat digital polyarthritis[69]. After more than 50 years of success, transdermal Delivery has been examined as a powerful method for delivering diverse compounds, including macromolecules[67 68]. A piezoelectric crystal or similar electromechanical device is vibrated by alternating current through the material, which is how it is formed. Quartz or any polycrystalline material like lead-zirconate-titanium or barium titanate may be used as the crystal material. Controlled, improved, and safe percutaneous absorption are all dependent on frequency. The skin permeability of various active compounds has been enhanced by applying ultrasound at frequencies ranging from 20 kHz to 16 MHz. Physicochemical factors such as lipophilicity and molecular weight also have a role in ultrasonic medication penetration. Ultrasound does not improve the transport of tiny lipophilic medicines readily diffusing through the skin under passive settings.[70]

4.2.4 Magnetophoresis

It is an active means of enhancing medicine penetration through the skin or other biological barriers, and it is based on the law of electromagnetism. It argues that charged particles are susceptible to forces whenever they travel through a magnetic field [71]. In this way, charged molecules of substances being permeated may be provided with a driving force by using appropriate magnetic fields of such magnitude, direction, and polarity to enhance the process of transcutaneous permeation. To produce magnetic fields, the approach makes use of a device known as a magnetic field generator. This device creates magnetic fields by directing electric currents via coils built for use inside. By serving as an external driving force, the magnetic field is used to elevate the diffusion coefficient of diamagnetic substances over the skin's surface. Magnetophoresis is the process that occurs when magnetic fields generate forces on charged particles that cause them to be drawn into the skin. This is the last fundamental concept that may be used to increase flux[72]. As shown in Table 3, we enlisted and discussed the various penetration enhancers discovered for transdermal preparation, which we can use to formulate transdermal patches.

Table 3: Penetration Enhancers discovered for transdermal preparation.

Chemical Classification	Enhancers
Alcohols	Long Chain Alcohols: Decanol, Hexanol, Myristyl Alcohol Short Chain Alcohols: Isopropyl Alcohol, Ethanol[73]
Esters	Ethyl acetate, isopropyl myristate, propylene glycol, monocaprylate, Octyl salicylate, ethyl acetate
Amides	Azones
Fatty Acids	Isostearic Acid, Palmitic Acid , Linoleic Acid, Lauric Acid, Oleic Acid
Glycols	1,2-butylene glycol, propylene glycol, propylene glycol
Pyrrolidone	2-pyrrolidone ,N-Methyl-2-Pyrrolidones
Sulphoxide	Decylmethyl Sulphoxide, Dimethyl sulphoxide
Surfactants	Sodium lauryl sulfate Anionic Surfactant Cationic surfactants Alkyl Dimethyl benzyl ammonium halides, Alkylpyridinium halide Non-ionic surfactants, Tween 80, Span 80,
Miscellaneous	Cyclodextrins, water, vitamin e, phospholipids
Urea	Carbamide[73]
Terpenes	Cineole, Eugenol ,D-limonene , linanoal, Menthol , Menthone

5. ADVANCEMENT IN MATERIALS AND FABRICATION TECHNIQUES IN THE TRANSDERMAL DRUG DELIVERY SYSTEM

5.1. Various TDDS Preparation Methods

Asymmetric TPX membrane method: The backing membrane for this prototype patch will be a heat-sealable polyester sheet of type 1009 measuring 3 meters in length and featuring a 1-centimetre concave. A sample of the medicine is first placed into the concave membrane, which is then adherently sealed after being covered with an asymmetric TPX poly (4-methyl-1 pentene) membrane and then covered again. (The preparation of an asymmetric TPX membrane): They are produced by a process known as the inversion of dry and wet conditions. At a temperature of sixty degrees Celsius, TPX is heated to dissolve it in a solvent (cyclohexane), but there are no additions. After being heated to 40 degrees Celsius for twenty-four hours, the polymer solution is poured onto a glass plate using a Gardner knife and cooled to the desired thickness. After that, the casting film is allowed to evaporate at a temperature of 50 degrees Celsius for thirty seconds before the glass plate is immediately immersed in a coagulation bath at 25 degrees Celsius. After soaking for ten minutes, the membrane may be removed and air dried in an oven with circulation at a temperature of fifty degrees Celsius for twelve hours[74].

