

Development of Polymer-Based Nasal Gel of Selegiline Hydrochloride for Alzheimer's Disease Management

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and loss of functional abilities. Effective treatment of AD is often limited by poor drug penetration across the blood–brain barrier. The present study aimed to develop and evaluate a polymer-based nasal gel of Selegiline Hydrochloride for enhanced nose-to-brain delivery. Preformulation studies confirmed the suitability of Selegiline Hydrochloride for nasal administration, demonstrating favorable physicochemical properties, pH-dependent solubility, moderate lipophilicity, and acceptable flow characteristics. Nasal gel formulations (SNG1–SNG6) were prepared using Carbopol 934 and guar gum in combination with selected natural oils and evaluated for physicochemical and performance parameters. All formulations exhibited satisfactory appearance, homogeneity, pH, spreadability, viscosity, extrudability, and drug content. Drug content ranged from $96.84 \pm 0.68\%$ to $99.12 \pm 0.43\%$, while cumulative drug release after 12 h ranged from $81.74 \pm 1.35\%$ to $94.68 \pm 0.96\%$. Among all formulations, SNG4 demonstrated superior characteristics, including optimum pH, highest spreadability, viscosity, extrudability, drug content, and maximum drug release. The findings suggest that the optimized nasal gel formulation can provide prolonged nasal residence, sustained drug release, and enhanced brain targeting, offering a promising therapeutic approach for Alzheimer's disease management.

Keywords: Alzheimer's disease; Selegiline Hydrochloride; Nasal gel; Nose-to-brain delivery; Carbopol 934;

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Introduction:

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by gradual impairment of memory, cognition, language, and executive functioning [1]. Nasal drug delivery offers several advantages, including rapid onset of action, avoidance of first-pass hepatic metabolism, ease of administration, improved patient compliance, reduced systemic adverse effects, and potential for self-administration. These advantages make the nasal route particularly attractive for chronic neurodegenerative diseases such as Alzheimer disease, where long-term treatment is required [2]. Nasal gels are semisolid formulations designed to increase residence time within the nasal cavity, enhance mucosal adhesion, improve drug absorption, and provide sustained drug release [3]. Alzheimer disease is a multifactorial neurodegenerative disorder involving complex molecular and cellular mechanisms. The disease progresses slowly over several years and is characterized by a continuum from preclinical

stages to mild cognitive impairment and eventually severe dementia. Brain drug delivery remains one of the greatest challenges in pharmaceutical sciences due to the presence of the blood–brain barrier (BBB), a highly selective physiological barrier that restricts the entry of most therapeutic agents into the central nervous system (CNS). Neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, brain tumors, multiple sclerosis, and stroke affect millions of individuals worldwide, yet effective treatment remains limited by poor drug penetration into the brain [4]. Neurological disorders constitute a major global health burden and are among the leading causes of disability and mortality worldwide. Diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), glioblastoma, epilepsy, Huntington's disease, multiple sclerosis, and stroke continue to present significant therapeutic challenges. Although numerous potent therapeutic molecules have been developed, their clinical effectiveness

