ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

A Potential Use of Dopamine Agonist and Monoamine Oxidase B Inhibitor in Parkinson's Disease as Apply by Transdermal Patch.

Received: 16 October 2022, **Revised:** 19 November 2022, **Accepted:** 22 December 2022

Shubhrajit Mantry1*, Suvarna Deshmukh2, Kiran Mahajan3, Shital Bidkar4, Ganesh Dama5

1,2,3,4,5 Department of Pharmaceutics SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi (Otur), Tal-Junnar, Dist.- Pune, Maharashtra, India, 410504.

***Corresponding Author: Dr. Shubhrajit Mantry**

Email: manu28pharamcy@gmail.com

Key words:

Parkinson's disease, Transdermal patch, MAO inhibitors, Dopamine agonist,

Abstract

Parkinson's disease (PD) is an advancing neurological disorder. The characteristic physical symptoms, which also include dopaminergic neuron loss and Lewy pathology, include rigidity, postural instability, bradykinesia, and resting tremors. Clinical symptoms in the elderly worsen over time due to decreased neurotransmitter levels, protein homeostasis disruption, mitochondrial malfunction, and oxidative stress. Parkinson's disease (PD) pathogenesis is likewise reliant on protein misfolding. and malfunction of the ubiquitin-proteasome system. The main purpose of continuous drug administration in PD is to maintain continuous dopaminergic activation, provide higher drug concentrations, prolong benefits, and reduce side effects. For example, transdermal delivery of monoamine oxidase-B or dopamine agonists inhibitors the drug delivery method itself may have an impact on a drug's bioavailability, which may therefore have an impact on a drug's effectiveness and tolerability, as well as on patient compliance. Additionally, examine the pharmacological and pharmacokinetic characteristics of dopamine agonists and MAO-B inhibitors for the treatment of Parkinson's disease in both its early and advanced stages

1. Introduction

Parkinson's disease (PD) is a neurological condition that causes restlessness, rigidity, hyperkinesia, and an overall impairment of body balance. The most prevalent neurological disease, primarily influences people more than 65 years old. Even though Parkinson's disease is influenced by a many more different circumstances, its aetiology is still unknown. Parkinson's symptoms appear in patients when around 80% of striatal dopamine and 50% of the substantial nigra are gone, according to the disease's pathogenesis, which depicts the degeneration or necrosis of dopaminergic nerve cells. Levodopa is a starting point for the production of dopamine, and it takes about 5 years to finish a course of treatment. Antiparkinson's monotherapeutic agents is an alternative to levodopa. Dopamine metabolism is controlled by MAO-B, and its suppression results in a steady supply of dopamine. [1]

Older people have a different medication metabolization process compared to less age patients [2] Drugs with short half-lives necessitate frequent administration, which is quite inconvenient for individuals with PD. Treatment discontinuation would cause anomalies, which would make movement and simple tasks challenging for people with PD. Patients would have longer treatment times if ineffective time was reduced. Time allotted for routine daily chores it

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

has been reported that activating the brain helps lessen motor problems. [3]

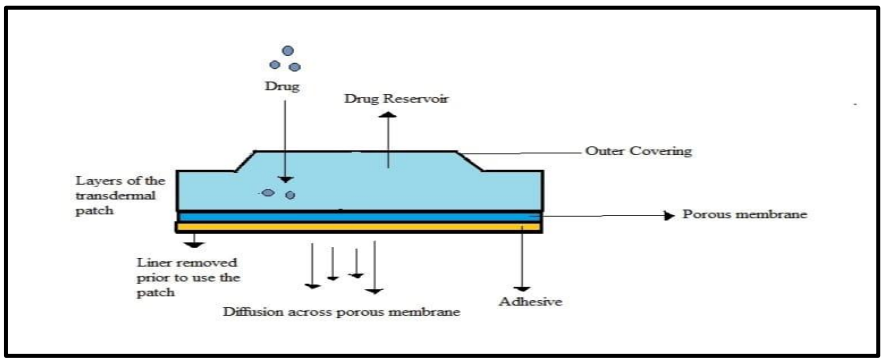

Figure 01. Transdermal patch and its parts

Transdermal drug delivery systems are a best option for PD patients because they maintain a relatively constant plasma concentration, reduce the liver first-pass impact, reduce side effects, and improve patient compliance. [3] Transdermal distributions of Parkinson's medications seems to be the most appealing alternate method for treating PD and neuroleptic-induced extrapyramidal responses due to the probable toxicity and metabolic behaviour of the oral route. [4] The clinical effectiveness of transdermal patch for this disease is a stand-alone treatment also a supplement to levodopa in advanced stages. [5] Comparing the transdermal patch to an oral tablet, a longer dosage interval may be possible due to the transdermal patch's prolonged half-life, greater area under the curve, and more stable plasma drug concentration. [6]

