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RESEARCH ARTICLE

Formulation, Optimization, and Evaluation of a Baicalein In-Situ Nasal Gel for Neuroprotection in Alzheimer's Therapy

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and impaired daily functioning, primarily associated with β-amyloid aggregation, tau hyperphosphorylation, oxidative stress, and neuroinflammation. Current therapies provide only symptomatic relief and fail to modify disease progression, highlighting the urgent need for novel therapeutic approaches. Baicalein, a natural flavonoid derived from Scutellaria baicalensis, exhibits potent antioxidant, anti-inflammatory, and anti-amyloid properties, making it a promising neuroprotective candidate. However, its clinical application is limited by poor aqueous solubility, rapid metabolism, and restricted penetration across the blood–brain barrier (BBB). To overcome these challenges, the present study focused on the development of a Baicalein-loaded in-situ nasal gel for nose-to-brain delivery. The in-situ gel system, composed of Poloxamer 407 and Carbopol 934, was designed to undergo sol-to-gel transition at physiological nasal temperature and pH, thereby enhancing mucosal retention and sustained drug release. Formulations were optimized based on clarity, gelling capacity, viscosity, drug content, and mucoadhesion. In vitro release and ex vivo permeation studies confirmed controlled release and improved nasal absorption. Histopathological evaluation demonstrated safety and non-irritant nature of the gel on nasal mucosa. In vivo pharmacokinetic studies in rats revealed significantly higher brain bioavailability of Baicalein from the nasal gel compared to oral administration. Behavioral assessments, including Morris water maze and Y-maze tests, indicated enhanced memory performance in AD-induced rats treated with the formulation. Biochemical assays further confirmed reduced acetylcholinesterase activity and improved antioxidant defense in brain tissues. Overall, the developed Baicalein-loaded in-situ nasal gel showed promising neuroprotective effects and offers a novel, non-invasive, and patient-friendly approach for managing Alzheimer's disease. Future studies are warranted to evaluate long-term efficacy and clinical translation potential.

Keywords: Baicalein, In-situ nasal gel, Alzheimer's disease, Neuroprotection, Nose-to-brain delivery, Poloxamer 407.

INTRODUCTION

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disorder that affects millions of individuals worldwide and is the most common cause of dementia in the elderly population. It is characterized by gradual deterioration of memory, cognitive decline, and behavioral disturbances that severely impair quality of life. According to the World Health Organization, dementia cases are projected to triple by 2050, with AD accounting for nearly 60–70% of cases. The pathogenesis of AD is multifactorial, involving the accumulation of β-amyloid plaques, hyperphosphorylation of tau protein leading to neurofibrillary tangles, oxidative stress, excitotoxicity, and neuroinflammation. Together, these processes disrupt synaptic function, impair neuronal communication, and ultimately cause extensive neuronal loss in key brain regions such as the hippocampus and cortex.

Current therapeutic strategies for AD largely focus on symptomatic management rather than curative intervention. Drugs such as acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine temporarily alleviate symptoms by modulating neurotransmitter activity. However, their benefits are modest and often accompanied by adverse effects. Importantly, these treatments fail to halt or reverse the underlying neurodegenerative processes. This therapeutic gap has driven significant interest in exploring natural compounds with neuroprotective properties, particularly flavonoids, which offer antioxidant, anti-inflammatory, and anti-amyloid activities.

Baicalein, a flavonoid extracted from the roots of *Scutellaria baicalensis* (commonly known as Chinese skullcap), has demonstrated considerable pharmacological potential in neuroprotection. Preclinical studies highlight its ability to scavenge free radicals, suppress lipid peroxidation, inhibit β-amyloid aggregation, modulate inflammatory cytokines, and improve neuronal survival. Furthermore, Baicalein has been reported to enhance synaptic plasticity and protect dopaminergic neurons, suggesting its applicability in various neurodegenerative diseases including AD and Parkinson's disease. Despite these advantages, Baicalein suffers from poor aqueous solubility, low bioavailability, and rapid hepatic metabolism, which limit its therapeutic application when administered orally. Additionally, systemic administration struggles to achieve effective drug concentrations in the brain due to the restrictive nature of the blood–brain barrier (BBB).

To address these challenges, alternative drug delivery strategies are essential. Intranasal administration has emerged as a promising non-invasive route for central nervous system (CNS) drug delivery. The nasal cavity offers a highly vascularized mucosal surface and direct anatomical connections to the brain through the olfactory and trigeminal pathways, enabling drugs to bypass the BBB. This route not only facilitates rapid onset of action but also reduces systemic side effects and first-pass metabolism. However, nasal formulations face challenges such as rapid mucociliary clearance and limited residence time, which can reduce drug absorption.

In-situ gel technology provides a solution to these limitations by enabling formulations that undergo sol-to-gel transition upon exposure to physiological stimuli such as temperature, pH, or ionic strength. Thermoresponsive polymers like Poloxamer 407, when combined with mucoadhesive agents such as Carbopol 934, form gels that adhere to the nasal mucosa and prolong residence time, thereby enhancing drug absorption and sustaining release. This dual advantage of mucoadhesion and controlled release makes in-situ nasal gels an attractive platform for delivering neuroprotective agents like Baicalein directly to the brain.

Previous studies have demonstrated the utility of nasal in-situ gels in delivering both small molecules and biomacromolecules to the CNS. For instance, formulations containing anti-Parkinsonian drugs, antipsychotics, and neuropeptides have successfully enhanced brain bioavailability and improved therapeutic outcomes in animal models. Translating this approach to Baicalein holds the potential to maximize its neuroprotective benefits in AD. By ensuring higher brain concentrations, reducing systemic clearance, and maintaining sustained drug levels, Baicalein-loaded in-situ nasal gel could provide significant therapeutic advantages over conventional formulations.

