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RESEARCH ARTICLE

Formulation Development and Evaluation of Intranasal Delivery of Imperatorin-Loaded Nanoemulgels for Attenuating Neurodegeneration in Rotenone-Induced Parkinson's Disease

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Abstract: The therapeutic management of Parkinson's disease therapy is challenging due to the restrictive nature of the blood-brain barrier and the systemic side effects associated with conventional oral medications. Imperatorin, a furanocoumarin bioactive, possesses potent antioxidant and neuroprotective properties, yet its clinical utility remains hampered by poor aqueous solubility and limited cerebral bioavailability. This work involves development of an Imperatorin-loaded nanoemulgel designed for direct nose-to-brain delivery to enhance therapeutic outcomes in a Parkinson's-like rat model. Optimization through a Box-Behnken experimental design identified an ideal nanoemulsion comprising oleic acid, Tween 80, and Transcutol P, processed via high-energy ultrasonication. The optimized formulation exhibited a hydrodynamic droplet size of 71.05 nm, a polydispersity index of 0.202, and a high negative zeta potential of -60.0 mV, ensuring colloidal stability. Upon incorporation into a Carbopol 974P matrix, the resulting nanoemulgel showed shear-thinning rheological behavior and a sustained biphasic drug release profile, reaching 95.6% over 24 hours. *In vivo* evaluation in a rotenone-induced Parkinsonian model revealed that intranasal administration significantly restored motor coordination and locomotor activity in rotarod and open-field assessments. Biochemical analysis confirmed the mitigation of oxidative stress through reduced malondialdehyde levels and the restoration of superoxide dismutase activity, alongside a marked decrease in neuroinflammatory markers such as TNF-α. These results indicate that the Imperatorin nanoemulgel platform successfully bypasses systemic barriers, offering a direct and effective non-invasive strategy for neuroprotection in neurodegenerative disorders.

Keywords: Nanoemulgel; Imperatorin; Parkinson's disease; Intranasal delivery; Neuroprotection.

1. Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, characterized by the progressive loss of dopaminergic neurons within the substantia nigra pars compacta [1]. This neuronal attrition leads to a profound depletion of dopamine levels in the striatum, manifesting as classic motor symptoms including bradykinesia, resting tremors, postural instability, and muscular rigidity [2]. Beyond motor dysfunction, the disease involves complex molecular pathways involving oxidative stress, mitochondrial dysfunction, and neuroinflammation, which contribute to the persistence of neurodegeneration [3]. While current pharmacotherapy primarily relies on dopamine replacement strategies such as Levodopa, these treatments are often symptomatic and fail to halt disease progression [4]. Long-term systemic administration is frequently limited by fluctuating plasma levels, peripheral side effects, and the formidable challenge posed by the blood-brain barrier (BBB), which restricts the cerebral entry of many therapeutic agents.

The emergence of nanotechnology has provided innovative avenues to circumvent the limitations of traditional drug delivery. Nanoemulsions, characterized by droplet sizes in the sub-200 nm range, offer enhanced surface area and improved solubilization of lipophilic compounds [5]. However, the low viscosity of nanoemulsions often limits their residence time on mucosal surfaces. To address this, nanoemulgels a hybrid system where a nanoemulsion is incorporated into a hydrogel matrix have been developed to provide controlled release and improved bioadhesion [6]. For neurodegenerative conditions, the intranasal route has gained importance as a non-invasive pathway that facilitates direct nose-to-brain transport via the olfactory and trigeminal nerve pathways, effectively bypassing the BBB and reducing systemic exposure [7].

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Imperatorin, a natural furanocoumarin derived from various medicinal plants, has showed significant pharmacological potential, particularly in the context of neuroprotection [8]. Its ability to modulate oxidative stress and suppress inflammatory cytokines makes it a candidate for treating PD pathology [9]. Nevertheless, the clinical translation of Imperatorin is hindered by its hydrophobic nature and rapid first-pass metabolism, resulting in poor oral bioavailability. It is possible to enhance its solubility, protect it from degradation, and ensure its efficient delivery to the central nervous system by encapsulating Imperatorin within a nanoemulgel. The primary aim of this research work involves the development, optimization, and evaluation of an Imperatorin-loaded nanoemulgel for the management of Parkinson's disease. The study utilizes a Box-Behnken design to refine the physicochemical attributes of the nano-carrier and employs a rotenone-induced rat model to validate its neuroprotective efficacy [10]. This work aims to establish a robust technique for improving the delivery of bioactive coumarins to the brain.