Circular Teflon mould method: Different polymer solution ratios are combined with the solvent in an organic solvent. To dissolve the prescribed quantity of medication, just one-half of the organic solvent used initially is required. The enhancers are dissolved in the organic solvent left behind and then added in varying proportions. To make the drug-polymer solution more plastic-like, di-N-butyl phthalate is added. It is necessary to stir the liquid continuously for twelve hours before putting it into a circular mould made of Teflon. In a model of a laminar flow hood with an air speed of 0.5 meters per second, moulds have to be placed on a level platform and covered with an inverted funnel to regulate the vaporization of the solvent. A whole day is given to the process of the solvent evaporating. Before examining the dried films, they should be kept for a further 24 hours at 250.5 degrees Celsius in silica gel desiccators. This will erase any effects of ageing that may have occurred. The film evaluation must occur one week after they have been finished[75].

The Mercury Substrate method involves dissolving the medication in a polymer solution while simultaneously adding a plasticizer. The aforementioned solution should be agitated for ten to fifteen minutes to create a uniform dispersion before being put onto a flat surface made of mercury and covered with an inverted funnel to control the amount of solvent lost via evaporation[76].

"IPM membranes" method: For 12 hours, a magnetic stirrer spins a mixture of propylene glycol and water containing carbomer 940 polymers to mix the drug. The application of triethanolamine will reduce the dispersion's viscosity. A solution gel may be formed if the drug's buffer pH is 7.4 and its water solubility is weak. As soon as it's ready, the gel will be added to the IPM membrane[77].

EVAC membranes method: As rate control membranes in developing the transdermal treatment system for the target, carbopol reservoir gel with 1% carbopol concentration, polyethene, and ethylene vinyl acetate copolymer membranes are all viable options. Propylene glycol is used in gel production if the medication is insoluble in water. Propylene glycol is used to dissolve the drug before carbopol resin is added. The mixture is neutralized with a sodium hydroxide solution containing 5 per cent by weight sodium hydroxide. A backing layer sheet is covered with the appropriate region before the drug, which is in the form of a gel, is applied to the sheet. To create a device that cannot leak, a rate-controlling membrane will be placed on top of the gel, and the boundaries will then be sealed using heat[78].

Aluminium-backed adhesive film method: The transdermal drug administration approach may produce unstable matrices if the loading dosage is more than 10 mg. The aluminium-backed adhesive film technique is suitable for its production, and the solvent of choice is Chloroform because most pharmaceuticals and adhesives may be dissolved in Chloroform. After dissolving the medicine in Chloroform, the adhesive component is added to the drug solution, which undergoes dissolution before being used[79]. Aluminium foil has adhered to the inside of the ends of the custom-made

aluminium former, and the ends themselves are blocked off with cork blocks that fit.[80,81]

Free film method: When casting is done on the surface of mercury, a free sheet of cellulose acetate is produced. 2% W/W Chloroform will be used to create a polymer solution. Plasticizers need to be added at a concentration of forty per cent by weight of the polymer before they can be used[82]. Five millilitres of polymer solution were placed into a glass ring positioned above the mercury surface in a glass petri dish. The crew was inverted so that the mercury surface was facing up. The pace of solvent evaporation may be controlled by positioning an upside-down funnel on the petri dish. This allows for more precise control. The creation of a coating may be seen on the surface of the mercury when it is seen after the solvent has been completely evaporated. After it has dried, the film will be cut into pieces and stored in desiccators between sheets of wax paper until it is required. Multiple thicknesses may be achieved by adjusting the quantity of free film used in the process.

Table 4: Manufacturers available across the world for industrial-scale production of TDDS[83].

Company	Country	Founded In
Arecor	United Kingdom	2007
Sirnaomics.Inc	USA	2007
Zynerba pharmaceuticals	USA	2014
Medherant	United Kingdom	2015
Direct corporation	USA	1998
Radius Health, Inc	USA	2003
TSRL, Inc	USA	1986
Agile therapeutics	USA	1997
Kind of drug delivery	USA	2020
Sparshapharma international	India	2008
Mycrodose therapeutics	USA	2021
Botanix pharma	Australia	2015

As shown in Table 4 above, it listed the various manufacturers in different countries with their established years.

