Advancements of Polymer-Based Transdermal Drug Delivery Systems in Drug Bioavailability and Patient Compliance in United States

Hunny Dabas [1], Deepika Singh [1], Faraat Ali [2], Dipanjan Koley [1], Mohammed. Aslam [3], Esra Tariq Anwer Bayrakdar [3], Manvi Singh [1*]

Abstract

Transdermal drug delivery system (TDDS) helps in overcoming drug molecule barriers such as particle size, lipophilicity, permeability, and transports the medication directly to the blood circulation by employing physical and chemical penetration enhancers using polymers. The use of skin as a drug delivery route is challenging due to the stratum corneum's barrier properties that restrict the therapeutic bioavailability of the medications. Both, natural and synthetic polymers are used in TDDS to transport the medication into circulation via diffusion, and swelling control. TDDS is generally achieved by using transdermal patches containing one or more pharmaceutical active entities that are placed on unbroken skin for delivering active entities directly to the bloodstream by crossing the skin barrier. TDDS is the trendiest -delivery system as it is painless, non-invasive, self-administrative, avoids hepatic first-pass metabolism, and delivers poorly soluble drugs and increases the bioavailability. An overview of TDDS is provided in this review article, including its advantages over traditional dosage forms, limitations, different components of transdermal patches, modern techniques as well as transdermal products available in US market.

Keywords: Transdermal, Permeability, Transdermal patch, US Market, Polymer-based drug delivery.

Significance | This review comprehensively discusses the transdermal drug delivery systems (TDDS) in the area of drug administration, for non-invasive, precise, and efficient delivery, overcoming oral limitations.

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Introduction

Skin is the largest organ in the human body in terms of mass, accounting for an area of 1.5 - 2.0 m2 in adults. In ancient Egyptian and Babylonian medicine (around 3000 BC), medical records show that for treating superficial disorders, drugs were applied to the skin. These cosmetic products such as ointments, salves, potions, patches that were applied consisted of plant, animal and mineral extracts (Pastore *et al.*, 2015). However, in late 20th century the routine use of transdermal delivery systems became a common practice when drug delivery technology was developed to produce a precise, accurate, reproducible and controllable administration through the skin for systemic effects. Polymers are widely used in the pharmaceutical sector for various purposes i.e., in tablets they are used as a binder and disintegrant; oral liquids use them as thickeners and diluents; suspensions use them as protective colloids; gels use them as gelling agents; and suppositories use them as bases (Drupal *et al.*, 2016, Aslam *et al.*, 2016). However, because of their vast availability, economic, chemical adaptability, and

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potential degradability, natural polymers are still the most favoured choice among the formulation scientists. The capacity to control and sustain medicine release has been investigated in polymers produced from natural gums or mucilages (Pal *et al.,* 2010). Drug delivery systems are pharmaceutical formulations used to transfer active chemicals into the body and aims to deliver an active entity to its target site of action at a predefined rate and concentration in order to reduce the adverse effects and improves the therapeutic advantages. Transdermal route of drug delivery can help to achieve local as well as systemic therapeutic effects. It is an attractive substitute for oral drug delivery as it bypasses first pass metabolism, helps to overcome the poor patient compliance when compared to other administration routes and gastrointestinal effects. These methods have a number of drawbacks, including a higher risk of systemic toxicities, the risk of GIT irritation, and the presence of hepatic first-pass metabolism (Abruzzo *et al*., 2017). Transdermal drug delivery is self-administered, allowing the drug to pass through intact skin over a controlled period of time to achieve a local or systemic Drugs may be delivered via the skin at a predefined and regulated pace using TDDS, which falls under controlled drug delivery. This kind of patch, which is put to the skin, delivers a specified amount of drug to the bloodstream via the skin at a predetermined time interval. Transdermal distribution lessens the burden on the digestive system and liver with enhancing the patient compliance and the reduction of dangerous side effects (Sandeepthi & Satyanarayana, 2017). This review will give insights into the journey of the transdermal patch from its basic characteristics to the finalized product approved by Food and Drug Administration (FDA) and marketed in the United States. Advantages and disadvantages of Transdermal drug delivery system are described in **Table 1.**

