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Feasibility Assessment of Transdermal Drug Delivery Systems for Treatment of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is defined as the second most prevalent neurodegenerative disorder that has been characterized with a loss of dopaminergic neurons severely in cytoplasmic inclusions and substantia nigra. To treat both early and advanced stages of PD several therapeutic agents are available. However, the transport of therapeutic actives in to the brain has been a consistent challenge for researchers, because of the presence of blood-brain barrier (BBB). Various novel delivery carriers have been designed to deliver the drugs across BBB and the systems have been designed with an object to effectively target the drugs and overcoming the BBB. In some last decades, transdermal delivery carriers have gained extensive deliberations across the globe. These transdermal systems are depicted to be the most recent modalities in treating PD as they offer constant drug delivery, immediate effect as intestinal absorption in unneeded, and ease of application being a non-invasive technique. The present review explores the potential of transdermal delivery systems in order to deliver numerous therapeutic actives researched for PD therapy via transdermal route. Various trans-carriers such as patches, oil-based nanocarriers, nanoemulsions have been observed for the treatment of PD. The write up traces the reports on transdermal delivery carriers in PD and clinical study data to define the feasibility transdermal carriers.

Keywords: Transcarriers; Transdermal delivery; Parkinson's disease; Drug delivery systems; Clinical status

Introduction

Parkinson's disease (PD) is defined as a chronic and progressive neurological disease that has been characterized with the symptoms of stiffness, tremors, and slow or hesitant speech. Though the disease is most commonly related and seen in old aged people, it has been reported that around one in ten people are diagnosed with the disease before the age of 50. Parkinson's disease is depicted by striatal dopamine depletion as a result of dopaminergic neurons degeneration in the substantia nigra pars compacta. Besides the lack of dopamine at the cellular level the formation of Lewy bodies in the substantia nigra, which are cytoplasmic inclusions composed of fibrils, ubiquitin, and alpha-synuclein may appear [1,2]. Medication employed for the treatment of PD only provides patients with temporary symptomatic relief, where access to care and treatment differs widely depending on where the patients live [3]. Pharmaceutical agents that are used to treat PD include levodopa, entacapone, pramipexole, ropinrole, benserazide, carbidopa, tolcapone, entacapone, selegiline, rasagiline, and safinamide [4]. However, several drugs among these are not able to reach the brain completely and can undergo metabolism instead, partially or completely by liver. This inefficient utilization of drug may require ingestions of higher drug concentrations that can produce toxic effects in the heart, liver, or kidney. Also, many therapeutic agents are poorly soluble or insoluble in aqueous solutions. These drugs provide challenges to deliver them orally or parentally, however, these compounds can have significant benefits when formulated through other delivery systems like transdermal systems [5].

Transport of therapeutic actives via transdermal route is a well established route of administration valued by patients as well as physicians for comfort and convenience [6]. Drug transport via transdermal route has been approved and widely accepted for the systemic drug delivery. This non-invasive approach avoids the hepatic first-pass metabolism, maintains a steady drug concentration (extremely important both in the case of drugs with a short half-life and in the case of chronic therapy), allows the use of drugs with a low therapeutic index, and improves patient compliance. However, the outermost layer of the skin, stratum corneum prevents transdermal permeation of most drugs at clinically useful rates. To facilitate this transdermal transport of drugs, numerous

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Table 1: Effective transdermal delivery of therapeutic actives via novel carriers in treating PD.

Drug	Transdermal System	Inference	Ref.
Rotigotine	Patch	Rotigotine containing transdermal system was found to be effective in reducing the morbidity in early and advanced PD patients.	[14]
Rotigotine	Patch	Continuous rotigotine delivery through transdermal patch exhibited stable mean steady-state 24-h plasma concentrations.	[15]
Ropinirole	Oil based nanocarriers	Enhanced relative bioavailability of ropinirole enhanced more than two fold.	[16]
Selegiline	Liposomal gel	Improved bioavailability with maximum therapeutic effect was observed.	[17]
Levodopa	Vehicles and permeation enhancer based system	Proved to be a good adjuvant therapy for PD.	[18]
Ropinirole Hydrochloride	Ethosomes	Effective transdermal drug delivery was observed.	[19]
Levodopa	Alginate membranes	Progressive supply of drug to the systemic circulation was observed.	[20]
Ropinirole Hydrochloride	Modulated iontophoresis and microneedles	Significantly higher delivery of ropinirole hydrochloride was observed via combination of modulated iontophoresis and microneedles [46.50 ± 6.46 μg/cm^2] than modulated iontophoresis alone.	[21]
Rotigotine	Film forming gel	Effective transdermal delivery was observed with improved patients' compliance and better efficacy.	[22]
Nicotine, fentanyl, rivastigmine and ketoprofen	Patches	Findings suggested that the Skin Parallel Artificial Membrane Permeability Assay based system served as a useful tool for evaluation and classification of the transdermal patches.	[23]
Rotigotine	Microspheres	The addition of palmitic acid to the microspheres significantly affected the release profile of rotigotine from microspheres.	[24]

systems have been investigated to treat PD.

