TRANSDERMAL DRUG DELIVERY SYSTEM: AN ATTRACTIVE APPROACH FOR TREATMENT OF NEUROLOGICAL DISORDERS

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ABSTRACT: The gradual deterioration of certain nerve cells, leading to ataxias and dementia, is a symptom of neurodegenerative disorders. These illnesses impact millions of individuals around the globe. "Patches" that distribute drugs transdermally are a promising new alternative to the old ways of doing things and have helped a lot of people with different kinds of medical issues. One way to administer medication topically is via a transdermal patch.the bloodstream in a regulated manner. An rise in the number of medications authorized was caused by the introduction of several advanced transdermal delivery systems. Many different types of patients, especially those with problems of the neurological system, may benefit from this method of administration due to its inherent and significant benefits. In order to address chronic neurological diseases, the transdermal route is suitable since it allows for sustained medication administration and a stable plasma concentration of medicines, which reduces side effects.
In addition to improving drug treatment and patient compliance, transdermal patches are easy to use and provide significant benefits. This article provides a comprehensive overview of transdermal medication administration, including its rationale and scope in neurological disorders, as well as the numerous methods to transdermal formulation and innovative techniques used in this drug delivery.

Keywords: Transdermal patch, Neurological disorder; Alzheimer's disease, Parkinson's disorder, Depression Migraine

INTRODUCTION: Transdermal drug delivery system (TDS) is defined as a self-content discrete dosage form, which when applied to intact skin delivers the drug to the systemic circulation at a controlled rate. TDS is an appealing alternative route of administration of a drug. The development of a successful 3- day transdermal patch of scopolamine to treat motion sickness in 1979 boosted research in the field of transdermal patch. Later in the year 1984, the FDA approved a nicotine patch for the cessation of smoking.

In the following decade, various transdermal patches for analgesia, contraception and hormone replacement therapy were approved by the FDA. Transdermal drug delivery holds great potential in the market of medical devices. The Transdermal drug delivery market was 4200 million USD acrossthe world in 2016 and is projected to increase everyyear by 7.5%, up to 2024 [1].

TDS has proven to be a successful alternative over various routes of administration such as oral, intravenous, intramuscular, hypodermal, and rectal. Neurological disorders are diseases of the peripheral and central nervous systems. It isrecognized by electrical, biochemical, and structural anomalies of nerves or the spinal cord. Reports insinuate that there are more than 600 kinds of neuropathological conditions. Symptomsof neurological disorder include confusion, muscle

weakness, cognitive failure, dementia [2]. TDS is particularly beneficial in the case of chronic neurological diseases encompassing symptoms of motor and cognitive loss that causes a challenge of adherence to treatment [3]. Adherence to medication can be influenced by several factors such as dosing regimen, route of administration, type of disease, and undesirable side effects. TDS lowers gastrointestinal adverse effects that are generally associated with the oral route of administration thereby enhancing tolerability [4]. TDS enables sustained release, evade patient unwillingness or inability to swallow oral formulation, and the painful and unpleasant experience of injections. A transdermal patch is capable of providing continuous and controlled release, minimizing the side effects caused by fluctuation in blood plasma concentration of drugs that are generally observed with oral dosage form [5].

