

Formulation And Evaluation of Nelumbo Nucifera Plumule-Loaded Thermosensitive Nasal Spray for Parkinsonism

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ABSTRACT:

Parkinson's disease is a degenerative disorder of the nervous system characterized by the deterioration of dopaminergic neurons in the brain, resulting in compromised motor functions. Using the intranasal route for nose-to-brain delivery offers a promising method, as it enables quick absorption, avoids liver metabolism, and provides direct access to the brain. This research investigated the development of a thermosensitive nasal spray utilizing plumule from *Nelumbo nucifera* to enhance the treatment of Parkinson's disease. The plumules are rich in neuroactive alkaloids like nuciferine and neferine, which possess antioxidant and anti-inflammatory properties, inhibit cell death, and offer nerve protection. Initially, the plumules were extracted using a hydroethanolic solvent, followed by testing for specific phytochemicals like alkaloids, flavonoids, tannins, and terpenoids. To improve solubility and absorption, the extract was formulated into a nanosuspension via anti-solvent precipitation. The resulting nanosuspension was mixed with a thermosensitive nasal spray composed of Poloxamer 407, Carbopol 934, and HPMC to enhance the retention time of the gel within the nasal cavity. The formulation underwent testing for various parameters, including pH, viscosity, gelation temperature, gelation time, drug content, and spray characteristics. FTIR, TLC, UV-Visible spectroscopy, and SEM analyses confirmed the existence of alkaloids, nanosized particles, and the compatibility of the excipients. The F2 formulation demonstrated an appropriate pH, rapid gelation at nasal temperature, high drug content, and a consistent spray pattern. Additionally, molecular docking studies indicated the potential of nuciferine in combating Parkinson's disease.

KEYWORDS: *Nelumbo nucifera*, Parkinson's disease, Nanosuspension, Nasal spray, Thermosensitive gel, Molecular docking

I. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterised by the degeneration of dopaminergic neurons, which results in the loss of motor activity. In the management of PD, the primary aim is to increase the dopamine content in the brain either by delivering the precursors of dopamine or by inhibiting the molecules responsible for dopamine degradation [1]. Levodopa is the drug of choice in the treatment of Parkinson's disease, but it exhibits low oral bioavailability (30%) and very low brain uptake due to its extensive metabolism by aromatic Amino acid decarboxylase in the peripheral circulation. Hence, levodopa is co-administered with carbidopa, a peripheral amino acid decarboxylase inhibitor [2].

The most effective approach is the nose-to-brain delivery for targeting drugs directly to the brain. This delivery bypasses the blood-brain barrier [1]. The intranasal route has recently been introduced as an alternative route of administration for systemic purposes rather than the delivery of local drugs. The nasal cavity provides the advantages of a large surface area, fast absorption, a rapid onset of action, and avoidance of the first-pass metabolism. Besides, the nasal cavity is a safe and convenient route of administration [3].

The plumule (seed embryo) of *Nelumbo nucifera* is pharmacologically well-justified for Parkinsonism-oriented, as it is the richest source of key neuroactive alkaloids, especially neferine and related bisbenzylisoquinoline/isoquinoline alkaloids with documented neuroprotective antioxidant, anti-inflammatory, anti-apoptotic, and calcium-modulating effects, protects neurons from glutamate-induced oxidative stress, and improves cognition in

experimental models, which are all relevant to dopaminergic neurodegeneration actions. This constitution show antioxidant, anti-inflammatory, anti-apoptotic, and calcium-modulating effects, protects neurons from glutamate-induced oxidative stress, and improves cognition in experimental models, which are all relevant to dopaminergic neurodegeneration[4].