is often compromised by poor penetration across the blood–brain barrier (BBB) [5]. Medicated gels are semisolid pharmaceutical dosage forms in which drug substances are dispersed or dissolved within a three-dimensional network of hydrophilic or hydrophobic polymers. Owing to their non-greasy nature, ease of application, enhanced patient compliance, and ability to provide controlled drug release, medicated gels have become increasingly important in topical, transdermal, ophthalmic, oral, nasal, vaginal, and rectal drug delivery systems. The development of novel polymers and nanotechnology-based gel systems has further expanded their applications in pharmaceutical and biomedical fields [6]. The term "gel" is derived from the Latin word *gelu*, meaning frost or freezing. Pharmaceutical gels are widely used as drug delivery systems because of their ability to incorporate both hydrophilic and hydrophobic drugs and provide localized or systemic therapeutic effects. Medicated gels have gained considerable attention in pharmaceutical formulations due to their unique characteristics such as ease of application, excellent spreadability, cooling effect, transparency, and prolonged residence time at the site of application [7]. These dosage forms are particularly useful for delivering drugs through the skin and mucosal surfaces, thereby enhancing therapeutic efficacy while minimizing systemic side effects. The proposed work is focused on the formulation, development, and evaluation of a mucoadhesive in situ nasal gel for effective drug delivery through the nasal route [8]. The study encompasses the selection of suitable polymers, gelling agents, and excipients capable of producing a formulation that remains in liquid form during administration and undergoes rapid gelation upon contact with the nasal environment. The present study aims to develop a medicated nasal gel formulation that can be conveniently administered into the nasal cavity and undergoes gelation to attain semisolid properties upon contact with the nasal mucosa. The drug delivery is to enhance drug delivery to the brain through the nose-to-brain pathway, thereby increasing drug concentration in the central nervous system and improving therapeutic efficacy. This is also achieved the efficient systemic and/or brain-targeted drug delivery while minimizing dose-related fluctuations and improving overall clinical performance. Selegiline hydrochloride is a selective irreversible MAO-B inhibitor primarily used in the management of Parkinson's disease. The drug exhibits good therapeutic effectiveness,

a favorable safety profile at recommended doses, and potential neuroprotective benefits, making it an important agent in the treatment of neurodegenerative disorders.

Material and methods:

Preformulation Studies: The preformulation studies of Selegiline Hydrochloride were conducted to evaluate its physicochemical properties and to assess its suitability for incorporation into nasal gel formulations. These studies provide essential information regarding drug characteristics that may influence formulation development, stability, and performance.

Organoleptic Evaluation: The organoleptic properties of Selegiline Hydrochloride, including color, odor, and taste, were evaluated through visual and sensory inspection. Such assessments are important for establishing the identity and purity of the drug and for detecting any potential abnormalities or degradation.

Microscopic Examination Microscopic analysis was carried out to determine the morphological characteristics of the drug powder. A small quantity of the sample was placed on a clean glass slide and examined under a phase-contrast microscope. The examination provided information regarding particle shape, surface characteristics, and aggregation behavior, which may influence flowability, solubility, and formulation performance [9].

Physical Characterization: The flow characteristics of the powder were assessed using Carr's Compressibility Index, Hausner's Ratio, and Angle of Repose, which are widely accepted indicators of powder flow behavior.

Carr's Index was calculated using the following equation:

$$\text{Carr's Index (\%)} = \left[\frac{(\rho_{\text{tapped}} - \rho_{\text{bulk}})}{\rho_{\text{tapped}}} \right] \times 100$$

Hausner's Ratio was determined as:

$$\text{Hausner's Ratio} = \rho_{\text{tapped}} / \rho_{\text{bulk}}$$

The Angle of Repose was measured using the fixed funnel method and calculated using:

$$\text{Angle of Repose } (\theta) = \tan^{-1} (2H/D)$$

where H represents the height of the powder heap and D represents the diameter of the powder cone [10].

Particle Size Distribution: Particle size distribution was determined using laser diffraction analysis with a Malvern Mastersizer instrument. The sample was dispersed using the dry dispersion technique, and parameters such as mean particle size and particle size distribution profile were recorded. Particle size analysis is

critical for predicting dissolution behavior, drug release, and formulation uniformity.

Solubility Determination: The saturation solubility of Selegiline Hydrochloride was evaluated in distilled water, 0.1 N hydrochloric acid, phosphate buffer (pH 6.4), and phosphate buffer (pH 7.4). Excess drug was added to each medium and maintained at $37 \pm 0.5^\circ\text{C}$ with continuous stirring until equilibrium was attained. The solutions were subsequently filtered and analyzed spectrophotometrically to determine drug solubility ($\mu\text{g/mL}$) [11].

Partition Coefficient: The partition coefficient of Selegiline Hydrochloride was determined using an n-octanol/phosphate buffer (pH 6.4) system. The drug was equilibrated between the two phases for 24 hours. Following phase separation, drug concentrations in both the organic and aqueous phases were quantified spectrophotometrically, and the partition coefficient ($\log P$) was calculated to assess the lipophilicity of the drug.