6. NEWER DELIVERY SYSTEMS AND NANOSYSTEMS FOR TDDS

Macroflux: These devices have an area of approximately 8 cm and 300 micro projections per cm^2, with individual micro projection lengths of < 200m. There are three different forms of macro flux. They are as follows:

- Dry-coated macro flux system-This system is utilized for short-term distribution and comprises a micro projection array coated with medication and attached to an elastic polymer adhesive backing.
- D-TRANS Macroflux system-also for short-term administration, this system comprises a micro projection array paired with a drug reservoir.
- E-TRANS Macroflux system-for on-demand Delivery, this technology combines a tiny projection array with an electron transport system.

- **Metered Dose Transdermal Spray:**It is a liquid preparation that is administered topically and takes the form of a solution. The solution comprises a vehicle, which may or may not be volatile, and a dissolved medication contained inside the solution. When you use a metered dose transdermal spray (MDTS), you may expect a consistent level of medicine absorption via your skin. In addition, the MDTS may provide the following advantages: It increases delivery potential while reducing the risk of skin irritation due to its non-occlusive nature [84].
- Dose adjustability.
- Simple to produce

7. CURRENT STATUS AND NEW TECHNOLOGIES IN TRANSDERMAL DRUG DELIVERY SYSTEMS

Microfabricated microneedles are hybrids of transdermal patches and hypodermic needles utilized for efficient medication delivery with these minuscule needles. Because of their small size, giant molecules can even be transmitted over the stratum corneum [85,86]. ALZA Corporation created another transdermal medication delivery technique known as the Macroflux. This Macroflux is used to administer biopharmaceutical medications in a regulated way, increasing effectiveness and bioavailability while causing no pain to the patients. Significant efforts are being made collectively to address obstacles associated with Aliza's technology [87]. Since the initial generation in 1981, systems based on patch matrices and reservoir forms have been increasingly prominent in the worldwide market in years of FDA clearance. The device employs a titanium-based micro projection array that aids in creating a superficial route surrounding the skin for transporting proteins and vaccinations for sampling. Another technique developed at the Victorian College of Pharmacy is the MDTS. It can increase the overall expansion of the TDDS by widening patient acceptability and the use of pharmaceuticals for the much-improved form of TDDS. Another approach is the Electrically-Based Enhancement Technique, which uses Iontophoresis to facilitate medication diffusion all over the skin using an electrical application[88].

8. MARKETED POTENTIAL AND NEWER DRUGS INCORPORATED IN TDDS

There are several advantages to transdermal medication delivery systems, such as overcoming the limits imposed by traditional dosage forms. For TDDS to be effective, the medicine must be able to penetrate through the skin barrier. Compared to topical drug delivery, TDDS delivers the medication to the whole body at a controlled rate, while topical drug delivery targets just a small portion of the body. When administering medicine, dose type and drug absorption at the delivery site affect the intended therapeutic benefit and any undesirable side effects. There was $12.7 billion in revenue in 2005, $21.5 billion in 2010 and $37.79 million by 2018, and $49.37 million by 2024 for TDDS, according to industry figures. [8990]

New developments

- ImQuest Biosciences has announced the release of an antiretroviral (ARV) transdermal delivery patch in September 2021.
- Luye Pharma Group introduced the Rivastigmine Transdermal Patch in China in June 2021 to treat mild to moderate Alzheimer's disease.
- Agile Therapeutics Inc. to launch Twirla (Levonorgestrel and Ethinyl Estradiol) transdermal system, a novel non-daily, non-invasive contraceptive patch, in the United States in December 2020.
- In June 2020, Vektor Pharma introduced a generic transdermal Neupro patch (Rotigotine), often used to treat Parkinson's disease symptoms[91].

9. ADVANCEMENTS IN QUALITY ASSURANCE IN TDDS

The evaluation of a transdermal drug delivery system in critical quality attributes is adequately discussed in Table 5 below with tests and regulatory requirements.

Table 5: Critical Quality Attributes Evaluation of Transdermal Drug Delivery System[92.]

