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

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ABSTRACT: Neurodegenerative diseases are progressive degeneration of certain nerve cells causing ataxias and dementia affecting millions of people worldwide. Transdermal drug delivery systems – "patches" represent an attractive alternative to the conventional method and have made an important contribution to the management of the various medical conditions. A transdermal patch is a medicated adhesive patch which delivers drug *via* skin to the systemic circulation in a controlled manner. The advancement of various sophisticated transdermal delivery technologies led to of increase in the number of approved drugs. This route of administration has several innate and major advantages that have the potential to benefit various patient populations, including those with nervous system disorders. The transdermal route is an ideal route for the management of chronic neurological conditions as they are capable of providing continued drug delivery and maintaining steadier plasma concentration of drugs thereby reducing adverse events. Moreover, a transdermal patch is convenient, efficient in enhancing medication therapy and patient compliance. This article reviews the rationale and scope of the transdermal route in neurological disorder, the different transdermal formulation approaches and various novel techniques employed in transdermal drug delivery.

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.

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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 across the world in 2016 and is projected to increase every year 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 is recognized by electrical, biochemical, and structural anomalies of nerves or the spinal cord. Reports insinuate that there are more than 600 kinds of neuropathological conditions. Symptoms of 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].

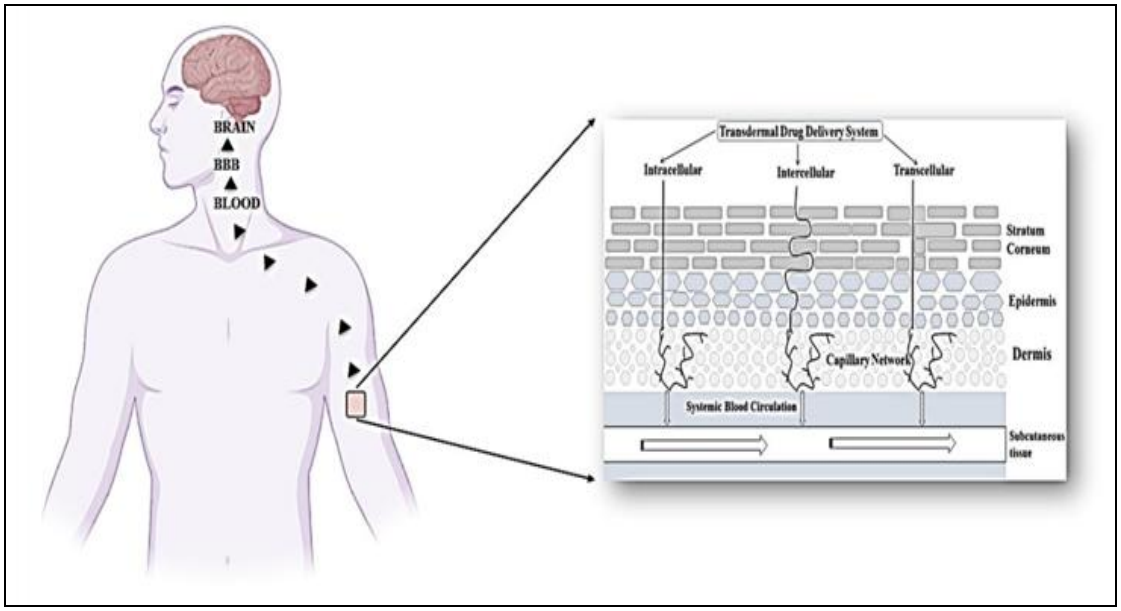

FIG. 1: PERMEATION OF DRUG MOLECULES ACROSS SKIN THROUGH THE TRANSDERMAL PATCH

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 of drug 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].