Melting Point Determination: The melting point of Selegiline Hydrochloride was determined using the capillary tube method. A small quantity of the drug was filled into a capillary tube and heated in a melting point apparatus. The temperature range at which the drug began to melt and completely liquefied was recorded, providing information regarding drug purity and thermal characteristics [12].

Method of Preparation of Topical Nasal Gel: Selegiline Hydrochloride nasal gel formulations were prepared by the dispersion and neutralization method. Accurately weighed Carbopol 934/ guargum was gradually dispersed in approximately 70% of the required quantity of distilled water under continuous stirring using a magnetic stirrer to avoid lump formation. The dispersion was allowed to hydrate and swell for 2–4 h to obtain a clear gel base. Carbopol-based nasal gels are commonly prepared by hydration followed by neutralization to achieve optimum viscosity and mucoadhesive properties. Selegiline Hydrochloride was dissolved separately in a small quantity of distilled water. Polyvinylpyrrolidone (PVP), glycerine, polyethylene glycol (PEG 400), methyl paraben sodium, and the required quantity of neem oil were added to the drug solution with continuous stirring until a homogeneous mixture was obtained. The prepared drug solution was then slowly incorporated into the hydrated Carbopol 934 dispersion under continuous stirring. The pH of the formulation was adjusted to 5.5–6.5 by the dropwise addition of triethanolamine, which

neutralized Carbopol / guargum and facilitated gel formation. The final volume was adjusted with distilled water and the formulation was stirred continuously until a smooth, homogeneous gel was obtained. The prepared gel was allowed to stand overnight to remove entrapped air bubbles and to ensure complete hydration of the polymer. The formulations were then filled into suitable nasal containers, sealed, and stored at room temperature for further evaluation [13-14].

Table 1: A various composition of different topical nasal gel

Ingredients	SN G1	SN G2	SN G3	SN G4	SN G5	SN G6
Selegiline Hydrochloride (mg)	100	100	100	100	100	100
Carbopol 934 (g)	1.5	1.5	1.5	1.5	1.5	1.5
Guargum (g)	-	-	-	1.5	1.5	1.5
Neem Oil (mL)	1	-	1	1	-	1
Clove Oil (mL)	1	1	-	1	1	-
Almond Oil (mL)	-	1	1	-	1	1
PVP (mg)	50	50	50	50	50	50
Methyl Paraben Sodium (mg)	75	75	75	75	75	75
Glycerine (mL)	5	5	5	5	5	5
PEG (mL)	5	5	5	5	5	5

Triethanolamine (mL)	1	1	1	1	1	1
Distilled Water (q.s. to)	100 g	100 g	100 g	100 g	100 g	100 g

Characterization of selegiline hydrochloride topical nasal gel: The preparing systems was evaluated with various parameters such as Organoleptic Evaluation, physical Evaluation of gel, determination of pH, spread ability, tube Extrude ability, viscosity, in Vitro Diffusion Studies, skin irritation study, drug release kinetic data analysis: The release data was fitted to following mathematical models.

Physical Examination: The prepared topical gel formulations were visually evaluated for color, appearance, consistency, homogeneity, and extrudability. Homogeneity was assessed by visual inspection before filling the formulations into containers. The gels were also examined for the presence of aggregates, phase separation, and overall aesthetic appearance. Additionally, the feel of the gel after application on the skin and pH were evaluated.

Globule Size and Polydispersity Index (PDI): The mean globule size and polydispersity index (PDI) of the formulations were determined using the Dynamic Light Scattering (DLS) technique. Measurements were performed to assess the particle size distribution and uniformity of the dispersed phase within the gel formulations [15].

Viscosity Determination: Viscosity was measured using a Brookfield cone-and-plate viscometer fitted with spindle No. 7. The instrument was connected to a thermostatically controlled water bath maintained at $25 \pm 1^\circ\text{C}$. An adequate quantity of gel was placed in a wide-mouth container, and the spindle was immersed completely. Measurements were recorded at a rotational speed of 2.5 rpm, and the viscosity values were expressed in centipoise (cP).