Nanosuspensions (NS) hold tremendous potential for nose-to-brain drug delivery by increasing the absorption and bioavailability of many poorly soluble drugs by intranasal administration. Nanosuspensions are considered a dispersion of drug nanoparticles in suitable surfactants with sizes smaller than 1 µm (most commonly between 200 and 500 nm). Because of the small particle size and large surface area, NS offer some advantages for enhancing the solubility and dilution velocity of poorly soluble drugs. However, liquid suspension suffers from short retention times in the nasal cavity due to rapid mucociliary clearances. This problem can be solved by using smart stimuli-responsive systems[5]. A thermosensitive nasal spray will increase the retention time of the formulation at the site of action. Poloxamer is one of the most important thermosensitive polymers. Therefore, the present study aimed to prepare a thermosensitive nasal spray containing *Nelumbo nucifera* plumule nanosuspension to improve bioavailability[6]

Plant profile:

Nelumbo nucifera is one of the well-known medicinal plants (family: Nelumbonaceae), also termed as "Tamarai" in Tamil. The parts of *Nelumbo nucifera* plumule are traditionally used for Nervous disorders, Diarrhoea, High blood pressure, Fever, Insomnia and bleeding problems

Synonyms: Sacred Lotus, Indian Lotus, Oriental Lotus, and simply Lotus

| | |
|-------------|---------------|
| Kingdom | Plantae |
| Sub Kingdom | Tracheobionta |
| Kingdom | Streptophyta |
| Division | Magnoliophyta |
| Class | Magnoliophyta |
| Super order | Protaenae |
| Order | Proteales |
| Family | Nelumbonaceae |
| Genus | Nelumbo Adans |

| | |
|---------|--------------------------------|
| Species | <i>Nelumbo nucifera Gaertn</i> |
|---------|--------------------------------|

Table 1: Taxonomical classification

Phytoconstituents:

The plant *Nelumbo nucifera* contains numerous phytoconstituents, including alkaloids (like liensinine, nuciferine), flavonoids (quercetin, astragalin), phenolics (tannins, hydroxybenzoic acid), terpenoids, steroids, polysaccharides, and glycosides. The plant extract alkaloids have anti-Parkinson activity[

Pharmacological Activity:

The plumule of *Nelumbo nucifera* exhibits various pharmacological actions like anti-inflammatory, neuroprotective, anti-cancer, and anti-obesity activities[7]. The primary goal of this research is to formulate a *Nelumbo nucifera* extract and nanosuspension-based thermosensitive nasal spray to investigate its ability to manage Parkinson's disease.



Figure1: *Nelumbo nucifera*

II. MATERIALS AND METHODS

2.1 Materials

Poloxamer 407, HPMC K100, Tween80, Ethanol, Carbopol 934, benzalkonium chloride

2.2. Methods

2.2.1 Preparation of *Nelumbo Nucifera* Plumule Extract

After collecting and drying *Nelumbo nucifera* seeds for 14 days, the plumules were extracted from the seeds and gathered separately. The plumules of *Nelumbo nucifera* were then shade-dried and ground into powder using a mechanical grinder. The

powdered plumules were macerated with a hydroalcoholic solution (70:30) for three days. The macerated sample was subsequently evaporated using a rotary evaporator at 40°C.

2.2.2 Preparation Of Nanosuspension:

Nanosuspension was prepared using the anti-solvent precipitation technique. The organic phase of ethanol was used to add the extract, and the aqueous phase of distilled water was used to add 2 % v/v Tween 80. Using a mechanical stirrer, the organic phase was gradually introduced to the aqueous phase and stirred for approximately three hours at room temperature at 6000 rpm[8].

2.2.4 Characterisation of *Nelumbo nucifera* nanosuspension:

2.2.4.1 Screening of *Nelumbo nucifera* plumule extract:

The phytochemical analysis of *Nelumbo nucifera* was performed using established methods, including tests for flavonoids (Shinoda test, alkaline reagent test, and zinc hydrochloride test), alkaloids (Dragendroff's reagent, Hager's reagent, Mayer's reagent, and Wagner's reagent), glycosides, saponins (Froth test), tannins (Ferric chloride test), as well as steroids and triterpenoids (Liebermann-Burchard test and Salkowski test) was carried[9].