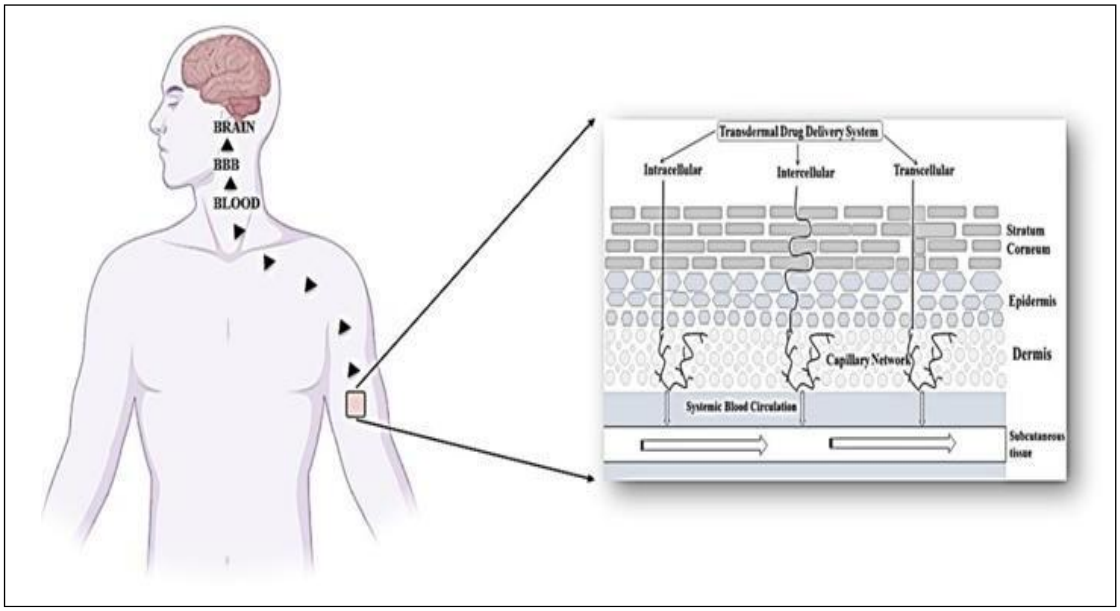

FIG. 1: PERMEATION OF DRUG MOLECULES ACROSS SKIN THROUGH THE TRANSDERMAL PATCH

Another advantage of TDS is it bypasses hepatic first-pass metabolism. It also aids dose reduction, increases therapeutic value, and efficacy. It is painless, non-invasive, cost-effective and convenient as compared to other routes of administration [6]. TDS is of great help for patients with dementia who fail to take the dosage as recommended. Transdermal drug delivery can provide local as well as systemic therapeutic effects [7].

For a drug molecule to be formulated into a transdermal dosage form, it should follow certain criteria. It should have low molecular weight and high lipophilicity so that they are liposoluble and permeates easily through the layers of skin. Another criterion is that the drug should be highly potent8. These criteria restrict the number of drug molecules that can be formulated as TDS. Many recent advances have been made to enhance the skin penetration of drugs which may facilitate the wider option for drugs to be formulated as TDS [9].

The main aim of TDS is to achieve systemic circulation through intact skin [10]. Hence it is necessary to review the biochemical and structural features of human skin. Anatomically human skin can be categorized into three main layers - epidermis, dermis, and subcutaneous layer. The outermost layer of the epidermis is the stratum corneum which possesses a major barrier [11]. The three major ways through which drug molecules cross the stratum corneum and reach systemic circulation are intracellular, intercellular, and via skin appendages (shunt routes) [12]. Typically, the transdermal patch consists of three components: polymer matrix, actives and adhesive. To enhance penetration of the drug certain penetration enhancers such as sulphoxide (Dimethyl sulfoxide DMSO), fatty acids (oleic acid, decanoic acid), alcohol (ethanol), glycol (propylene glycol) and surfactant (anionic surfactant), azone (lauracapran), *etc.* are added. Depending on the release pattern required various patches can be formulated **Fig. 1**.

- **Drug-in-Adhesive (DIA):** A homogenous dispersion of drug molecules in a polymer with adhesive properties is formulated. It can be further categorized into single layer drug- in- adhesive and multilayer drug- in – adhesive [13]. *e.g.*: Daytrana® patch of methylphenidate [14].

- **Matrix System:** A homogenous dispersion ofdrug molecules in a lipophilic or hydrophilic polymer matrix is formulated [15]. *e.g.*: Nitro – dur®patch of nitroglycerine [16].

- **Reservoir Type:** A drug reservoir in the form of a solution, suspension, or gel is embedded between an impervious backing membrane and a rate controlling membrane [17]. *e.g.*, CATAPRES-TTS® patch of clonidine [18].