Spreadability: Spreadability was determined using a modified extensometer apparatus consisting of two glass slides. Approximately 2 g of gel was placed between the slides, and a weight of 1 kg was applied for 5 min to obtain a uniform film. Excess gel was removed from the edges. A weight of 100 g was then attached to the upper slide, and the time required for the slide to move a distance of 7 cm was recorded

[16]. Spreadability was calculated using the following equation:

$$S = (m \times l)/t$$

where S is spreadability, m is the weight tied to the upper slide (g), l is the length moved by the slide (cm), and t is the time taken for separation (s). Lower separation time indicated better spreadability.

Drug Content Determination: One gram of gel formulation was accurately weighed and dissolved in methanol, followed by sonication for 1 h. The resulting solution was filtered through a $0.45 \mu\text{m}$ membrane filter and analyzed using a UV-Visible spectrophotometer at 350 nm to determine the drug content [17].

In Vitro Permeation Study: In vitro permeation studies were carried out using excised porcine ear skin mounted on Franz diffusion cells with a diffusion area of 3.8 cm^2 . The receptor compartment was filled with 75 mL phosphate buffer (pH 6.8) and maintained at $37 \pm 0.5^\circ\text{C}$ under continuous stirring at 100 rpm. The skin was positioned between donor and receptor compartments with the stratum corneum facing the donor side and equilibrated for 30 min. Gel formulation equivalent to 100 mg was applied to the donor compartment. Samples (1 mL) were withdrawn at predetermined intervals up to 24 h and replaced with fresh buffer. Drug permeation was quantified spectrophotometrically at 350 nm. After completion of the study, drug retained on and within the skin was extracted using methanol, followed by sonication, vortexing, centrifugation, filtration, and UV analysis for drug content determination [18-19].

Results:

Preformulation studies were carried out to evaluate the physicochemical properties of Selegiline hydrochloride and to assess its suitability for the development of nasal gel formulations. These investigations provide essential information regarding the drug's identity, purity, flow behavior, solubility, and compatibility with formulation processes. Selegiline hydrochloride was found to be a white to off-white crystalline powder that was odorless and possessed a bitter taste. Microscopic examination confirmed the crystalline nature of the drug, indicating a well-defined particulate structure. The crystalline morphology suggests good physicochemical stability and serves as an important parameter influencing drug dissolution and formulation performance. Micromeritic properties of both unmilled and milled drug samples were evaluated to determine the effect of particle size reduction on powder flow

characteristics. The bulk density increased slightly from 0.612 g/cm³ for the unmilled drug to 0.646 g/cm³ for the milled sample, indicating improved packing efficiency and reduced interparticulate void spaces following milling. The particle size of the unmilled powder was found to be 134 μ m, representing relatively coarse particles. Milling resulted in particle size reduction and improved particle uniformity, which contributed to enhanced flow behavior. The flow characteristics were further assessed using Carr's Index, Hausner's Ratio, and Angle of Repose. The unmilled drug exhibited moderate flow properties with a Carr's Index of 12.38 $\pm$ 0.018%, Hausner's Ratio of 1.12 $\pm$ 0.014, and Angle of Repose of 26.4 $\pm$ 0.121°. In contrast, the milled drug demonstrated significantly improved flowability, as evidenced by a lower Carr's Index of 9.06 $\pm$ 0.016%, a Hausner's Ratio of 1.03 $\pm$ 0.007, and an Angle of Repose of 18.9 $\pm$ 0.093°. These values indicate excellent flow characteristics and suggest that particle size reduction effectively minimized interparticle friction and enhanced powder handling properties. Such improvements are advantageous during pharmaceutical processing steps including mixing, granulation, and dosage form manufacturing. The solubility profile of Selegiline hydrochloride was investigated in distilled water, 0.1 N hydrochloric acid, phosphate buffer pH 6.4, and phosphate buffer pH 7.4. The results revealed a marked dependence of drug solubility on the pH of the medium. Maximum solubility was observed in 0.1 N HCl due to complete ionization of the drug under strongly acidic conditions. Moderate solubility was recorded in distilled water, attributable to the hydrochloride salt form of the drug, which enhances aqueous dispersion. A reduction in solubility was observed in phosphate buffer pH 6.4, while the lowest solubility was obtained in phosphate buffer pH 7.4. This decline can be attributed to decreased protonation of the amine group and increased prevalence of the unionized form of the drug at higher pH values. The overall solubility order was found to be: 0.1 N HCl > Distilled Water > Phosphate Buffer pH 6.4 > Phosphate Buffer pH 7.4, confirming the pH-dependent solubility behavior of Selegiline hydrochloride. The partition coefficient was determined using the shake-flask method in an n-octanol/water system. The drug exhibited a partition coefficient value of 2.05 $\pm$ 0.18, indicating moderate lipophilicity. This characteristic suggests a favorable balance between aqueous solubility and membrane