2. Materials and Methods

2.1. Materials and Reagents

Imperatorin (purity ≥98%) was obtained as the primary bioactive from Yucca Enterprises, Mumbai, India. Excipients including various oils (oleic acid, almond oil), surfactants (Tween 80, Tween 20), and co-surfactants (PEG 400, Transcutol P, propylene glycol) were procured from the same source. Carbopol 974P was utilized as the gelling agent to provide the desired mucoadhesive properties. Rotenone, used for the induction of Parkinsonian symptoms, and analytical-grade biochemical kits for superoxide dismutase (SOD) and malondialdehyde (MDA) assays were acquired from Sigma-Aldrich. All other reagents and solvents, including triethanolamine and methyl/propyl parabens, were of analytical grade.

2.2. Preformulation Studies

The selection of oil, surfactant, and co-surfactant was based on the equilibrium solubility of Imperatorin. Excess amounts of the drug were added to 5 mL of various vehicles in stoppered vials and agitated for 48 hours at 25 ± 0.5°C to achieve saturation [11]. The mixtures were سپس centrifuged at 3000 rpm for 15 minutes, and the supernatant was filtered and analyzed via UV spectrophotometry at 324 nm to quantify the dissolved drug.

2.3. Preparation of the Imperatorin Nanoemulsion

The nanoemulsion was prepared using a combination of the titration method and high-energy ultrasonication. Briefly, Imperatorin was dissolved in the lipid phase (oleic acid) and the surfactant/co-surfactant mixture (S_{mix}). Deionized water was added dropwise under constant vortexing to form a coarse emulsion [12]. To refine the droplet size, the mixture was subjected to an ultra-homogenization process, followed by probe sonication, ensuring the formation of a transparent and stable nano-dispersion.

2.4. Formulation of the Nanoemulgel

A hydrogel base was prepared by dispersing 1% Carbopol 974P in distilled water and allowing it to hydrate for 6 hours. The optimized Imperatorin nanoemulsion was then incorporated into the gel base in a 1:10 ratio under slow magnetic stirring [13]. Triethanolamine was added to adjust the pH to a range suitable for the nasal mucosa (5.5–6.5), which also served to neutralize the Carbopol and initiate the gelation process.

2.5. Experimental Design and Optimization

A three-factor, three-level Box-Behnken design was implemented using Design Expert software (Version 13) to evaluate the influence of independent variables on the formulation's performance. The independent factors included oil concentration (A), Smix ratio (B), and homogenization speed (C). The dependent variables or responses determined were particle size (Y1), polydispersity index (Y2), and percentage drug content (Y3). A total of 18 experimental runs were generated to map the response surface and identify the optimal formulation parameters.

Table 1. Experimental levels for Box-Behnken Design

Factors	Low (-1)	Medium (0)	High (+1)
A: Oil (%)	2	5	8
B: Smix (Ratio)	1:1	2:1	3:1
C: Homogenization Speed (RPM)	5000	10000	15000

Table 2. Composition of the 18 Experimental Runs as per BBD

Formulations	A: Oil%	B: Smix	C: Homogenization speed
IMF1	-1	0	-1
IMF2	0	-1	1
IMF3	1	1	0
IMF4	1	0	-1
IMF5	-1	-1	0
IMF6	0	1	-1
IMF7	0	0	0
IMF8	0	-1	-1
IMF9	1	-1	0
IMF10	0	0	0
IMF11	0	0	0
IMF12	0	1	1
IMF13	1	0	1
IMF14	0	0	0
IMF15	0	0	0
IMF16	-1	0	1
IMF17	-1	1	0
IMF18	0	0	0

2.6. Physicochemical Characterization

2.6.1. Size, Morphology, and Zeta Potential

The mean droplet diameter and PDI of the nano-formulations were determined using a dynamic light scattering (DLS) analyzer. The surface charge, or zeta potential, was measured to assess the physical stability of the colloidal system [14]. The homogeneity of the final nanoemulgel was visually inspected for phase separation and gritty textures through microscopic evaluation of thin smears.