2.2.4.2 Thin-layer chromatography:

TLC was carried out to qualitatively assess the hydroethanolic extract of the powdered plumule. After development, the chromatographic spots were visualized under normal daylight and UV illumination. The retention factor (Rf) for each spot was calculated using the formula:

$R_f = \frac{\text{distance travelled by the sample}}{\text{distance travelled by the mobile phase}}$

Stationary phase: Silica gel G.

Mobile phase: Toluene: Ethyl acetate: Acetic acid: Ethanol (7:2:1)

Detecting agent: Dragendroff's reagent[10].

2.2.4.3 Fourier transmission infrared spectroscopy (FTIR):

The FTIR spectrum of the hydroethanolic extract of *Nelumbo nucifera* (HENN) was acquired, and the sample was dried at 45°C. The dried HENN sample was combined with KBr to create a fine powder, which was then pressed into a thin pellet. FTIR spectra were recorded by placing the pellet into the holder of the spectrophotometer[11]

2.2.4.4 UV -Visible spectrophotometric analysis:

Hydro-ethanol extract of *Nelumbo nucifera* was dissolved in 10ml ethanol. The absorbance of the sample solution was scanned within the wavelength range 200-400nm using a model UV-visible spectrophotometer.

2.2.4.5 Scanning Electron Microscope (SEM):

The surface morphology of the formulated beads was analysed by scanning electron microscope (SEM)

(CarlZEISSEVO18-Germany) - operating modes: secondary electron (SE) and Backscattered electron (BSD) modes. Up to 200 nm resolution depends on the sample. It is attached to the AMETEK Team V.4.3 EDS detector[12].

2.2.5 Preparation of thermosensitive nasal spray:

A thermosensitive nasal spray was prepared by using the cold method.

The poloxamer 407 is slowly added to cold water while stirring. Keep in refrigerator overnight until a clear solution forms. Dissolve Carbopol in distilled water and allow to hydrate for 2-3 hours. Add HPMC slowly with continuous stirring until a uniform solution is obtained.

Add nanosuspension slowly with gentle stirring. Do not heat, keep cold. Add sodium chloride and benzalkonium chloride separately to 10 mL of water. Adjust pH to 5.5-6.0 using dilute sodium hydroxide. Make the final volume 100 ml using distilled water and fill it into the nasal spray container.

| S. No | Ingredient | F1 | F2 |
|-------|-----------------|-------|-------|
| 1. | Nanosuspension | 30 % | 30 % |
| 2. | Poloxamer | 15% | 20% |
| 3. | Carbopol | - | 0.3% |
| 4. | HPMC | 0.5% | 0.5% |
| 5. | BKC | 0.02% | 0.02% |
| 6. | Sodium chloride | 0.4% | 0.4% |
| 7. | Distilled water | q.s | q.s |

Table 2: Composition of thermosensitive nasal spray

2.2.5.1 Characterisation of thermosensitive nasal spray:

2.2.5.2 Determination of PH:

To accurately measure the PH of the samples, the nasal sprays were diluted. 1 ml of the prepared nasal spray was transferred into a 10 ml volumetric flask. The solution was diluted with distilled water. The PH of the resulting solution was determined using a digital PH meter[3].

2.2.5.3 Determination of viscosity:

The viscosity of the prepared formulation was assessed using a Brookfield DV-II Pro Plus viscometer equipped with a T-bar spindle. Viscosity measurements were performed across various temperatures and shear rates. To examine temperature-dependent behaviour, the formulation was subjected to a constant shear rate within a temperature range of 25°C–40°C.

The viscosity of the sol state was measured at room temperature (25°C) using spindle L2, while gel state measurements were conducted at nasal temperature (34°C) due to the observed increase in viscosity[12].

2.2.5.4 Determination of Gelation Time

Sol-gel transition temperature (T sol-gel) of the prepared in situ gel formulations was evaluated by transferring 2 ml of the prepared formulation to a test tube (10 ml), with a diameter of 1.0 cm. After sealing with parafilm, the tube was kept in a circulating water bath at 37 °C. Following each temperature setting, equilibration was allowed for 10 min. Finally, the test tube was placed horizontally to observe the state of the sample[2].

