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Original Research Article

Intranasal Solid Lipid Nanoparticles of Selegiline for Early-Stage Parkinson's Disease Brain-Targeted Administration

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Abstract: ***Background and Objectives***: The blood-brain barrier limits the effective delivery of drugs to the brain in Parkinson's disease (PD), a neurodegenerative ailment that progresses over time. One non-invasive method that has shown promise for direct brain targeting is the intranasal administration of systems based on nanocarriers. The current research set out to design and test solid lipid nanoparticles (SLNs) loaded with selegiline for improved intranasal transport to the brain in patients with early-stage Parkinson's disease. ***Methods:*** Selegiline-loaded solid lipid nanoparticles (SLNs) were made via heat homogenization and ultrasonication. The formulations' particle size, polydispersity index, zeta potential, entrapment efficiency, and drug loading were extensively characterized. The SLNs' selegiline release behavior was examined in vitro, and the nasal membrane's penetration efficiency was assessed ex vivo using isolated nasal mucosa. In vivo pharmacokinetic and brain distribution experiments assessed systemic exposure, brain targeting efficiency, and nose-to-brain transport capacity after intranasal administration of the improved formulation. ***Results:*** An optimized SLN formulation showed a homogeneous particle size distribution with a mean particle size of 148.6 ± 6.4 nm and a low polydispersity index of 0.21 ± 0.03. The colloidal stability was indicated by a zeta potential of -28.3 ± 2.1 mV. Efficiency of entrapment was 86.4 ± 3.2% and drug loading was 9.1 ± 0.6%. Studying selegiline release in vitro revealed a persistent pattern of 78.2 ± 4.5% over 24 hours. In goat nasal mucosa, ex vivo permeation experiments showed stronger drug penetration (65.7 ± 3.8%) than the drug solution. After intranasal administration, brain drug concentration increased with a brain-to-plasma ratio of 4.6, DTE of 312%, and DTP of 68.4%. A PD rat model revealed significant motor coordination improvements and oxidative stress reductions compared to controls. ***Conclusion:*** Efficacy, nose-to-brain transport, and sustained drug release were improved by intranasal selegiline-loaded solid lipid nanoparticles. This method is promising for early Parkinson's disease intervention.

Keywords: Intranasal delivery; Solid lipid nanoparticles; Selegiline; Brain targeting; Parkinson's disease; Nose-to-brain transport; Nanocarrier system.

INTRODUCTION

Degeneration of dopaminergic neurons in the substantia nigra pars compacta is a hallmark motor symptom of Parkinson's disease (PD), a progressive neurodegenerative disorder (Ahmad et al., 2016). Additionally, resting tremor, stiffness, and postural

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instability are other hallmarks of PD. Existing pharmaceutical treatments mainly aim at alleviating symptoms by means of dopaminergic therapies; however, when taken orally over an extended period of time, these drugs can cause fluctuations in plasma levels, peripheral side effects, and restricted brain availability as a result of the BBB's restrictive properties. The need for new medication delivery methods that can reduce systemic exposure while increasing brain targeting is highlighted. (Alam et al., 2010; Singh, Dash and Sahoo, 2020; Pal et al., 2017). People with early-stage Parkinson's disease often use selegiline, an irreversible monoamine oxidase-B (MAO-B) inhibitor, to improve dopaminergic neurotransmission and slow the disease's progression. Oral administration of selegiline has several drawbacks, including a low and fluctuating bioavailability, lower drug concentration in the brain, and substantial first-pass metabolism, which hinders its therapeutic potential. Alyautdin et al. (2014) noted that these limitations render it clinically ineffective and highlight the necessity of a drug delivery technology capable of avoiding the BBB and reaching the central nervous system directly (Behera et al., 2010; Bhoumik, 2023).

To circumvent hepatic first-pass metabolism and achieve direct nose-to-brain transport, intranasal medication administration was developed as a potential non-invasive method for brain targeting by utilizing the olfactory and trigeminal nerve pathways (Abrha et al., 2015; Arora et al., 2015; Mekonnen et al., 2025). For long-term neurological conditions like Parkinson's disease, this approach is ideal because of its quick beginning of action, decreased systemic side effects, and increased patient compliance. On the other hand, the nasal epithelium generally limits drug permeability and mucociliary clearance is quick, which might make efficient intranasal delivery difficult (Andrade et al., 2019; Bhoumik, 2024).