Transdermal drug delivery system

To provide a certain dosage of medication, a transdermal patch medicine enters the bloodstream through the skin. Transdermal the FDA initially approved patches in 1981.[7]

Motor function variations are lessened by the constant release of dopamine agonists and MAO-B inhibitors. The primary goals of continuous medication administration are to maintain constant drug concentration, prolong the benefits, and reduce unwanted effects. [8]

The drug content in a blood compaired oral with the transdermal is much more. [9]

Types of patch designs

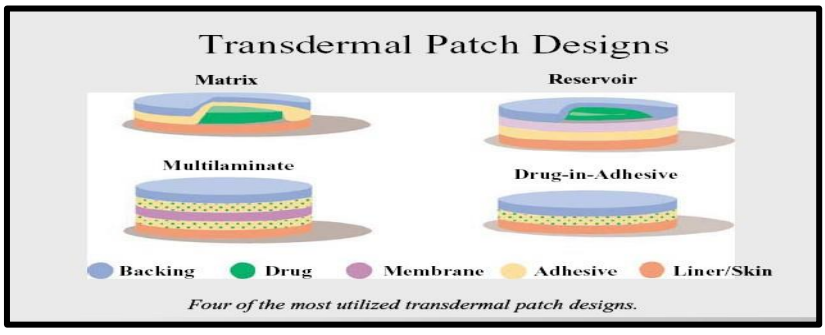

Figure 02. Transdermal patch designs

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

A) Drug in matrix

This transdermal type has no membrane. In between the release liner and backing layers, there is a layer that contains the drug. [10]

B) Drug in reservoir with membrane

It contains rate controlling membrane with drug reservoir, mainly used for the higher molecular weight drugs. [10]

C) Drug in adhesive

Here is no separate layer of drug; drug is directly incorporated into adhesive. This system mainly used for small molecular compounds. [10]

D) Multi-layer Drug-in-adhesive

Transdermal systems use layers of the drug, membranes, and adhesives to regulate the rate of drug administration. Useful for prolong release of drug delivery. [10, 11]

Table 01- The advantages of the MAO-B inhibitor transdermal system (TDS) over the oral MAO-B inhibitor oral formulation [12]

1	Enhancements to MAO- B inhibitor
2	Targeting particular tissues with drugs - Targeted, selective MAO inhibition in the brain
3	Increased brain drug delivery by bioavailability - Without first-pass metabolism
4	A simple administration approach - Skin patch
5	Comfort and simplicity - A single daily dose that is simple to stop using if unwanted side effects develop
6	Suitable alternate uses based on the patient's health - For swallowing issues
7	Reduced gastrointestinal adverse effects - No first-pass metabolism and skin absorption
8	Prevent major side effects - Lowering the hypertensive.
9	Less dietary restrictions - No restrictions on a recommended diet

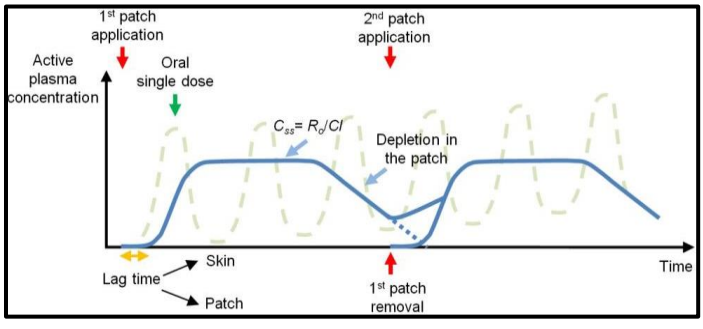

Figure 02. Transdermal drug release profile over oral drug release

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

The mechanism involved in medication delivery from transdermal administered formulation into and through the skin.

