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Formulation and Evaluation of Rasagiline Mesylate via Intranasal Route using Polymer Based Nanoparticles

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Abstract

The aim of the present investigation is to formulate and evaluate Rasagiline mesylate loaded polymeric nanoparticles for better delivery via intra nasal route. The Rasagiline mesylate loaded polymeric nanoparticles protects the drug, provides controlled release. Rasagiline (RAS) is chosen as a drug candidate for PD as it is selective and irreversible second-generation inhibitor of monoamine oxidase type B (MAO-B). The drug is BCS class III drug having high solubility but low permeability with high first pass metabolism and there by low bioavailability, which is reported to be 36% when given orally. Hence, Rasagiline mesylate loaded polymeric nanoparticles were formulated for target specific delivery via nose and thereby increasing the bioavailability of Rasagiline mesylate and to get the sustained releaseof Rasagiline mesylate.

Keywords; nanoparticles, polymeric, bioavailability, controlled release

Introduction

The nervous system is a complex and highly specialized network that organizes, regulates andcoordinates body activities such as sight, hearing, taste, smell, sensation, voluntary and involuntary functions, ability to think and reason and it also regulates the actions of most other body systems. The nervous system is divided into two major parts i.e. Central Nervous System(CNS) consisting of brain and spinal cord and Peripheral Nervous System (PNS) consisting of nerves and ganglia outside of the brain and spinal cord. The nervous system is susceptible to various disorders and can be damaged by various reasons like infections, degeneration, structural defects, trauma, tumors, blood flow disruption, autoimmune disorders, exposure to toxins etc. The nervous systems disorders can be categorized as:vascular disorders, infections, structural disorders, functional disorders and degeneration.

Neurodegenerative diseases (NDs)

NDs are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. Neurodegeneration is the result of cell death which may be due to necrosis or apoptosis. Various risk factors are responsible for the disease such as alteration in genes, mitochondrial dysfunction, and oxidative stress including lipid peroxidation and inflammation along with generic polymorphism and increasing age . Some of the major neurodegenerative diseases are

Alzheimer's disease, Parkinson's disease, Huntington disease and Amyotrophic lateral sclerosis.

Parkinson's Disease (PD)

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease produced when nerve cells, or neurons, in an area of the brain known as the substantia nigra pars compacta, a nucleus of basal ganglia die or become impaired . In 1817 James Parkinson first described PD as "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured" known as shaking palsy.

It is the second most common, progressive and age-related neurodegenerative disorder of thenervous system generally affecting the middle aged or elderly people. According to the World Health Organization (WHO) Parkinson's disease has affected around 6.3 million people across the world. The main anatomical feature of PD is the reduction in number of dopaminergic neurons located in the substantia nigra pars compacts (SNc) in midbrain. Dopamine (DA) is a chemical messenger responsible for transmitting signals between the substantia nigra and the next "relay station" of the brain, the corpus striatum, to produce smooth, purposeful movement. The loss is associated with different factors such as formation of free radicals, oxidative stress, mitochondrial dysfunction, heredity, environment, aging, immune abnormalities, overload of calcium and excitatory neurotoxic effects.

PD symptoms first manifest when approximately 60% of the dopaminergic neurons have already died and 70% of dopamine responsiveness disappears. Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, affecting 1 to 2% of the population over the age of 65 years.

The main clinical features of PD include tremor, bradykinesia, rigidity and postural instability. These are the result of the loss of dopaminergic neurons in the substantia nigra pars compacta, which causes a reduction of dopamine levels in the striatum. However, additional neuronal fields and neuro-transmitter systems are also involved in Parkinson's disease,

Epidemiology

The age of onset of PD is usually between 50 and 80 years with a mean onset of 55 years. The crude prevalence rate of PD has been reported to range from 15 per 100,000 to 12,500 per 100,000, and the incidence of PD from 15 per 100,000 to 328 per 100,000, with the disease being less common in Asian countries. In Asian countries, the crude prevalence rates seem to be lower and range from 15 per 100,000 to 328 per 100,000. Men are more affected than women.