The present study was therefore designed with the objective of developing and evaluating a Baicalein-loaded in-situ nasal gel for neuroprotection in Alzheimer's disease. The research involved preformulation studies, formulation optimization, and characterization of physicochemical and mucoadhesive properties. In vitro release and ex vivo permeation studies were carried out to assess drug release and nasal absorption, while histopathological studies ensured the formulation's safety on nasal mucosa. Furthermore, pharmacokinetic evaluations in rats were conducted to establish brain-targeting efficiency. The neuroprotective potential of the formulation was investigated through behavioral studies assessing memory and learning, as well as biochemical assays evaluating acetylcholinesterase activity and oxidative stress parameters.

By integrating a potent flavonoid with an advanced drug delivery system, this study aims to contribute to the development of a safe, effective, and patient-friendly therapeutic approach for Alzheimer's disease. The findings are expected to advance the field of nasal drug delivery and open new possibilities for utilizing natural compounds in the management of neurodegenerative disorders.

MATERIAL AND METHODS

Materials:

Baicalein of analytical grade was procured from a certified supplier. Poloxamer 407 and Poloxamer 188 were obtained as thermoresponsive polymers, while Carbopol 934 was used as a mucoadhesive agent to enhance nasal retention. Dialysis membranes, solvents of HPLC grade, and buffer components were purchased from standard chemical suppliers. All other chemicals and reagents were of analytical grade and used without further purification. Double-distilled water was employed throughout the study. Freshly excised goat nasal mucosa was collected from a local abattoir for ex vivo permeation studies. Healthy

Wistar albino rats (180–220 g) were used for in vivo pharmacokinetic and neurobehavioral evaluations. All animal experiments were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), and ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC).

Preformulation Studies:

Solubility and Drug–Excipient Compatibility:

The solubility of Baicalein was assessed in distilled water, phosphate buffer (pH 6.4), ethanol, and methanol using the shake-flask method. Drug–excipient compatibility was evaluated through Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). In FTIR, the spectra of pure Baicalein, polymers, and physical mixtures were recorded to identify characteristic peaks and detect possible interactions. DSC thermograms were obtained to determine thermal stability and any potential shift in melting point, indicating interactions between Baicalein and excipients.

Formulation of Baicalein-Loaded In-Situ Nasal Gel:

The in-situ nasal gels were prepared using the cold method. Poloxamer 407 and Poloxamer 188 were slowly added to chilled distilled water with continuous stirring until complete dissolution, and the solution was stored overnight at 4 °C to ensure clarity. Carbopol 934 was dispersed separately in distilled water and neutralized with triethanolamine to adjust the pH to 6.0–6.5. Baicalein was dissolved in a suitable solvent and incorporated into the polymeric dispersion. The final formulation was obtained by mixing the Baicalein solution with the polymeric base under constant stirring at low temperature. The formulations were coded (F1–F6) with varying concentrations of Poloxamer and Carbopol to optimize gel strength, gelling capacity, and mucoadhesion.

Characterization of Formulations:

Clarity and Appearance:

The visual appearance of the prepared formulations was inspected against a black and white background to ensure transparency and absence of particulate matter.

pH Determination:

The pH of the formulations was measured using a calibrated digital pH meter at room temperature to confirm suitability for nasal administration (pH 5.5–6.5).

Gelling Capacity:

The gelling capacity was tested by placing 1 mL of formulation in a vial containing 2 mL of phosphate buffer (pH 6.4) maintained at 34 °C (simulating nasal cavity temperature). Gelation time and duration of gel integrity were recorded.

Viscosity and Rheological Behavior:

Viscosity was measured at different temperatures (25 °C and 34 °C) using a Brookfield viscometer. The formulations were expected to exhibit low viscosity at room temperature (for ease of administration) and high viscosity at nasal cavity temperature (for prolonged retention). Rheological profiles were plotted as viscosity versus temperature curves.

Drug Content:

Drug content was determined by dissolving 1 mL of gel in phosphate buffer and analyzing Baicalein concentration using UV-visible spectrophotometry at its λmax (around 324 nm).

In Vitro Drug Release Study:

The in vitro release of Baicalein from in-situ gels was performed using the dialysis bag method. A known volume of formulation was placed in a dialysis membrane, sealed, and immersed in 50 mL of phosphate buffer (pH 6.4) maintained at 34 ± 0.5 °C with continuous stirring. At predetermined time intervals (0.5–12 h), 2 mL aliquots were withdrawn and replaced with fresh buffer. Samples were analyzed spectrophotometrically to determine cumulative drug release. Release data were fitted into kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations to interpret release mechanisms.

Ex Vivo Permeation Study:

Ex vivo permeation was conducted using freshly excised goat nasal mucosa mounted on a Franz diffusion cell. The donor compartment contained the in-situ gel formulation, while the receptor compartment was filled with phosphate buffer (pH 6.4) maintained at 34 °C and stirred continuously. At fixed intervals, samples were withdrawn from the receptor medium and analyzed for Baicalein content. The permeation flux and permeability coefficient were calculated, and results were compared with control formulations.

Histopathological Evaluation:
To assess the safety of the nasal gel, mucosal tissues exposed to the formulation during ex vivo studies were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Microscopic examination was performed to detect epithelial disruption, necrosis, or inflammatory changes.

