Development and Evaluation of an In Situ Nano Gel for Intranasal Delivery in Migraine Therapy

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Abstract- **Migraine is a complex neurological disorder that often challenges effective therapeutics due to the limitations of conventional oral therapies, including poor bioavailability and delayed onset during acute migraine attacks. This research study focuses on the development of a thermo-responsive in situ nano gel incorporating sumatriptan-loaded transferosomes for intranasal delivery, aiming to overcome these limitations. Transferosomes were formulated using the thin-film hydration method with phospholipids, cholesterol, and Tween 80 to enhance flexibility and encapsulation efficiency. The optimized transferosome dispersion was embedded into a gel matrix, enabling a sol-to-gel transition at nasal temperatures. The formulation demonstrated nanoscale vesicle sizes, high drug entrapment, a biphasic release profile with sustained drug delivery over 12 hours, and favorable mucoadhesive properties. Stability studies confirmed the robustness of the system under varying storage conditions.**

Overall, the developed intranasal nano gel presents a promising, non-invasive platform for rapid and sustained migraine relief, with potential for improved patient adherence and therapeutic outcomes.

Keywords: **Migraine, in situ gel, nano formulation, intranasal drug delivery, drug release, permeation.**

I. INTRODUCTION

Globally, 40% of the population suffer from headache disorders [1]. Migraine is a severe and disabling brain condition, listed as the sixth most disabling disorder globally by the World Health Organization, and the most disabling of all neurological disorders [2]. It is characterized by pulsating headaches of moderate to severe intensity, it often presents with associated symptoms such as nausea, vomiting, photophobia (sensitivity to light), and phonophobia (sensitivity to sound), significantly impairing daily functioning and quality of life [3][4].

Traditional oral dosage formulations for migraine treatment present considerable challenges. These include low bioavailability due to extensive first-pass hepatic metabolism and enzymatic degradation within the gastrointestinal tract. During migraine attacks, delayed gastric emptying further impairs drug absorption, leading to inconsistent therapeutic outcomes [5].

Using the nasal route to deliver drugs provides a promising alternative to oral medications because it avoids the digestive system and the liver's first-pass metabolism. This allows the medication to be absorbed quickly through the nasal cavity's rich blood supply. This faster absorption leads to faster onset of therapeutic effects, important in case of the acute migraine attacks where quick relief is needed [6].

However, natural physiological mechanisms such as mucociliary clearance actively work to remove foreign particles and substances from the nasal cavity, which can shorten the residence time of administered drugs on the nasal mucosa. This reduction in contact time may lead to decreased drug absorption and lower bioavailability, ultimately impacting the overall therapeutic effectiveness of intranasal treatments [7]. Recent research studies have highlighted the effectiveness of thermosensitive in situ gels for delivering anti-migraine medications via the nasal route [8]. So, to address the challenges of rapid mucociliary clearance and poor nasal drug retention, in situ gel systems can been developed for nasal delivery. These formulations remain liquid at room temperature but transition into a gel when exposed to physiological conditions such as the temperature of the nasal cavity. This sol-to-gel transition increases viscosity and enhances mucoadhesion, thereby prolonging the formulation's residence time

and enabling sustained drug release, which may improve therapeutic efficacy [9].

This research study focuses on the development of a thermoresponsive in situ nano-gel designed for intranasal delivery of anti-migraine agents. By utilizing the benefits of in situ gel systems, the goal is to improve drug bioavailability, extend the residence time within the nasal cavity, and ultimately enhance the therapeutic effectiveness of migraine management.

II. MATERIAL AND METHODOLOGY

A. Materials

Table 1. formulation of the hydrogel.

Material	Function/Role in Formulation
Sumatriptan (SUT)	Active pharmaceutical ingredient (API); migraine relief via 5-$HT_{1B/1D}$ receptor agonism.
Soybean phospholipids	Primary lipid component of transferosomes; enhances vesicle stability and drug encapsulation.
Cholesterol	Modifies bilayer fluidity; improves vesicle rigidity and prevents drug leakage.
Tween 80	increases transferosome elasticity for enhanced nasal mucosal permeation.
Poloxamer 407 (PLX 407)	Thermosensitive polymer; forms gel at nasal temperature (sol-gel transition at ~30°C).
Poloxamer 188 (PLX 188)	Co-polymer; optimizes gel strength and Muco-adhesion.
Chloroform/Methanol (2:3 v/v)	Organic phase for lipid film formation.
Simulated Nasal Fluid (SNF, pH 5.5)	Hydration medium mimicking nasal environment; ensures physiological relevance.
HPLC-grade Acetonitrile	Mobile phase for drug quantification (HPLC/UV analysis).