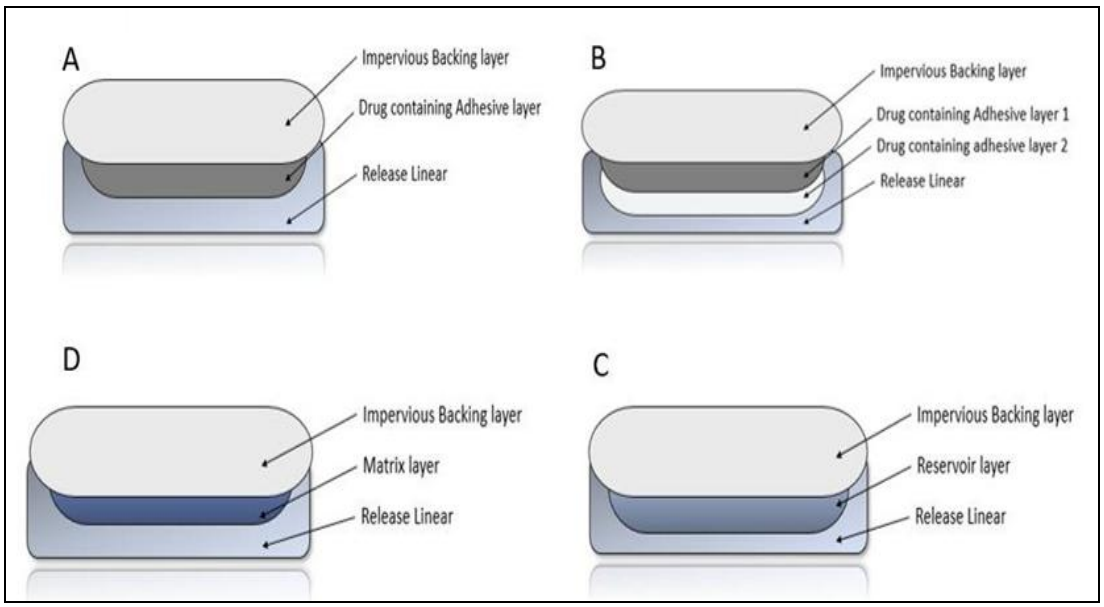

FIG. 2: DIFFERENT TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEMS. A. Single-layer drug-in-adhesive system, B. Multiple layer drug-in-adhesive system, C. Reservoir system, D. Matrix system

Depending on the size of drug molecules and type of penetration enhancers, various advances in transdermal 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 also observed. 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 a narrow 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 patients for 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 under brand 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 action as a selective reversible acetylcholinesterase inhibitor 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 concen-tration 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 times across 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 $\mu g/cm^2/h$ 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 drug exposure 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% and that of the patch was 63%. The amount of memantine absorbed into systemic circulation was higher *via* patch administration than oral administration [44].

Parkinson's Disorder: Parkinson's disease (PD) is the second most prevalent, progressive neuro-degenerative disorder following Alzheimer's disorder that has been characterized by a loss of dopaminergic neurons severely in substantia nigra [45]. It is characterized by symptoms like movement retardation, tremors, stiffness, and muscle rigidity, and posture instability. Pharmaceutical agents that are used to treat PD include naxagolide, levodopa, carbidopa, Piribedil, Apomorphine and pramipexole. Some of these drugs undergo extensive first-pass metabolism and several drugs among these are not able to reach the brain in sufficient quantity. This insufficient utilization of drugs often requires the ingestion of higher concentrations of drugs which in turn manifest toxicity in certain organs like the heart, kidney, or liver. Another limitation of these therapeutic agents is that they cannot be administered parenterally because they are highly lipophilic in nature. Poor solubility of these therapeutic agents is the major drawback of oral or parenteral administration. Therefore, transdermal drug delivery can prove to be beneficial in Parkinson's disorder [46].

Naxagolide is a potent dopamine agonist and the first anti-Parkinson agent that was investigated for the transdermal route of administration owing to its high solubility in lipid as well as an aqueous medium. A study was conducted using a naxa-golide transdermal patch on 4 patients with idiopathic Parkinson's. It was observed that plasma concentration of naxagolide increased after 4-6 hours of application of the patch, whereas steady-state plasma concentration was achieved only after 24 h of patch application, possibly due to the time needed for skin permeation of the drug [47]. Regardless of the promising preliminary results, no further studies are conducted to demonstrate its clinical efficacy.