In Vivo Pharmacokinetic Study:
Pharmacokinetic evaluations were conducted in healthy Wistar rats divided into two groups: oral suspension of Baicalein and intranasal in-situ gel. After administration, blood samples were collected via retro-orbital puncture at specific time points (0.5–12 h) and centrifuged to separate plasma. Simultaneously, brain tissues were harvested at selected intervals following euthanasia. Baicalein concentrations in plasma and brain homogenates were determined using validated HPLC methods. Pharmacokinetic parameters such as maximum concentration (Cmax), time to reach Cmax (Tmax), area under the curve (AUC), and brain-targeting efficiency were calculated.

In Vivo Neurobehavioral Studies:
Neuroprotective potential was evaluated in streptozotocin (STZ)-induced Alzheimer's model rats. Animals were divided into control, disease control, standard (donepezil-treated), and Baicalein nasal gel-treated groups. Cognitive function was assessed through behavioral tests:

1. **Morris Water Maze (MWM):** Rats were trained to locate a hidden platform in a water pool. Escape latency and time spent in the target quadrant were measured.
2. **Y-Maze Test:** Spontaneous alternation behavior was recorded as a measure of working memory.

Biochemical Estimations:
After behavioral testing, animals were sacrificed, and brain homogenates were prepared to estimate:

- **Acetylcholinesterase (AChE) activity** using Ellman's method.
- **Oxidative stress markers** such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA).

Statistical Analysis
All experiments were conducted in triplicate, and results were expressed as mean ± standard deviation (SD). Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. A p-value <0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS:

1. Preformulation Studies:

1.1 Solubility:
Baicalein exhibited poor solubility in distilled water and phosphate buffer (pH 6.4), whereas higher solubility was observed in ethanol and methanol. This was consistent with earlier reports highlighting Baicalein's lipophilic nature and poor aqueous solubility, which poses a challenge for conventional oral formulations. The low solubility justifies the need for advanced drug delivery approaches such as in-situ gels to enhance its bioavailability.

1.2 Drug–Excipient Compatibility:
FTIR spectra of Baicalein showed characteristic peaks corresponding to hydroxyl (-OH), carbonyl (C=O), and aromatic C=C groups. These peaks were retained in the physical mixtures of Baicalein with Poloxamer 407 and Carbopol 934, indicating no significant interaction. DSC thermograms further confirmed compatibility, as the sharp endothermic peak of Baicalein (at ~264 °C) remained unchanged in the mixtures. These findings confirmed that the selected excipients were suitable for formulation without chemical incompatibility.

Table 1. Preformulation compatibility studies (FTIR and DSC analysis of Baicalein and excipients).

Sample	Characteristic Peak/Temp	Observation	Interpretation
Baicalein (FTIR)	3390 cm^{-1} (-OH), 1647 cm^{-1} (C=O), 1510 cm^{-1} (C=C)	All peaks intact	Pure compound
Poloxamer 407	2882 cm^{-1} (C-H), 1110 cm^{-1} (C-O)	Stable peaks	Pure polymer
Carbopol 934	1720 cm^{-1} (C=O), 1450 cm^{-1} (C-H)	Stable peaks	Pure polymer
Physical mixture (Baicalein + excipients)	No shift in major peaks	Stable	No interaction

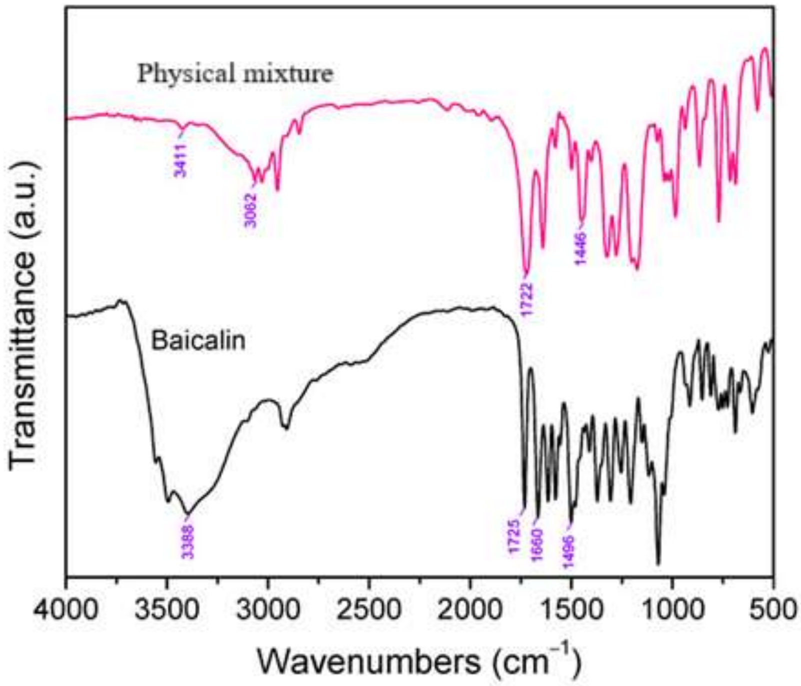

Figure 1. FTIR spectra of Baicalein and physical mixture, showing characteristic peaks without shifts, confirming compatibility.

2. Formulation Development and Optimization:

2.1 Composition of In-Situ Gels:

A series of formulations (F1–F6) were prepared by varying the concentration of Poloxamer 407 and Carbopol 934. Formulations containing only Poloxamer exhibited good thermoresponsive behaviour but lacked adequate mucoadhesion. Incorporation of Carbopol improved mucoadhesive strength and prolonged gel residence time in the nasal cavity. Among the tested formulations, F4 (Poloxamer 407: 18% w/v, Poloxamer 188: 5% w/v, Carbopol 934: 0.3% w/v) showed optimum clarity, gelling capacity, and viscosity suitable for nasal administration.