2.6.2. Rheological and pH Assessment

The viscosity of the nanoemulgel was evaluated using a Brookfield digital rheometer at various shear rates to determine the flow behavior. The pH was measured using a calibrated digital pH meter to ensure compatibility with the nasal environment.

2.6.3. Spreadability and Mucoadhesion

The spreadability was quantified using a parallel plate method, measuring the time required for the gel to spread over a predefined area under a specific weight [15]. This parameter is critical for ensuring uniform coverage of the nasal mucosa.

2.7. *In Vitro* Drug Release Studies

The release kinetics of Imperatorin from the nanoemulgel were investigated using Franz diffusion cells. A dialysis membrane (MWCO 12,000–14,000 Da) was used as the barrier between the donor compartment containing the formulation and the receptor compartment filled with phosphate-buffered saline (pH 6.4) [16]. Aliquots were withdrawn at regular intervals (3, 6, 9, 12, 15, 18, 21, and 24 hours), and the drug concentration was determined spectrophotometrically.

2.8. *In Vivo* Pharmacological Evaluation

2.8.1. Animal Models and Dosing

Adult albino rats were utilized following ethical approval (Approval Number: SSIPSR/IAEC/2025/05) and adherence to ARRIVE guidelines. Parkinsonism was induced via subcutaneous injection of rotenone (0.5 mg/kg) daily for 28 days [17]. The animals were

divided into four groups: healthy control, PD model (diseased), placebo-treated, and nanoemulgel-treated. The Imperatorin nanoemulgel was administered intranasally at a dose of 10 mg/kg.

2.8.2. Behavioral and Biochemical Assays

Motor coordination was assessed using the rotarod test and open-field activity counts. Post-behavioral testing, brain tissues were harvested for biochemical analysis, including the measurement of MDA for lipid peroxidation, SOD for antioxidant capacity, and TNF-α levels for neuroinflammation.

3. Results and Discussion

3.1. Preformulation Studies

3.1.1. Calibration

The quantitative determination of Imperatorin was performed using UV-visible spectrophotometry at a λmax of 324 nm. The calibration curve showed high linearity within the tested concentration range, yielding a regression equation of $y = 0.0276x + 0.089$. The correlation coefficient (R^2) was calculated at 0.9889, confirming the accuracy and reproducibility of the analytical method for subsequent drug content and release studies.

3.1.2. Solubility

The successful development of a nanoemulsion-based system necessitates the identification of vehicles that maximize the solubilization of the lipophilic bioactive. Among the various oils screened, oleic acid exhibited the highest solubility for Imperatorin (0.964 mg/mL), followed by almond oil and isopropyl myristate. For the surfactant phase, Tween 80 showed superior solubilizing capacity (0.753 mg/mL) compared to Tween 20. Among co-surfactants, Transcutol P provided the most favorable results (0.738 mg/mL). Consequently, a ternary system consisting of oleic acid, Tween 80, and Transcutol P was selected for further optimization through the Box-Behnken design.

Table 3. Solubility of Imperatorin in Various Oils, Surfactants, and Co-surfactants

S. No.	Components	Uses	Solubility (mg/ml)*
1	Almond oil	Oil	0.63852 ± 0.012
2	Oleic acid	Oil	0.96421 ± 0.025
3	Isopropyl myristate	Oil	0.43854 ± 0.009
4	PEG 400	Co-surfactant	0.66169 ± 0.015
5	Propylene glycol	Co-surfactant	0.52804 ± 0.011
6	Transcutol P	Co-surfactant	0.73802 ± 0.018
7	Tween 80	Surfactant	0.75384 ± 0.021
8	Tween 20	Surfactant	0.70238 ± 0.014

*Mean ± SD values (n=3)

3.2. Optimization using Response Surface Methodology

3.2.1. Influence of Factors on Particle Size (Y1)

The application of the Box-Behnken design allowed for the systematic evaluation of the interactions between oil concentration, Smix ratio, and homogenization speed. The quadratic model was found to be statistically significant, with a Model F-value of 4.22. The analysis revealed that an increase in the Smix ratio and homogenization speed significantly reduced the globule size. This phenomenon is attributed to the reduction in interfacial tension and the high shear forces that effectively disrupt the oil droplets into the nanometric range. The regression equation indicated that while individual factors A and B had a negative effect on size (reducing it), the interaction between homogenization speed and time played a crucial role in preventing droplet coalescence.