permeability, which is beneficial for nasal drug delivery and subsequent absorption across biological membranes. The melting point of Selegiline hydrochloride was determined by the capillary tube method and was found to be 175°C. This value closely corresponds with the reported literature value, confirming the purity and identity of the drug. Overall, the preformulation studies demonstrated that Selegiline hydrochloride possesses suitable physicochemical properties for the development of nasal gel formulations intended for effective drug delivery.

The developed Selegiline Hydrochloride nasal gel formulations (SNG1–SNG6) were evaluated for various physicochemical and performance parameters, and the results are presented in Table 2. All formulations exhibited a smooth gel appearance with colors ranging from pale yellow, off-white, light yellow, to creamish white. The formulations were found to be homogeneous, free from grittiness, and showed good to excellent consistency and washability, indicating successful incorporation of the drug and excipients into the gel matrix. The drug content of the formulations ranged from 96.84 $\pm$ 0.68% to 99.12 $\pm$ 0.43%, demonstrating uniform drug distribution throughout the gels. Among all formulations, SNG4 exhibited the highest drug content (99.12 $\pm$ 0.43%), whereas SNG1 showed the lowest (96.84 $\pm$ 0.68%). The pH values of all formulations were found within the range of 6.12 $\pm$ 0.05 to 6.45 $\pm$ 0.02, which is compatible with the nasal mucosal environment and suggests minimal risk of irritation upon administration. Spreadability values ranged from 17.95 $\pm$ 0.48 to 21.84 $\pm$ 0.46 g·cm/sec. Formulation SNG4 demonstrated the highest spreadability (21.84 $\pm$ 0.46 g·cm/sec), indicating ease of application and better surface coverage, while SNG2 showed the lowest spreadability (17.95 $\pm$ 0.48 g·cm/sec). Extrudability studies revealed values between 142 $\pm$ 3.2 and 162 $\pm$ 2.4 g/cm², suggesting satisfactory ease of extrusion from the container. The highest extrudability was observed with SNG4 (162 $\pm$ 2.4 g/cm²), whereas SNG1 exhibited the lowest value (142 $\pm$ 3.2 g/cm²). The viscosity of the prepared gels varied from 12,480 $\pm$ 112 cP to 15,890 $\pm$ 145 cP. An increase in viscosity was observed in formulations containing optimized concentrations of formulation components, with SNG4 showing the highest viscosity (15,890 $\pm$ 145 cP), which is advantageous for prolonged nasal residence time. In vitro drug release studies performed over 12

hours demonstrated cumulative drug release ranging from $81.74 \pm 1.35\%$ to $94.68 \pm 0.96\%$. The highest drug release was obtained from SNG4 ($94.68 \pm 0.96\%$), followed by SNG5 ($91.24 \pm 1.08\%$) and SNG6 ($89.76 \pm 1.12\%$). The lowest release was observed for SNG2 ($81.74 \pm 1.35\%$). Overall, formulation SNG4 emerged as the optimized formulation, exhibiting excellent homogeneity and consistency, highest drug content, favorable pH, superior spreadability and extrudability, optimum viscosity, and maximum drug release at 12 hours. These results indicate that SNG4 possesses the most suitable characteristics for effective nose-to-brain delivery of Selegiline Hydrochloride.