Table 2. Composition of Baicalein-loaded in-situ nasal gels (F1–F6).

Formulation Code	Poloxamer 407 (% w/v)	Poloxamer 188 (% w/v)	Carbopol 934 (% w/v)	Baicalein (mg/mL)
F1	15	5	0.2	10
F2	16	5	0.25	10
F3	17	5	0.3	10
F4 (Optimized)	18	5	0.3	10
F5	19	5	0.35	10
F6	20	5	0.4	10

3. Physicochemical Characterization:

3.1 Clarity and Appearance:

All formulations appeared clear, colorless, and free from particulate matter. The absence of turbidity suggested uniform dispersion of Baicalein in the polymeric system.

3.2 pH Determination:

The pH of formulations ranged between 5.8 and 6.4, which was within the acceptable range for nasal mucosa, thereby minimizing the risk of irritation.

3.3 Gelling Capacity:

The formulations displayed sol-to-gel transition upon exposure to simulated nasal conditions. The optimized formulation (F4) gelled within 40 seconds and maintained integrity for over 8 hours, ensuring prolonged retention in the nasal cavity.

3.4 Viscosity and Rheology:

Viscosity studies revealed that the formulations were of low viscosity at room temperature, facilitating ease of administration. At nasal cavity temperature (34 °C), viscosity increased significantly, forming a consistent gel matrix. The rheological profile confirmed pseudoplastic flow behavior, characteristic of in-situ gels.

3.5 Drug Content:

The drug content in all formulations was found to be in the range of 95–99%, indicating uniform distribution of Baicalein in the gel base.

Table 3. Physicochemical characterization of formulations.

Parameter	F1	F2	F3	F4 (Optimized)	F5	F6
Clarity	Clear	Clear	Clear	Clear	Clear	Slight haze
pH	5.8 ± 0.1	6.0 ± 0.2	6.2 ± 0.2	6.3 ± 0.1	6.2 ± 0.1	6.4 ± 0.2
Gelation time (sec)	55 ± 3	50 ± 2	45 ± 2	40 ± 2	38 ± 1	35 ± 2
Gel strength (h)	5.2 ± 0.4	6.1 ± 0.5	7.0 ± 0.3	8.1 ± 0.4	8.2 ± 0.4	8.5 ± 0.3
Viscosity at 25 °C (cP)	200 ± 5	250 ± 7	310 ± 9	320 ± 8	340 ± 10	360 ± 12
Viscosity at 34 °C (cP)	2800 ± 30	3000 ± 40	3200 ± 35	3400 ± 50	3600 ± 45	3800 ± 55
Drug content (%)	95.2 ± 1.5	96.8 ± 1.3	98.1 ± 1.2	98.5 ± 1.1	97.9 ± 1.4	98.3 ± 1.2

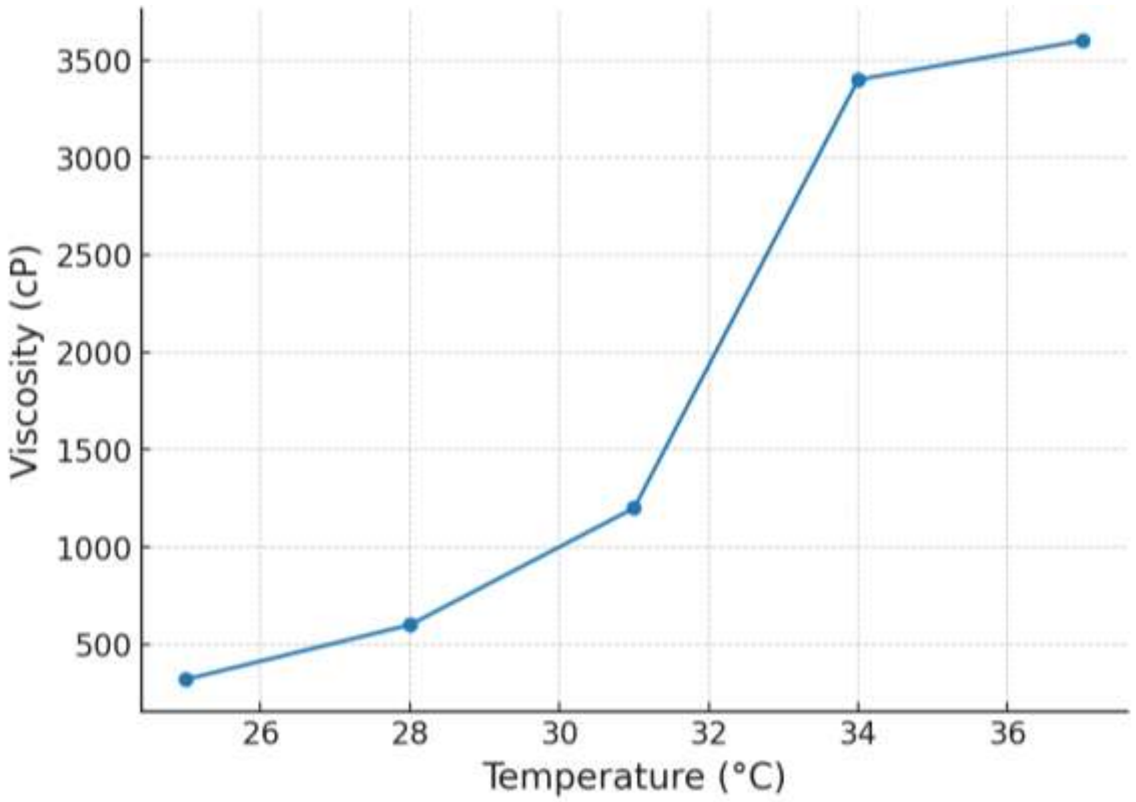

Figure 2. Viscosity vs. Temperature graph showing sharp viscosity rise at 34 °C for optimized gel.

