



RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ZOLMITRIPTAN NASAL SPRAY FOR RAPID MIGRAINE RELIEF

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ABSTRACT

Background: Migraine is a common neurovascular disorder with severe headaches, nausea, and photophobia. Oral triptans like zolmitriptan can be effective but may have delayed onset due to gastric stasis. Nasal delivery bypasses the gut, providing rapid relief. **Objective:** To formulate and evaluate a zolmitriptan nasal spray for the quick treatment of acute migraine, focusing on rapid drug release and onset of action. **Methods:** Zolmitriptan nasal spray formulations used different polymers (hydroxypropyl methylcellulose, methylcellulose, or chitosan) as viscosity modifiers. They were characterized for pH, viscosity, spray content uniformity, in vitro drug diffusion through the nasal membrane, and drug-excipient compatibility (FTIR). A UV spectrophotometric method quantified the drug after constructing a calibration curve of zolmitriptan in pH 5.8 buffer. **Results:** All formulations had pH 5.5–6.0 suitable for nasal mucosa, with uniform drug content. FTIR confirmed drug-excipient compatibility. In-vitro diffusion showed chitosan formulation (F3) released about 20% of drug in 5 min and 61.86% in 85 min, much faster than HPMC or MC formulations. This rapid release correlated with quicker action. The spray delivered about 0.15 mL per actuation with consistent dosing. **Conclusion:** A zolmitriptan nasal spray with chitosan as a mucoadhesive polymer provides rapid drug release, achieving significant drug diffusion within minutes. This formulation offers a promising approach for quick relief in acute migraine, potentially benefiting patients who require a rapid onset of effect and those with migraine-induced gastric stasis. The nasal route thus combines the efficacy of zolmitriptan with an improved delivery profile for managing acute migraine.

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INTRODUCTION

Migraine constitutes an episodic neurological disorder impacting approximately 15% of the general population.^[1] The condition involves the activation of the trigeminovascular system and the subsequent release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), which contributes to neurogenic inflammation and pain. Zolmitriptan is a selective agonist targeting the serotonin receptors (5-HT_{1B} and 5-HT_{1D}) located in the cranial arteries and sensory nerves of the trigeminal system (Fig. 1). Its administration induces vasoconstriction and diminishes inflammation of the trigeminal nerves, thereby alleviating migraine symptoms.^[2] Zolmitriptan (4S-4-[(3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl]-1,3-oxazolidin-2-one) is a second-generation triptan effective in treating acute migraine with or without aura.^[3] It is available in oral and nasal spray formulations; the nasal route can provide a rapid onset of relief (as quick as 10 minutes post-dose) by avoiding gastrointestinal delays.^[4,5] A non-oral route of administration can benefit some migraine patients by reducing the impact of gastric stasis (a common feature of migraine) on

absorption.^[6] A nasal spray delivers the drug directly into the systemic circulation through the highly vascularised nasal mucosa, offering faster relief and assisting patients with nausea or vomiting who cannot tolerate oral medication. Zolmitriptan nasal spray has demonstrated good clinical effectiveness, with some patients experiencing headache relief within 10 minutes.^[5] Many patients also prefer it over oral therapy because of its rapid action and similar tolerability. Several clinical studies support the use of zolmitriptan nasal spray for acute migraine.

Few reports indicate that complete relief of headache occurs in approximately 60% of patients, with at least partial relief in 85%, after using zolmitriptan nasal spray, and side effects are minimal. In an open-label study, around 68% of migraine sufferers preferred continuing with zolmitriptan nasal spray over their previous treatments, citing a faster onset of action; even among those who had previously used sumatriptan, over 70–90% opted to switch to zolmitriptan nasal spray.^[8] These findings emphasise that a well-formulated nasal spray of zolmitriptan can deliver rapid and effective migraine relief, improving patient satisfaction and treatment outcomes.

OBJECTIVE

This work aimed to formulate a zolmitriptan nasal spray and evaluate its pharmaceutical properties and in-vitro performance. The goal was to develop a nasal formulation that delivers zolmitriptan rapidly and efficiently, providing quick relief in acute migraine. The study focused on comparing different polymer gelling agents in the spray (hydroxypropyl methylcellulose, methyl cellulose, and chitosan) to optimise viscosity and drug release profile, and on assessing parameters critical for nasal sprays such as pH, viscosity, content uniformity, spray output, and diffusion through the nasal membrane.