Levodopa is the metabolic precursor of the neurotransmitter dopamine. The most widely available oral route has the disadvantage of rapid rise and fall of plasma concentration of levodopa. This pulsatile stimulation of dopamine receptors is the reason for treatment-related problems of levodopa, limiting its effectiveness. The transdermal route offers continuous medication administration, thereby averting dyskinesia and motor fluctuation due to pulsatile drug delivery. Absorption of L-dopa is also affected by diet and other gastric factors such as gastric emptying and food intake [48]. To overcome these complications, various types of transdermal delivery systems were investigated. An in-vitro study was performed to investigate the effect of various permeation enhancers along with fatty acid and PSA TDS. The *in-vitro* study demonstrated that the ester-type vehicles (propylene glycol monocaprylate and propylene glycol monolaurate) had a relatively higher permeation enhancing effect. It was observed that the addition of fatty acid like 10% linolenic acid led to an increase in AUC (76.2 times) and a decrease in clearance value (86.8 times) and prolonged Tmax of levodopa as compared to an oral formulation. This increased AUC and subsequently the therapeutic efficacy of the transdermal patch [49]. An attempt was made to develop a transdermal patch of a frequently used combination of levodopa-carbidopa. Levodopa (5%) in combination with carbidopa (2.5%) was fabricated as a drug-in-the adhesive transdermal patch and assessed for drug permeation, drug release, and pharmacokinetics in rats.

Permeation study demonstrated the rapid permeation of levodopa and carbidopa without any lag time. However, the formulation did not achieve the therapeutic range of levodopa. It also failed to maintain steady-state drug concentration throughout the duration of the study. Further investigations are required to increase levodopa's permeation and achieve steady-state plasma concentration for a longer duration [50]. Rotigotine (Neupro®) is a dopamine agonist developed as a silicone-based transdermal patch. The FDA approved transdermal rotigotine (Neupro®, Schwarz) as monotherapy to be used during the early stages of Parkinson's disorder in 2007 and for restless leg syndrome in 2008.

The patch delivered rotigotine for a period of 24 hours [51]. Rotigotine transdermal patches are available in various sizes, *e.g.,* 10,20,30,40 cm^2 patch that delivers various doses of 2,4,6,8 mg of rotigotine respectively for 24 h. Along with Parkinson's disorder, the rotigotine transdermal patch is also indicated for the management of moderate to severe idiopathic restless leg syndrome [52]. Rotigotine patch has high adherence and tolerability, with mild to moderate side effects,

mostly local skin reactions and nausea. Piribedil, a centrally acting anti-Parkinson's dopamine agonist, acts on D2 and D3 dopamine receptors. A randomized double-blind study was carried out with piribedil transdermal patch. 27 patients with idiopathic Parkinson's disease received 3 different treatments. One group received a placebo, and the other two groups were administered a single patch (1PP) or two piribedil patches (2PP). The plasma concentration of piribedil was 6.74 ± 1.10 and 9.31 ± 3.33 ng/mL in 1 PP and 2 PP, respectively. This plasma level is low to manifest clinical efficacy. Pharmacokinetic-pharmacodynamic studies of intravenous administration of piribedil suggested that the critical range for clinical efficacy was between 10 ng/mL to 30 ng/mL [53]. However, another study conducted in MPTP-induced Motor Deficits in the Common Marmoset demonstrated a reduction of motor deficits for a prolonged duration [54]. Further investigation is required to determine the feasibility of Piribedil as a transdermal delivery system.

Apomorphine is a potent D1 and D2 agonist used as an adjunct medication for Parkinson's disease. The limitation with the oral of apomorphine orally, is its short half-life of 30 minutes, rapid clearance, and very poor bioavailability of 5% due to high first-pass metabolism after oral administration. Sublingual, subcutaneous, rectal, and intranasal dosage forms were explored but failed to provide sustained release for a prolonged period [55].

To overcome this limitation, a transdermal patch of apomorphine was formulated. To achieve the controlled delivery of apomorphine, the iontophoretic transdermal patch of apomorphine was developed. The significant feature and a major advantage of transdermal iontophoresis is that it possesses the potential to deliver apomorphine as per the need, not only by measuring patient's pharmacokinetics but by the possibility of measuring their pharmacodynamic output. This particular study demonstrated that the rate of delivery of apomorphine could be controlled by moderating current. However, after applying current for 1-h, plasma concentration attained was 1.3 ng/ml at 250 µA/cm^2 and 25 ng/ml at 375 µA/cm^{2,} which was lower than the therapeutic limit (10 ng/mL) [56]. Another iontophoretic study was conducted in 16 patients with advanced Parkinson's disorder employing a current density of 250 µA/cm2 for 3.5 h. 8 out of 16 patients received pre-treatment with a non-occlusive surfactant formulation before application of iontophoresis patches. It was observed that pre-treatment with a surfactant formulation increased the plasma level of apomorphine. Bioavailability was enhanced to 13.2% in the group receiving pre-treatment with a surfactant, as compared to that of 10.6% in the control group (without surfactant pre-treatment). The results of this study confirmed the effectiveness of iontophoresis in the delivery of apomorphine in combination with pre-treatment with surfactant [57]. This patient-customized apomorphine delivery system with iontophoresis could hold great potential for optimizing the drug dose of apomorphine. Pramipexole is a highly active agonist of dopamine receptors and is used as a first-line antiparkinsonian agent for early and advanced Parkinson's disease. Even though pramipexole has a high bioavailability of 90%, it has a short half-life of 8 h.

