EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 12
Issue: 12
Year: 2025

FORMULATION AND EVALUATION OF PROPRANOLOL HYDROCHLORIDE INTRANASAL *INSITU* GEL FOR THE TREATMENT OF MIGRAINE

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DOI: https://doi.org/10.5281/zenodo.17799412

How to cite this Article: Bhavyashree T., Srjan C. S. Rai*, Megha G., Rashmitha Rai E., Vandana Ishwar Patagar, Gururaj, A. R. Shabaraya. (2025). Formulation And Evaluation Of Propranolol Hydrochloride Intranasal Insitu Gel For The Treatment Of Migraine. European Journal of Biomedical and Pharmaceutical Sciences, 12(12), 320–323.

Article Received on 05/10/2025 **Article Revised on 25/11/2025** **Article Published on 01/12/2025**

ABSTRACT
Intranasal in situ gels represent an innovative pharmaceutical formulation designed to address challenges related to drug delivery through nasal route. The aim of the present study was to formulate and evaluate intranasal in situ gel of propranolol hydrochloride. Intranasal in situ gel of propranolol hydrochloride was prepared by cold method. In the present study four different formulations were prepared using different concentrations of poloxamer 407 as a polymer. The formulations were evaluated for physical parameters like clarity, pH, gelation temperature, viscosity, drug content analysis and in vitro drug diffusion studies. FTIR spectra revealed that, there was no interaction between drug and excipients. All the formulation were light white and clear. The drug content of all the formulations was ranged between 93.2% - 96.5% and cumulative drug release was ranged between 66.45% to 72.50%. Among the four formulations, F2 was identified as the potential candidate due to its immediate gelation at nasal temperature, optimum pH, viscosity and increased cumulative drug release.

KEYWORDS: *In situ* gel, propranolol hydrochloride, poloxamer 407, cold method.

INTRODUCTION
Migraine is a neurological condition in which a person suffers from tremendous headache marked by intense, usually one-sided headaches that can last between 4 to 72 hours. Generally, this headache affects only one side of the head and body. It often affects individual under high stress and is more common in women. These headaches may be accompanied by symptoms like nausea, vomiting, immense pain and sensitivity to light or sound. Although the exact cause remains unclear, various triggers such as stress and changes in blood flow can provoke an attack.[1,2]

Migraineurs are much more likely to have metabolic disorders, than non - migraineurs which are speculated and connected to carbohydrate disturbance of electrolytes. Additionally, supporting the theory that migraineurs have hyper sensitive sensory organs. Hypersensitive sensory organs thus result in more receptor connections among sensory neurons. Brain containing hyper sensitive sensory organs with multiple receptor connections would need more voltage generating nutrients to accommodate the increased frequency of action potentials.[3]

Antimigraine drugs are the drugs used in migraine therapy which can be divided into two groups that reduce the number of migraines attacks they are either specific or nonspecific. The drugs that are used to treat the migraine are ergot alkaloids (ergotamine, dihydroergotamine) agonist (sumatriptan) or partial agonists (methysergide) at a specific subtype of $5HT_1$-like receptors, β adrenoreceptor antagonist (propranolol, metoprolol) calcium agonist (flunarizine) and anti-inflammatory agents.[4]

Propranolol is beta-blocking drugs may have an impact on cerebral blood flow. The effectiveness of beta-blocking drugs in the management of migraine headache has been demonstrated clinically and *via* controlled studies proved clinically the potency of propranolol hydrochloride (PN) in the prophylactic management of both classic and common migraine.[5]

An *in-situ* gel is a drug delivery system that exhibit sol-to-gel phase transition due to change in specific physiochemical parameters such as ionic concentration, temperature or pH. Nasal *in situ* gels are instilled as low viscosity solutions into the nasal cavity. Upon contact with the nasal mucosa, the polymer changes conformation producing a gel, so that it not only prolongs the contact time between the drug and the absorptive sites in the nasal cavity, but also releases drug slowly and continuously.[6]