The skin and stratum corneum (SC) are superior layers and the primary barrier to drug absorption; they are made up of multi-laminate tissue. The SC is a thin, heterogeneous layer with keratinized epidermal cells that are separated from one another by an intercellular lipid domain. A medicine can traverse the SC using a variety of methods. Following diagram can show the three pathway of transdermal route. [13]

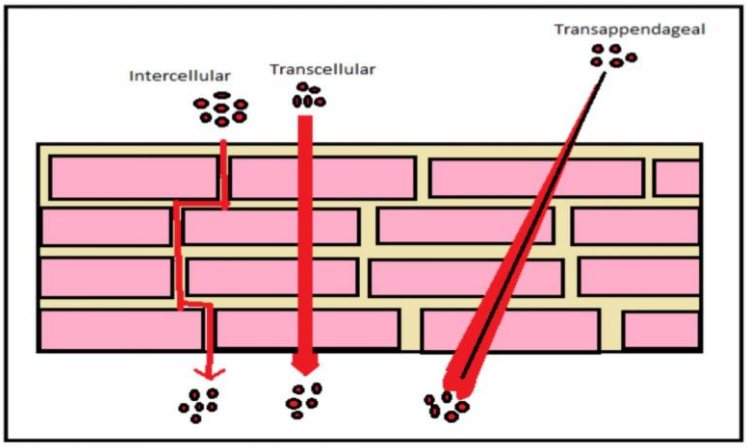

Figure 03. Potential routes of transportation via the stratum corneum

Fig. 3 illustrates the possible processes that could happen after applying a topical product to the skin. The medication is first released from vehicle, and then it partition into the SC. The molecules will first go through the SC then partition into epidermis and continue to diffuse toward dermis. Medicine will be removed from the skin by the dermal lymphatic and vascular systems. This procedure is effective and, in essence, results with a very low active concentration in the skin layers beneath the SC. [13]

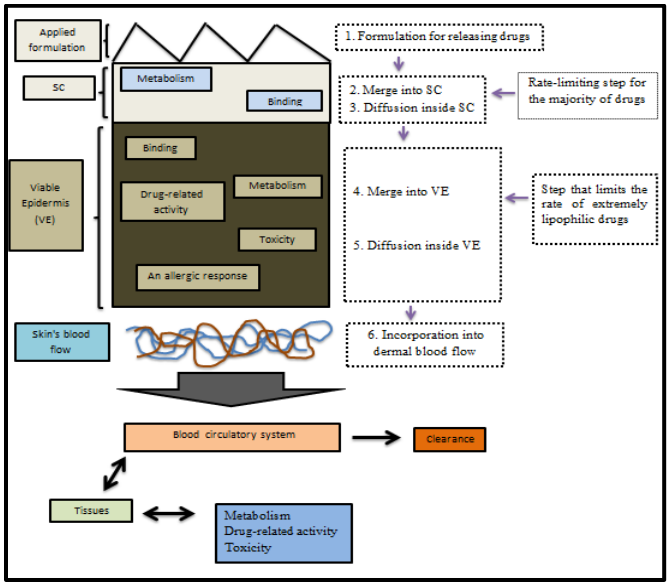

Figure 04. A diagram showing the processes by which the drug in any topical or transdermal treatment is delivered to and spread across the skin

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

All transdermal patches have a multi-layered design that makes it unique. Patches are a convenient delivery method for medications with short elimination half-lives due to their regulated release, which prevents fluctuating blood levels. The patch can be removed at any time to prevent the delivery of medication. [9]

Pathophysiology of Parkinson's disease

1. **Features of PD neuropathology and neurochemistry.**

The pathological signs of PD include low levels of dopamine, demise of neurons that produce dopamine, and intraneuronal known cytoplasmic aggregates as "Lewy bodies" (LB) in substantia nigra pars compacta (SNpc) neurons. When symptoms first appear, 80% of the putamen's dopamine is gone, and 60% of the SNpc's dopaminergic neurons have already died. PD very mildly affects cells of mesolimbic dopaminergic neurons and reduces dopamine level. Dopaminergic neuron loss and dopamine depletion are the neuropathology hallmarks of Parkinson's disease. [14]