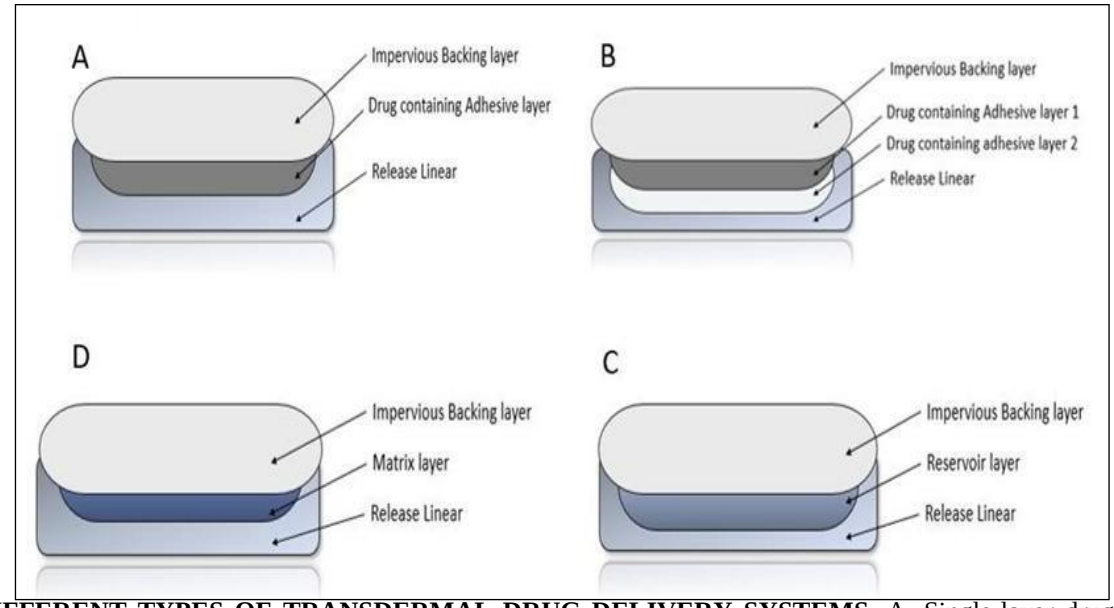

FIG. 2: DIFFERENT TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEMS. A. Single-layer drug-in-adhesive system, B. Multiple layer drug-in-adhesive system, C. Reservoir system, D. Matrix system

Depending on the size of drug molecules and type of penetration enhancers, various advances intransdermal drug delivery systems were made [19]. These advances are to be categorized into three generations. First-generation involves the formulation of drug molecules that were topically applied and had therapeutic efficacy without the aid of any penetration enhancers. The second- generation acknowledged the need to enhance skin permeability of drugs and used penetration enhancers such as chemicals [20] or methods like iontophoresis [21] and ultrasound [22]. Third generation aimed at the delivery of macromolecules like certain proteins and vaccines. This could be achieved with aid of novel chemical enhancers, electroporation [23], microneedles [24], thermal ablation
[25], and micro dermabrasions [26].

This article addresses five neurological disorders: Alzheimer's disease, Parkinson's disorder, schizophrenia, depression, and migraine. It provides a methodical analysis of the rationale, efficacy, clinical and pharmacokinetic studies of the transdermal drug delivery system currently under investigation for these conditions (from 2000-2020). Thus, the review provides a strong basis for the development of transdermal formulations in treating neurological disorders.

Alzheimer's disease: Alzheimer's disease is characterized by intracellular neurofibrillary tangles and extracellular amyloidal protein deposits that contribute to senile plaques [27]. A decrease in cortical neurotransmitters, such as norepinephrine, serotonin, acetylcholine, somatostatin, and an elevation in the levels of glutamate is linked with Alzheimer's disease. Cholinesterase inhibitors (ChEIs): donepezil, rivastigmine, galantamine, tacrine, and other memantine are the anti- Alzheimer drugs approved by the FDA. Mostly all these anti-Alzheimer agents are available as dosage forms containing high doses of drugs that lead to adverse effects such as nausea, vomiting, anorexia, and abdominal pain. Some incidences of renal failure, hepatotoxicity, or asthenia are alsoobserved. Since, the disease is associated with

memory loss and dysphagia, there is poor medication adherence by patients. TDS can overcome these drawbacks by providing a novel therapeutic approach by improving patient compliance [28]. Physostigmine was the first anticholinesterase to be formulated as a transdermal patch for Alzheimer's disease. Physostigmine has anarrow therapeutic window and short half-life. Formulating physostigmine into a patch helped overcome these shortcomings. The transdermal patch of 20% physostigmine in propionic acid as an enhancer vehicle was developed and a single-blind study was carried out on 12 Alzheimer's patientsfor 2 weeks. The results exhibited that the plasma concentration of physostigmine was found to be relatively stable and showed comparable inhibition of blood cholinesterase in comparison to the oral formulation [29].