3.2.2. Influence on Polydispersity Index (Y2) and Drug Content (Y3)

The polydispersity index (PDI) serves as an indicator of the uniformity of the droplet size distribution. The optimized runs yielded PDI values as low as 0.202, suggesting a narrow and homogenous distribution. Faster homogenization speeds were found to correlate with lower PDI values by ensuring a more uniform energy distribution throughout the emulsion. Regarding drug content,

the percentage remained consistently high across the optimized formulations, ranging from 93% to 95.8%. The Smix ratio showed a positive influence on drug loading, likely due to the enhanced solubilization capacity provided by the surfactant-co-surfactant combination.

Table 4. Experimental Runs and Observed Responses (Y1, Y2, Y3) for BBD

Formulations	Particle size (nm)*	PDI *	Drug content (%) *
IMF1	155.0 ± 4.2	0.50 ± 0.02	93.02 ± 1.15
IMF2	104.2 ± 3.8	0.70 ± 0.03	95.13 ± 1.08
IMF3	67.51 ± 2.1	0.30 ± 0.01	95.18 ± 0.95
IMF4	117.0 ± 3.5	0.50 ± 0.02	94.34 ± 1.22
IMF5	148.0 ± 4.1	0.63 ± 0.03	93.08 ± 1.10
IMF6	53.43 ± 1.8	0.32 ± 0.01	95.44 ± 0.88
IMF7	98.4 ± 2.9	0.20 ± 0.01	95.08 ± 0.92
IMF8	143.0 ± 3.9	0.20 ± 0.01	93.11 ± 1.05
IMF9	138.1 ± 3.7	0.40 ± 0.02	93.18 ± 1.14
IMF10	84.4 ± 2.4	0.40 ± 0.02	95.69 ± 0.85
IMF11	126.3 ± 3.2	0.53 ± 0.03	93.58 ± 1.25
IMF12	127.2 ± 3.1	0.49 ± 0.02	93.24 ± 1.30
IMF13	104.2 ± 2.8	0.57 ± 0.02	94.53 ± 1.02
IMF14	123.0 ± 3.0	0.65 ± 0.03	93.94 ± 1.18
IMF15	133.0 ± 3.4	0.45 ± 0.02	93.22 ± 1.28
IMF16	92.65 ± 2.2	0.43 ± 0.02	95.83 ± 0.75
IMF17	114.8 ± 3.0	0.43 ± 0.02	94.53 ± 1.12
IMF18	120.7 ± 3.3	0.37 ± 0.01	94.26 ± 1.06

*Mean ± SD values (n=3)

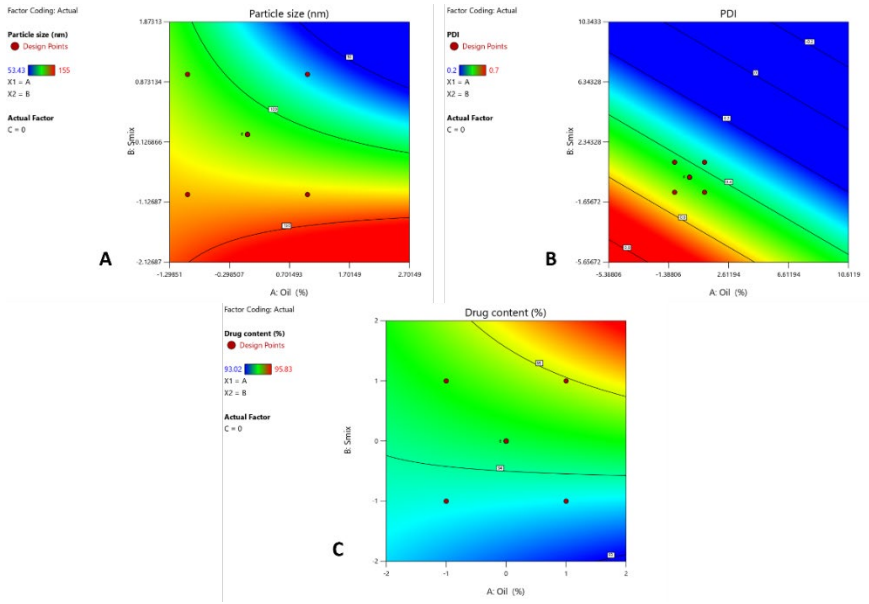

Figure 1. 3D Response Surface Plots showing the Effect of Independent Variables on A. Particle Size B. PDI and c. Drug Content