Parkinson's Disease and Its Treatment Approaches

Parkinson's relates to a category of neurodegenerative disorders that affects several brain regions, including pigmented nuclei in the midbrain and brainstem, cerebral cortex, olfactory tubercle, and peripheral nervous system [7]. The pathological and clinical manifestations of PD include depletion of dopaminergic neurons in the midbrain, and deficiency of dopamine in the areas of brain areas that receive dopaminergic inputs from these neurons [8]. Clinically, the indications of the disease can be grouped into motor, cognitive and psychiatric; each group with its own set of symptoms. The usual occurrence of PD in late midlife or marked increase is prevalent at older ages, suggests the possible role of aging in the pathogenesis of PD [9]. Many cellular mechanisms are believed to be involved in neuronal death in PD, such as endoplasmic reticulum stress, proteasomal and mitochondrial dysfunction [10].

Treatments are effective in managing the early motor symptoms of the disease, mainly through the use of levodopa (L-DOPA) and dopamine agonists. As the disease advances and dopaminergic neurons continue to get depleted, these drugs eventually become ineffective in treating the symptoms, and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements; thereby making the treatment difficult. More recently, nose to brain delivery of nanoformulations and transdermal systems have gained tremendous potential to provide effective therapy in treating PD. Nano-formulations delivered via nose to brain route are the upcoming formulations in PD treatment as they offer targeted drug delivery, enhanced therapeutic efficacy and decreased systemic side effects of neurotherapeutics. These formulations provide effective intranasal transport by encapsulating drug, protecting it from biological/ chemical degradation and extracellular transport through P-glycoprotein (P-gp) efflux thus, and enhancing CNS availability for drugs as highlighted in our extensive published review article [11]. However, in the preceding text transdermal systems has been highlighted for treating PD.

Transdermal Therapy in PD

Skin is the largest and easily accessible organ of the body and

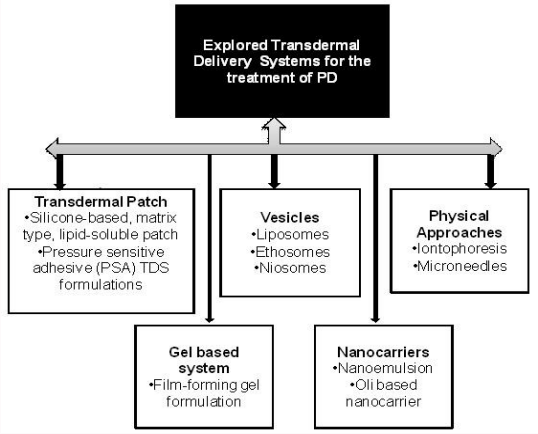

Figure 1: Various approaches for transdermal delivery in the treatment of Parkinson's disease.

therefore can be extensively used as a prominent route of delivery for local and systemic effects. Though it presents a multifunctional barrier between body and surrounding particles, there are chances to deliver therapeutic carriers, particularly in diseased skin. For dermal and transdermal drug delivery, the horny layer, i.e, the uppermost layer of the skin serve as the most resistant layer to be crossed. To circumvent this barrier, different perforation techniques are used that relatively widen the skin opening and allow the passage of drug (≤ 10 mg) and micromolecules, but this amateur disruption of the skin can be avoided in order to preserve this barrier against cutaneous microbiota by using deformable carriers [12]. Transdermal drug delivery system (TDDS) in this context provides a means to sustain drug release as well as reduce the intensity of action and thus minimize the side effects associated with its oral therapy. Transdermal systems are self-contained, discrete dosage form. It delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system.