The intranasal administration of lipophilic pharmaceuticals has attracted a lot of interest in nanotechnology-based carriers, particularly solid lipid nanoparticles (SLNs), because of their biocompatibility, controlled drug release, and improved stability. To increase drug accumulation in the brain, SLNs can increase the amount of time a drug stays in the nasal cavity and make transport across neuronal pathways easier. Beg et al. (2019) predicted that selegiline's nasal absorption, protection from enzymatic breakdown, and sustained therapeutic levels in the brain might all be improved by including it into SLNs (Bhoumik, 2025; Hooda et al., 2017; Abrha et al., 2017; Saini et al., 2016; Bahre et al., 2016).

Here, we set out to create and assess intranasal solid lipid nanoparticles loaded with selegiline for use in targeted brain delivery during the early stages of Parkinson's disease. Bhavna et al. (2014) state that the study's overarching goal is to determine whether the formulation can be optimized, characterized for its physicochemical properties, and evaluated in vitro, ex vivo, and in vivo in order to prove that it can be a patient-friendly and effective treatment strategy for managing Parkinson's disease.

MATERIAL AND METHODS:

Materials:

We received a complimentary sample of selegiline hydrochloride from a well-known pharmaceutical company. We utilized Glyceryl monostearate (GMS) as the solid lipid and soy lecithin and Poloxamer 188 as the surfactant and co-surfactant, respectively. Other than that, all solvents and chemicals utilized in the study were analytical grade and did not undergo any additional purification processes. Promptly following isolation, fresh goat nasal mucosa was sourced from a nearby butcher for the purpose of conducting ex vivo permeation experiments.

Preparation of Selegiline-Loaded Solid Lipid Nanoparticles:

Solid lipid nanoparticles (SLNs) loaded with selegiline were synthesized using the hot homogenization followed by ultrasonication technique. In a nutshell, the solid lipid (GMS) was dissolved in the melted lipid phase after being heated to 70–75 °C. The lipid phase was homogenized with the water-based phase containing Poloxamer 188 and soy lecithin at the same temperature for 10 minutes using high-speed homogenization at 15,000 rpm. In order to decrease the particle size, the produced pre-emulsion was probe ultrasonicated for 5 minutes. Solid lipid nanoparticles were formed when the produced nanoemulsion was allowed to cool to ambient temperature (Bloodworth and Bateman, 2019; Khulbe et al., 2023).

Optimization of Formulation:

Minimal particle size, low polydispersity index (PDI), and high entrapment efficiency were achieved by optimizing formulation variables such as lipid concentration, surfactant concentration, and homogenization speed. According to Costantino et al. (2007), the results of the physicochemical characterisation were used to determine the optimal formulation (Keservani and Gautam, 2020).

Physicochemical Characterization:

Dynamic light scattering (DLS) using a Zetasizer was used to assess the zeta potential, polydispersity index, and mean particle size of the produced SLNs following the required dilution with distilled water. Gadhave et al. (2020) used transmission electron microscopy (TEM) to look at the optimized formulation's morphology (Keservani and Gautam, 2022).

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Determination of Entrapment Efficiency and Drug Loading:
Ultracentrifugation was used to find the entrapment efficiency (EE%) and drug loading (DL%). After centrifuging the SLN solution at 20,000 rpm for 30 minutes, the concentration of free drug in the resulting supernatant was measured using a UV-visible spectrophotometer set at the correct wavelength. We used the conventional equations (Illum, 2004) to determine the EE% and DL%.

***In-Vitro* Drug Release Study**:
The dialysis bag diffusion method was used to conduct in-vitro drug release experiments. A dialysis membrane was used to hold a known quantity of SLN formulation, which was equal to the dosage of selegiline, and it was immersed in phosphate buffer (pH 6.4) kept at 37 ± 0.5 °C with constant stirring. At regular intervals, samples were removed and replaced with new media. Spectrophotometry was used to determine the dosage of the medication that was released (Jain et al., 2010).

***Ex-Vivo* Nasal Permeation Study:**
The permeation investigations were carried out in a controlled environment utilizing Franz diffusion cells and freshly removed nasal mucosa from goats. Inserting the SLN formulation into the donor chamber, the mucosa was mounted between the donor and receptor compartments. The pH of the phosphate buffer was 6.4 and the temperature was kept at 37 ± 0.5 °C in the receptor compartment. The researchers tested the samples for the presence of drugs at predetermined intervals (Khan et al., 2017).