MATERIALS AND METHODS

Zolmitriptan was obtained as the active pharmaceutical ingredient (API). Hydroxypropyl methylcellulose (HPMC), methyl cellulose (MC), and chitosan were used as polymeric viscosity modifiers and mucoadhesive agents. Polyethylene glycol (PEG-400) served as a lubricant to minimise nasal irritation in a dry nasal cavity. Glycerine was added as a humectant to keep the nasal mucosa moist, and menthol was included as a flavouring and refreshing agent. Citric acid (0.1%) was added to adjust the pH to the slightly acidic range (5.5–6.0), optimal for stability and comfort. Sodium chloride (0.9%) was used to adjust tonicity to physiological levels. Benzalkonium chloride (0.01%) was added as an antimicrobial preservative. Ethanol and distilled water were used as solvents. All other reagents were of analytical grade.

Preformulation studies

Solubility study: The solubility of Zolmitriptan was assessed qualitatively in various solvents, including distilled water, ethanol, and acetone. An excess of the drug was added to 10 mL of each solvent in separate stoppered conical flasks, and the mixtures were shaken manually.

Melting point determination: The melting point of Zolmitriptan was determined using an automatic melting point apparatus. The measured melting point was compared with standard literature values.

IR Spectrophotometer: The IR spectrum of pure Zolmitriptan was obtained by outsourcing to Nargund College of Pharmacy. The spectrum was analysed and compared against the standards specified in the Indian Pharmacopoeia (IP) to verify the drug's structural identity.

Determination of λ max: A UV-visible spectrophotometric method was employed to determine the λ max of zolmitriptan. Known concentrations of zolmitriptan were prepared in phosphate buffer (pH 5.8) and scanned between 200–400 nm to determine the λ max.

Preparation of Standard Calibration Curve of Zolmitriptan: Primary Stock Solution: Precisely 10 mg of Zolmitriptan was dissolved in 10 mL of phosphate buffer (pH 5.8). Secondary Stock Solution: 10 mL of the primary stock was dissolved in 10 mL of phosphate buffer (pH 5.8). Tertiary Dilutions: From the secondary solution, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL, 0.7 mL and 0.8 mL aliquots were taken and diluted to 10 mL with phosphate buffer to achieve final concentrations. The absorbance of the prepared solutions was measured at 222.5 nm using a UV spectrophotometer with phosphate buffer as the blank. A standard calibration curve was plotted, and the slope of the line was calculated and reported.^[9]

FORMULATION DEVELOPMENT

Three formulations of 0.5% w/v zolmitriptan nasal spray were prepared using HPMC, MC, and chitosan, a polymer, at a concentration of 0.1%. These polymers were selected to modulate the spray viscosity and drug release. The sprays were formulated by dissolving zolmitriptan in the water-ethanol solvent along with citric acid, sodium chloride, and other soluble components. PEG-400, glycerine, and menthol were then incorporated. Finally, dimethyl sulfoxide and benzalkonium chloride were added, and the solution was brought to volume with distilled water. The different compositions of all the formulations are listed in Table 1. The mixtures were stirred until homogeneous. Each formulation was transferred into a nasal spray bottle equipped with a metered dose pump (delivering approximately 0.1–0.15 mL per actuation). The filled bottles were stored at room temperature and protected from light until they were evaluated.

EVALUATION OF NASAL SPRAY

The formulated nasal sprays were evaluated for the following parameters:

Clarity and Appearance: Each formulation was examined for clarity through visual inspection against light and dark backgrounds.^[10]

pH: The pH of all the formulations was measured using a digital pH meter.^[11]

Viscosity: The viscosity of all formulated samples was measured using an Ostwald viscometer at room temperature.^[12]

Spray Volume and Uniformity (Pump Delivery): The spray bottles were actuated multiple times, and the volume delivered per actuation was measured by weight difference.^[10, 11]

Drug Content Uniformity: The drug content in all formulations was analysed by diluting a known concentration of spray in phosphate buffer, and the absorbance was measured at 222.5 nm using a UV-Spectrophotometer.^[10]

In-vitro Diffusion Study: The in-vitro drug release of zolmitriptan nasal spray formulations was examined using the egg membrane within a Franz diffusion cell. The membrane was placed between the donor and receptor compartments to simulate the nasal mucosal barrier. Phosphate buffer at pH 5.8 served as the medium, with the temperature consistently maintained at 37 ± 0.5 °C and continuous stirring at 300 rpm. The donor compartment was loaded with 5 mL of the prepared nasal spray, while the receptor compartment was filled with phosphate buffer at pH 5.8. At specified time intervals, 1 mL of the sample was withdrawn from the receptor compartment and immediately replaced with fresh phosphate buffer to maintain sink conditions. The collected samples were analysed at 222.5 nm using UV spectrophotometry, and the cumulative percentage release of zolmitriptan nasal spray across the membrane was calculated over time.^[10, 11]

RESULTS AND DISCUSSION

Preformulation studies: The solubility of Zolmitriptan was analysed using various solvents, including distilled water, ethanol, and acetone. The drug was found to be highly soluble in ethanol and acetone. The melting point of Zolmitriptan was determined to be 141.1 ± 0.4 °C, indicating its purity. The IR spectrum of the pure drug closely resembled the standard spectrum of Triptans as outlined by I.P. standards (Fig. 2).