1. Ideal Characteristics of Drug in TDDS

Skin has a pH in the range of 4.2 to 5.6, hence products within this range are used to protect the skin from injury. The following are the ideal requirement for drug to be incorporated into transdermal patch. It should have an optimal partition coefficient for the drug to produce a therapeutic effect, drug should have a low melting point (less than 2000°C), patch size should be less than 40 cm^2, shorter half-life (t½) of the drug should be short, drug should be non-irritating and non-allergic, drug should have a molecular weight of less than 1000 Daltons and both hydrophilic and lipophilic drugs can be targeted by this system (Sudam & Suresh, 2016). Transdermal patches consist of hydrophobic drugs which have a molecular weight above the lower Berner–Cooper boundary = 500, < 1000 Daltons with a log P ranging between 1-5, and melting point < 250 °C. Transdermal patch was prepared for fentanyl with a molecular weight of 337 Da, melting point of 83°C with a log P of 3.9. Drugs having low dose strength, facile hydrolysis in acidic media, and which show hepatic metabolism, are not suitable to be delivered by transdermal patches (Al Hanbali *et al*., 2019, Aslam *et al*., 2016, Lakhan *et al.* 2023).

2. Skin Anatomy

2.1 Skin

Skin is the body's biggest organ, covering an area of around $2m^2$ and receives 1/ 3^{rd} of the blood flow. Microorganisms, pollutants, allergies, and water loss are all prevented by the skin's fundamental role as a barrier between the internal environment and the outside world. (Zaid et al., 2015). The anatomical and structural characteristics of the skin have a significant impact on its diffusional resistance (Sandeepthi & Satyanarayana, 2017).The skin is composed of three histological tissues as shown in **Figure 1** (Akhtar *et al*., 2020)**.**

3.1.1 Epidermis: Hand and foot skin is covered by an epidermis that is around 0.8 millimetres thick on the palms and soles. Approximately 95% of the cells in the epidermis are keratinocytes, with the remainder comprising melanocytes, Langerhans cells, and Merkel cells.

3.1.2 Dermis: Collagenous and elastin fibres make about 70 percent of the dermis approximately 0.1–0.5 cm^2 thickness. Proteinoglycans in the dermis are formed by the covalent attachment of glycosaminoglycans or acid mucopolysaccharides with peptide chains. The dermis also contains the nerves, arteries, and lymphatic vessels (Mali *et al*., 2018).

3.1.3 Hypodermis: The hypodermis is the subcutaneous layer of the superficial fascia, which is referred to as the fascia superficialis. In this layer, glycosaminoglycans and proteoglycans are abundant, serving as a link between both the skin, muscle, and bone. In the winter, adipose tissue in the epithelial tissue serves as a thermal insulator, keeping the body warm (Ramadon *et al*., 2022).

3. Principle of transdermal drug permeation

TDDS uses epidermis and skin appendages i.e., hair follicles and sweat glands as a route for drug delivery. Only 0.1 percent of the human skin's surface is covered with skin appendages, and their contribution to drug penetration flow is negligible (Ruela *et al*., 2016, Alam *et al*., 2016). Initially, the skin was thought to be an impenetrable barrier, but subsequent studies demonstrated that the skin could be used as a method of administering drugs to the body. Only a few millimetres of tissue separate the skin's surface from its underlying capillary network, making it the body's most intensive and easily accessible organ. Drug release into the systemic circulation from TDDS involves the diffusion of drug from the drug reservoir to the membrane. This is the rate controlling step. Further, the drug is transferred and permeated from the membrane to dermal capillary network and impact the target organ. (Figure 2).

4. Components of transdermal patch

Generally, a transdermal patch consists of five components-

Table 1. Advantages and Disadvantages of TDDS.

Advantages of TDDS	Disadvantages of TDDS	References
Prevents absorption in the gastrointestinal tract (GIT).	There is no way to take a huge amount of drug every day.	(Jadhev *et al.*, 2018)
Reduces the total number of intakes	Uncomfortable to put into practise.	(Mohan *et al.*, 2013)
Avoid first pass metabolism	May not be economical.	(Jadhev *et al.*, 2018; Sandeepthi & Satyanarayana, 2017)
Minimizing undesirable side effects.	Ionic drugs cannot be delivered by the transdermal drug delivery method.	(Sudam & Suresh, 2016)
Provide access to drugs with short half-lives, restricted therapeutic windows, and inter- and intra-patient variability.	It is unable to achieve large drug concentration in to the bloodstream.	(Mohan *et al.*, 2013; Tanwar, & Sachdeva, 2016)

Table 2. The polymers used in transdermal system.