However, local adverse effects like dermal irritation are one of the major problems, this formulation requires further investigation in a larger group of patients and greater optimization of physostigmine dosages and application areas. A study was conducted to investigate the pharmacokinetics of single application of the transdermal patch, IV infusion, and oral solution of physostigmine in 6 healthy male volunteers. It demonstrated that the therapeutic plasma level was maintained for about 18 h after a single application of the patch. The transdermal patch enhanced bioavailability to 36% as against 3% for oral solution. Also mean elimination half-life of physostigmine was enhanced by the use of a transdermal patch to 4.5 h, as compared to that of
I.V infusion signifying sustained and continuous physostigmine absorption from skin depot. This study proved the efficacy and advantage of a once- a-day patch application of the drug over several times of oral administration [30].

Another study conducted on 204 patients assessed the tolerability and safety of the physostigmine patch. Reports indicated that the plasma concentration of 100 pg / mL was too low to show adequate cholinesterase inhibition. The transdermal system failed to maintain the therapeutic plasma concentration of physostigmine in Alzheimer's disease for the expected period [31]. Further investigation is necessary to develop a successful transdermal drug delivery system of physostigmine. Donepezil is most commonly used in the treatment of Alzheimer's disease. Currently, available formulations are in the form of immediate release, sustained release, and orally disintegrating tablets. However, oral donepezil is associated with adverse events of the gastrointestinal system and exhibits plasma fluctuations [32]. To overcome this limitation, two different approaches were attempted. In the first approach, drug-in-adhesive was formulated wherein lag time was reduced. This decrease in lag time increased the flux of drugs in the bloodstream [33]. Further feasibility for iontophoresis transdermal delivery of donepezil using Wearable Electronic Drug Delivery (WEDD) patches was explored and different current levels of 0, 0.13, 0.26, and 0.39 mA were supplied.

It was observed that increasing the strength of the current, increased bio-availability, and plasma concentration of drug [34]. A phase 3 clinical trial in 2017 was conducted in Alzheimer's patients to evaluate the efficacy and safety of donepezil transdermal patch by Icure pharmaceuticals. Improvement in cognitive function was evaluated based on the Alzheimer's Disease Assessment Scale
- Cognitive (ADAS-cog) and global assessment as evaluated by Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus). The results are awaited [35]. Rivastigmine is an acetylcholinesterase inhibitor approved by the FDA in 2007 for dementia in Alzheimer's and Parkinson's disorder. Higher dose and fluctuation in plasma concentration of rivastigmine lead to unwanted side effects of the gastrointestinal tract. This hampered the patient's adherence to treatment.

With a motive of increasing compliance with rivastigmine, the transdermal patch was developed, approved by FDA in 2007, and marketed underbrand name Exelon® patch in 3 dose strengths *i.e.* 4.6 mg/ 24 h.; 9.5 mg/24 h; 13.3 mg/ 24 h [36]. Patches of all strengths demonstrated steadier and smoother release of rivastigmine in comparison to rivastigmine capsules. Pharmaco-kinetic data showed lower Cmax and absorption efficiency showing similar efficacy of both the patch and capsule [37]. Analysis of data from a 48-week randomized, double-blind phase (13.3 *vs.* 9.5 mg/24 h rivastigmine patch) in declining patients with mild-to-moderate AD (OPTIMA), a 24-week,

randomized, double-blind evaluation of 13.3 *vs.* 4.6 mg/24 h rivastigmine patch in severe AD (ACTION), and a 72- to 96-week study comprising an initial open-label (IOL) phase was done. It was observed that application site reaction was experienced by <25% of patient in both the studies, generally in mild-to-moderate severity and do not cause significant discomfort. This reaction can be managed by using proper patch site rotation, treatment, and skin care [38]. Galantamine is a first- line treatment for mild-to-moderate Alzheimer's disease and is available in the form of tablets and capsules. It possesses a dual mechanism of actionas a selective reversible acetylcholinesteraseinhibitor and nicotinic receptor modulator [39].

Various side effects like gastrointestinal disturbances, vomiting, and nausea are associated with these formulations. A drug-in-adhesive transdermal patch of galantamine was formulated to avoid these side effects. The effect of formulation factors such as pressure-sensitive adhesive, enhancers, and drug concentration was evaluated. Permeation enhancers like N-methyl-2- pyrrolidone, Transcutol, isopropyl myristate, oleic acid, benzyl alcohol; various PSA like acrylic PSA with no functional group, two with hydroxyl functional group and with carboxyl functional group and different concentrations of drug (3, 7, 8, 9, and 10%, w/w) were evaluated. It was reported that the most optimized transdermal patch contained 8% galantamine, 3% oleic acid, and acrylic PSA with a hydroxyl group (DT-2510).