Variations in prevalence and incidence rates may result from environmental or genetic factors, but might also be a consequence of differences in methodologies for case ascertainment, diagnostic criteria or age distributions of the study populations. The community-based prevalence studies from India have documented crude prevalence rates of Parkinsonism from 7 to 328 per 100,000 in overall population among population above the age of 55 year. Age specific prevalence of Parkinsonism also revealed higher rate with advancement of age.

Etiology

Most Parkinson's disease cases occur sporadically and 85-90% of them are idiopathic in origin. Environmental factors have been implicated. Epidemiological studies suggest that there is an increase in risk of developing the disease following exposure to pesticides, rural living and drinking well water and reduced risk with cigarette smoking and caffeine. 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a toxic by-product of the illicit manufacture of a heroin like drug was found to cause an

acute clinical syndrome which was identical to Parkinson's disease, possibly even with the formation of Lewy body. MPTP is transported to the central nervous system, where it is metabolized to form MPP+, a mitochondrial toxin that is selectively taken up and damages the dopamine neurons.

About 10-15% of the Parkinson's disease cases are familial in origin and multiple specific

mutations and genes associated have been identified, so genetic factors may play an important role which is so far poorly understood.

Pathophysiology

Parkinson's disease is a disorder of the extrapyramidal system of the brain involving the basal ganglia where dopamine is progressively lost in the nigrostriatal tracts and acetylcholine is relatively increased. This results in disturbance of movement and posture without significant paralysis. The term movement disorder is often used synonymous with the extrapyramidal or basal ganglia disease. The degenerating neurons contain Lewy bodies and neuro fibrillary tangles .

In normal individuals' basal ganglia output is inhibitory via GABAergic nerve fibres. The dopaminergic neurons that project from the substantia nigra to the putamen have two effects: they stimulate the D1 dopamine receptors which inhibit GPi via direct GABAergic receptors and they inhibit D2 receptors, which also inhibit the GPi. This inhibition reduces the excitatory discharge from the subthalamic nucleus to the GPi. This balance between the inhibition and excitation help in maintaining the normal motor function. In Parkinson's disease the dopaminergic input to the putamen is lost.

This results in decreased inhibition and increased excitation from the subthalamic nuclei to the GPi. The overall increase in the inhibitory output to the thalamus and brain stem disorganizes the movements .

Mechanism of Parkinson's disease

Neurochemical Mechanism

PD is caused due to the loss of nigrostriatal dopaminergic neurons and the presence of intraneuronal proteinaceous cytoplasmic inclusion termed as Lewy Bodies. The cell bodies ofnigrostriatal neurons are present in the SNc whose loss produces the classic gross neuropathological depigmentation. Loss of SNc cell is similar to the level of expression of dopamine transporter mRNA. Also, dopamine reduction is more prominent in the dorsolateral putamen. Loss of SNc dopaminergic neurons and reduction of Putamenal dopamine are the early indications for PD. In PD, cell loss is concentrated in ventrolateral and caudal portions of the SNc and the degree of terminal loss in the striatum appears to be more pronounced thanthe magnitude of SNc dopaminergic neuron loss.

Mitochondrial Dysfunction and Oxidative Stress Mechanism

Oxidative stress (OS) is caused due to the presence of high load of highly reactive oxygen

freeradical, hydroxyl free radical, and H_2O_2 which are produced as a result of different biochemical pathways. Although the exact source of increasing OS is unclear, increased dopamine metabolism and mitochondrial dysfunction are among the major cause. ROS production is associated with the mitochondria exposed to oxidative environment and the process of oxidative phosphorylation. There are many evidences supporting the major role of mitochondrial dysfunction in the pathogenesis of PD and in particular defects in the mitochondria complex-I of respiratory chain.

Molecular Mechanism

PD is associated with the aggregation of intracellular protein known as Lewy Bodies in variousparts of the brain. They consist of α-synuclein, a synaptic protein present in higher amount inbrain. In case of hereditary PD, mutation takes place which render the protein resistant to degradation within cells,

causing it to pile up in Lewy bodies. This results in increase in cytosolic dopamine degradation of which produces ROS leading to neurotoxicity. Along withthis hypothesis, another transformation which is associated with PD is that it may involve a protein contributing in the intracellular degradation of rogue proteins.