Critical Quality Attributes	Justification	Regulatory Requirements
Physiochemical test		
"Assay	Variability in the test will impact the product's safety and efficacy.	BP, USP, JP, EP
Content Uniformity test	To define dosage unit homogeneity, dosage forms are supplied in single-unit TPS containers. (9 out of 10 TPS packed in pre-metered dose forms have a content between 85 and 115 per cent, with one having a range between 75 and 125 per cent)[93]	BP, EP, JP, USP
Moisture Content	In general, the water content can influence product deterioration and microbial development. Having an impact on product safety and stability	EP, USP, JP
Thickness	TPS thickness influences drug release and peel adherence. Affecting product quality and efficacy	-
Tensile Strength	The amount of force necessary to shatter the patch. TPS folding resistance is heavily influenced by tensile strength. Influencing product stability	-
Elongation	The extent to which the TPS may be stretched without breaking is usually stated as %	-
Water vapour permeation test	Measuring water vapour permeability influences quality control and drug delivery rate optimization. Having an impact on product efficacy and stability	BP, USP
Flatness test	A TPS should have a smooth surface and not become constrictive with time. Influencing product quality	-
Folding Endurance	The intensity is given as the number of diffractions from the fold to the cutting TPS. Having an impact on product stability and quality. When TPS is applied to the skin, folding endurance will impair skin integrity and overall skin folding.	-
Presence of Impurities	Determine the presence of residual solvents or other contaminants and if the remaining levels are dangerous.	EP, JP, USP
Microbial test	Even if some TPSs do not allow microbial growth, bioburden is necessary for product validation if any post-approval alterations are done.	USP
***In vitro* test (drug delivery test)**		
Drug Release test	The *in vitro* performance test must determine drug release from the completed product. Having an impact on product efficacy and quality	EP, USP, JP
Drug Permeation test	The medicine enters the TPS, travels to the target skin, and penetrates the skin to have a therapeutic effect. Having an impact on product efficacy and quality	EP
Adhesive property test		
Tack test	Allows an adhesive to bind with another material's surface after brief contact under slight pressure. TPS has a tack feature that will enable it to adhere to the skin or surface with little force.	EP, JP, USP
Peel adhesion test	The amount of force required to detach TPS adhesive from a rigid substrate.	EP, USP, JP
Shear adhesion test	The force measurement of an adhesive's cohesive strength indicates the adhesive's flow resistance. The characteristic is related to TPS matrix thickness.	EP, JP
Cold flow test	Assess the mobility of the adhesive beyond the TPS's edge, both qualitatively and numerically. It affects the product's stability, effectiveness, and safety	EP, USP

leak test	TPS reservoir leakage has an impact on product stability and quality. It is critical for the patient's safety.	USP
TPS integrity	TPS seal integrity test throughout the packing process. Examine the package for flaws. Side effects may develop from unintentional medication release in the event of a defect.	-
Degradation test and Impurities	It must be proved that the product's rationale and risk factors have been minimized so that safety and efficacy are not compromised.	USP
Sensitive test and Skin irritation test	The incidence of erythema and oedema during TPS administration is [9495]".	-

It represents transdermal drugs use in clinical development, as shown in Table 6 below.

Table 6:Transdermal drugs in clinical development

Drug	Indication	Delivery technology	Clinical Phase	Company
Fertility hormone	Female infertility	Iontophoresis	Phase I	Veterans/Ferring(Fair Lawn,NJ,USA)
Granisetron	Nausea and Vomiting	Passive	Pre-registration	Prostrakan(UK)
Insulin	Diabetes Mellitus	Thermal ablation	Phase I	Altea Therapeutics (Atlanta, GA, USA)
Testosterone	Female Sexual dysfunction	Metered dose transdermal spray	Phase 2	Acres/VIVUS (west Melbourne, Australia, USA)
Sufentanil	Chronic pain	Passive	Phase 2	Durect/Endo(Cupertino,CA,USA)
Ketoprofen	Osteoarthritis	Heat enhancement	Phase 3	ZARS (salt lake city, UT, USA)