The advantages of in situ nasal gel over other nasal formulations it helps in the reduction over post-nasal drip into the back of the throat and therefore minimization of bad taste problems and loss of drug from the nasal cavity, reduction in anterior leakage of the drug out of the nasal cavity and localization of formulation on the mucosa thereby providing a better chance for the drug to be absorbed.[7]

Hence the present study aims to develop an intra nasal in situ gel of propranolol hydrochloride for achieving improved residence time and patient compliance.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride, Poloxamer 407, HPMC K4M, Methyl paraben, PEG 400 and Distilled water were used in the preparation of intranasal *in situ* gel. All the ingredients are obtained from Yarrow chem products, Mumbai. The ingredients used in the preparation were of analytical grade.

Methods

Formulation of Nasal *in situ* gel by cold method.[6]

Poloxamer 407 and HPMC K4M was dissolved in small quantity of water. Then drug, PEG 400 and Methyl paraben were incorporated and stirred until a clear solution was obtained. The volume was adjusted to 30ml with distilled water and kept overnight at freezing condition (4 to 10°C).

Table No. 01: Formulation table for preparation of *in situ* gel.

Formulation Code	Drug (g)	Poloxamer 407	HPMC K_4M (g)	PEG 400 (ml)	Methyl Paraben (g)	Distilled Water (q.s to)
F1	1.5	15%	0.106	0.05	0.05	30ml
F2	1.5	16%	0.106	0.05	0.05	30ml
F3	1.5	17%	0.106	0.05	0.05	30ml
F4	1.5	18%	0.106	0.05	0.05	30ml

EVALUATION OF *IN SITU GELS*

Prepared *in situ* gel formulation were subjected to various evaluation parameters as follows.

Clarity[6]

Clarity can be examined by Clarity Test Apparatus by observing under white and dark background.

pH[6]

The pH of the prepared formulations was measured using calibrated Digital pH meter.

Viscosity[6]

The Viscosity of *in-situ* gel was determined by using Brookfield viscometer. The measurement was made before and after gelation using spindle no 27 and 64 respectively at shear rate ranging from 0.3 to 20 rpm. The procedure was repeated three times.

Gelation temperature[8]

A magnetic bead and 10ml of sample solution were put into 30ml beaker. A thermometer was placed into the sample solution. The solution was heated at the rate of 1°C/min with continuous stirring using magnetic stirring. Temperature at which magnetic bead stops moving due to gelation was considered as gelation temperature.

Drug content analysis[6]

Drug content of formulations was determined by using double beam UV Visible spectrophotometer. Two millilitre of formulation was taken in capacity of 10ml volumetric flask and diluted with phosphate buffer of pH 6.8 and volume adjusted to 10ml. After suitable dilutions, the absorbance of the prepared solution was measured using a double beam UV visible spectrophotometer.

In vitro drug diffusion studies[6]

The drug release from the propranolol HCl *in situ* gel was measured using Franz diffusion cell. Assembly was set and the temperature was maintained at 37± 0.5°C, then 1ml of nasal in situ gel of propranolol HCl was applied in the donor compartment, which was separated by the receptor compartment with the cellophane membrane. The 1ml aliqouts of sample were withdrawn at regular time intervals and replaced with an equal volume of phosphate buffer pH 6.8 as fresh receptor medium. The duration of the study was carried up to 6hr. For every 1hr the sample was been withdrawn. The sample were appropriately diluted with phosphate buffer pH 6.8 and analysed spectrophotometrically (Double beam UV Visible spectrophotometer).

RESULTS AND DISCUSSIONS

Clarity test

The clarity of all the formulations was observed under ambient lighting with black and white background. The observations in the given table no: 2 shows that all the formulations were found to be clear.

Table No. 02: Clarity test.

Formulation	F1	F2	F3	F4
Clarity	Clear	Clear	Clear	Clear

pH and viscosity

The pH of the *in-situ* gel was determined by using digital pH meter. From the results it was found that pH value of all formulations was within the range of nasal secretions.