2.2.5.5 Determination of Gelation Temperature

The gelation temperature of the prepared formulation was determined using the tube inversion method. A 10 ml sample was placed in sealed glass vials and gradually heated in a temperature-controlled water bath. The temperature was increased at a controlled rate (1°C/ min), and the temperature at which the solution stopped flowing on inversion was noted as the gelation temperature[2].

2.2.5.6 Determination of drug content

An accurate measure of 1ml of sample was transferred into a 25ml volumetric flask, and the final volume was made up with phosphate buffer, PH 6.4. The drug content was determined by UV-Visible spectrophotometry[6].

2.2.5.7 Molecular Docking

A silicon-based protein-ligand docking software named Autodock Vina 1.5.6 was used to evaluate the binding affinities and interaction patterns between the compound and its proposed targets. The molecular structure of nuciferine, PubChem CID 10146, was retrieved from the PubChem database. The 3D coordinates for the target proteins human alpha synuclein, were sourced from the PDB website. The molecular and protein files were converted into PDBQT format by eliminating water molecules and adding polar hydrogen atoms. Grid boxes were created to cover the protein domains and permit the free movement of the molecules. Autodock Vina 1.5.6 was utilised for conducting the docking studies. We extracted the lowest binding energies and estimated inhibition constants (pKi) from the docking log files.[13].

III. RESULT AND DISCUSSION:

3.1 Phytochemical screening:

| S. No | Phytoconstituents | Hydroethanolic extract |
|-------|-------------------------------|------------------------|
| 1. | Alkaloids | + |
| 2. | Flavonoids | + |
| 3. | Tannin and phenolic compounds | + |
| 4. | Carbohydrates | + |
| 5. | Glycosides | - |
| 6. | Proteins | - |
| 7. | Saponins | + |
| 8. | Terpenoids | + |

Table 3: Phytochemical screening of HENN

3.2. Thin-layer chromatography (TLC):

TLC analysis of *Nelumbo nucifera* plumule hydroethanolic extract performed using silica gel G as the stationary phase and toluene: ethyl acetate: ethanol (7:2:1) as mobile phase showed 0.60, which

confirms the presence of alkaloids 0.60, which confirms the presence of alkaloids

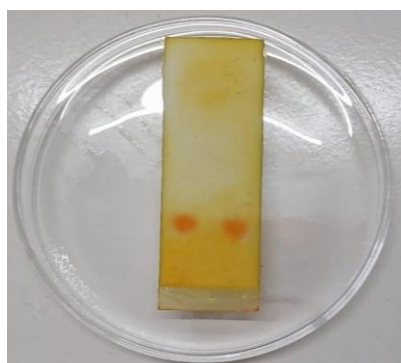
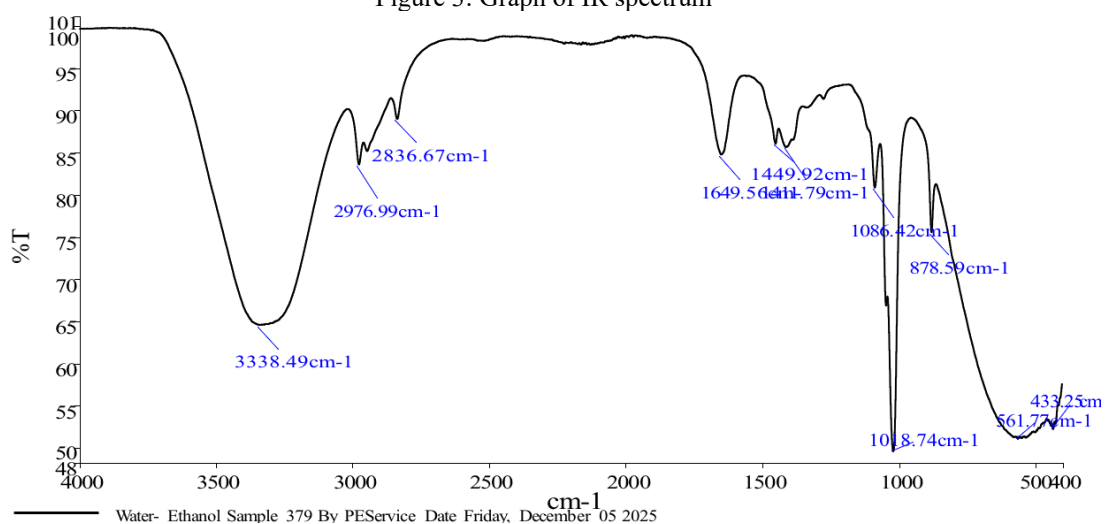