10. THE FUTURE OF TRANSDERMAL DRUG DELIVERY

Although transdermal medication administration is excellent for injectable and orally administered pharmaceuticals, many chemicals cannot travel through the skin due to the skin's limited permeability[9697]. Pharmaceutical firms create novel adhesives, penetration enhancers and molecular absorption to improve the permeability of skin and so broaden the variety of medications that may be given transdermally[98,99]. Iontophoresis and Phonophoresis are well-known technologies that can significantly enhance skin permeability (Sonophoresis). During Iontophoresis, an electrical current is passed between 2 electrodes on the skin's surface. Ultrasonic frequencies are used in Phonophoresis to assist the transport of high molecular weight medicines through the skin. Micro needle-enhanced Delivery is a newer and more promising method. An array of small needle-like features is used in these systems to open pores in the stratum corneum and enhance medication delivery. The structures are so little they do not reach the nerve ends; hence there is no pain feeling. These technologies have significantly improved "up to 100,000 fold" macromolecule penetration through the skin. The transdermal drug delivery systems market is predicted to grow at 4.5 per cent of CAGR from an estimated 5.7 billion in 2018 to USD 7.1 billion by 2023[100,] as shown in Figure 4.

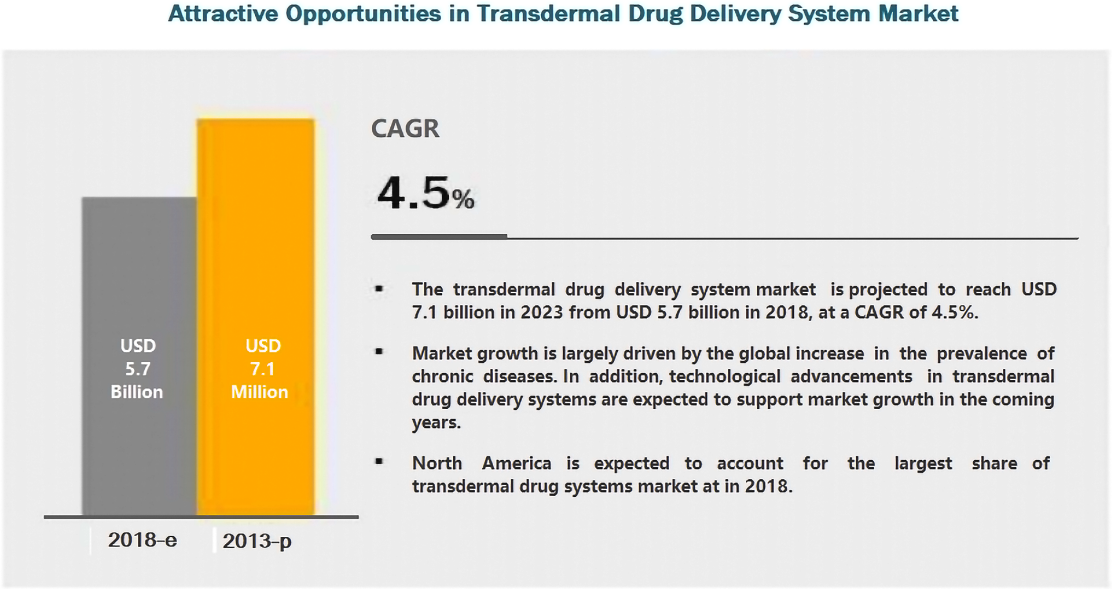

Fig 4: Attractive opportunities in the TDDS market[101]

This figure shows the market value prediction to grow from 2018 to 2023. North America is expected to account for the largest share of the transdermal drug delivery system market in 2018.TDDS market is divided into two types: transdermal semisolids and transdermal patches. Transdermal patches, on the other hand, are predicted to increase faster throughout the projection period.

This is due to the advantages of transdermal patches, such as lower dose frequency, higher bioavailability, fewer side effects, and drug input cessation at any moment by removing the patch.

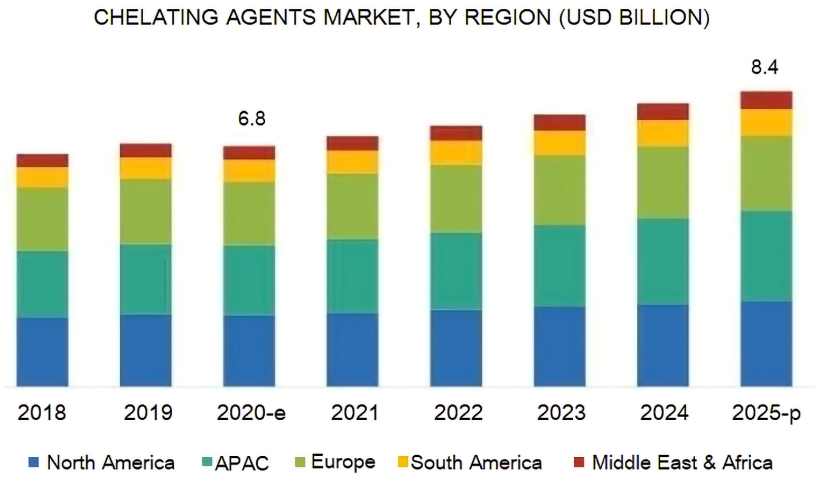

Fig 5: chelating agents market by region (USD BILLION)

North America is expected to have the most significant market share over the projection period.