The dosing frequency of the drug is thrice a day, causing patient non-compliance, which can be solved by formulating a transdermal patch. Hence, a simple drug in adhesive type transdermal patch of pramipexole was formulated. It was reported that a combination of PSA, DUROTAK ® 87-2852, and DURO-TAK® 87-2510 gave a prolonged release of the drug owing to their high stability, drug loading, and release capacity.

The most optimized pramipexole patches maintained continuously *in vitro permeation* flux of 6.0 µg/(cm^2•h) through human skin for 7 days [58]. Another study involving a long-acting pramipexole transdermal patch on the mouse with Parkinson's disease exhibited a neuroprotective effect [59]. Further studies in humans are required to examine the clinical efficacy of the patch.

Schizophrenia: Schizophrenia is a psychological condition that affects perceptions and interpretations of reality. Common symptoms are hallucination, delusion, inability to think coherently, and disordered thinking [60]. Genetic and environmental factors are responsible for this condition. Currently available antipsychotic drugs for schizophrenia are marketed in the form of conventional tablets.

Low bioavailability due to high first-pass metabolism and gastrointestinal irritation leads to patient nonadherence to treatment. The major purpose of the transdermal patch in schizophrenia is to resolve patient non-compliance associated with the route of administration [61]. Asenapine is a second-generation atypical antipsychotic that is nearly completely metabolized in the first pass through the liver. Hence it is available in the form of sublingual then again, some problematic issues with sublingual administration (complex instruction, bitter taste, and potential for mouth ulcers) occur. Once a day transdermal patch of asenapine has been approved by the FDA for a patient with schizophrenia [62]. A Phase III study evaluated the efficacy and safety of the asenapine patch in adults with schizophrenia. The trial aimed to assess the safety and efficacy of the asenapine patch in comparison with the placebo.

The primary efficacy objective was Week 6 PANSS score change from baseline versus placebo. The key secondary objective was Week 6 CGI-Score change from baseline versus placebo. The results demonstrate that the asenapine patch is safe, efficacious and well-tolerated, and met primary and secondary endpoints. However, headache, extrapyramidal disorder, and reaction as application were reported as adverse events [63]. Blonanserin is a second-generation antipsychotic developed for the treatment of schizophrenia in adults [64]. Phase 3 clinical trial was conducted to evaluate the safety of the patch in comparison with placebo [65].

Patients were treated with a placebo patch, 40 mg, or 80mg patch of blonanserin. Efficacy and irritation scores were assessed using the PANSS scale. This clinical trial reported that the blonanserin transdermal patch was well tolerated showing dose-dependent psychopathology and treatment completion rates over placebo. The incidence of skin-related AEs increased in a dose-dependent manner [66]. Sumitomo Dainippon Pharma received the approval of the blonanserin transdermal patch in June 2019 in Japan. Olanzapine is a second-generation antipsychotic used during the onset and maintenance of therapy in schizophrenia. Studies were conducted using various permeation enhancers like natural oils, surfactants, and vegetable oil. In a study employing matrix-type transdermal patch of olanzapine, natural oils like corn oil, jojoba oil, and ground oil were tested as permeation enhancers across rat skin. All the selected enhancers demonstrated enhanced permeability and reduced lag time. However, the highest permeation was exhibited by corn oil. The reason could be the presence of a high amount of unsaturated fatty acid in corn oil, as fatty acids are known to enhance permeation through the human epidermal membrane [67]. Pharmacokinetic studies conducted on rabbits showed better relative bioavailability (113.6% as compared to oral olanzapine) and more sustained release (8 hours as against 4 hours of oral olanzapine) than oral marketed preparation. Due to the long elimination half-life of olanzapine, the drug accumulated in skin tissue showed slow depletion resulting in a mild reservoir effect [68].