S.No.	Polymers	Examples	References
01.	Natural Polymers	Zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes, and chitosan, etc.	(Drupal *et al.*, 2016)
02.	Synthetic Polymers	Polyvinylchloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, etc.	(Tanwar & Sachdeva, 2016; Tiwari *et al.*, 2007)
03.	Synthetic Elastomers	Hydrin rubber, polyisobutylene, polybutadiene, silicon rubber, nitrile, neoprene, butyl rubber, acrylonitrile, etc.	(Kumar et al., 2010; Sharma *et al.*, 2011)

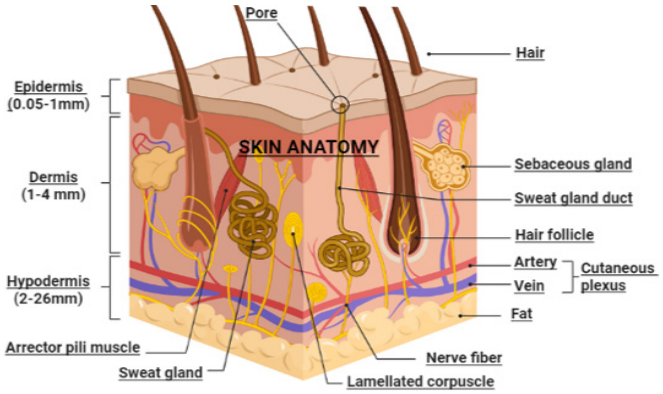

Figure 1. Anatomy of the Human Skin

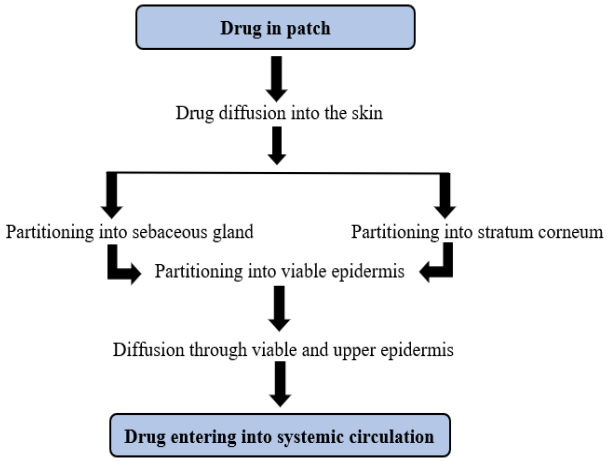

Figure 2. Drug absorption routing through the skin

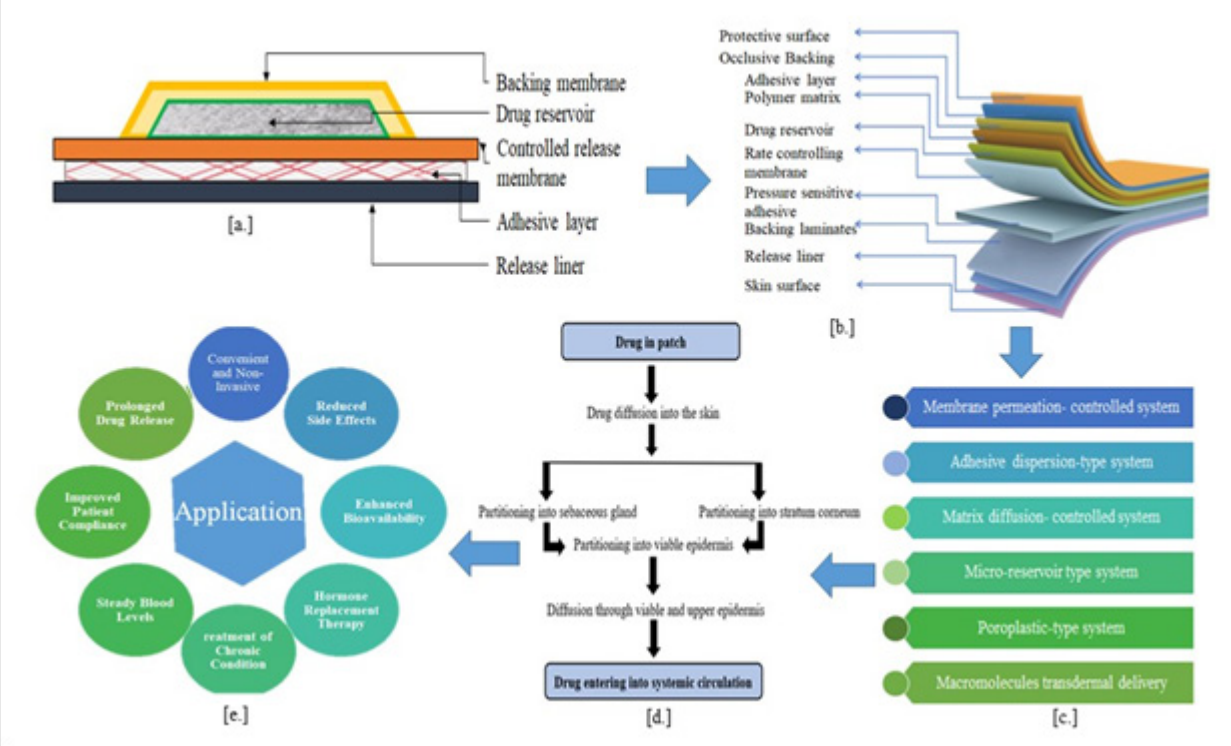

Figure 3. Portfolio picture of TDDS a.b. Components of transdermal drug delivery system c. Types of transdermal patch d. Mechanism of drug permeation through the skin layers e. Application of TDDS in different biomedical field.

Table 3. List of Transdermal products currently in the US market.

Active ingredients	Name	Company	Type of patch	Dose and application	Uses	References
Estradiol	Alora®	Watson Laboratories	Adhesive matrix drug reservoir	9–36-cm² patches deliver 0.025–0.1 mg/day and continuous delivery for twice-weekly dosing Applied to the lower abdomen	Menopause, postmenopausal, and osteoporosis, in case of lowered estrogen levels	(Radhakrishnan *et al.*, 2020)