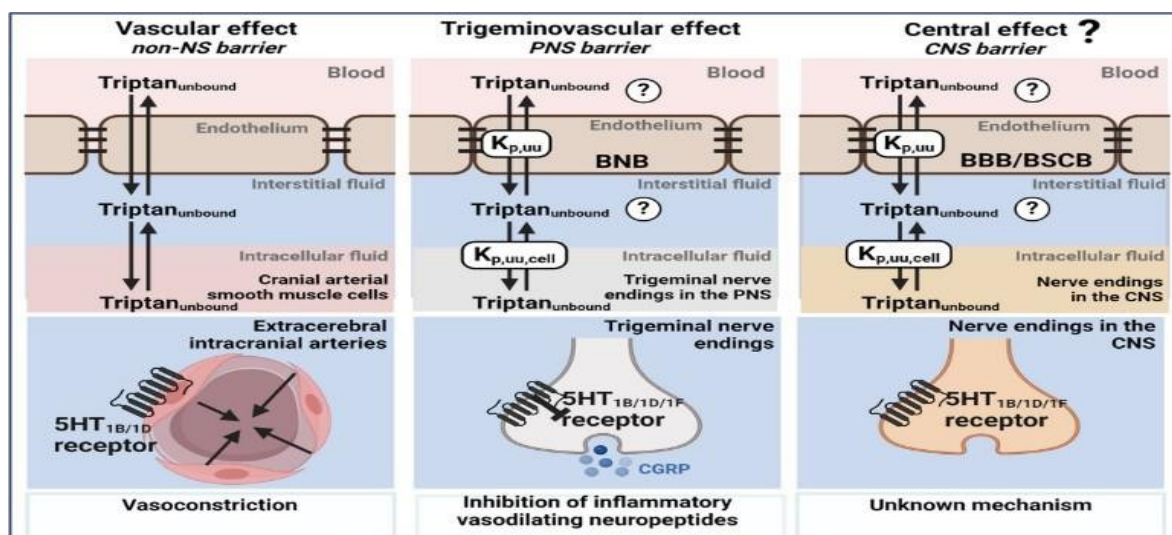


Fig. 1. Illustrates the proposed mechanism of action of zolmitriptan in migraine therapy. It targets 5-HT_{1B/1D} receptors located on intracranial arteries and trigeminal nerve endings. Triptan-induced cranial vasoconstriction and the inhibition of CGRP release serve to interrupt the migraine pain pathway (7)