Another matrix type transdermal patch for olanzapine was formulated, and an increase of permeation was evaluated by the use of permeation enhancers like non-ionic (span-20), anionic (sodium lauryl sulphate), cationic surfactant (benzalkonium chloride), and vegetable oil (olive oil). A patch containing olive oil and span 20 exhibited greater permeation through rat skin as compared to sodium lauryl sulphate and benzal-konium chloride. During in vitro release test, a patch containing span 20 showed the greatest cumulative release in 72 h period.

Pharmacokinetic studies done on rabbits indicate significantly enhanced bioavailability [69]. A drug in a pressure-sensitive adhesive patch was formulated using sorbitan monooleate as permeation enhancers. It leads to an increase in permeability as well as the release of olanzapine from the transdermal patch because sorbitan monooleate destroyed hydrogen bonding between pressure-sensitive adhesive (PSA) and drug. A pharmaco-kinetic study done on rats demonstrated enhanced bioavailability of the patch as compared to an oral formulation [70]. Thus, the transdermal administration of olanzapine would help circumvent the first-pass metabolism of the drug and enhance bioavailability. An attempt was made to formulate risperidone as a drug-in-adhesive transdermal patch. Four different types of acrylic PSA, one without a functional group, 2 with hydroxyl, and one with a carboxyl group were tested. It was reported that PSA with hydroxyl

group demonstrated greater permeation through rabbit skin in comparison to PSA without functional group or carboxyl group. To inhibit the crystallization of risperidone in the patch, various crystallization inhibitors like Polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), surfactant, and fatty acids were added. Fatty acid showed maximum inhibition of crystallization due to interaction between the amino groups of risperidone and carboxyl groups of fatty acid. Pharmacokinetic studies of the patch conducted in rabbits showed prolonged plasma concentration and higher bioavailability [71]. With promising preliminary results, development of risperidone transdermal drug delivery system holds a great potential.

DEPRESSION: Depression is one of the critical conditions that affect various people across the world. It can affect any age group from young to elderly and can prove to be terminal if not treated [72]. The Monoamine hypothesis suggests that depression occurs due to an imbalance or dysfunction of monoamine neurotransmitters like dopamine, serotonin, norepinephrine [73]. Symptoms include an anxious mood, loss of interest, or constant sadness. Physical symptoms include fatigue, loss of appetite, declining attention, and energy level [74]. Management of depression includes treatment with tricyclic antidepressants, serotonin reuptake inhibitors, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors. Available therapy has limitations, most of which are related to the oral route of administration.

Some of the drawbacks are high first-pass metabolism, variation in absorption in the GI tract, short half-life, high dosing rate, and dietary restriction. All this limitation could be surmounted by exploring other routes of administration, such as the transdermal drug delivery system [75]. Current, available patches are not ideal for acute situations such as asthma, a myocardial infarction for which rapid onset of action is needed; however, for chronic conditions like depression once optimal plasma levels of money, they remain steady as long as the patch is applied. Imipramine is a tricyclic antidepressant extensively used for the management of unipolar depression. The drawback associated with the oral route of administration is variation in absorption of the drug in the GI tract, high first-pass metabolism, which leads to patient noncompliance [76]. A drug in matrix reservoir transdermal formulation of imipramine incorporated in a hydro-alcoholic gel of HPMC along with penetration enhancers (oleic acid and menthol 2.5% w/v) was formulated and tested in rats. Reservoir gel formulation investigation showed that the plasma concentration in rats was 3.0 µg/mL, 15 to 35 times higher than the therapeutically effective concentration window (85-25 ng/mL). This showed that the problem associated with variation in absorption in the GI tract was circumvented [77]. However, rat skin is more permeable compared to human skin, so further studies are required to prove the efficacy of patches in humans.