Figure 2: Thin layer chromatography

3.3. Fourier transform infrared spectroscopy (FTIR):

FTIR spectrum of *Nelumbo nucifera* plumule hydroethanolic extract is displayed in the figure. within the range of 400-4000 cm^{-1} . In this figure, the wavenumber 3338.49 cm^{-1} indicates OH, NH stretching, 2976.99 cm^{-1} indicates CH stretching, 1649.56 cm^{-1} indicates C=N stretching, 1449.92 cm^{-1} indicates C=C stretching, 1086.42 cm^{-1} indicates C-N stretching, 878.59 cm^{-1} indicates CH bending, and 561.77 cm^{-1} indicates C-N deformation. These wavenumber confirms the presence of phytoconstituents in *Nelumbo nucifera* plumule hydroethanolic extract, and the spectrum confirms the presence of nitrogen-containing functional groups and aromatic rings, which confirms the presence of alkaloids in *Nelumbo nucifera* plumule hydroethanolic extract.

Figure 3: Graph of IR spectrum



| Source Spectra Results | |
|------------------------|-----------------|
| Spectrum Name | Number Of Peaks |
| Water- Ethanol | 11 |

3.4. UV-Vis spectroscopy:

The hydroethanolic extract of *Nelumbo nucifera* with UV-Vis Spectroscopy. They found an absorption peak between 230-270 nm, suggesting the extract contains alkaloids. A clear peak at 270 nm appeared, typical of alkaloidal compounds. This technique offers a simple and quick way to spot alkaloids, proving their existence in the herbal extract.

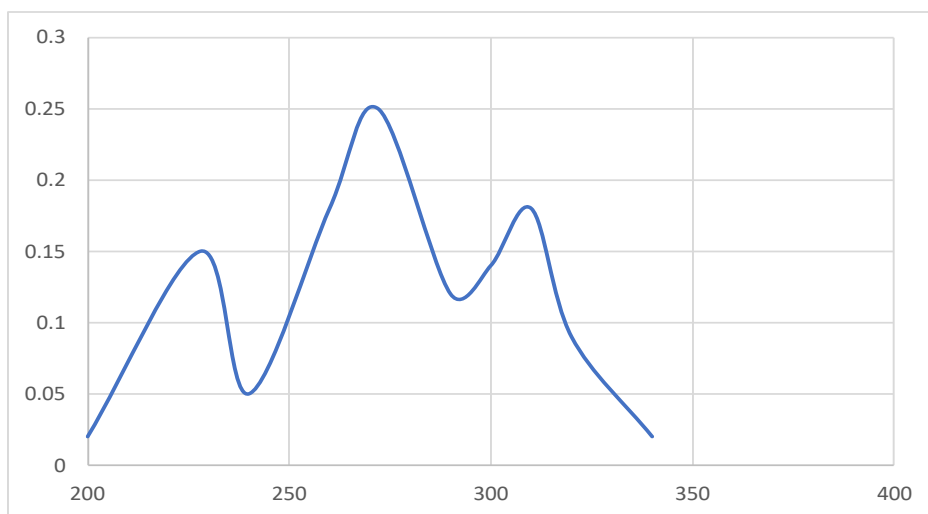


Figure 5: Graph of UV absorbance of HENN

3.5 Scanning Electron Microscopy (SEM):

The SEM study showed that nanoprecipitation works well to shrink the nanosuspension to a nano size. It proved that the new nanoparticles have a regular shape and smooth surface. These traits help deliver drugs better and make them more available in the body. The particles' appearance suggests they could work well in future drug formulations.