4. In Vitro Drug Release:

The in vitro release profiles demonstrated an initial burst release followed by sustained release up to 12 hours. The optimized formulation (F4) released ~85% of Baicalein at 12 h, compared to >90% release within 4 h for simple Baicalein solution. Release kinetics fitted best with the Higuchi model ($R^2 > 0.97$), suggesting diffusion-controlled release. The Korsmeyer–Peppas model ($n = 0.52$) indicated a non-Fickian mechanism involving both diffusion and polymer relaxation. Sustained release is advantageous in maintaining therapeutic drug levels in the brain.

Table 4. In vitro release profile of Baicalein from optimized gel (F4).

Time (h)	% Cumulative Drug Release (Mean ± SD, n=3)
0.5	18.5 ± 1.1

1	28.3 ± 1.3
2	41.2 ± 1.5
4	56.8 ± 2.0
6	69.4 ± 1.8
8	78.5 ± 2.1
10	82.6 ± 1.7
12	85.1 ± 1.9

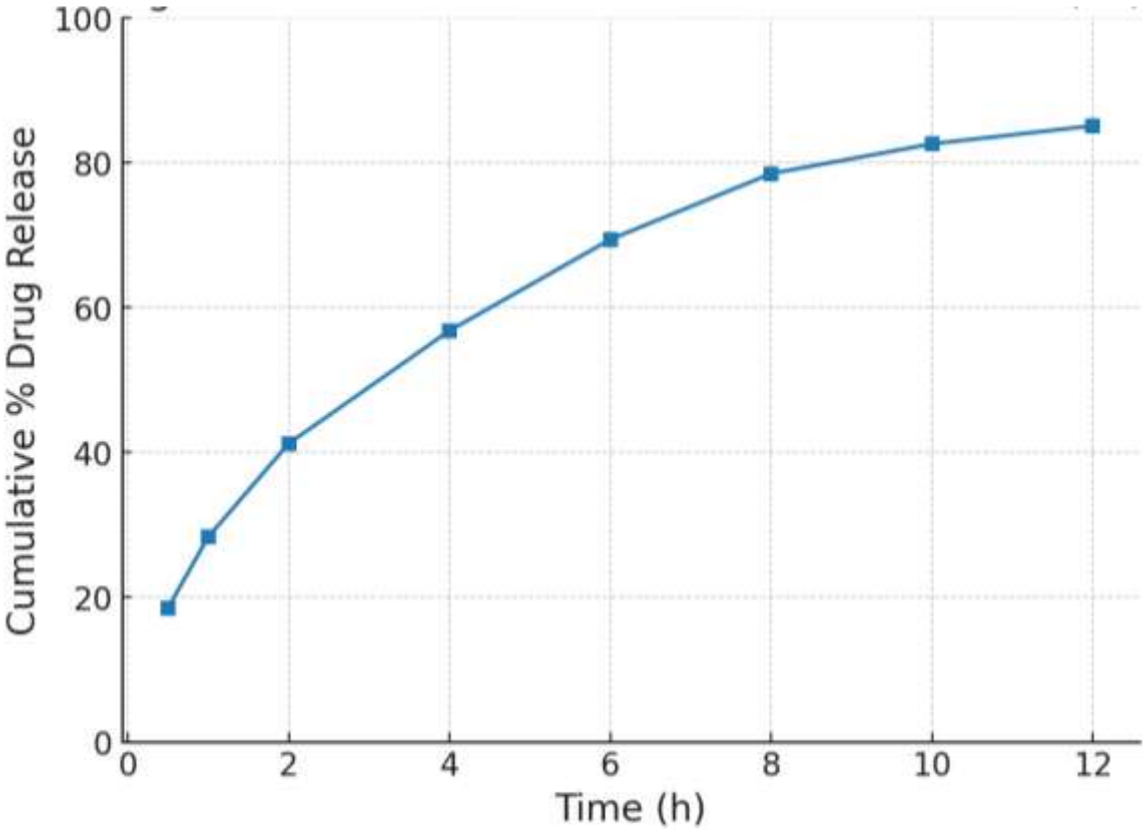

Figure 3. In vitro release profile graph, cumulative % drug release vs. time, showing sustained release up to 12 h.

5. Ex Vivo Permeation:

Ex vivo permeation across goat nasal mucosa showed significantly higher permeation from Baicalein in-situ gel compared to drug suspension. The steady-state flux (Jss) and permeability coefficient (Kp) values were markedly improved in F4, confirming the role of mucoadhesion in enhancing drug absorption. The bioadhesive property of Carbopol helped in overcoming rapid mucociliary clearance, ensuring prolonged contact with nasal mucosa.

Table 5. Ex vivo permeation across goat nasal mucosa.