Paroxetine is a serotonin reuptake inhibitor and the most potent marketed antidepressant. However, the pharmacokinetics of paroxetine administered via the oral route is unfavourable. Paroxetine is absorbed effectively from the gastrointestinal tract but is readily metabolized by the first-pass metabolism in the liver [78]. The reverse-phase evaporation technique was used to formulate Paroxetine liposomal gel in a reservoir transdermal patch. The main objective of the formulation was to enhance bioavailability and maintain the therapeutic response of the drug. The prepared paroxetine transdermal patch did not show any skin irritation when tested in rabbits. It was observed that the administration of the transdermal patch in rabbits increased the bioavailability of the drug by 2.8 times as compared to that of oral dosage forms [79].

Fluoxetine is a selective serotonin reuptake inhibitor and is extensively used to treat and manage various psychiatric diseases like bipolar depression, major depression, obsessive-compulsive disorder, bulimia nervosa, and panic disorder [80]. Fluoxetineinduces dose-related side effects due to enhanced serotonin response such as insomnia, anxiety, sexual dysfunction, vomiting, and nervousness81. These side effects are more dominant as fluoxetine is prescribed for the long term. A formulation of a drug-in-adhesive transdermal patch with 20% (w/w) fluoxetine was prepared. DuroTAK 87-502B was used as adhesive in the formulation, and the pharmacokinetic study was conducted in rats. C_{max} of 52.38 ng/ml was

attained at approximately 11 h after transdermal administration. This demonstrated that transdermal delivery can minimize side effects caused by the high plasma concentration of fluoxetine [82].

Trazodone, a serotonin reuptake inhibitor, specifically used for depression in schizophrenic patients, and have a short plasma half-life of 6 hours [83]. Consequently, it becomes necessary to increase the dosing frequency. Consequently, the occurrence of side effects like dry mouth, dizziness, nausea, muscle ache increased due to fluctuation in the plasma concentration of trazodone [84]. These side effects can be avoided by maintaining steady-state plasma concentration for a longer period. Hence matrix type transdermal patch was formulated, wherein different penetration enhancers like isopropyl palmitate, isopropyl myristate, octanol, and butanol were used. The enhancing effect on the permeation of Trazodone was determined using the mouse and human cadaver skin. The presence of all the enhancers at 10% showed a significant increase in the flux of Trazodone. IPM exhibited the highest flux (0.092 ± 0.03 mg/cm^2/h) as compared to other enhancers used [85]. Technical problems related to the large size of the patch required to deliver adequate dosages of the drug ceased further development of this patch. In another study, the biopharmaceutical behaviour of matrix-based transdermal formulation of trazodone form was evaluated. Pharmacokinetic studies conducted on healthy rabbits indicated the controlled release of drugs by maintaining the plasma level of trazodone for 24 h. The steady-state plasma concentration attained in rabbits was higher (2.5 µg/mL) in comparison to humans (0.75 µg/ml) [86]. This was observed because the rabbit's skin was more permeable in nature as compared to that of human skin [87]. Thus, further studies are needed to demonstrate the efficacy of patches in humans.

Selegiline is a MAO-B inhibitor used to treat Parkinson's disease in later stages. However, clinical trials have indicated the efficacy of selegiline in depression [88]. Selegiline causes a hypertensive crisis, a critical side effect known as the "cheese effect," which limits its use. Selegiline's low molecular weight and high lipophilicity are well-suited for transdermal absorption and rapid crossing of the blood-brain barrier without accumulation in the skin. A randomized, double-blind, placebo-controlled flexible-dose, parallel-group trial was conducted for evaluation of the safety and efficacy of the selegiline transdermal system in adolescents. Results demonstrated selegiline patch was well tolerated and safe to use [89]. MAOI selegiline TDS received marketing authorization for the treatment of depression in 2006 by the FDA for patients unable to swallow, absorb, or tolerate other available oral formulations. Thus, the Selegiline patches are used in depression associated with Parkinson's disease. Application of patch avoids dietary restrictions as safety and tolerability of selegiline patch were improved [90]. Selegiline transdermal patch is available as EMSAM® patches of 6 mg, 9 mg, and 12 mg per 24 h [91]. Selegiline TDS is a three-layered matrix-type adhesive patch that allows the continuous release of drugs from the patch for 24 h.

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 is usually 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 prominently used route of administration used in migraine. Even though 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 used for 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 its potential for "severe burn and permeant skin lesion". A subsequent application was approved by the agency despite the concern of local adverse events 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 current density 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 the transdermal 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. The dosing 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 arrival of 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 enable individual 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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CONFLICTS OF INTEREST:

The authors declare that there is no conflict of interest.

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