	Evamist™	KV Pharm/Ther-Rx	Topical application to the skin of a rapidly drying homogeneous solution of 1.7% drug from a metered-dose pump	One, two, or three sprays/day (90 µl/spray) to adjacent non-overlapping 20-cm² areas on the inner surface of the arm between the elbow and the wrist and allowed to dry	Menopause, postmenopausal, and osteoporosis, in case of lowered estrogen levels	(Paudel *et al.*, 2010)
Ethinyl estradiol and norelgestromin	Ortho Evra®	Ortho McNeil Janssen	An adhesive matrix containing drug	6.00 mg norelgestromin and 0.75 mg Ethinyl estradiol in each 20-cm2 patch and delivers for 7 days Applied to buttock, abdomen, upper outer arm, or upper torso	Contraception	(Kováčik et al., 2002)
Estradiol and norethindrone acetate	Combipatch®	Novartis	The adhesive layer contains both drugs	9–16-cm² patches deliver 0.05/0.14 or 0.05/0.25 mg estradiol/norethindrone acetate per day and are applied twice weekly to the lower abdomen	Menopausal symptoms	(Jung *et al.*, 2020)
Estradiol and levonorgestrel	Climara Pro™	Bayer Healthcare Pharmaceuticals	The drug in adhesive layer	22-cm² Climara Pro™ system contains 4.4 mg estradiol and 1.39 mg levonorgestrel and delivers 0.045 mg estradiol and 0.015 mg levonorgestrel/day for 7 days applied to the lower abdomen	Menopausal symptoms	(Radhakrishnan *et al.*, 2020; Kováčik *et al.*, 2002)