***In-Vivo* Pharmacokinetic and Brain Distribution Studies**:
The Institutional Animal Ethics Committee gave their blessing before any in-vivo experiments were conducted on Wistar rats. As a control, some animals received selegiline solution orally or intranasally, while others received selegiline SLNs intraperitoneally. We used a proven analytical approach to quantify the drug concentrations in blood and brain samples obtained at preset time periods. The effectiveness of nose-to-brain administration was assessed by calculating the brain targeting efficiency (DTE) and the direct transport percentage (DTP) (Kaur et al., 2016).

Statistical Analysis:
The results were presented as the mean ± standard deviation, and each experiment was carried out three times. Appropriate tests were used for statistical analysis, and differences were deemed significant when $p < 0.05$.

RESULTS

Physicochemical Characterization of Selegiline-Loaded SLNs:
The hot homogenization-ultrasonication process was used to successfully create solid lipid nanoparticles loaded with selegiline. With nanoscale particle size, limited size distribution, and sufficient surface charge, the improved formulation demonstrated good physical stability. The results of the dynamic light scattering examination showed that the nanoparticles were evenly dispersed, with an average size of 148.6 ± 6.4 nm and a low polydispersity index of 0.21 ± 0.03. Particle aggregation could not occur due to the strong electrostatic repulsion, as shown by the zeta potential of −28.3 ± 2.1 mV. Because of its high affinity for the lipid matrix and its lipophilic nature, selegiline has a high entrapment efficiency.

Table 1. Physicochemical properties of optimized selegiline-loaded SLNs

Parameter	Value (Mean ± SD)
Particle size (nm)	148.6 ± 6.4
Polydispersity index (PDI)	0.21 ± 0.03
Zeta potential (mV)	−28.3 ± 2.1
Entrapment efficiency (%)	86.4 ± 3.2
Drug loading (%)	9.1 ± 0.6

Morphological Analysis:
Transmission electron microscopy (TEM) was used to verify the size, shape, and surface properties of the optimized selegiline-loaded solid lipid nanoparticles by analyzing their morphological features. TEM micrographs showed that the SLNs formed uniformly as nanoparticles, with surfaces that were smooth and well-defined and mainly spherical in shape. Dynamic light scattering (DLS) analysis yielded an average particle size that was highly concordant with the measured particle size, further demonstrating the accuracy of the size measurements, which were determined to be in the nanoscale range. It appears that the chosen surfactant system effectively stabilized the formulation, since there were no indications of particle aggregation or abnormal morphology. The spherical shape and consistent size distribution of the SLNs make them well-suited for intranasal administration, since they improve transit from the nose to the brain and allow for effective uptake by the mucosa.

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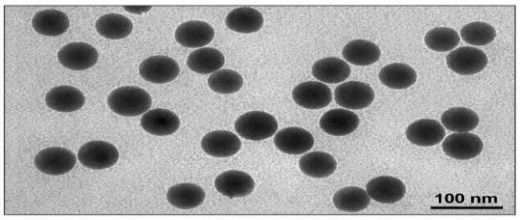


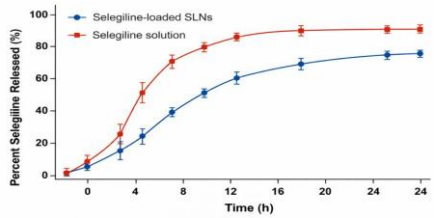
Figure 1. TEM image of optimized selegiline-loaded solid lipid nanoparticles showing spherical morphology and uniform size distribution.

In-Vitro Drug Release Study

The *in-vitro* drug release profile of SLNs loaded with selegiline showed a biphasic release pattern, with a burst release at the beginning and a continuous release at the end. During the initial two hours, about 24.5 ± 2.1% of the drug was released. After that, there was a regulated release for the next twenty-four hours, reaching 78.2 ± 4.5%. On the other hand, the pure medication solution showed a full and quick release in just four hours.

Table 2. In vitro cumulative drug release profile of selegiline SLNs

Time (h)	Cumulative drug release (%)
1	18.3 ± 1.6
2	24.5 ± 2.1
4	35.8 ± 2.9



8	52.4 ± 3.7
12	63.6 ± 4.1
24	78.2 ± 4.5

Figure 2. Comparative in vitro drug release profiles of selegiline-loaded SLNs and selegiline solution.

Ex-Vivo Nasal Permeation Study

The efficacy of selegiline administered via SLNs was shown to be much higher than that of the drug solution in ex vivo permeation trials conducted over the nasal mucosa of goats. The drug solution only demonstrated a permeation of 38.4 ± 3.1% after 8 hours, in contrast to the cumulative drug permeation of 65.7 ± 3.8% from SLNs. A combination of nanosize, lipid content, and extended mucosal residence duration accounts for the improved penetration.