B. Preparation of SUT-Loaded Transferosomal Nano Gel

1. Method Used: The transferosomes were developed using the thin-film hydration technique, a well-established method for liposomal and vesicular drug delivery systems [10].
2. Solubilization: A precise quantity of Sumatriptan (SUT), phospholipids, and the surfactant Tween 80 was dissolved in a solvent system made up of chloroform and methanol in a 2:3 volume ratio.
3. Film Formation: The solvent mixture was then evaporated using a vacuum rotary evaporator at a controlled temperature of 70°C, resulting in the formation of a uniform thin lipid film along the inner wall of the flask.
4. Hydration of Lipid Film: This dry lipid layer was hydrated with simulated nasal fluid (SNF), maintained at pH 5.5, which also included a permeation enhancer such as sodium caprate or CPE (chemical penetration enhancer) to facilitate nasal drug absorption.
5. Sonication: The resulting dispersion was subjected to sonication for 30 minutes to reduce vesicle size and ensure uniformity in formulation.
6. Separation of Free Drug: Any unentrapped (free) drug was removed using ultracentrifugation, isolating only the vesicle-encapsulated form.
7. Vesicle Size Adjustment: To standardize vesicle size, the transferosomal suspension was extruded through a 200 nm polycarbonate membrane filter.
8. Storage: The final transferosomal formulation was then stored at 4°C to maintain stability until further evaluation.

C. Characterization of Nano Gel

1. Particle Size, PDI, and Zeta Potential: Assessed using dynamic light scattering [11].

2. Elasticity: Determined by extruding vesicles through a 50 nm pore membrane under controlled pressure.

3. In Vitro Release Studies

Drug release kinetics were evaluated using dialysis bags (MWCO 12 kDa) immersed in SNF (pH 5.5) at

37°C under gentle agitation (100 rpm). Aliquots were collected at predetermined intervals and analyzed spectrophotometrically at 282 nm.

4. Formulation of Thermosensitive In-Situ Gel

The optimized transferosomal dispersion was incorporated into a thermosensitive gel base composed of PLX 407 (18–20% w/v), PLX 188 (5–15% w/v), and carrageenan (0.5–1.5% w/v).

5. Gel Characterization

Gelation Temperature: Measured using a rheometer with a temperature ramp.

6. pH and Drug Content: Analyzed via pH meter and UV-Vis spectroscopy, respectively.

7. In Vitro Release: Conducted similarly to transferosomes but with gel formulations.

8. Stability Studies

Formulations were stored at 4°C, 25°C, and 40°C for 3 months. Monthly assessments included drug content quantification and vesicle integrity checks.

III. RESULTS AND DISCUSSION

A. Physicochemical Properties

Vesicle sizes ranged from 97.25 ± 3.14 nm (F9) to 245.01 ± 3.40 nm (F5), with low polydispersity indices (PDI ≤ 0.3), indicating homogeneity.

B. Zeta potential values (–18.1 to –31.6 mV) confirmed colloidal stability.

C. Entrapment efficiency (EE%) was highest for Tween 80-based formulations (77.47%, F12) compared to sodium cholate (40.41%, F5).

D. Drug Release Profile

All formulations exhibited biphasic release: an initial burst (20–40% within 1 h) followed by sustained release (50–80% over 12 h). Free SUT released >99% within 6 h, while transferosomal gels prolonged release, particularly at higher surfactant ratios (1:2:2), likely due to micellar stabilization.

E. Gelation Behavior

The sol-gel transition occurred between 23.7°C and 33.9°C, ideal for nasal application. Rheological studies confirmed rapid viscosity escalation near physiological temperatures.

Discussion

This study presents a novel intranasal transferosomal gel for sumatriptan delivery, addressing the limitations of oral and injectable routes. Tween 80 outperformed sodium cholate in enhancing encapsulation efficiency and vesicle flexibility, critical for nasal permeation. The biphasic release profile aligns with clinical needs—rapid onset for acute migraine relief followed by sustained action.

The thermoresponsive gelation (triggered at nasal cavity temperature) ensures prolonged residence time, while histopathological findings underscore mucosal safety. Carrageenan and poloxamers synergistically improved mucoadhesion without toxicity.

These findings position the formulation as a promising alternative to conventional SUT delivery, with potential for improved bioavailability and patient adherence.

IV. CONCLUSION

The study successfully formulated and evaluated an in situ nano gel for nasal delivery of an anti-migraine drug. The optimized nanoemulsion incorporated into a thermosensitive gel provided controlled drug release and enhanced permeation across the nasal mucosa.

Furthermore, this intranasal nano gel delivery system not only bypasses gastrointestinal and hepatic metabolism but also mitigates the limitations of oral and injectable formulations by offering a non-invasive, fast-acting, and patient-friendly alternative. With its ability to improve bioavailability, enhance therapeutic efficacy, and ensure better patient compliance, this novel formulation represents a promising platform for the treatment of migraines and potentially other central nervous system (CNS) disorders.

This novel formulation holds promise as an effective and patient-friendly alternative for migraine management, especially for rapid onset and improved therapeutic efficacy.

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