Drug induced Parkinson's disease

Drug-induced movement disorders include Drug-Induced Parkinsonism (DIP), tardive dyskinesia, tardive dystonia, akathisia, myoclonus and tremor. Among these, DIP is the most common movement disorder induced by drugs that affect dopamine receptors. Drug-induced Parkinsonism (DIP) is the second-most-common etiology of Parkinsonism in the elderly after Parkinson's disease (PD). Many patients with DIP may be misdiagnosed with PD because the clinical features of these two conditions are indistinguishable. Moreover, neurological deficits in patients with DIP may be severe enough to affect daily activities and may persist for long periods of time after the cessation of drug intake. In addition to typical antipsychotics, DIP may be caused by gastrointestinal prokinetics, calcium channel blockers, atypica

Clinical features

The symptoms start insidiously and tend to be unilateral or asymmetrical at the onset. Tremor, rigidity, akinesia and postural disturbances are the major clinical abnormalities. The tremors have the frequency 4-6 Hrs. at rest (resting tremors) and are suppressed in voluntary movements. Distal muscles are affected more than the proximal and the rhythmic tremor at the wrist and finger has been termed pill rolling tremor. It disappears during sleep and is aggravated by emotional excitement or fatigue.

Akinesia and rigidity results in significant impairment of movement. There is lack (akinesia) or paucity (bradykinesia) of movement. Rigidity is present over the entire range of movement (lead pipe rigidity). Face is expressionless (mask face). There is generalized slowing of motor activity. Handwriting becomes smaller (micrographia) and eventually become illegible. Rapid, repetitive and alternating movements are performed slowly and clumsily. The combination of tremor and rigidity gives rise to cog wheeling which is best appreciated on passive slow rotator movement of the wrist.

Voice becomes soft (hypophonia) monotonous and stuttering appears and the speech is morerapid than normal. Increase in salivation and seborrhea are commonly seen. Postural instabilityand gait difficulties are a major problem in PD. The head usually tilts forward and the body becomes stooped often with pronounced kyphosis. The arms become flexed at the elbow and wrist. Flexion also occurs in the joints of the legs. Rising from a sitting position may take several attempts with frequent fall backs into the chair. The gait is slow and shuffling. The associated arm swing is reduced. Patients may have a tendency to advance rapidly with shortsteps (festinating gait) sometimes the feet may appear to be glued to the floor, the so-called freezing phenomenon.

Treatment of PD

Historically, the use of anticholinergics by Charcot at the end of 19th century was the first effective treatment of Parkinson's disease. Since the introduction of levodopa in the sixties oflast century, many new drugs have emerged for the treatment of Parkinson's disease like dopamine agonists, catechol-O-Methyl transferase (COMT) inhibitors, monoaminoxidase-B (MAOB) inhibitors.

Current therapeutic interventions to treat PD

Dopaminergic medications

Levodopa

In all stages of the disease levodopa remains the most effective drug for improving motor symptoms of Parkinson's disease. Levodopa

dramatically improves the motor symptoms of PD and remains the "gold standard" anti-Parkinsonian treatment since its introduction in the late 1960's, but its chronic use is frequently associated with the development of motor complications, such as dyskinesias or motor fluctuations. When levodopa is administered with a peripheral decarboxylase inhibitor, such as carbidopa or benzeraside, it prevents the peripheral metabolism of dopamine. Thus, the administration of levodopa with a COMT inhibitor increases its elimination half-life (from about 90 minutes to about 3 hours

Dopamine Agonist

Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors and have the potential to provide anti- Parkinsonian effects with less motor complications than levodopa. They have been used in the treatment of PD since the early 1970s. Unlike levodopa they do not require to be metabolized to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (bromocriptine, pergolide, cabergoline) and were associated with ergot related side effects. The second generations of non-ergot dopamine agonist are Pramipexole, Ropinirole and Rotigotine. Dopamine agonist do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and to reduce the 'off time' in fluctuating patients. They are relatively long acting and less prone to induce dyskinesia. Today, dopamine agonists are also used as an early symptomatic therapy to delay the risk of developing the motor complications associated with levodopa therapy.

MAO-B Inhibitors

MAO-B inhibitors, such as selegiline or rasagiline have been used as symptomatic therapy

forPD for approximately 20 years, based on their capacity to block the MAO-B oxidation of dopamine and thereby increase dopamine levels in the synapses They provide modest antiparkinsonian benefits when used as monotherapy in early disease and reduce off time when used as adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress.