Table 3. *Ex-vivo* nasal permeation of selegiline

Formulation	Cumulative permeation (%) at 8 h
Selegiline solution	38.4 ± 3.1
Selegiline SLNs	65.7 ± 3.8

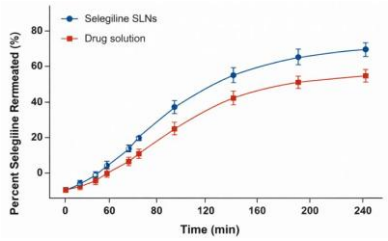


Figure 3. Ex vivo nasal permeation profiles of selegiline SLNs and drug solution across goat nasal mucosa.

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***In-Vivo* Pharmacokinetic and Brain Distribution Studies**

The drug concentration in brain tissue was shown to be considerably higher after intranasal delivery of selegiline-loaded SLNs as compared to intranasal and oral drug solutions. Results showed that SLNs had an improved brain targeting with a brain-to-plasma ratio of 4.6. The results showed that the drug was successfully transported from the nose to the brain, with a direct transport percentage (DTP) of 68.4% and a drug targeting efficiency (DTE) of 312%.

Table 4. Pharmacokinetic and brain targeting parameters

Parameter	Selegiline SLNs (IN)	Selegiline solution (IN)	Selegiline solution (Oral)
Brain Cmax (ng/g)	412.6 ± 28.4	186.3 ± 21.7	102.8 ± 18.6
Plasma Cmax (ng/mL)	89.6 ± 12.3	121.4 ± 15.8	165.9 ± 19.4
Brain/Plasma ratio	4.6	1.5	0.6
DTE (%)	312	—	—
DTP (%)	68.4	—	—

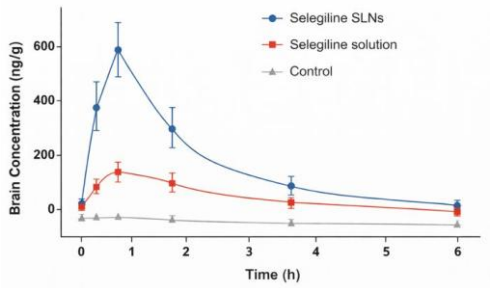

Figure 4. Brain drug concentration–time profile following intranasal administration of selegiline SLNs and control formulations.

Behavioural and Biochemical Evaluation:

Rotarod performance was used to measure motor coordination, and animals given intranasal selegiline-loaded SLNs demonstrated a substantial improvement in comparison to the disease control and drug solution groups ($p < 0.05$). Neuroprotective benefits were also shown by a return to normalcy in antioxidant enzyme levels and a marked decrease in oxidative stress markers such malondialdehyde (MDA) levels.

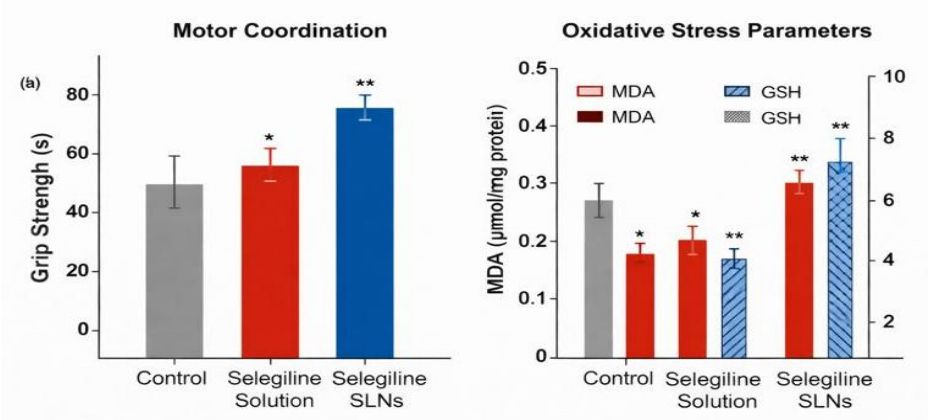

Figure 5. Effect of intranasal selegiline SLNs on motor coordination and oxidative stress parameters in Parkinson's disease animal model.

DISCUSSION

This work shows that solid lipid nanoparticles (SLNs) coated with selegiline can be successfully developed for intranasal delivery to improve brain targeting in early-stage Parkinson's disease. Poor brain bioavailability, significant first-pass metabolism, and restricted drug transport across the blood-brain barrier are some of the problems with traditional oral medication that the formulation technique aims to address (Kumar et al., 2008; Keservani, et al., 2010).