Figure 3. continued

Fentanyl	Fentanyl transdermal system	Actavis, Mylan Technologies, Lavipharm Labs, Noven, Watson Laboratories, and Teva Pharms	Matrix type (Mylan technologies and Teva Pharms) and reservoir (Actavis and Watson laboratories)	10–40-cm^2 patches deliver 25–100 μg/h	Chronic pain (opioid tolerant) that cannot be managed by any other means	(Lashmar *et al*., 1994)
	Duragesic®	Ortho McNeil Janssen	The drug in reservoir and adhesive formulation	5–40-cm^2 patches deliver 12.5–100 μg/h continuous systemic delivery for 72 h applied to a flat surface such as the chest, back, flank, or upper arm		
Granisetron	Sancuso®	Prostraken	An adhesive matrix containing drug	52-cm^2 patch containing 34.3 mg of granisetron. The patch releases 3.1 mg of granisetron per 24 h for up to 7 days Applied to upper outer arm	Chemotherapy-induced nausea and vomiting	(Paudel *et al*., 2010)
Methylphenidate	Daytrana®	Shire	Adhesive-based matrix type patch	12.5–37.5-cm^2 patches deliver 10–30 mg/9 h per patch applied to the hip area 2 h before an effect is needed and should be removed 9 h after application	Attention-deficit hyperactivity disorder	(Zhao *et al*., 2006)
Nicotine	Nicoderm® CQ	Aventis	Matrix type patch	7–21 mg over 24 h at different stages of the treatment	Smoking cessation	(Akhtar *et al*., 2020; Zhao *et al*., 2006)
	Habitrol®	Novartis and Novartis Consumer	Reservoir type	17.5–52.5 mg that delivers 7–21 mg/day for the duration of treatment		
Nitroglycerin	Nitro Dur®	Key Pharmaceuticals	Drug in adhesive	5–40-cm^2 patch delivers 0.1–0.8 mg/h for 12–14 h	Angina prophylaxis	(Savoji *et al*., 2014)
	Nitroglycerin	Noven, Hercon Laboratories, Kremers Urban, and Mylan Technologies	Drug in adhesive	Delivers nitro-glycerine at 0.2 mg/h		(Wang *et al*; 1998)
	Nitroglycerin	Fougera	2%	7.5–30 mg applied in the morning and again 6 h later to a 36-inch^2 area of truncal skin		
Oxybutynin	Oxytrol®	Watson Laboratories	An adhesive matrix containing drug	39 cm^2 system containing 36 mg and has a nominal *in vivo* delivery rate of 3.9 mg oxybutynin per day consistently for 3–4 days Applied to the abdomen, hip, or buttock	Bladder muscle dysfunction	(Azmana *et al*., 2022)
Scopolamine	Transderm Scop®	Novartis	Matrix reservoir containing drug	2.5-cm^2 patch delivers 1.0 mg for 3 days Applied to the hairless area behind one ear	Motion sickness, Postoperative nausea, and vomiting (prophylaxis).	(Zhao *et al*., 2006)
Rivastigmine	Exelon®	Novartis	Matrix reservoir containing drug	4.6–9.5 mg/24 h from 5–10-cm^2 patches Preferable application to upper or lower back	Dementia is associated with Alzheimer's disease and Parkinson's disease	(Radhakrishnan *et al*., 2020)
Oxybutynin chloride	Gelnique®	Watson Labs	10% gel	100 mg applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs (area of application rotated)	Bladder muscle dysfunction	(Paudel *et al*., 2010)
Selegiline	Emsam®	Somerset	Drug in adhesive	6–12 mg/24 h from 20–40-cm^2 patch Applied to the upper torso, upper thigh, or the outer surface of the upper arm	Major depressive disorder	(Kováčik *et al*., 2002)
Testosterone	Androderm®	Watson Laboratories and Watson Pharma	Reservoir type	2.5 or 5 mg/day from 37–44-cm^2 patch	Hypogonadism (testosterone deficiency)	(Jung *et al*., 2020)
	Androgel®	Unimed Pharma and Solvay/Abbott	1% gel	5–10 g contains 50–100 mg, 10% of the applied testosterone dose is absorbed across the skin of average permeability during a 24-h period Applied 5 g once daily to shoulders and upper arms and/or abdomen		

5.1 Backing layer: Prevents contamination of the patch from the outside. These components of the transdermal patch cannot pass through them; thus, the patch may move freely.

5.2 Drug releasing membrane: Drugs are released from the reservoir via many layers into the skin, controlled by this device. These polymers are either natural or synthetic.

5.3 Drug reservoir: contains the drug to be released.

5.4 Adhesive: Patches are held in place by this adhesive layer. Permeation enhancers may be added to the product to increase the skin permeability (Akhtar *et al*., 2020; Gorain *et al*., 2012, Aslam et al., 2016)

5.5 Liner: It serves as a storage cover for the patch, which is then removed for use on the skin.

5. Polymers used in TDDS

6.1 Degradable Polymers: Hydrolytic polymers are either natural or synthetic, which may be used to perform hydrolysis *in vivo*. Among the most often used polymers are natural sugars like chitosan and -hydroxy acids. Synthetic degradable polymers have less batch-to-batch variability and immunogenicity than natural degradable polymers. For degradable polymers, surface erosion and diffusion are the drug release mechanisms (Kamaly *et al*., 2016).