Pharmacokinetic studies done on rabbits demonstrated prominent absolute bioavailability of 80% and a stable level of galantamine in plasma for
24 h [40]. A reservoir-type transdermal patch was formulated using galantamine hydrobromide gel as a reservoir. It was observed that when a low amount of polymer, crosslinker, and a higher amount of drug and penetration enhancer was employed, drug release was highest as against the high amount of polymer and crosslinker. It was deduced that the gel drug reservoir can be employed to fabricate a reservoir-type transdermal patch [41]. In another study, matrix type transdermal patch employing PSA was developed. Four diverse pressure-sensitive adhesives with different functional groups, ten penetration enhancers, and four drug loadings were tested to determine the

optimized patch. It was reported that an optimized patch was composed of 10% w/w galantamine, 5% w/w oleic acid as crystallization inhibitor, 5%w/w limonene as a penetration enhancer, and GELVA GMS 788 as PSA. It was observed that the use of limonene enhanced flux of galantamine to 1.7 timesacross human cadaver skin whereas the use of a combination of limonene and oleic acid enhanced flux to 2.7 times. The optimized patch demonstrated a permeation rate of 32.4 ± 1.41 μg/cm^2/h across human cadaver skin [42]. However, no pharmacokinetic studies were conducted to demonstrate its clinical efficacy. Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been used in patients with moderately severe to severe Alzheimer's disease.

In-vitro studies were performed on pig ear skin to investigate the feasibility of memantine formulated as a transdermal patch. The outcome indicated that transdermal flux is enhanced after pre-treating skin with various chemical enhancers like R- (+)- limonene, decanoic acid, laurocapram, or oleic acid. The use of R- (+)-limonene demonstrated maximum transdermal flux. In another study, iontophoretic transdermal delivery of memantine hydrochloride was also investigated. The application of 0.5 mA/cm^2 current density exhibited maximum transdermal flux, 22.5 times greater in comparison to passive diffusion of memantine across layers of skin. Evidently, iontophoresis was seen to significantly increase the flux of memantine across the skin [43].

Subsequent comparative investigation of memantine pharmacokinetics after oral, IV, and patch administration in rats, after multiple- or single- oral dose and transdermal administration was conducted. It was reported that the patch showed lower drug plasma concentration, lower Cmax, and prolonged half-life with similar drugexposure as oral and IV administration.

Thus, patch formulation was found to show fewer side effects than oral formulations. In single-dose studies, it was noted that the absolute bioavailability of oral formulation was 41% andthat of the patch was 63%. The amount ofmemantine absorbed into systemic circulation was higher *via* patch administration than oral administration [44].

TABLE 1: MARKETED TRANSDERMAL PATCHES FOR NEUROLOGICAL CONDITIONS

Year	Drug Trade Name	Patch design	Indication	Manufacturer	Dose and size of a patch	Frequency of application	References
1981	Scopolamine Transderm Scop®	Reservoir/ membrane	Motion Sickness	Novartis. Baxter Healthcare Corporation, SandozInc. GlaxoSmithKline Consumer Healthcare Holdings (US)LLC	1.5 mg in 2.5 cm²	72 hours	[92, 93]
2006	Methylphenidate Daytrana®	DIA	ADHD	Shire, Noven therapeutics LLC	27.5 mg in 12.5 cm² 41.3 mg in 18.75 cm² 55 mg in 25 cm² 82.5 mg in 37.5 cm²	Up to 9 hours in a day	[94, 95]
2006	Selegiline	DIA	Major	Mylan Specialty L.P.	20 mg in	24 hours	[96]

	Emsam®		depressive disorder	Somerset Pharmaceuticals Inc.	20cm² 30 mg in 30cm² 40 mg in 40cm²		
2007	Rivastigmine Exelon®	Matrix	Parkinson's and Alzheimer's disease	Novartis Europharm Limited Actavis Pharma Company Strides Pharma Canada Inc	9 mg in 5 cm² 18 mg in 10cm² 27 mg in 15cm²	24 hours	[97]
2007	Rotigotine Neupro®	DIA	Parkinson's disease Restless legs syndrome	Ucb Inc	2.25 mg in 5cm² 4.5 mg in 10cm² 6.75 mg in 15 cm² 9 mg in 20 cm² 13.5 mg in 30 cm² 18 mg in 40 cm²	24 hours	[98]
2013 - 2017	Sumatriptan Zecuity®	Iontophoretic system	Migraine	Teva pharmaceuticals	36 mg in 7 cm²	4 hours	[99]
2019	Asenapine SECUADO®	DIA	schizophrenia	Noven Therapeutics, LLC	6.4 mg in 20 cm^2 9.6 mg in 30 cm^2 12.8 mg in 40 cm^2	24 hours	[63]