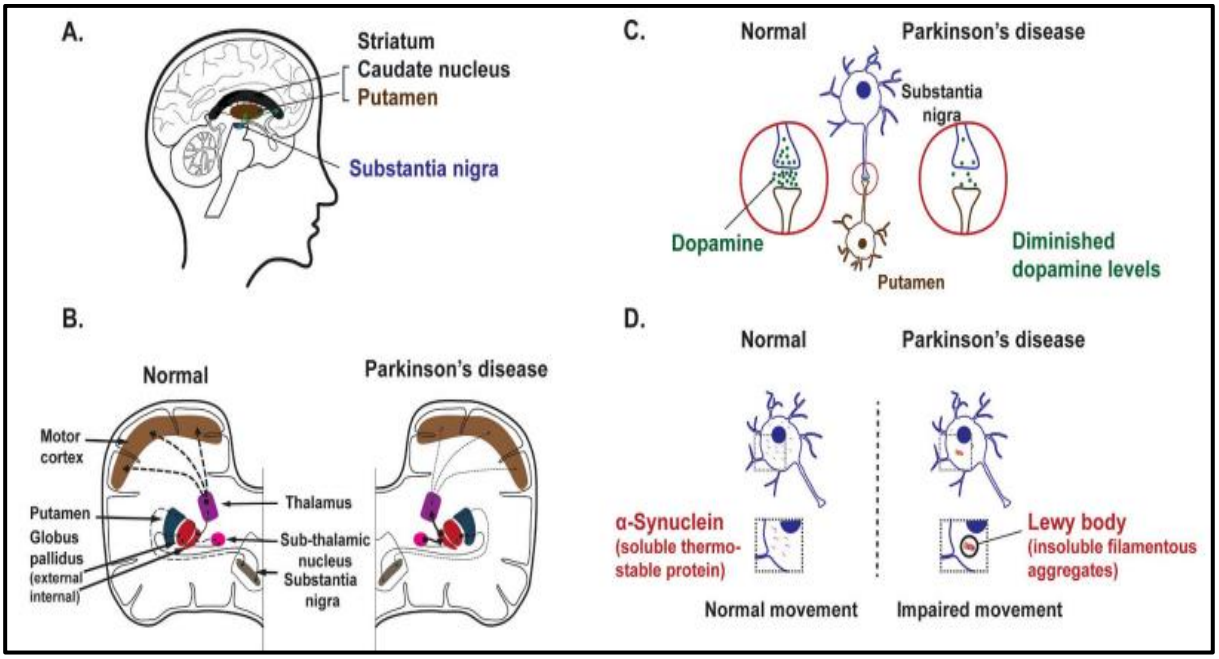

Figure 05. Neuropathology and neurochemistry in PD

Parkinson's disease's neurochemical, neuropathological, and dopaminergic pathways figure number 05 shows the synthesis of dopamine in the substantia nigra (blue) and transmission of synapses to the striatum (green) (A). Target suppression (continuous line) and target stimulation (dashed lines) are present in the dopaminergic pathway in the healthy brain. whereas Parkinson's disease causes the substantia nigra to deteriorate, impairing cortico-striatal circuits and causing the accompanying symptoms (B). Dopaminergic neurons in the Substania nigra (C). Produce less dopamine, and α-synuclein aggregates develop into Lewy bodies (D).

2.1. Molecular processes causing PD

It consists of impaired protein homeostasis (inducing protein aggregations) as well as mitochondrial abnormalities (which degrade bioenergetics)

2.1.1 PD and abnormal protein homeostasis

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

For quick detection of changed proteins and their processing or removal, protein homeostasis is governed by internal monitoring systems. Synuclein interacts with proteins such as chaperones, ubiquitin proteasomal, and lysosomal proteins in its native state, and its mutant variations lead to the breakdown of security mechanisms. Phosphorylated α-synuclein promotes the formation of LB includes. The malfunction of α-Synuclein, causes aggregation. The formation of LB and subsequent harm to SNpc neurons is caused by a change in the nature of α-synuclein. Because α-synuclein is sequestered in the LB, it inhibits the function of surveillance proteins. α-Synuclein aggregation may play a role in autophagy dysfunction. These studies unequivocally show that altered protein homeostasis caused by either monitoring system Malfunction or α-synuclein mediated failure is a major cause of disease. [14]