6.2 Biodegradable Polymers: To provide temporary support, biodegradable polymers break down in the body in a short span of time (Patil *et al*., 2021). Non-enzymatic or enzymatic decomposition of biodegradable polymers may yield biocompatible and harmless by-products that are removed by the regular metabolic routes of the organism and non-immunogenic while using synthetic polymers as basic materials (Jain 2000, Middleton *et al*., 2000; Song *et al*., 2018).Some of the important properties of a biodegradable biomaterial polymer can be summarized as, accumulation of the metabolites should not cause a long-term inflammatory or toxic reaction, it is important that the substance should have mechanical characteristics for its intended use and its breakdown activity should be timed with the healing or rejuvenation process in order to be effective (Huang *et al*., 2015, Nair & Laurencin , 2007). Polymers used in transdermal system are shown in **Table 2**.

6.2.1 Cellulose and its derivatives:

Various cellulose derivatives such as ethyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethylcellulose (CMC), and methylcellulose (MC), have been used for the fabrication of transdermal patches. Polyvinylpyrrolidone (PVP) in combination with HPMC and chitosan encapsulated with gentamycin showed a drug release of >70% and upto 90% the biofilm growth was inhibited (Jaber, 2023). Repaglinide was incorporated into the transdermal patch fabricated from HPMC polymer and PVP K30. The patch showed a release of 92.343% up to 12 hr (Prajapati *et al*., 2011).

6.2.2 Acrylic-acid complexes:

Acrylic-acid complexes such as different varieties of Eudragits have been used with plasticizers to form transdermal patch. Losartan potassium patch was formed with Eudragit® E100 and hydrophilic polymer PVP and showed 90% of drug release in 4h. Penetration studies showed a passive diffusion and good bioadhesion property (Almazan *et al*., 2020). Carvedilol transdermal patch was developed using solvent evaporation technique. Eudragit RS-100 was used in combination with Span 80 to reduce the blood pressure and showed maximum bioavailability (Mo *et al*., 2020). Eudragit L 100 was found to be the most efficient formulation while developing transdermal patch of topiramate (Cherukuri *et al*., 2017).

6.2.3 Polyethylene glycol:

Polyethylene glycol (PEG) is an excellent polymer in terms of its bioavailability and biocompatibility. Matrix type of transdermal patch was developed using heparin sodium along with 30% (w/w) PEG 400 LR using different hydrophilic polymers. Highest flux was observed for the formulation with 1.369-fold increase in permeation of the drug through the rat skin (Patel *et al*., 2014). Montelukast sodium transdermal film was formed using lignosulphonic acid, sodium alginate and PEG-400 for matrix formation and glycerine as the plasticizer. The film showed a controlled drug release designed specifically for the paediatric and elderly population (Reddy *et al*., 2023). Transdermal patches of lornoxicam were designed to increase the bioavailability of the drug. It was prepared with ethyl cellulose: polyvinylpyrrolidone and Eudragit RL 100: Eudragit RS 100 in different ratios along with propylene glycol as plasticizer (5%) and tween 80 as permeation enhancer. The results showed that lornoxicam bioavailability was increased 3.1-fold when compared to oral dosage forms (Baviskar *et al*., 2013).

7. Types of transdermal patches

7.1 Single-layer drug in adhesive: Drug is present inside the adhesive layer in this design. A liner and a backing membrane are used to protect the adhesive layer. In addition to sticking to the other layers, this layer also releases the medicine directly to your skin (Chandrashekhar et al., 2008; Prausnitz *et al*., 2004; Kumar *et al*., 2010).

7.2 Multi-layer drug in adhesive: Similar to the single-layer, this design has an instant drug release layer and a controlled release layer. In order to release the medicine, the adhesive layer must be in place. This patch has a transient liner layer or a persistent backing layer (Kumar *et al*., 2010).

7.3 Vapour patch: Aside from adhering the layers together, the adhesive layer is also responsible for releasing any trapped vapour. An essential oil decongestant known as a vapour patch has just been introduced to the market (Priya *et al*., 2023).