The viscosity of all the formulations before and after formation of gel was measured by using Brookfield viscometer. From the observed results it was found that as the concentration of poloxamer 407 was increased, the viscosity of the gel also increased.

Table No. 03: pH and Viscosity readings of formulations.

Formulations	**F1**		**F2**		**F3**		**F4**	
pH *	6.5± 0.2		5.6± 0.1		5.9± 0.1		6.0± 0.1	
Viscosity(cps)*	Solution	Gel	Solution	Gel	Solution	Gel	Solution	Gel
	142± 0.46	16698± 0.57	134± 0.812	16745± 0.81	115± 0.1	17797± 0.81	125± 0.1	18199± 0.81

*All values are represented as mean of 3 readings ± SD(n=3)

Gelation temperature

The gelation temperature of prepared gel formulation was found to be in the range of 30-36°C. Hence it is considered as optimum temperature for development of thermosensitive *in situ* gelling formulation.

Table No. 04: Gelation Temperature.

Formulation Code	F1	F2	F3	F4
Gelation Temperature (°C)*	30±0.47	32±0.47	34±0.81	36±1.24

*All values are represented as mean as of 3 readings ± SD(n=3)

Fig. No. 01: Formulation before and after gelation temperature.

Drug content studies

The drug content in all the formulations was found to be in the range of 93.32 to 96.05%. The highest drug content was observed in the formulation F2 i.e., 96.05% and the lowest was 93.2% in F4.

Table No. 05: Drug Content of prepared formulations.

Formulation Code	F1	F2	F3	F4
Drug Content (%) *	94.5±0.126	96.5±0.077	95.2±0.057	93.2±0.114

*All values are represented as mean as of 3 readings (n=3)

***In vitro* drug diffusion studies**

The percentage cumulative drug release after 6 h of study was studied and found to be 66.45%, 67.77%, 72.50% and 70.20% for formulations F1, F2, F3 and F4 respectively. The maximum cumulative drug release was shown by formulation F3 followed by F4.

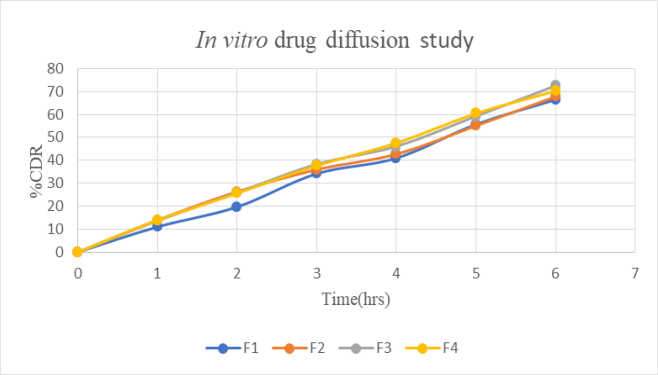

Fig. No. 02: *In Vitro* drug diffusion profile of the formulations (F1-F4).

CONCLUSIONS

The present study successfully developed intranasal in-situ gels of propranolol hydrochloride using Poloxamer 407, creating a promising drug delivery system for migraine treatment aimed at improving patient compliance through reduced dosing frequency. The formulations demonstrated excellent compatibility, confirmed by FTIR studies showing no drug-polymer interaction, and adhered to necessary physicochemical properties for nasal administration, including an appropriate pH and an acceptable gelation temperature (30–36°C) within the physiological range of the nasal cavity. Furthermore, the gels exhibited high drug content (93.2% to 96.5%) and favourable viscosity after gelation, leading to a desirable sustained release profile with 66.45% to 72.50% cumulative drug release over 6 hours, confirming the system's viability as an efficient, prolonged-action alternative for propranolol delivery**.**

ACKNOWLEDGEMENT

Authors are thankful to Management of Srinivas college of Pharmacy, Mangalore for providing necessary facilities to carry out the research work. Authors also extend their thanks to Vision Group on Science and Technology for the grants provided to establish the laboratory setup.

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