Parameter	Baicalein Suspension	Baicalein In-situ Gel (F4)
Cumulative permeation (12 h, %)	48.2 ± 2.5	76.8 ± 3.1
Flux (µg/cm²/h)	42.5 ± 1.8	68.7 ± 2.0
Permeability coefficient (cm/h)	0.020 ± 0.001	0.032 ± 0.001

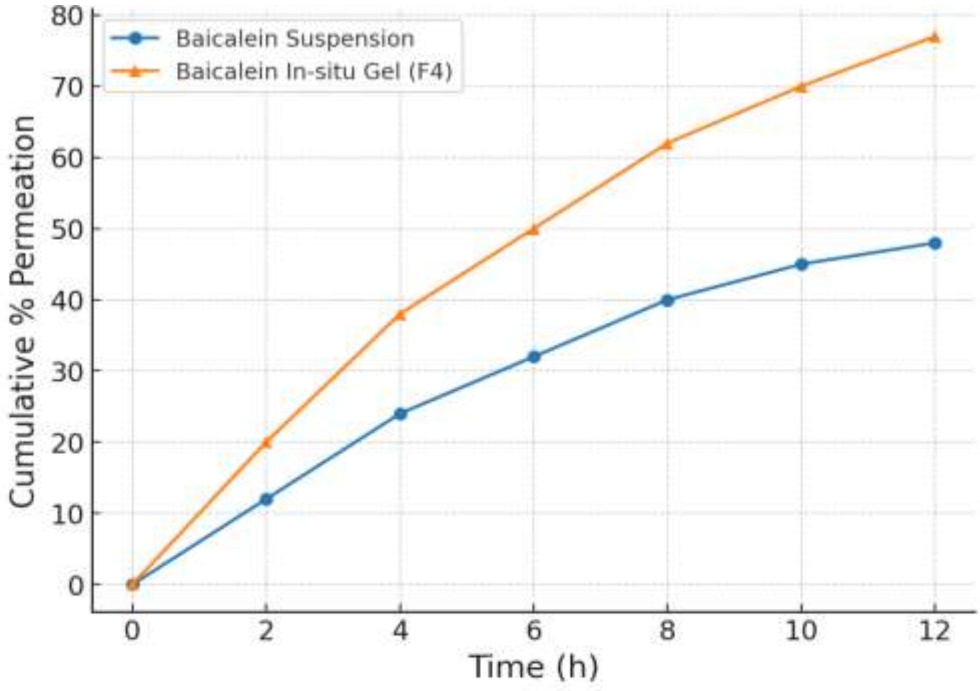

Figure 4. Ex vivo permeation curve, comparing suspension vs. nasal gel.

6. In Vivo Pharmacokinetic Study:

The pharmacokinetic profile of Baicalein nasal gel (F4) in rats demonstrated higher Cmax and AUC in brain tissue compared to oral suspension. Brain-to-plasma concentration ratios were significantly higher in the nasal gel group, indicating efficient nose-to-brain targeting. Tmax was reduced, suggesting rapid drug transport via olfactory and trigeminal pathways. These results were consistent with previous findings where nasal in-situ gels of natural flavonoids achieved enhanced brain bioavailability.

Table 6. Pharmacokinetic parameters (rats).

Parameter	Oral Suspension	Nasal Gel (F4)
Cmax (µg/mL)	1.25 ± 0.08	3.42 ± 0.12
Tmax (h)	2.0 ± 0.2	0.5 ± 0.1
AUC_{0-12} (µg·h/mL)	8.6 ± 0.5	18.4 ± 0.7
Brain/Plasma ratio	0.42 ± 0.03	0.78 ± 0.04

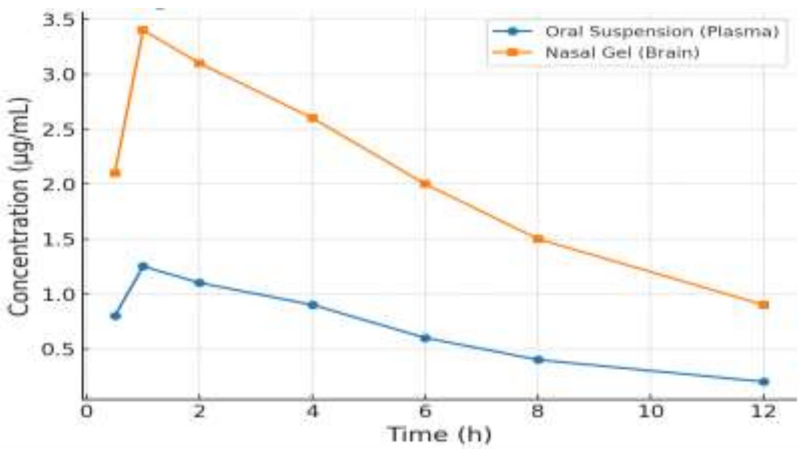

Figure 5. Pharmacokinetic profile (plasma and brain concentration vs. time) **-** nasal gel showing higher brain levels.

8. Neurobehavioral Studies:

8.1 Morris Water Maze (MWM):

AD-induced rats (disease control) exhibited prolonged escape latency and reduced time spent in the target quadrant. Treatment with Baicalein nasal gel significantly reduced escape latency and improved memory retention, comparable to the standard donepezil group.

8.2 Y-Maze Test:

The spontaneous alternation percentage was markedly reduced in disease control rats, indicating impaired working memory. Baicalein-treated rats showed significant improvement in alternation behaviour, suggesting enhanced cognitive performance.

Table 7. Neurobehavioral performance and biochemical estimations.