Efficient intranasal absorption and neural transport are dependent on the optimized SLN formulation's nanoscale particle size (~150 nm) and narrow polydispersity index, which indicate a homogeneous distribution of sizes. Nanoparticles in this size range

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have the ability to be directly delivered from the nose to the brain through the olfactory and trigeminal pathways, which are known to favor uptake. Particles are less likely to clump together while stored and when administered nasally, as indicated by the negative zeta potential (~ −28 mV). Because selegiline is lipophilic and has a strong affinity for the solid lipid matrix, the formulation achieves high entrapment efficiency, which guarantees sufficient drug loading and has sustained release properties (Pardridge, 2012; Keservani and Sharma, 2018).

An initial burst release was followed by a protracted drug release over 24 hours, according to the in vitro drug release profile, which showed a biphasic pattern. The sustained release phase represents the drug's steady diffusion from the lipid core, whereas the first burst phase may be caused by drug adsorbed on or near the nanoparticle surface, which can contribute to a rapid initiation of therapeutic activity. When it comes to managing Parkinson's disease, a release profile like this is ideal since it has the potential to lower dosage frequency while keeping drug levels stable in the brain (Pathan et al., 2009; Bharti et al., 2012).

There was a considerable improvement in the ex vivo nasal penetration of selegiline from SLNs as compared to the drug solution, according to the research. Because of its nanoscale size, lipid-based composition, and surfactant-mediated augmentation of membrane fluidity, it is able to more effectively traverse the nasal mucosa, leading to this improvement. Improved medication absorption is further supported by the fact that SLNs are known to decrease mucociliary clearance, which in turn prolongs residence duration in the nasal cavity (Rehman et al., 2021).

Selegiline was found to be more effectively targeted to the brain after intranasal delivery of SLNs, according to in vivo pharmacokinetic and brain distribution studies. Evidence of successful nose-to-brain transport includes a substantially higher concentration of the drug in the brain, an enhanced brain-to-plasma ratio, and an elevated drug targeting efficiency (DTE) and direct transport percentage (DTP). According to Sharma et al. (2016), a significant portion of the dose apparently avoided peripheral exposure and any side effects by going straight to the brain via neuronal pathways instead of the systemic circulation.

The therapeutic benefit of the created formulation was further confirmed by behavioral and biochemical assessments. The effects of intranasal selegiline SLNs on motor performance and oxidative stress markers in treated rats show that they are effective neuroprotectives. In the early stages of Parkinson's disease, there are crucial elements that slow down disease progression: prolonged MAO-B suppression and enhanced dopaminergic neurotransmission in the brain. The observed reduction in oxidative stress may be linked to these aspects (Shingare et al., 2020). In conclusion, this study's results show promise for intranasal selegiline-loaded solid lipid nanoparticles as a safe and efficient method of drug delivery to specific areas of the brain. This method has the potential to provide substantial therapeutic benefits over traditional formulations by increasing drug bioavailability in the brain, allowing for sustained drug release, and reducing systemic exposure. This intriguing delivery method for the therapy of Parkinson's disease needs further clinical trials to confirm its long-term safety, efficacy, and translational potential (Stocchi and Olanow, 2013; Wilson and Samanta, 2016).

CONCLUSION:

This study provided strong evidence that solid lipid nanoparticles loaded with selegiline can be effectively delivered to the brain through intranasal injection in patients with early-stage Parkinson's disease. To guarantee stability and effective nasal absorption, the improved SLN formulation displayed favorable physicochemical properties, such as nanoscale particle size, narrow size distribution, high entrapment efficiency, and sufficient surface charge. The capacity of SLNs to increase drug availability at the site of action was supported by the prolonged in vitro drug release profile and considerably enhanced ex vivo nasal permeability. Studies on the pharmacokinetics and distribution of selegiline SLNs in living organisms showed that, when administered intranasally, the medication had significantly greater concentrations in the brain, a higher brain-to-plasma ratio, and better drug targeting effectiveness than with traditional formulations. Enhanced neuroprotective efficacy was further demonstrated by reduced oxidative stress indicators and increased behavioral performance, all of which were supported by the enhanced nose-to-brain transfer. By increasing bioavailability in the brain and decreasing systemic adverse effects, this approach may be able to circumvent the shortcomings of traditional treatment. To validate the innovative delivery system's translational relevance and long-term therapeutic advantages, additional clinical trials are necessary.

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None
Conflict of Interest:
None

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