7.4 Matrix System: This system is divided in to two types of matrix systems, one is drug-in-Adhesive Systems in which the medication may be dispersed in an adhesive polymer, which is then placed over

an impermeable backing layer through solvent casting or melt-casting (in the case of hot-melt adhesives) and other is Matrix-Dispersion System where compartment is constructed of a drug-impermeable backing layer, the drug is enclosed with the enclosing polymer (as a matrix) and attached to an occlusive base plate (Gaur *et al*., 2009).

7.5 Micro-reservoir systems: An aqueous solution of a water-soluble polymer is used to disperse the drug into thousands of un-leachable tiny spheres, which are subsequently coated with a lipophilic polymer to create the drug reservoir (Gaur *et al*., 2009).

6. Modern techniques for fabricating transdermal drug delivery system

8.1 Iontophoresis: While the electrode stays in contact with the formulation, the skin receives a few milliamperes of electrical current, which is confined to a particular location. To promote sweating in the diagnosis of cystic fibrosis, pilocarpine might be used as an example of the Iontophoretic administration (Gaur *et al*., 2009).

8.2 Electroporation: Transient aqueous holes in the skin are created using the electroporation method, which makes use of high-voltage brief electrical pulses (Jassim *et al*., 2018). These holes allow drugs to penetrate the horny layer without having to go through the horny layer first. These compounds, which include biopharmaceuticals with molecular weights more than 7kDA, have been employed to increase skin permeability using this method (Bhowmik *et al*., 2012).

8.3 Ultrasounds or Sonophoresis: Sonophoresis is a process in which ultrasound or ultrasonic energy is utilised to increase the transdermal transfer of different medicines, including macromolecules, via the skin by disrupting the stratum corneal lipid barrier (Jassim *et al*., 2018).

8.4 Magnetophoresis: Using a magnetic field as an external force, diamagnetic solutes may be more easily absorbed through the skin in this method. Magnetic fields affect the structure of the skin, which may lead to greater permeability. It is shown that raising the magnetic field intensity enhances drug diffusion flow by using benzoic acid as a diamagnetic material (Agarwal *et al*., 2020).

8.5 Microneedles: These are created on the micron scale, ranging from 1 micron in length to 100 millimetres in diameter. These are transdermal patches with micro-sized needles. A microneedle patch is a bandage-like device with microneedles attached to a backing membrane. Transdermal microneedles produce holes in the skin with a diameter of a few hundred nanometers in order to improve medication delivery. Transdermal transport of tiny and big molecules may be improved with the use of microneedles (Sharma *et al*., 2018).

8.6 Laser ablation: Pores are created in the stratum corneum using a high-energy laser. A wavelength absorbed by tissue proteins (2940 nm) and one absorbed by tissue water (2560 nm) are the two ideal wavelengths for skin ablation (mid-infrared; 2790 nm). Vibrational heat is produced when laser energy is applied to the skin, which then absorbs it (Joshi *et al*., 2012).

8.7 Skin Abrasion: Using this method, the top layers of skin are removed or disturbed, making it easier for topically administered medications to penetrate the skin (Sudam & Suresh, 2016) and procedure has been used by dermatologists to treat acne, hyperpigmentation, scars, and other skin imperfections.

7. Transdermal products currently in the US market

Fentanyl patch known as Duragesic® was launched in 1990 and manufactured by Johnson and Johnson which made a historic global sale in 2004 of about $2 (Watkinson, 2013). This product represented a blueprint for the TDDS and showed a great success at the biomedical field in treating pain as well as commercial front giving high economic returns. Another breakthrough in the market of transdermal patch was the fabrication of Androgel® - a transdermal testosterone replacement product which generated a revenue of $900 million in the year 2010 (Watkinson, 2013).

Several manufacturing defects such as seal and membrane defect which causes drug leakage led to recall of the patches in 2004 and 2008, which caused the patients to expose themselves to the overdose of the drug. In 2009, the Duragesic showed a leakage problem which was solved by redesigning of the patch to a DIA design (Prodduturi *et al*., 2010).

In 2022, donepezil loaded transdermal patch was formed for the treatment of mild to severe Alzheimer's-related dementia. The product is known as Adlarity from Corium which became available in the United States on producing a prescription. The patch was applied on the skin on weekly basis which delivers constant doses of donepezil. In the same year, Rivastigmine was given approval by the National Medical Products Administration (NMPA) to be applied twice weekly for the treatment of Alzheimer's disease.