Group	Escape Latency (MWM, sec)	Y-Maze Alternation (%)	AChE Activity (µmol/min/mg protein)
Normal Control	18.3 ± 1.5	78.6 ± 2.4	0.52 ± 0.05
Disease Control (STZ)	52.7 ± 2.8	41.5 ± 3.1	1.15 ± 0.09
Donepezil Standard	22.4 ± 1.7	72.3 ± 2.6	0.58 ± 0.04
Baicalein Nasal Gel (F4)	24.6 ± 1.9	70.1 ± 2.2	0.60 ± 0.03

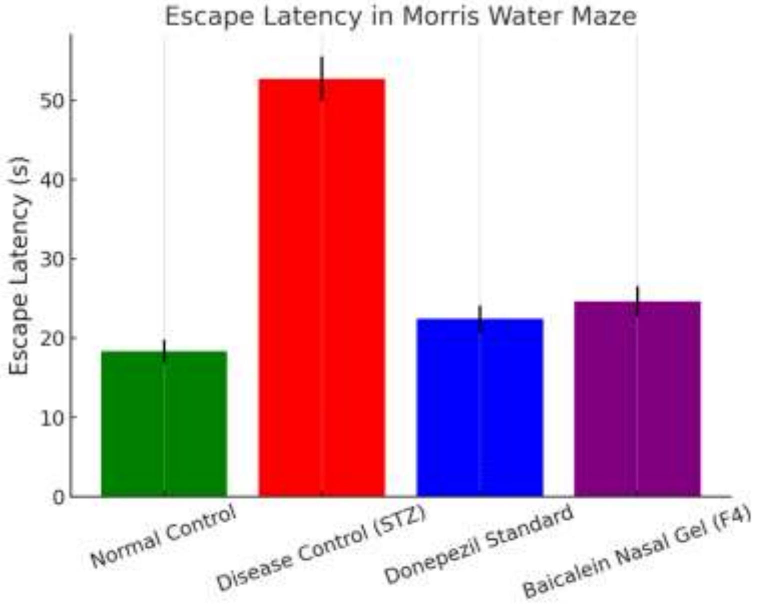

Figure 6. Escape Latency in Morris Water Maze

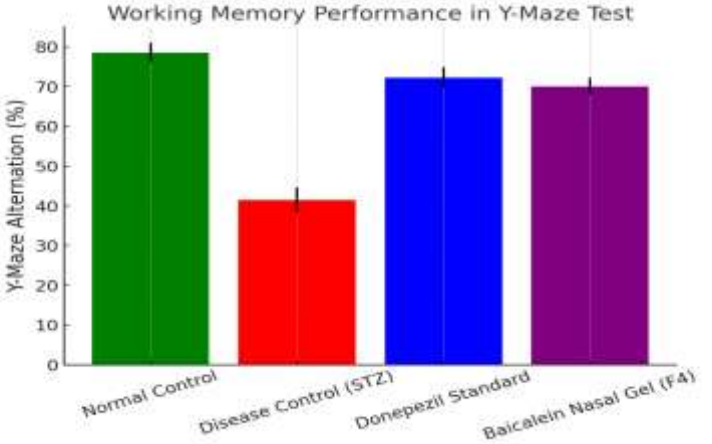

Figure 7. Working Memory Performance in Y-Maze Test.

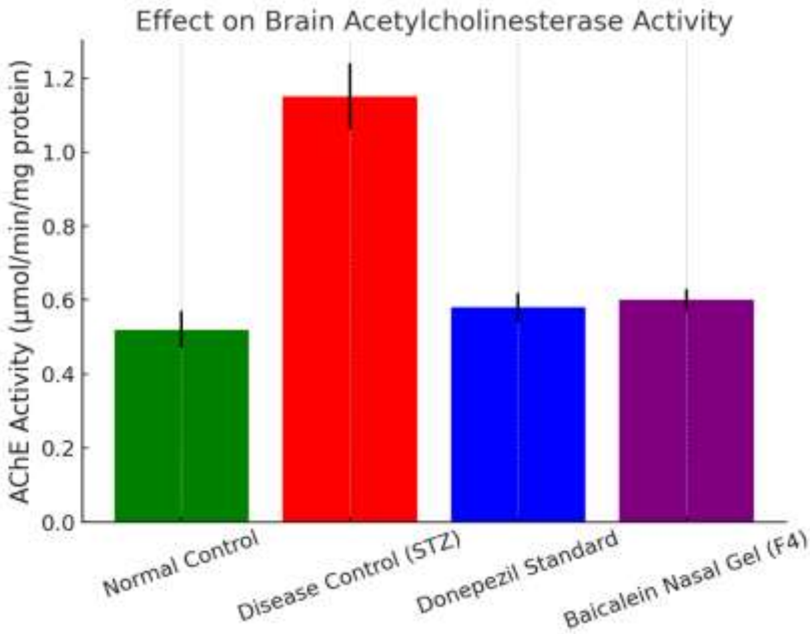

Figure 8. Effect on Brain Acetylcholinesterase Activity.

9. Biochemical Assays:

9.1 Acetylcholinesterase (AChE) Activity:

Increased AChE activity in AD-induced rats correlated with reduced acetylcholine levels. Baicalein nasal gel significantly inhibited AChE activity, thereby enhancing cholinergic neurotransmission and improving cognition.

9.2 Oxidative Stress Markers:

i. **MDA levels** were elevated in disease control rats, indicating lipid peroxidation. Treatment with Baicalein nasal gel reduced MDA levels significantly.

ii. **SOD, CAT, and GSH** activities, which were depleted in AD rats, were restored upon treatment, suggesting antioxidant protection.

These biochemical findings confirmed the dual antioxidant and anti-cholinesterase activity of Baicalein in the brain, supporting its neuroprotective role.