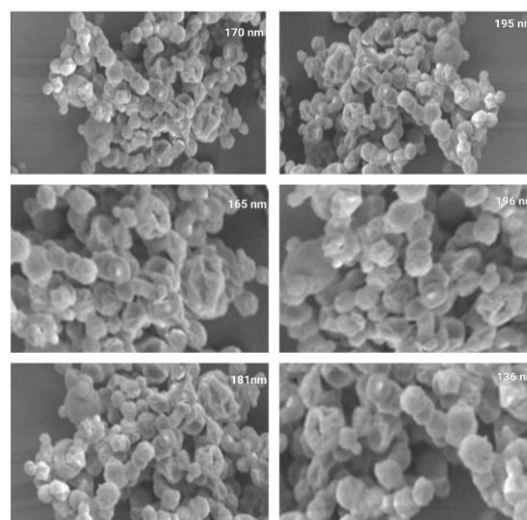


Figure 6: SEM analysis of nanosuspension

3.6. Characterisation of thermosensitive nasal spray: The thermosensitive nasal spray formulations F1 and F2 were evaluated for physiochemical characteristics to conform their suitability for nasal spray and stability

| CHARACTERISTICS | F1 | F2 |
|----------------------|-------------|----------------|
| Appearance | Clear | Clear |
| pH | 5.6 | 5.4 |
| Viscosity | Sol- 120cp | Sol- 160cp |
| | Gel- 1155cp | Gel- 1920cp |
| Gelation temperature | 32°C | 34°C |
| Gelation time | 3 mins | 1 min |
| Drug content | 92% | 97% |
| Spray pattern | Uniform | Fine particles |

Table 4: Physiochemical results of thermosensitive nasal spray

3.7 Molecular docking

Molecular docking analyses were conducted to explore the binding interaction of nuciferine with α -synuclein, an essential protein connected to the development of Parkinson's disease. The results of the docking analysis showed that nuciferine had a binding affinity of -8.19 kcal/mol, signifying a strong attraction to the target.

| S. No | PARAMETER | α -synuclein |
|-------|--------------------------------|---------------------|
| 1 | Binding energy (Kcal/mol) | -8.19 |
| 2 | Ligand efficiency | -0.41 |
| 3 | Inhibition constant (μ M) | 998.56 |

Table 5: Docking results with target protein

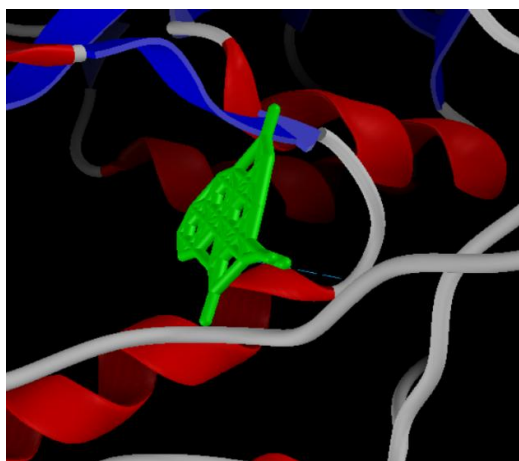


Figure 7: Docking studies with target protein human alpha synuclein

IV. CONCLUSION:

This study successfully developed and tested a thermosensitive nasal spray containing *Nelumbo nucifera* plumule extract for Parkinsonism treatment. The formulation aims to improve nose-to-brain drug delivery, addressing the limitations of traditional oral and parenteral methods. Phytochemical analysis confirmed the presence of bioactive compounds, especially alkaloids, known for their neuroprotective, antioxidant, and anti-inflammatory effects relevant to Parkinson's disease. Among the formulations tested, F2 was identified as the best, showing ideal pH, viscosity, spray pattern, drug content, and gelation temperature, which collectively enhanced nasal retention and mucoadhesion. Molecular docking studies revealed that nuciferine has a strong affinity towards human alpha-synuclein for anti-Parkinsonism potential.

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