The drugs which are available in market and studied widely for the use of TDDS are nifedipine (Thacharodi *et al*., 1996), nitro-glycerine, (Savoji *et al*., 2014; Wang *et al*., 1998) captopril, (Duraivel *et al*., 2014; Mohabe *et al*., 2011), chlorpheniramine (Gajbhiye *et al*., 2021), propranolol (Sirisha *et al*., 2012; Thacharodi & Rao, 1995), aspirin (Chorghe *et al*., 2013; Ammar *et al*., 2006), norethindrone (Barichello *et al*., 2006), hydrocortisone (Lashmar *et al*., 1994; Abruzzo *et al*., 2017), acyclovir (Zhao *et al*., 2006), fentanyl (Lashmar *et al*., 1994), theophylline (Akhtar *et al*., 2020; Zhao *et al*., 2006), nicotine (Akhtar *et al*., 2020; Zhao *et al*., 2006) etc. Detailed elaboration in **Table 3.**

8. Discussion

The ultimate outcome of this review was deeper understanding of the facts of transdermal drug delivery system which has evolved over the years to provide an efficacious and sustainable drug delivery system. This system helps in achieving a greater

bioavailability of the drugs that lack to reach the blood levels when compared with their oral administration. Different conventional methodologies are being used to deliver the drug in to systemic circulation, but have to face major issues with GI metabolism, frequent administration and variable clinical efficacy with a load of several other side effects. Polymeric TDDS have emerged as a powerful technology for delivering suitable chemical entities to large complex biotherapeutics while addressing the short coming associated with oral and parental pathways and providing an established clinical efficacy. The whole concepts of development and working of a TDDS orbits around the selection, biocompatibility with drug, utilisation and physiochemical properties of the polymers. Polymers plays a crucial role in development and functioning of the transdermal patches like formation of drug core, sustained and controlled release of drug, drug entrapment, targeted delivery, adhesive properties, chemical adaptability, and potential degradability without causing allergic reactions. These polymers severe as a drug carrier or a functional excipient that helps in drug permeation across the cell membrane. Drugs selected for use in TDDS have to accomplish many specified criteria to be used in the transdermal patches, that's why the number of medications produced in the patches has hardly risen over the last decade, but the drug delivery mechanism has seen several developments. Because only a small number of medications meet the molecular weight and potency criteria for transdermal absorption, the majority of modifications have focused on improving the substance itself. Different types of trandermal patches are prepared which has made the drug delivery system more biocompatible and biodegradable. These multilayer patches also help to deliver hydrophilic and hydrophobic drug components. Newer practices are being employed which utilise the mechanical energy to boost drug flow across the skin barrier or raising drug molecule's energy level, ultimately increasing the penetrability of drug to across different skin barriers. Transdermal delivery is helpful in producing clinical effects, such as anti-inflammatory activity and local anaesthesia deep within or beneath the layers of the skin. It also helps in encapsulating drug molecules of cardiovascular disease, depression, hormone replacement therapy. This review outlines the different transdermal products available in the market which has their own success and limitations. TDDS have shown a tremendous market share and opportunities to be explored for the betterment of the healthcare science. A detailed snapshot of the transdermal patch, its components, types of transdermal patch, the permeation mechanism and various applications have been given in Figure 3.

9. Conclusion

In conclusion, the utilization of polymer-based systems for transdermal drug delivery has witnessed remarkable advancements in recent years, particularly in the highly dynamic and competitive US market. These innovative systems have not only transformed the way medications are administered but have also addressed several critical challenges associated with traditional drug delivery methods. Such practices are known as active transdermal technologies, and they include opportunity to explore in the segment like electroporation and therml energy. Additionally, the idea is to use this purported platform to raise the awareness related to use of Transdermal drug delivery among the potential users, encouraging them for more preclinical and clinical studies and to explore its therapeutic potential in order to understand the current extremities and overcome the present limitations thereby helping in increasing the commercialization of more transdermal patches.

Author contribution

H.D., D.S., D.K., M.A., E.T.A.B. made substantial contributions to the conception and design of the manuscript, review of the literature, and drafting of the manuscript and figures. F.A., M.S. supervised every step in the design, structure and preparation of the manuscript and gave the final approval of the version to be published. All authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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