Various transdermal drug delivery systems have been developed to treat PD using several carriers, penetration enhancers and vehicle based system. The most commonly used transdermal system is the skin patch using various types of technologies. Formulations

Table 2: Clinical development in the treatment of Parkinson's disease via transdermal systems**.**

Therapeutic Agent/Product developed	Title	Objective/ Purpose	Clinical Status/ verified date
Intravenous Levodopa, Lisuride transdermal system	Lisuride patch to treat Parkinson's disease	To evaluate the effectiveness of a skin patch formulation of the dopamine agonist Lisuride in controlling parkinsonian symptoms and dyskinesias	Phase 2/ January 24, 2017
Neupro® [Rotigotine] and L-dopa	Evaluating the effectiveness of Neupro® [Rotigotine] and L-dopa combination therapy in patients with Parkinson 's disease [NEUPART]	To depict the effectiveness of Rotigotine and Levodopa combination therapy for younger and older patients with Parkinson 's disease under real life conditions	Phase 4/ July 1, 2016
Rotigotine, Placebo patch, L-dopa	Rotigotine versus placebo, a study to evaluate the efficacy in advanced stage idiopathic Parkinson's disease [PD]	To demonstrate that rotigotine transdermal patch is efficacious in chinese subjects with advanced-stage idiopathic PD as an adjuvant therapy	Phase 3/ January 29, 2016
Rotogotine transdermal patch	Anxiety in Parkinson's: use of quantitative methods to guide rational treatment [ANXPD]	To assess efficacy and safety of rotigotine in patients with late onset of PD, starting at age 70 or later, on motor symptoms	Phase 2/ January 22, 2016
Rotigotine, Placebo	Possible use of rotigotine in subjects 70 years and older with late onset of disease [PARROT]	To assess efficacy and safety of rotigotine in patients with late onset of PD, starting at age 70 or later, on motor symptoms	Phase 2/ January 22, 2016
Nicotine transdermal patch	Disease-modifying potential of transdermal nicotine in early PD	To demonstrate that transdermal nicotine treatment retards disease progression	Phase 2/ September 28, 2015
Rotigotine, Placebo	Randomized evaluation of the 24-hour coverage: efficacy of Rotigotine [RECOVER]	To assess the effects of transdermal rotigotine on the control of early morning motor function and sleep disorders compared to placebo in subjects with idiopathic PD	Phase 3/ May 26, 2015
Rotigotine, Placebo Patch	Rotigotine versus placebo as double blind study to evaluate the efficacy in early stage idiopathic PD patients	To demonstrate that the Rotigotine transdermal patch is efficacious in Chinese subjects with early-stage idiopathic PD	Phase 3/ July 14, 2015
Rotigotine [Test product PR 2.3.1], Rotigotine [Reference product PR 2.1.1]	A study to compare the adhesiveness of two different Rotigotine patches used for the treatment of PD	To compare the adhesiveness of 2 different patch formulations of Rotigotine using the largest patch size of 40 cm^2	Phase 1/ October 1, 2015
Exelon Patch [rivastigmine transdermal system], Placebo Patches	Mild cognitive impairment in PD	To study the usefulness of Exelon [rivastigmine] Patch in treating mild cognitive impairment in patients with PD	Phase 4/ February 24, 2015
SPM 962	A dose-finding study for SPM 962 in advanced PD patients	To investigate efficacy and safety of SPM 962 in advanced PD patients in a multi-centre, placebo-controlled study following once-daily multiple transdermal doses of SPM 962 within a range of 4.5 mg to 36.0 mg	Phase 2/ February 3, 2014
Rotigotine	Safety and tolerability trial of switching from ropinirole to rotigotine	To assess the safety and tolerability of switching from ropinirole therapy to the Rotigotine transdermal system and its effect on symptoms in subjects with idiopathic PD	Phase 3/ September 24, 2014
SPM 962	A long-term extension trial from late Phase II of SPM 962 in advanced PD patients	To investigate the safety of SPM 962 in advanced PD patients in a multi-centre, open-label, non-controlled study following once-daily multiple doses of SPM962 via transdermal route within a range of 4.5 to 36.0 mg. Efficacy is also investigated	Phase 2/ February 3, 2014
Placebo, Rotigotine	Sleep efficiency assessed by polysomnography in advanced PD	To evaluate the effect of Rotigotine with Polysomnography [PSG] and subjective measures on sleep efficiency, maintenance, insomnia, nocturnal akinesia and night-time movement in bed, in patients with advanced PD	Phase 4/ January 29, 2014
SPM 962	A long-term extension trial of SPM 962 in advanced PD patients	To investigate the safety and efficacy of once-daily transdermal repeated administration of SPM 962	Phase 3/ February 3, 2014
SPM 962	A long term extension trial from phase II/ III of SPM 962 in early PD patients	To analyze the safety of SPM 962 in a once-daily repeated long-term treatment in PD patients who are not concomitantly treated with L-dopa.	Phase 2 Phase 3/ February 3, 2014
Rotigotine	A phase 4, open-label study to assess the feasibility and efficacy on motor and non-motor symptoms of switching from Pramipexole or ropinirole to Rotigotine transdermal patch in subjects with advanced idiopathic PD	To assess the safety and feasibility of switching subjects with advanced PD from Pramipexole or Ropinirole to Rotigotine	Phase 4/ February 25, 2014
SPM 962, Ropinirole	A placebo and ropinirole controlled study for SPM 962 in advanced PD patients	To demonstrate the superiority, safety and tolerability of SPM 962 to placebo in terms of efficacy	Phase 3/ April 23, 2014
SPM 962, placebo	A placebo controlled study for SPM 962 in early PD patients	T o investigate the superiority of SPM 962 over placebo in early PD patients in a multi-centre, placebo-controlled, double-blind study	Phase 2 Phase 3/ February 3, 2014
Rotigotine	A trial of Neupro® [Rotigotine Transdermal patch] with PD undergoing surgery	To evaluate the efficacy and safety of rotigotine in patients suffering from PD during and after surgery requiring general anaesthesia	Phase 4/ September 24, 2014
Rotigotine	A trial to assess switching from ropinirole, Pramipexole or Cabergoline to the Rotigotine transdermal system in idiopathic PD	To assess the switching of drugs from ropinirole, pramipexole and cabergoline to Rotigotine transdermal system [SPM 962] overnight without worsening of PD symptoms	Phase 3/ September 24, 2014