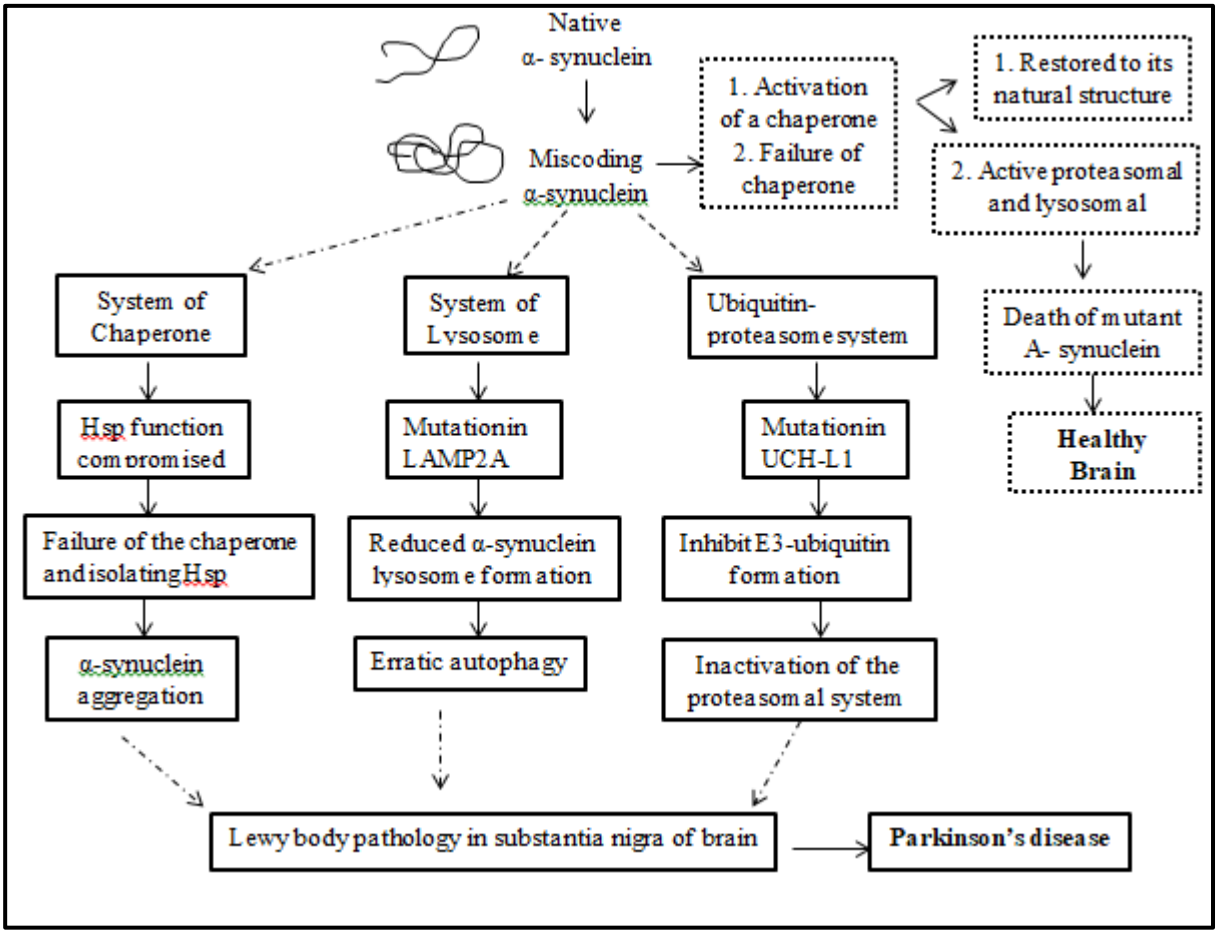

Figure 06. Mutated α-synuclein's disturbed homeostasis the configuration is restored by a system with a chaperone, but if it fails, aggregation results. Lewy body formation and abnormal protein clearance are caused by gene mutations, which eventually result in Parkinson's disease.