Table 2: Various characterization of selegiline hydrochloride topical nasal gel

Formulation	Appearance	Color	Homogeneity	Consistency	Drug Content (%)	Homogeneity	Grittiness	Washability	pH (Mean $\pm$ SD, n=3)	Spreadability (g/cm ² /sec)	Extrudability (g/cm ²)	Viscosity (cP)	Drug Release at 12 h (%)
SNG1	Smooth gel	Pale yellow	Good	Good	96.84 ± 0.68	Good	Absent	Good	6.12 ± 0.05	18.62 ± 0.54	14.2 ± 3.2	124.80 ± 11.2	84.36 ± 1.22

SNG2	Smooth gel	Off-white	Good	Good	97.25 ± 0.54	Good	Absent	Good	6.18 ± 0.03	17.95 ± 0.48	14.5 ± 2.8	128.60 ± 13.8	81.74 ± 1.35
SNG3	Smooth gel	Light yellow	Good	Good	97.88 ± 0.71	Good	Absent	Good	6.20 ± 0.04	18.20 ± 0.51	14.8 ± 3.1	130.50 ± 12.4	85.92 ± 1.18
SNG4	Smooth gel	Pale yellow	Excellent	Excellent	99.12 ± 0.43	Excellent	Absent	Excellent	6.45 ± 0.02	21.84 ± 0.46	16.2 ± 2.4	158.90 ± 14.5	94.68 ± 0.96
SNG5	Smooth gel	Creamish white	Excellent	Excellent	98.64 ± 0.56	Excellent	Absent	Excellent	6.39 ± 0.03	20.56 ± 0.39	15.8 ± 2.7	154.20 ± 13.6	91.24 ± 1.08
SNG6	Smooth gel	Light yellow	Excellent	Excellent	98.08 ± 0.56	Excellent	Absent	Excellent	6.35 ± 0.02	20.12 ± 0.2	15.5 ± 2	150.80 ± 8.0	89.76 ± 1.12

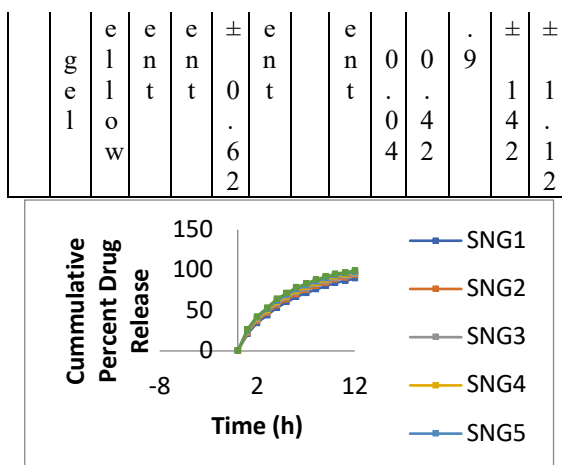


Figure 1: Zero-order plots for in-vitro drug release profile of prepared selegiline hydrochloride topical nasal gel (SNG1-SNG6)

Conclusion: The present study successfully developed and evaluated Selegiline Hydrochloride-loaded nasal gel formulations intended for enhanced nose-to-brain drug delivery. Preformulation studies confirmed that Selegiline Hydrochloride possesses favorable physicochemical characteristics, including suitable solubility, moderate lipophilicity, acceptable flow properties, and good stability, making it an appropriate candidate for nasal administration. The prepared nasal gels exhibited satisfactory physicochemical attributes such as homogeneity, absence of grittiness, suitable pH, adequate spreadability, extrudability, viscosity, and uniform drug content. Among the developed formulations, SNG4 demonstrated superior performance with the highest drug content ($99.12 \pm 0.43\%$), optimum pH, maximum spreadability and extrudability, desirable viscosity, and the highest cumulative drug release ($94.68 \pm 0.96\%$) over 12 hours. These findings indicate that the optimized formulation can provide prolonged nasal residence time and sustained drug release, which are essential for effective nose-to-brain delivery. Overall, the study suggests that Selegiline Hydrochloride nasal gel, particularly formulation SNG4, represents a promising delivery system for improving drug transport to the brain and may offer enhanced therapeutic efficacy in the management of neurodegenerative disorders such as Alzheimer's disease. Further in vivo and pharmacokinetic studies are warranted to establish its clinical potential.

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