Migraine: Migraine is a neurological condition characterized by frequent recurrences of the headache of moderate to severe intensities. It isusually associated with nausea, vomiting,phonophobia, photophobia, and fatigue. Migraine attacks are linked with gastric symptoms and gastric dysfunction, subsequently causing delayed absorption of oral medication and affecting the time to reach maximum plasma concentration (Tmax). The nasal route is Another prominentlyused route of administration used in migraine. Eventhough the drug is sprayed nasally, a substantial amount of drug is absorbed through the gut after swallowing eventually resulting in gastroparesis. This impedes the efficacy of the drug administered via the oral route and nasal spray formulation.

Sumatriptan is the most widely used triptan usedfor the treatment of migraines. It is available as oral, nasal, and subcutaneous formulations. The delivery of drugs via oral and nasal routes exhibited gastrointestinal side effects and low bioavailability.The delivery of sumatriptan via subcutaneous route was inconvenient; thus transdermal delivery for sumatriptan was developed [100]. In September 2015, Teva pharmaceutical launched the Zecuity® patch for the management of migraines which used a drug/device combination of sumatriptan and iontophoresis. The FDA initially rejected NDA for the sumatriptan iontophoretic patch, citing itspotential for "severe burn and permeant skinlesion". A subsequent application was approved by the agency despite the concern of local adverseevents with a deliberation that modification to patch would tackle those risks. However, the FDA issued an alert warning and recalled the patch in less than 10 months due to reports of skin irritation and serious burns from patch application. The FDA announced in late 2017 the discontinuation of patch [101].

To avoid this kind of failure in the future and develop a successful transdermal drug delivery system for migraine treatment, it is important to evaluate all the adverse events reported in clinical trials before NDA approval. Zolmitriptan is a second-generation triptan and a highly selective 5- HT1B/1D receptor agonist.

It is marketed as a tablet and nasal spray. The limitation with available formulation was low bioavailability and reports of gastrointestinal distress [102]. An attempt was made to formulate a drug-in-adhesive transdermal patch of zolmitriptan. Different permeation enhancers like azone, span, tween, transcutol P, N-methyl-2-pyrrolidone, Isopropyl myristate, and oleic acid were used. The results of pharmacokinetic studies conducted on rabbits exhibited that the patch with azone as a permeation enhancer was higher than other permeation enhancers used and released the drug in
15 min of patch application. The plasma concentration of drugs was maintained at a relatively high level in comparison with the patch without azone. Also, the absolute bioavailability of the drug was 67% higher than oral administration (40%) [103]. To enhance bioavailability and reduce gastrointestinal symptoms, transdermal iontophoretic delivery zolmitriptan was investigated. The *in-vivo* studies were performed using multistep current profiles that employed change in current supplied with respect to time.

Results indicated the delivery of a therapeutic dose of zolmitriptan in a shorter duration of time and rapid drug uptake, allowing the early onset of therapeutic effect [104]. A formulation of zolmitriptan delivered utilizing the Adhesive Dermally Applied Microneedle™ (ADAM) technology is recently developed by Zosano pharma and approved by FDA105. Phase III trial of ADAM zolmitriptan versus placebo was conducted to determine efficacy, safety, and tolerability of ascending doses. ADAM zolmitriptan was found to be effective as 42% of patients were reported to be pain-free in 2 h after the treatment. 70% of patient-reported to be free from migraine-associated symptoms. Efficacy was reported to be dose-dependent, with a 3.8mg dose offering a better response than both 1.9 mg and 1 mg dose106. A post hoc analysis was conducted to understand the efficacy of ADAM zolmitriptan. It was observed that participants receiving ADAM zolmitriptan 3.8 mg showed a uniform better response within 2 hours of treatment
[107]. Thus, ADAM zolmitriptan holds the potential to be more effective than other routes of administration that are currently available for zolmitriptan. The exact rationale for enhanced efficacy is unknown but can be linked to a faster rate of absorption of zolmitriptan from ADAM