3.3. Physicochemical Characterization of the Optimized Nanoemulgel

3.3.1. Droplet Size and Colloidal Stability

The optimized formulation (IMF17) was characterized by a mean hydrodynamic diameter of 71.05 nm. Such small droplet sizes are advantageous for intranasal delivery, as they provide a large surface area for absorption and may facilitate paracellular transport through the nasal epithelium [18]. The zeta potential was recorded at -60.0 mV, which indicates a highly stable colloidal system. The strong negative charge generates sufficient electrostatic repulsion to prevent globule aggregation over time, ensuring the long-term physical stability of the nanoemulgel.

3.3.2. Morphological and Structural Studies

Visual and microscopic inspection of the nanoemulgel confirmed a homogenous, lump-free appearance. The FTIR studies showed no significant shift in the characteristic peaks of Imperatorin when formulated with Carbopol 974P, suggesting the absence of chemical interactions between the drug and the polymeric matrix. This compatibility ensures that the bioactive maintains its pharmacological integrity within the delivery system.

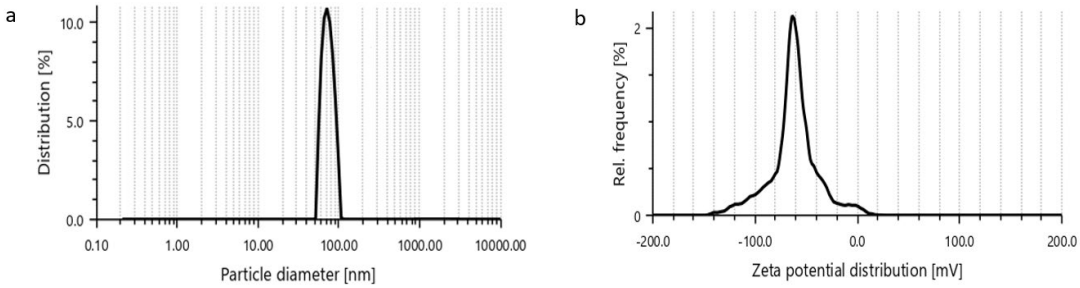

Figure 2. a. DLS Size Distribution and b. Zeta Potential Profiles of the Optimized Formulation (IMF17)