In the TDDSs sector, North America is a substantial income producer. The rising frequency of targeted diseases like chronic pain, cardiovascular diseases, and central nervous system disorders), the increasing use of contraception, and the growing number of TDDS research activities are driving the region's transdermal drug delivery systems market, as shown in Figure 5.

11. COMPARISON OF TRANSDERMAL DRUG DELIVERY SYSTEM

Most enhancement methods increase skin permeability without adding a driving factor for transdermal transport. Chemical enhancers are an exception because they can alter stratum corneum structure while increasing drug solubility and resulting in the drug concentration-gradient driving force. Microneedles are another exception since they penetrate the skin and deliver drugs into it via coating and encapsulation with solid microneedles or infusion with hollow needles. Although electrical delivery methods can affect skin permeability and provide an electrical driving force, Iontophoresis primarily drives drugs into the skin. In contrast, electroporation is used mainly to disrupt stratum corneum structure. Iontophoresis may be especially beneficial when combined with another approach that enhances skin permeability since it offers a transport driving force. Such integrated enhancing tactics have already been discussed in the literature. Achieving a good balance between efficient delivery and skin safety is essential for successful transdermal delivery. Some third-generation techniques are based on the assumption that relatively extensive, micron-scale flaws in the stratum corneum will be tolerated by patients as long as no significant harm is done to live cells in the viable epidermis and dermis. Based on evidence from a growing number of clinical trials that have progressed from phase I safety trials to phase 2 and 3 effectiveness studies (table 6), particularly employing microneedles and thermal ablation reports to date, imply that this theory is credible. Because most transdermal delivery systems are designed for self-administration at home, the clinical impact is dependent not only on a transdermal delivery system that distributes medications safely and effectively but also on one that is low-cost and simple to use. The numerous chemical boosters can be combined into compact, low-cost patches that patients find helpful. Physical enhancers may be more successful in delivering macromolecules and vaccines, but they are often powered by mobile devices that require electricity. As a result, most physical enhancers rely on inexpensive, reusable devices that communicate with a disposable drug reservoir component. Microneedles are an exception since they can transport macromolecules and vaccinations, are cheap to produce as single-use patches, and do not require a needle. On the other hand, Microneedles are physically intrusive, presenting further safety and sterility concerns.

12. CONCLUSION

TDDS have been used because they are rational drug treatment drug delivery devices, which means they are safe, effective, and cost-effective. Many new researchers are now striving to include innovative drugs into the TDDS due to the evident and multiple advantages the system provides. A transdermal patch comprises various essential components, such as drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers, and solvents. These fundamental components all play an important part in drug release through the skin and are essential to constructing a transdermal patch. These patches are prepared using various strategies, all of which use the vital components of TDDS. Once the transdermal patches have been manufactured, they are subjected to physicochemical investigations, in vitro permeation testing, skin irritation studies, and stability studies. On the other hand, the FDA has to approve every transdermal patch that is developed and tested before it can ever be marketed. It is expected that future TDDS advancements will concentrate on improving therapeutic regimen management and significantly expanding the number of available drugs. Transdermal dosage forms make it possible for medical professionals to provide their patients with a more significant number of treatment options, therefore improving the quality of care they get.

13. AUTHOR'S CONTRIBUTION STATEMENT

This paper is an outcome of the combined efforts of Dr Goswami and Dr Mittal's team. Dr Manish Goswami has been

working in the field of Transdermal drug delivery systems for the last 20 to around to decades. Similarly, Dr Mittal has worked in phyto, herbal medicines, and topical products. Both persons are involved in drafting this manuscript with Mr Jain and Ms Simran as students.

14. CONFLICT OF INTEREST

Conflict of interest declared none.

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