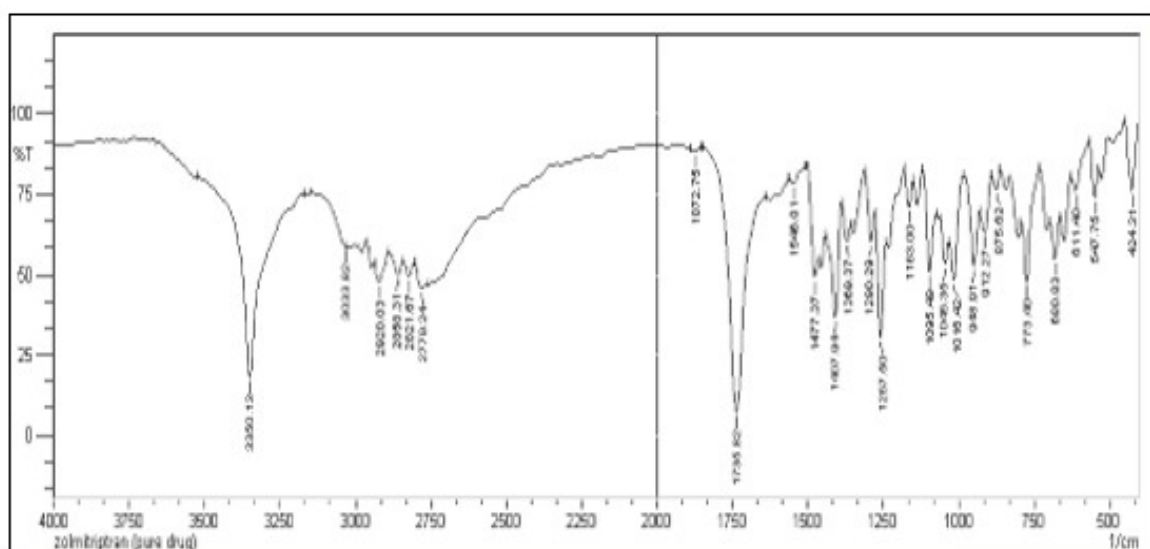


Fig. 2. IR-Spectroscopy of Zolmitriptan Pure Drug

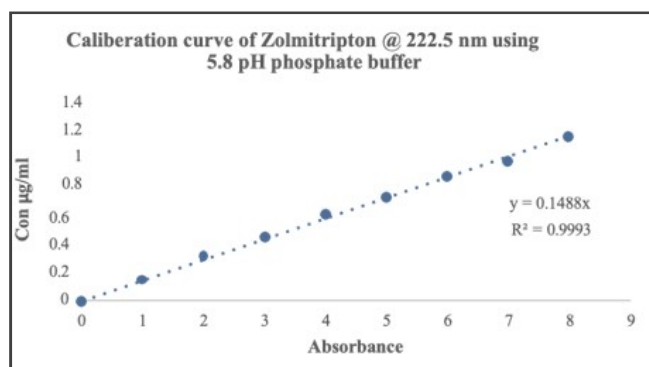


Fig. 3. illustrates the calibration curve of zolmitriptan in pH 5.8 phosphate buffer at 222.5 nm. The absorbance versus concentration plot exhibits a linear relationship ($R^2 \approx 0.9993$), confirming the reliability of the UV spectroscopic method for drug quantification

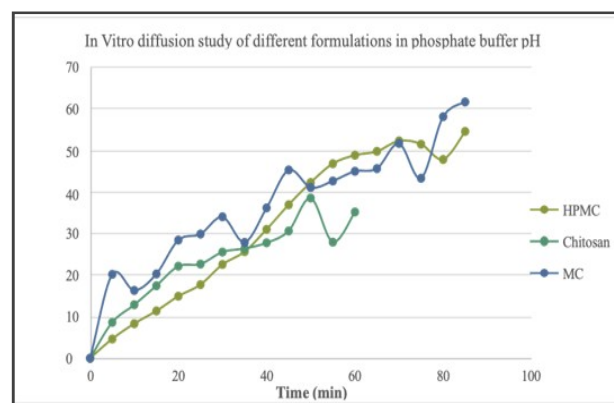


Fig. 4. In-vitro diffusion study of zolmitriptan nasal spray formulations

Table 1. Formulation of Zolmitriptan Nasal Sprays

Sl. No.	Ingredients	Category	Formulation codes (%)		
			F1	F2	F3
1.	Zolmitriptan	API	0.5	0.5	0.5
2.	HPMC	Polymer	0.1	--	--
3.	Chitosan	Polymer	--	0.1	--
4.	MC	Polymer	--	--	0.1
5.	PEG	Lubricant	4.8	4.8	4.8
6.	NaCl	Tonicity modifiers	0.9	0.9	0.9
7.	Glycerin	Humectant	0.4	0.4	0.4
8.	Citric acid	Antioxidant	0.1	0.1	0.1
9.	Dimethyl Sulfoxide	Penetration Enhancer	0.1	0.1	0.1
10.	Benzalkonium Chloride	Preservative	0.01	0.01	0.01
11.	Menthol	Flavoring agent	0.1	0.1	0.1
12.	Water	Solvent	q.s	q.s	q.s

Table 2: Standard plot of Zolmitriptan

Sl. No.	Concentration(μ g/ml)	Absorbance @ 222.5nm
1	1	0.156
2	2	0.323
3	3	0.459
4	4	0.623
5	5	0.754
6	6	0.898
7	7	1.004
8	8	1.186

Table 3. Determination of viscosity of formulations

Sl. No.	Formulation	Viscosity(η) in cps.
1	Distilled water	0.997
2	F1	4.4218
3	F2	4.5204
4	F3	4.6703

Table 4. Content uniformity test

Sl. No.	Formulation	Absorbance@222.5nm	Drug content (%)
1	F1	0.596	80.11 $\pm$ 0.5%
2	F2	0.623	83.74 $\pm$ 0.5%
3	F3	0.503	67.61 $\pm$ 0.5%

Table 5. Cumulative Drug Release Profile (%)