2.1.2 PD is characterised by mitochondrial dysfunction

Human post-mortem brain tissue analysis indicates evidence of mitochondrial malfunction, with oxidative stress A poison due to irreversible mitochondrial complex I inhibition, 1-methyl-4-phenyl-1,2,3,4-tertahydropyridine (MPTP) treatment, demonstrated

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

strong Parkinson characteristics and suggested that mitochondrial dysfunctions[3,15]

Decreased mitochondrial complex I activity leads to dopaminergic neuron degeneration. The presence of mitochondrial reactive oxygen species can harm dopaminergic neurons (ROS). In mammalian cells, mitochondria are the primary sources of ROS generation. Additionally, genetically removing TFAM (transcription factor A, mitochondria), a significant transcriptional component, has been shown to cause dementia in mice. [16, 14]

2.2 Genetics behind PD

Numerous genes have been linked to hereditary forms of Parkinson's disease (PD), including mutant versions of α-synuclein, LRRK2, UCHL1, ATP13A2, PINK1, Parkin, GBA1, and VPS35. Mutations in the α-synuclein gene cause family-based PD, which also causes LB, significant damage to the SNpc, and long-term motor deficits in animals.[13] LRRK2 controls mitochondrial activity in neurons. [15, 14] Similar to this, UCH-L1 changes are related to the underlying neurodegeneration of PD. [14]

There are many of other medicines which cause the disease. All of these medications have the potential to cause reversible Parkinsonism. [17]

Parkinson's disease treatment with dopamine agonists and MAO inhibitors The best therapy is L-dopa paired with a peripheral inhibitor of dopa decarboxylase and this should always be the first line of treatment. But L-dopa, when increased gradually, is typically well tolerated. [14] Parkinson's disease can be treated in two ways: via a transdermal patch. Selegiline, rasagiline are selective type B monoamine oxidase inhibitors, so they can be used once a day. [17]

The mitochondrial enzyme monoamine oxidase has been a major cause neurodegenerative disorder. MAO is an outer membrane mitochondrial enzyme existing in two isoforms; MAO-A and MAO-B. [18] [19] Studies on PD-affected animal models also shown that selegiline or rasagiline pre-treatment can significantly lessen the behavioural abnormalities brought on by neurotoxic MPTP and 6-hydroxydopamine injections. [20, 21]

Dopamine agonists are also effective as monotherapy treatments for patients with Parkinson’s disease. [22] [23]

Table 02- A summary of the main pharmacological characteristics of dopamine agonists

Pharmacodynamics characteristics	
A method of action	The activation of D3 receptors, D2 receptors, and D1 receptors in the caudate-putamen of the brain is assumed to be how the Dopamine D3/D2/D1 receptor agonist that is non-ergolinic exerts its beneficial effect in Parkinson's disease. [24, 25] Greater functional potency at D1 and D3 receptors compared to D4 and D5 receptors. [26,27]

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Other activities	Antagonism at 2β-adrenergic receptors agonist 5-HT1A but not 5HT2B receptors. [25]
Preclinical research	Improvements in motor deficits in PD animal models. [26] Animal and cellular effects of Neuroprotection exercised. [26 ,24 ,25]
Pharmacokinetic characteristics	
General	The application of dopamine agonist (Rotigotine) transdermal patch, the drug is continually released and absorbed through the skin. Similar pharmacokinetics of Rotigotine spanning the dosing range of 1-24 mg/24 hr. in healthy volunteers and patients with PD. Rotigotine has a 37% absolute bioavailability following Rotigotine transdermal patch administration. Within 1-2 days of daily treatment, steady-state plasma Rotigotine concentrations are attained, and they hold steady for the whole 24-hour application period.
Potential interactions between drugs	There are no clinically significant medication interactions when Rotigotine transdermal patch is administered concurrently with Levodopa/Carbidopa, Domperidone, oral contraceptives, or CYP 2C19 inhibitors (Cimetidine and Omeprazole). [26]

Table 03- Key pharmacological characteristics of MAO-B Inhibitors are summarised.

Pharmacodynamics characteristics	
A method of action	Good for beginning PD treatment because they can lessen the frequency of motor fluctuations and the typically moderate motor symptoms that occur in the early stages of PD. The brain's neurotransmitters norepinephrine, serotonin, and dopamine are eliminated by the monoamine oxidase enzyme. It is inhibited by the medicine MAO inhibitor. In the end, motor impairment necessitates more potent symptomatic therapy. [19]

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Other activities	Neuroprotection and antioxidants impact, anti-apoptotic activity Additionally, Rasagiline has demonstrated substantial anti-toxicity against 6-hydroxydopamine (6-OHDA). [20]
Preclinical research	Rasagiline protects dopaminergic cell and both rat and primates have been used in studies of the drug's in vivo effect. [28]
Pharmacokinetic characteristics	
Potential interactions between drugs	Avoid selegiline conversional tablet because its amphetamine metabolites can have adverse effects on the heart. [12] When treating individuals on rasagiline, CYP1A2 inhibitors like ciprofloxacin and fluvoxamine should be used cautiously because they may significantly raise rasagiline levels. [28]

2. Materials

The primary purpose of the polymer matrix is to regulate the drug's release from the formulation system. Natural polymers, synthetic polymers, and synthetic elastomers are the three different types of polymers. [27] The stratum corneum's barrier resistance is reversibly decreased by permeation enhancers. They facilitate medicine absorption into the bloodstream and access to live tissues. [26] Solvents are chemicals that may promote skin penetration by

1) Enlarging the polar routes.