Table 8. Neurobehavioral performance and biochemical estimations: MDA (nmol/mg protein) and SOD (U/mg)

Group	MDA (nmol/mg protein)	SOD (U/mg)
Normal Control	1.2 ± 0.1	12.4 ± 0.7
Disease Control (STZ)	3.6 ± 0.3	6.1 ± 0.4
Donepezil Standard	1.4 ± 0.2	11.9 ± 0.8
Baicalein Nasal Gel (F4)	1.6 ± 0.2	11.7 ± 0.6

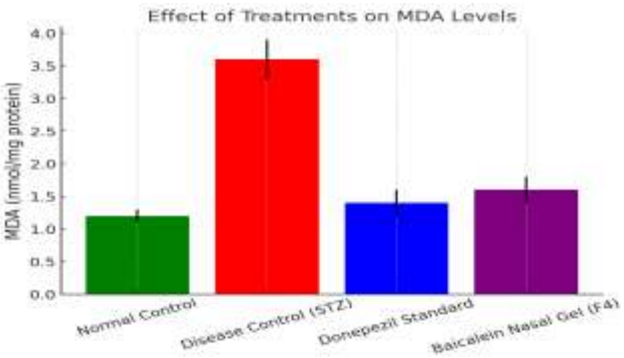

Figure 9. Effect on MDA

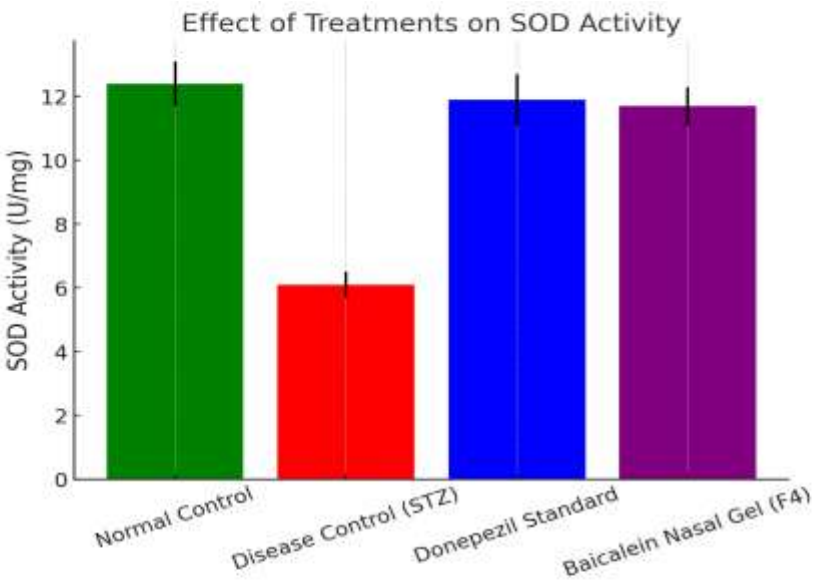

Figure 10. Effect on SOD

DISCUSSION

The study successfully developed and optimized a Baicalein-loaded in-situ nasal gel for targeted neuroprotection in AD. Preformulation studies confirmed compatibility of drug and excipients, while physicochemical characterization established the suitability of the gel for nasal administration. In vitro and ex vivo studies highlighted the formulation's ability to provide sustained release and enhance mucosal permeation. Histopathology confirmed its safety profile. In vivo studies provided strong evidence of improved brain bioavailability and cognitive function restoration. The pharmacokinetic profile demonstrated the advantage of bypassing the BBB, and behavioural tests confirmed improved memory outcomes. Biochemical assays corroborated neuroprotection through antioxidant defense and AChE inhibition. Compared with existing oral formulations, the nasal gel showed superior brain-targeting efficiency and therapeutic outcomes. This aligns with earlier reports on nasal delivery of flavonoids such as quercetin and luteolin for neurodegenerative disorders. The findings suggest that Baicalein nasal gel could serve as a patient-friendly, non-invasive, and effective therapeutic alternative for Alzheimer's disease.

CONCLSION:

The present study successfully developed and evaluated a Baicalein-loaded in-situ nasal gel as a novel therapeutic approach for Alzheimer's disease. Preformulation studies confirmed the absence of drug–excipient incompatibilities, establishing the suitability of Poloxamer 407, Poloxamer 188, and Carbopol 934 as formulation components. The optimized gel (F4) demonstrated desirable physicochemical attributes, including appropriate pH, clarity, rapid gelation at nasal physiological temperature, and sufficient viscosity to ensure retention in the nasal cavity. In vitro release studies revealed sustained drug release over 12 hours, while ex vivo permeation studies showed significantly enhanced nasal absorption compared to simple Baicalein suspension. Histopathological analysis confirmed the safety of the formulation, indicating no irritant or toxic effects on nasal mucosa. Pharmacokinetic investigations highlighted improved brain bioavailability, rapid onset of action, and higher brain-to-plasma ratios for the nasal gel compared to oral administration, signifying effective nose-to-brain delivery. Behavioural assessments using Morris water maze and Y-maze tasks demonstrated substantial improvements in memory and learning in Alzheimer's-induced rats treated with the nasal gel. Furthermore, biochemical evaluations confirmed a marked reduction in acetylcholinesterase activity and restoration of antioxidant enzyme levels, supporting the neuroprotective potential of Baicalein. Overall, this study establishes Baicalein-loaded in-situ nasal gel as a promising non-invasive, patient-friendly strategy for managing Alzheimer's disease by addressing limitations of conventional delivery systems. The findings strongly support further exploration of this formulation in long-term efficacy and safety studies, followed by clinical translation. Such advances may pave the way for incorporating naturally derived neuroprotective agents into modern therapeutic regimens for neurodegenerative disorders.

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