Sl No	Time (mins)	F1	F2	F3
1	0	0	0	0
2	5	4.63	8.62	20.22
3	10	8.32	12.87	16.35
4	15	11.39	17.48	20.31
5	20	14.96	22.20	28.52
6	25	17.75	22.70	29.95
7	30	22.63	25.63	34.11
8	35	25.70	26.47	27.97
9	40	31.10	27.85	36.28
10	45	37.05	30.73	45.45
11	50	42.43	38.65	41.20
12	55	46.97	28.01	42.78
13	60	48.99	35.29	45.12
14	65	49.93	34.76	45.77
15	70	52.46	34.51	51.84
16	75	51.69	34.35	43.45
17	80	47.97	34.21	58.33
18	85	54.76	34.02	61.86

Additionally, the diluted sample of Zolmitriptan in phosphate buffer was scanned within the wavelength range of 200–400nm, with the maximum absorbance observed at 222.5nm (Fig. 3). Calibration curve for zolmitriptan prepared in phosphate buffer at pH 5.8 in the concentration range of 1–8 μ g/ml at 222.5nm.

The correlation coefficient was found to be 0.9993. The results are presented in the Table 2.

Formulation Development: Nasal sprays containing Zolmitriptan, with varying combinations of polymers such as HPMC, MC, and Chitosan, were prepared and evaluated for different parameters.

Evaluation of Nasal Spray

Clarity and Appearance: All formulations were examined for clarity and appearance; the solutions were free of any visible particles or haze, indicating that the drug and excipients were completely dissolved and the formulation remained clear.

pH: The pH of all the formulations was measured using a calibrated digital pH meter. The values were adjusted to a range of 5.5–6.0 by adding citric acid, to mimic nasal physiology and ensure drug stability and patient comfort. All three formulations showed pH values within this range, considered optimal for nasal administration, as a slightly acidic pH helps prevent microbial growth and is well-tolerated by the nasal mucosa.

Viscosity: The viscosity of the formulation was maintained to improve mucosal adhesion and retention time within the nasal cavity, without significantly affecting sprayability. The formulations exhibited low viscosity, making them easy to deliver as a fine mist. The viscosity of all formulations ranged from 4.4218 to 4.6703 cps shown in Table 3.

Spray Volume and Uniformity (Pump Delivery): The spray bottles were actuated multiple times, and the volume delivered per actuation was measured by weight difference. Each pump dispensed approximately 0.14–0.15 mL per spray across all formulations, with minimal variability (the relative standard deviation of spray volumes was low). This demonstrates consistent dosing for the metered spray.

Drug Content Uniformity: The drug content in each formulation was analysed by diluting a known volume of spray and measuring absorbance at 222.5 nm. The drug content of all the formulations ranged from 67.61 $\pm$ 0.5% to 83.74 $\pm$ 0.5% shown in Table 4.

In vitro diffusion assay: All the prepared formulations underwent an in-vitro diffusion study using a Franz diffusion cell, and the drug released from the membrane ranged from 38.65 $\pm$ 0.28% to 61.86 $\pm$ 0.09% at 85 minutes (Fig. 4). The permeation data for all batches are shown in Table No. 5. As a result, the formulation coded as F3 was identified as the optimal formulation due to its maximum permeation of 61.86 $\pm$ 0.09% at 85 minutes, which exceeded the other formulations. Therefore, it is regarded as the most effective formulation for providing rapid relief from acute migraine.

CONCLUSION

A zolmitriptan nasal spray was successfully developed and evaluated. Among the three prototype formulations, the one with chitosan (F3) proved to be the most effective. It exhibited the fastest drug release – approximately 20% of zolmitriptan diffused within 5 minutes and around 61.86% in 85 minutes, compared to formulations containing HPMC or MC. This improved release profile is due to chitosan's mucoadhesive and permeation-enhancing properties. The F3 nasal spray is anticipated to provide a rapid onset of migraine relief, which is a crucial benefit for patients experiencing acute attacks. All formulations maintained appropriate pH, tonicity, and clarity,

and exhibited consistent drug content and dosing per spray. The use of benzalkonium chloride ensures the formulation remains preserved against microbial contamination, while other excipients like PEG and glycerine enhance the user experience by reducing dryness and irritation. The study concludes that the chitosan-based zolmitriptan nasal spray is a promising formulation for acute migraine therapy, as it offers a more rapid onset of action compared to conventional oral tablets. Further in vivo evaluations, including pharmacokinetic studies and clinical trials, are required to verify the enhanced performance of the optimised formulation.

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