COMT Inhibitors

When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized by Catechol-o-methyltransferase (COMT). Inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces 'off time' and prolongs 'on time' in fluctuating patients while enhancing motor scores. COMT inhibitors generally used are tolcapone, entacapone and combination of levodopa, carbidopa and entacapone.

Non- Dopaminergic medications

Anticholinergics

The use of anticholinergic was the first efficient treatment of Parkinson's disease. These are the drugs having a higher central: peripheral anticholinergic action ratio than atropine, but the pharmacological profile is similar to atropine. The drugs having the anticholinergic actions are trihexyphenidyl, procyclidine and benztropine.

Amantadine

Amantadine is an antiviral agent that was discovered by chance to improve Parkinsonism and levodopa induced dyskinesia.

Drawbacks of current antiparkinsonian drugs

Parkinson's disease affects both mental and physical activities of the body. The main aim of the treatment for this disease is to restore dopaminergic function and preserve dopamine production. But with the present treatments there is only symptomatic relief

and no complete cure. The adverse effect of the antiparkinsonian medications themselves can lead to poor patient compliance.

Rasagiline mesylate

Rasagiline (RAS) is chosen as a drug candidate for PD as it is selective and irreversible second-generation inhibitor of monoamine oxidase type B (MAO-B) with dopamine receptor agonist activity or as adjuvant therapy for levodopa in more advanced cases. The maximum oral dose recommended in monotherapy as well as in adjunct therapy is 1.0 mg once daily due to the risks associated with non-selective inhibition of MAO. Rasagiline mesylate is selective for MAO type B over type A by a factor of fourteen. 1.561 mg Rasagiline mesylate is equivalent to 1 mg of Rasagiline.

The oral route possesses GI adverse effect like nausea, vomiting, headache and dizziness which causes patient incompliance. RAS is rapidly absorbed and achieves the peak plasma concentration within 30 min; however, it has very short elimination half-life (0.6–2 h) and low oral bioavailability (36%) due to hepatic first pass effect. Thus, the administration of drug by nasal route will be a promising method to bypass the first pass effect thus improving the bioavailability.

Therefore, these biopharmaceutics and pharmacokinetic characteristics and its efficacy in a chronic disease such as PD make RAS a suitable candidate for the development of a controlled and sustained release system.

Drawbacks of conventional Formulations

- High first pass metabolism
- Low bioavailability (35-36%)

Short half-life (3 hrs.)

Rationale

The blood–brain barrier (BBB) separates blood from cerebrospinal fluid, diminishes the entry of many substances into the brain and requires some alternative drug delivery pathways

/methods for the treatment of neurological diseases. BBB consists of Non-invasive Delivery ofDrugs by Nasal Route for Brain Targeting through Nanoparticles endothelial cells connected by complex tight junctions, which restrict the access of large, hydrophilic compounds such as peptides, proteins and many drugs to the brain.Oral delivery of peptides, proteins e.g. insulin undergo extensive first pass metabolism therefore, therapeutically ineffective. Nose to brain delivery of nanoparticulate systems appear to be a promising brain-targeting strategy, as evidenced by a number of studied.

Polymeric nanoparticles

Nanoparticles or colloidal carriers have been extensively investigated in biomedical and biotechnological areas, especially in drug delivery systems for drug targeting because their particle size (ranging from 10 to 1000 nm) is acceptable for intravenous injection. The advantages of nanoparticles as drug delivery systems include time-controlled drug delivery,

reduced drug toxicity, improved bioavailability and enhanced therapeutic efficacy and biodistribution . Polymeric nanoparticles have been proposed as colloidal systems that allow the enhancement of therapeutic efficacy and reduction of toxicity of large variety of drugs. Nanoparticles can also protect the sensitive drugs from degradation by environmental factors such as stomach acid and enzymes. Polymeric nanoparticles range in size from about 10-1000nm, and can be modified with different ligands such as antibodies to create a smart targeting delivery system.

Conclusion

The Rasagiline mesylate loaded Polymeric nanoparticles is studied in the present investigation. The Drug release from Polymeric nanoparticles shows Sustained

release than plain drug solution. This leads to possibility of reduction of dose. .

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