



# Nose to brain delivery of selegiline loaded PLGA/lipid nanoparticles: Synthesis, characterisation and brain pharmacokinetics evaluation

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## ABSTRACT

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease that promotes neuronal cell death. The primary treatment strategy for Parkinson's disease involves the therapy of an MAO-B inhibitor molecule, selegiline. The present research aims to fabricate selegiline loaded polymeric (PLGA) nanoparticles (SPNPs) and selegiline loaded lipid-PLGA hybrid nanoparticles (SLPNPs) while using the single emulsion solvent evaporation method. The prepared SPNPs and SLPNPs formulations were subjected to preliminary optimisation using particle size, zeta-potential, and entrapment efficiency (EE%), and the selected formulations were subjected to further characterisation. Scanning electron microscopy (SEM) and high-resolution transmission electron microscopy (HRTEM) confirmed the particles' 2-D spherical morphology and size. ATR-FTIR was used to evaluate the physical interactions among the formulation ingredients. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies confirm that SPNPs and SLPNPs were in an amorphous state. *Ex-vivo* studies showed 77.56% and 80% of drug permeation in 24 h for optimised formulations of SPNPs-2 and SLPNPs-1, respectively, while pure selegiline showed 65% Permeation. *In-vivo* study revealed a steady and controlled release profile with a half-life of 13.5 h, and  $AUC_{0-24}$  was observed at  $130327.56 \pm 231.6$  ng/ml\*h for SPNPs-2. For SLPNPs-1 an immediate release was observed with a very short half-life and  $AUC_{0-24}$   $47548.57 \pm 434.8$  ng/ml\*h compared with pure selegiline HCl solution with 2.3 h and  $AUC_{0-24}$   $11116.52 \pm 345.7$  ng/ml\*h. SLPNPs-1 has a shorter half-life due to its immediate release properties with the presence of lipid. Meanwhile, SPNPs-2, which only has a polymeric layer, has a longer half-life due to its sustained release properties. Overall, SPNPs-2 and SLPNPs-1 are promising carriers for selegiline nasal uptake and increase its brain bioavailability compared to oral absorption by pure selegiline.

## 1. Introduction

A recent report from the World Health Organization shows that over 1.5 billion people worldwide are currently affected by neurological disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), stroke, headache, brain injuries, epilepsy, neuro infection, and multiple sclerosis [1,2]. Neurodegenerative diseases are conditions that affect the functioning of neurons in the brain by fluctuations in neurological functions [3]. The neuropathological hallmarks of PD are neuronal loss in the substantia nigra, which causes striatal dopamine deficiency, and intracellular inclusions containing aggregates of  $\alpha$ -synuclein [4]. PD comes under heterozygote gene diseases as it follows Mendel's law. A recent study concluded that PD is linked to  $\alpha$ -synuclein toxicity and to

lysosomal abnormalities. It indicated that idiopathic Parkinson's disease resembles Mendelian lysosomal storage disorders at a genetic and biochemical level [4]. PD is the second-most common neurodegenerative disorder, affecting 2–3% of a sexagenarian population [5].

Selegiline, an MAO-B inhibitor, was one of the first adjunct therapies in clinical neurology. It is also known as 2-propronylphenethylamine. As a specific, irreversible inhibitor of MAO-B, an enzyme that catalyses dopamine metabolism in the Central Nervous System (CNS) [6]. Selegiline also plays a double role in treating PD as well as depression caused by PD. The oral daily dose approved for the management of PD is 5–10 mg. However, for parenteral and transdermal routes, some studies have found that a lower dosage (1.5 mg–5 mg) is sufficient for the same amount of efficacy, which may also benefit in reducing side effects with

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