zolmitriptan formulation. Almotriptan is a highly selective serotonin 5- hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist used in moderate to severe migraine attacks. Although bioavailability of almotriptan was 69%, the time taken to attain Cmax was between 1.5 to 4 hours with a short half-life of 2.5-5 h [108]. A study was conducted to investigate the effect of iontophoresis on the permeation flux of transdermal almotriptan across pig ear skin. The permeation of almotriptan via passive diffusion and iontophoresis with a current density of 0.25 mA/cm2 and 0.50mA/cm2 was examined. It was demonstrated that permeation flux for almotriptan via iontophoresis was greater than passive diffusion. Application of currentdensity of 0.25 mA/cm^2 and 50mA/cm^2 enhanced the drug release to 280 and 411fold, respectively, compared to passive diffusion. This *in-vitro* study indicated almotriptan could be successfully delivered *via* an iontophoretic transdermal patch
[109]. Although, *in-vivo* studies are required to prove its efficacy in humans.

Conclusion: Achievements and Future Prospects: The transdermal drug delivery system has various advantages like reduced dosing frequency, bypassing hepatic first-pass metabolism, steady drug plasma concentration, avoidance of gastrointestinal irritation, increased bioavailability, the ease of use. All these advantages have led to the development of some successful transdermal patch for the management of Parkinson's disorder, Alzheimer's disease, Attention-deficit/hyperactivity disorder (ADHD), Depression, and migraine. It is evident from pharmacokinetic studies that thetransdermal route enhances bioavailability (10% – 80%) of various drugs such as physostigmine, donepezil, galantamine, rivastigmine, and zolmitriptan. Enhancement of bioavailability of these drugs is due to avoidance of the first-pass metabolism where a major amount of drug is metabolized. The fabrication of the transdermal system assists in the prolonged and controlled release of drugs from the patch through the skin. Rivastigmine, selegiline, rotigotine patches can provide a controlled rate of delivery for 24 h. Adverse events due to the pulsatile stimulation of dopamine receptors is solved by the rotigotine transdermal patch. Levodopa transdermal patch also showed promising results in reducing adverse events. Transdermal is a good alternative for drugs like apomorphine and almotriptan that have a short half-life of 30 min and 2.5 h, respectively. Thedosing frequency of such drugs can be reduced when administered transdermally. Clinical studies of drugs like selegiline, rivastigmine, rotigotine, asenapine, and zolmitriptan substantiates that TDS provides constant delivery of drug and persistent therapeutic plasma levels with good overall tolerability. A common symptom in various neurological disorders is dementia; thus a patient fails to recall their medication regimen. Hence transdermal therapy seems a practical choice that proves beneficial for both patient and caretaker, enabling visual check and, in some instances, may avoid the chances of overdose. The TDS approach has the potential to improve compliance, leading to better clinical outcomes.

It has already been evident that all of the drugs currently available in the market as transdermal patches possess stringent pharmacokinetic and physicochemical limitations, which are required for permeation through the skin barrier. With only a limited number of drug molecules available to be delivered *via* the transdermal route, the delivery of other molecules seems promising with the arrivalof new technologies in the transdermal delivery system. The latest development in technology (like iontophoresis, sonophoresis, microneedle patch, or ultrasound-mediated transdermal drug delivery) has increased the range of drug molecules that can be formulated and used clinically in a transdermal patch. This will allow clinicians to surmount the challenge of low bioavailability associated with oral formulations and discomfort and inconvenience of parenteral formulation, thereby increasing patient compliance. Transdermal therapy provides an effective alternative for a patient looking for a novel approach to better manage their symptoms.

Even with all the benefits, as mentioned earlier, the market presence of TDS is limited. This can be due to cost implications for the development of transdermal formulations. And for patients, patches prove to be more expensive in comparison to oral or parenteral drug delivery systems available in the market. The availability of less expensive generic options discourages the patient from opting for patch formulation as well as deter pharmaceutical companies from investing production of TDS.

Regardless of these ambiguities, the transdermal drug delivery system has offered the opportunity to explore the ability to exist drugs and a new drug in the treatment of neurological disorders.

The positive preliminary responses from patients and caretakers might bring attention to targeted research and novel ways of managing neurological disorders via the transdermal drug delivery system. Customized, programmable drug delivery *via* transdermal route may become available and enableindividual tailoring of drugs. With high-quality research and technological advancement, TDS will improve the quality of life for those suffering from neurological diseases and other chronic diseases.

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