2) Lipid fluidization

Examples include water alcohols such as methanol and ethanol, dimethyl acetamide, and dimethyl formamide etc. Surfactants are the substances that are suggested to improve the transport of hydrophilic medicines along polar pathways. There are two different kinds of surfactants anionic and non-ionic. Adhesive holds the patch to the skin so that the medicine can be delivered systemically. The backing layer shields the patch from the outside world. Adhesives that respond to pressure keep the transdermal system in close touch with the skin's surface. [29] [31]

Table 05- List of marketed transdermal patch [9]

Product (Drug, Tread name)	**Manufactured By**
Rivastigmine (Exelon)	Novartis India LTD
Rotigotine (Neupro)	ucb pharm
Selegiline (Emsam)	Apace Pharma

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Fentanyl (Mylafent)	Mylan
Glyceryl Trinitrate (Nitroderm TIIS)	Novartis Pharma Stein AQ

3. Conclusion-

Due to its simplicity, non-invasiveness, adaptability, patient compliance, and acceptability, TDDS, or transdermal drug delivery system, mainly preferred method of drug administration for systemic effects. Continuous drug administration is maintain, provide higher drug concentrations, prolong duration of action, and reduces dose fluctuation. In related literature, a transdermal patch is a collection of flat films that are placed surface of skin. TDDS provides a single daily dose that is easy to stop using if unwanted side effects, the elimination of variables influencing gut absorption and direct entry into the systemic circulation. As a result, transdermal patches are currently receiving a lot of attention for their versatility and availability in the delivery of a wide range of medications to patients who are bedridden, dysphagic, or neonatal. Using dopamine agonists and MAO inhibitors, transdermal method for Parkinson's disease not only aids in effective brain targeting but also prolongs the duration of drug release.

References

[1] Vicki Oldfield, Gillian M. Keating and Caroline M. Perry, Rasagiline A Review of its Use in the Management of Parkinson’s disease. Adis drug evaluation, Drugs 2007; 67 (12): 1725-1747

[2] Oertel W, LeWitt P, Giladi N, Ghys L, Grieger F, Boroojerdi B. Treatment of patients with early and advanced Parkinson's disease with rotigotine transdermal system: age-relationship to safety and tolerability. Parkinsonism & Related Disorders. 2013 Jan 1;19(1):37-42.

[3] Wang Y, Yu X, Zhang P, Ma Y, Wang L, Xu H, Sui D. Neuroprotective effects of pramipexole transdermal patch in the MPTP-induced mouse model of Parkinson's disease. Journal of Pharmacological Sciences. 2018 Sep 1; 138(1):31-7.

[4] Gorukanti SR, Li L, Kim KH. Transdermal delivery of antiparkinsonian agent, benztropine. I. Effect of vehicles on skin permeation. International journal of pharmaceutics. 1999 Dec 10;192(2):159-72.

[5] Claudine M. Baldwin and Gillian M. Keating, Rotigotine Transdermal Patch A Review of its Use in the Management of Parkinson’s Disease, Adis drug evaluation, CNS Drugs 2007; 21 (12): 1039-1055.

[6] Zhou W, Lv C, Zhang Q, Zong S, Wang M. Pharmacokinetics, pharmacodynamics, and safety of rasagiline transdermal patch: a preliminary study in healthy Chinese subjects. Clinical Drug Investigation. 2018 Feb;38(2):125-33.

[7] Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int J Pharm Pharm Sci. 2011;3(5):26-34.

[8] Senek M, Nyholm D. Continuous drug delivery in Parkinson’s disease. CNS drugs. 2014 Jan;28(1):19-27.

[9] Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

and pharmacology. British journal of pharmacology. 2015 May;172(9):2179-209.