Rotigotine [SPM 962]	A trial to compare efficacy of Rotigotine transdermal patch to that of ropinirole on early morning motor impairment and sleep disorders in subjects with early-stage, idiopathic PD	To compare the effect of rotigotine [SPM 962] and ropinirole on the control of early morning motor impairment and sleep disorders in subjects with early-stage PD	Phase 3/ September 24, 2014
Rotigotine	A trial to evaluate the effects of Rotigotine transdermal patch on early morning motor impairment and sleep disorders idiopathic PD	To assess the effect of rotigotine [SPM 962] on the control of early morning motor impairment and sleep disorders in subjects with idiopathic PD	Phase 3/ September 24, 2014
Rotigotine	An open-label extension trial to assess the safety of long-term treatment of Rotigotine in advanced stage PD	To assess the safety and tolerability of long-term treatment of the rotigotine patch in subjects with advanced-stage idiopathic PD	Phase 3/ September 24, 2014
Rotigotine, Placebo, Moxifloxacin infusion, Placebo infusion	Cardiac effects of Rotigotine transdermal system in subjects with advanced stage idiopathic PD	To assess whether rotigotine has an effect on the electrical activity of the heart or not. Moxifloxacin infusion is used as positive control to assess assay the sensitivity	Phase 1/ October 17, 2014
Nicotine patch, placebo	Nicotine treatment of impulsivity in PD	To examine whether treatment with transdermal nicotine improves computer-based laboratory and clinical measures of impulsive and compulsive behaviors in PD subjects who have recently experienced an impulse control disorder	Phase 4/ May 10, 2013
Rivastigmine, placebo	Study of rivastigmine to treat parkinsonian apathy without dementia	To assess the efficacy and acceptability of a 6 months treatment with rivastigmine on apathy in 60 patients with PD without dementia	Phase 3/ April 23, 2012 [25]

designed to deliver the drug at optimized rate into the systemic circulation should adhere to the skin for the expected duration and should not cause any skin irritation and/or sensitization, enhance the bioavailability and minimize the pharmacokinetic peaks and troughs [13]. The transdermal systems that have been explored till date for treating PD are highlighted in Figure 1. Table 1 revealed the reports based on these explored carriers in treating PD in recent years.

Clinical Status of Intranasal Delivery

Clinical trials reported on transdermal delivery systems are initiated with the finding that drugs administered via transdermal route could effectively deliver the therapeutic actives. Table 2 lists the clinical status of various drugs used in PD.

Conclusion

Transdermal drug delivery has proved to be an important treatment approach that is not only capable of providing a constant rate of drug delivery, but is also non-invasive and relatively simple to use. However, developing a drug to be delivered transdermally for the treatment of PD has been anything but easy. The techniques designed to enhance skin permeation and to improve the effectiveness of transdermal drug delivery are also potential sources for future treatment advances. Clinical trials of the said systems affirm their position in PD therapeutics.

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