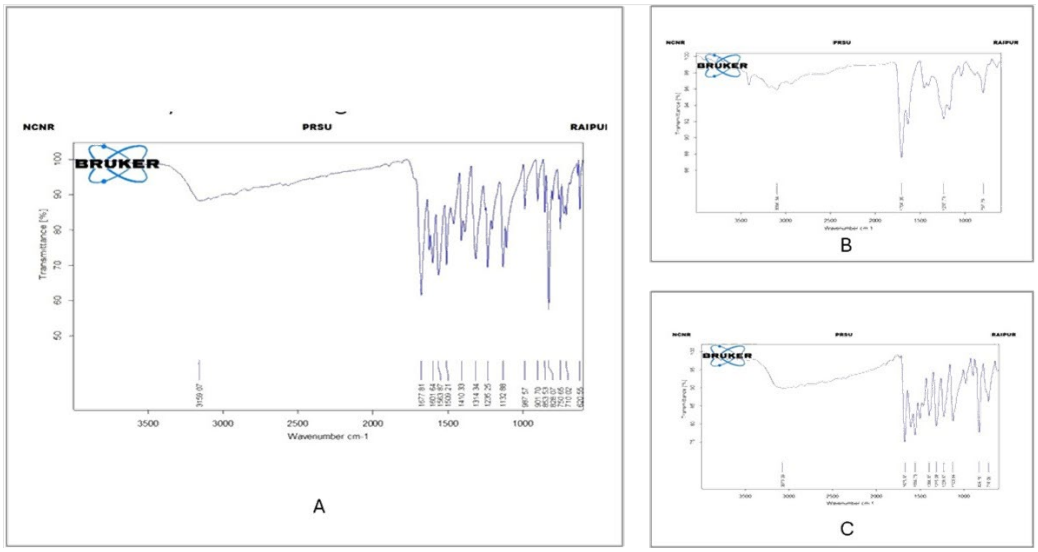

Figure 3. FTIR Spectra of A. Pure Imperatorin, B. Carbopol 974P Drug Mixture and C. Final Nanoemulgel

3.4. Rheological and Mechanical Properties

3.4.1. Viscosity

The rheological evaluation of the nanoemulgel showed a classic shear-thinning (pseudoplastic) behavior. As the rotational speed increased from 10 to 100 RPM, the apparent viscosity decreased significantly. This property is ideal for nasal application, as the gel remains viscous at rest to prevent leakage but flows easily during the application process. The pH of the formulations was maintained between 5.8 and 6.2, aligning with the physiological pH of the nasal mucosa to minimize irritation.

3.4.2. Spreadability and Mucoadhesion

The spreadability of the optimized nanoemulgel was measured at 21.57 g·cm/s. This value suggests that the formulation can effectively cover the nasal cavity surface, enhancing the contact area for drug absorption. The use of Carbopol 974P provides the necessary mucoadhesive strength to prolong the residence time in the nasal cavity, thereby counteracting the effects of mucociliary clearance [19].

Table 5. Results of Viscosity and pH of the prepared formulations

Formulation	Viscosity at 10 rpm (cP)*	Viscosity at 100 rpm (cP) *	pH*
IMF1	3567 ± 45.2	785 ± 12.5	5.8 ± 0.12
IMF2	3171 ± 38.5	689 ± 10.8	5.9 ± 0.09
IMF3	3678 ± 42.8	876 ± 14.2	6.2 ± 0.15
IMF4	3420 ± 40.1	750 ± 11.2	6.0 ± 0.10
IMF5	3250 ± 35.6	710 ± 10.5	5.7 ± 0.08
IMF6	3710 ± 44.2	890 ± 13.8	6.1 ± 0.14
IMF7	3590 ± 41.5	805 ± 12.1	5.9 ± 0.11
IMF8	3310 ± 37.8	725 ± 10.9	6.0 ± 0.13
IMF9	3480 ± 39.4	765 ± 11.7	5.8 ± 0.10
IMF10	3650 ± 43.1	840 ± 13.2	6.2 ± 0.12
IMF11	3380 ± 38.9	740 ± 11.4	5.9 ± 0.09
IMF12	3520 ± 40.7	790 ± 12.3	6.1 ± 0.11
IMF13	3280 ± 36.5	715 ± 10.7	5.8 ± 0.08
IMF14	3450 ± 39.8	770 ± 11.9	6.0 ± 0.14
IMF15	3610 ± 42.4	820 ± 12.8	5.7 ± 0.10
IMF16	3350 ± 37.2	730 ± 11.1	6.2 ± 0.13
IMF17	3490 ± 40.5	780 ± 12.2	6.0 ± 0.11
IMF18	3570 ± 41.9	810 ± 12.6	5.9 ± 0.12

*Mean ± SD values (n=3)

3.5. *In Vitro* Permeation and Release Kinetics

The drug release study revealed a biphasic pattern characterized by an initial burst release of approximately 15.2% within the first hour, followed by a sustained release reaching 95.6% over 24 hours. The initial burst may be attributed to the drug present at the surface of the nano-droplets, while the sustained phase is governed by the diffusion of Imperatorin from the inner oil core and through the gel matrix. This profile is beneficial for Parkinson's therapy, providing both rapid onset and prolonged therapeutic levels of the bioactive.