[10] Kanabar VB, Patel VP, Doshi SM. Formulation and evaluation of transdermal patch of Cefdinir with various polymers. The Pharma Innovation. 2015 Aug 1;4(6, Part B):74.

[11] Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The pharma innovation. 2012 Jun 1;1(4, Part A):66. Available at www.thepharmajournal.com

[12] Pae CU, Lim HK, Han C, Neena A, Lee C, Patkar AA. Selegiline transdermal system: current awareness and promise. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2007 Aug 15;31(6):1153-63.

[13] Lane ME. Skin penetration enhancers. International journal of pharmaceutics. 2013 Apr 15;447(1-2):12-21.

[14] Raza C, Anjum R. Parkinson's disease: Mechanisms, translational models and management strategies. Life sciences. 2019 Jun 1;226:77-90.

[15] Ho DH, Je AR, Lee H, Son I, Kweon HS, Kim HG, Seol W. LRRK2 kinase activity induces mitochondrial fission in microglia via Drp1 and modulates neuroinflammation. Experimental Neurobiology. 2018 Jun;27(3):171.

[16] Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003 Sep 11;39(6):889-909.

[17] Andrew J Lees, John Hardy, Tamas Revesz, Parkinson's disease, Lancet (British edition). 2009;373(9680):2055-66.

[18] Hong R, Li X. Discovery of monoamine oxidase inhibitors by medicinal chemistry approaches. Med ChemComm. 2019;10(1):10-25.

[19] Löhle M, Reichmann H. Controversies in neurology: why monoamine oxidase B inhibitors could be a good choice for the initial treatment of Parkinson's disease. BMC neurology. 2011 Dec;11(1):1-7.

[20] Blandini F, Armentero MT, Fancellu R, Blaugrund E, Nappi G. Neuroprotective effect of rasagiline in a rodent model of Parkinson's disease. Experimental neurology. 2004 Jun 1;187(2):455-9.

[21] Kupsch A, Sautter J, Götz ME, Breithaupt W, Schwarz J, Youdim MB, Riederer P, Gerlach M, Oertel WH. Monoamine oxidase-inhibition and MPTP-induced neurotoxicity in the non-human primate: comparison of rasagiline (TVP 1012) with selegiline. Journal of neural transmission. 2001 Sep;108(8):985-1009.

[22] Binde CD, Tvete IF, Gasemyr JI, Natvig B, Klemp M. Comparative effectiveness of dopamine agonists and monoamine oxidase type-B inhibitors for Parkinson's disease: a multiple treatment comparison meta-analysis. European journal of clinical pharmacology. 2020 Dec;76(12):1731-43.

[23] Le WD, Jankovic J. Are dopamine receptor agonists neuroprotective in Parkinson's disease? Leading article, Drugs & aging. 2001 Jun;18(6):389-96.

[24] Oster S, Radad K, Scheller D, Hesse M, Balanzew W, Reichmann H, Gille G. Rotigotine protects against glutamate toxicity in primary dopaminergic cell culture. European journal of pharmacology. 2014 Feb 5;724:31-42.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[25] Scheller D, Stichel-Gunkel C, Lübbert H, Porras G, Ravenscroft P, Hill M, Bezard E. Neuroprotective effects of rotigotine in the acute MPTP-lesioned mouse model of Parkinson's disease. Neuroscience letters. 2008 Feb 13;432(1):30-4.

[26] Frampton JE. Rotigotine transdermal patch: a review in Parkinson's disease. CNS drugs. 2019 Jul;33(7):707-18.

[27] Wood M, Dubois V, Scheller D, Gillard M. Rotigotine is a potent agonist at dopamine D 1 receptors as well as at dopamine D 2 and D 3 receptors. British journal of pharmacology. 2015 Feb;172(4):1124-35.

[28] Chahine LM, Stern MB. Rasagiline in Parkinson's disease. International Review of Neurobiology. 2011 Jan 1;100:151-68.

[29] Gore S. A., 1 Satpute V. V., 1 Gholve S. B., 1 Bhusnure O. G., 2 Bhosale P. H., 3 Phutke P. B, A Systematic Review on Transdermal Patches, Int. J. Pharm. Sci. Rev. Res., 45(2), July - August 2017; Article No. 08, Pages: 36-47.

[30] Tanwar H, Sachdeva R. Transdermal drug delivery system: A review. International journal of pharmaceutical sciences and research. 2016 Jun 1; 7(6):2274