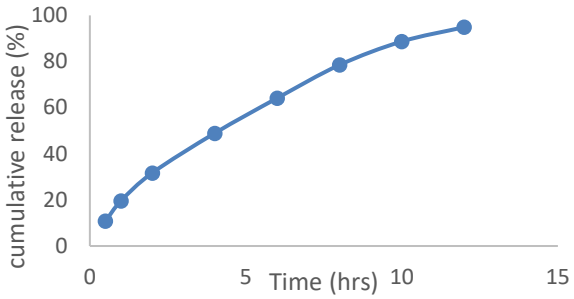

Figure 4. Cumulative *In Vitro* Drug Release of Optimized Formulation (IMF17) over 24 Hours

3.6. Pharmacological Validation in the Parkinsonian Model

3.6.1. Impact on Behavioral Performance

The neuroprotective efficacy of the Imperatorin nanoemulgel was validated using a rotenone-induced PD model. Behavioral studies showed that rats treated with the nanoemulgel exhibited a significant restoration of motor coordination compared to the diseased group. In the rotarod test, the performance time increased to 130 seconds in the treated group, a substantial improvement over the 60 seconds observed in the PD model group. Similarly, open-field activity counts were significantly higher in the treated animals, indicating a recovery in locomotor activity and a reduction in bradykinesia-like symptoms [20].

3.6.2. Biochemical Restoration and Neuroinflammation

Biochemical analysis of brain tissues further supported the behavioral findings. The nanoemulgel treatment led to a significant reduction in malondialdehyde (MDA) levels (1.5 nmol/mg), suggesting the attenuation of lipid peroxidation and oxidative stress.

Concurrently, the activity of superoxide dismutase (SOD) was restored to 48.5 U/mg, replenishing the endogenous antioxidant defense mechanism. The levels of the pro-inflammatory cytokine TNF-α were markedly reduced (12.4 pg/mg) in the treated group, confirming the anti-inflammatory potential of the formulation in preventing neurodegeneration.

Table 6. *In Vivo* Behavioral and Biochemical Parameters across Experimental Groups

Group	Rotarod Test (Seconds)*	Open Field Test (Activity Counts) *
Control (Healthy)	150 ± 10	300 ± 15
Disease (PD Model)	60 ± 8	120 ± 10
IMF17 Nanoemulgel Treated	130 ± 12	260 ± 18
Placebo Treated	70 ± 9	140 ± 12

*Mean ± SD values (n=3)

3.7. Discussion

The results of this study suggest that the Imperatorin-loaded nanoemulgel effectively addresses the challenges of brain-targeted delivery in neurodegenerative conditions. The direct nose-to-brain pathway, facilitated by the nanometric size of the droplets and the mucoadhesive nature of the gel, allows the bioactive to bypass the blood-brain barrier [21]. The recovery of motor functions and the normalization of oxidative markers in the rat model suggest that Imperatorin exerts its neuroprotective effects by mitigating the molecular cascades associated with dopaminergic cell death. Compared to conventional formulations, the nanoemulgel platform provides a superior pharmacokinetic profile, ensuring that the drug remains available at the target site for extended periods.

4. Conclusion

This work successfully developed an optimized Imperatorin nanoemulgel for improved brain delivery and neuroprotection in a Parkinson's-like model. The systematic application of the Box-Behnken design identified a stable and efficient nano-carrier with ideal physicochemical properties, including a sub-100 nm globule size and high colloidal stability. The formulation showed better performance in terms of sustained drug release and mucoadhesive properties, which are essential for effective intranasal administration. The *in vivo* results provided evidence that the nanoemulgel significantly restores motor function and alleviates oxidative stress and neuroinflammation in rotenone-induced rats. These results suggest that the Imperatorin nanoemulgel serves as a promising delivery system that overcomes the limitations of current Parkinson's treatments.

Compliance with ethical standards

Acknowledgements

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Conflict of interest statement

The authors declare that they have no known competing financial interests that could have appeared to influence the work reported in this paper. There are no conflicts of interest with any products or institutions mentioned in this manuscript.

Statement of ethical approval

The experimental protocol for the in vivo studies was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of the Shri Shankaracharya Institute of Pharmaceutical Sciences & Research (Approval Number: SSIPSR/IAEC/2025/05). All procedures were performed in strict accordance with the guidelines for the care and use of laboratory animals.

Statement of informed consent

The present research work does not contain any studies performed on human subjects by any of the authors. Informed consent was not required as the study exclusively involved animal models.

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