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Formulation and evaluation of intranasal mucoadhesive gel of Ibuprofen

Pankaj pal*, Pradeep Chauhan

IPS College of Pharmacy, Gwalior, Madhya Pradesh

*Corresponding Author

Email ID – pnkjpharm3204@gmail.com

Abstract

The objective of the investigation was to improvise the bioavailability of ibuprofen by formulating it as in situ intranasal gel delivery system thereby bettering the management of migraine. The *in situ* intranasal gel delivery system loaded with ibuprofen was prepared using cold stirring method and evaluated for various parameters. The concentration of poloxamer 407 to be used was optimized by gellation temperature study and it was found that 18% w/v of the same was able to gellify at temperature equivalent to the nasal temperature. The higher concentration of carbopol 934 increased the gel characteristics so much that they may not be pleasant for adminstration. The pH of all the formulations was found to be between 5.9 to 6.3, viscosity of the sol formulation ranged between 27 to 77 cps while that of the *in situ* gel ranged between 108 to 201 cps. The drug content ranged from 91.3 to 95.6 %. The *in vitro* release studies of different formulations of drug loaded *in situ* gels were carried out for 20 min in PBS pH 6.8. The maximum drug release from the formulations ranged from 76.7 to 101.2 % over the duration of in vitro release study.

Keywords: Intranasal, mucoadhesive, poloxamer, ibuprofen, migraine

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Introduction

Formulation of nasal sprays containing mucoadhesive polymers are and effective way to improve the bioavailability of drug by local or systemic delivery (Jansson et al., 2005). *In situ* forming mucoadhesive systems have been widely investigated for improving the bioavailability of drugs (Chavan et al., 2010; Butani et al., 2016; Kalita et al., 2016; Paul et al., 2017; Thakkar et al., 2014)

Ibuprofen is COX inhibitor belonging to class of NSAIDS and used for the treatment of migraine and cluster headache (drugbank, 2021). Ibuprofen undergoes extensive first pass metabolism. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, increase the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium, and act as a controlled release system resulting in prolonged blood concentrations.

It was therefore hypothesized that utilizing the intranasal mucoadhesive route for delivery of ibuprofen may be able to overcome the first pass metabolism and reduce the dose of ibuprofen needed for treatment of migraine.

Material and Methods

Ibuprofen was purchased from Yarrow Pharmaceuticals, Mumbai; poloxamer 407 from Sigma; carbopol 934 and all other reagents and chemical were obtained from Oxford Fine Chemicals.

The preformulation studies were carried out for confirming the identity of the drug and to ascertain the compatibility amongst the drug and the excipient (polymers) used in formulation.

Organoleptic Characters

The organoleptic properties of the procured drug sample were examined using sensory organs and include color, odor, taste and appearance. The solubility of the drug in various solvents was also observed.

FTIR spectroscopic analysis

The Fourier transformed infrared spectroscopic analysis of the procured drug sample was performed and the major absorption bands were compared with that of the spectral database of the drug to ascertain its identity. FTIR of physical mixture of the drug and the used polymers was also performed to observe to any possible interaction between the drugs and excipients (Carbopol 934, poloxamer 407).

Calibration curve of ibuprofen in phosphate buffer pH 6.8 solution

A stock solution containing 1 mg/ml of pure drug was prepared by dissolving 100 mg of ibuprofen in sufficient phosphate buffer pH 6.8 to produce 100 ml solution in a volumetric flask.

From the standard stock solution, 5 ml of the stock solution was further diluted to 50 ml with phosphate

buffer pH 6.8 into a 50 ml volumetric flask and diluted up to the mark with phosphate buffer pH 6.8. Aliquots of 1, 2, 3, 4, 5 and 6 ml of stock solution were pipette out into 10ml volumetric flasks. The volume was made up to the mark with phosphate buffer pH 6.8. These dilutions give 10, 20, 30, 40, 50 and 60 µg/ml concentration of ibuprofen respectively. The absorbance was measured in the UV-Visible spectrophotometer at 273 nm using phosphate buffer pH 6.8 as blank and graph of concentration versus absorbance was plotted.

Determination of gelation temperature

Temperature at which the liquid (sol) phase converts to gel form is termed as gelation temperature. The sol–gel transition temperature of the prepared *in-situ* gel formulations was determined by visual inspection method (Kempwade and Taranalli, 2014). Briefly, the solutions of poloxamer 407 in the concentrations (15–20 % w/v) were prepared by stirring on a magnetic stirrer in a transparent 10 ml glass bottle sealed with paraffin. The vial was heated at constant rate with an increment of 1°C and the temperature at which the magnetic bead stopped moving due to gelation was considered as gelation temperature. Gels which showed gelation temperature very close to nasal temperature (32-34°C) were selected for further evaluation. Effect of Carbopol 934 on phase transition temperature was evaluated by dispersing different concentration (0.1–0.5 % w/v) in optimized poloxamer 407 solutions.

Formulation of in situ nasal gel

Poloxamer 407 gel was prepared by dissolving the optimized poloxamer 407 concentration in cold (4°C) water. The hazy solution formed was kept in refrigerator (2–4°C) overnight for complete dissolution resulting in a clear solution. Carbopol 934 (0.1 to 0.4 % w/v) concentration was added slowly to the optimized poloxamer 407 solution (Schmolka, 1972) containing drug with continuous stirring at 4°C (Table 1). Formulated gels where then finally stored at 4°C for further evaluation.

Table 1 Composition of intranasal gel formulations

Formulation Code	Drug (% w/v)	Poloxamer 407 (%w/v)	Carbopol 934 (%w/v)
IS	Ibuprofen (0.5%)	--	--
ING	0.5	18	--
INGF1	0.5	18	0.1
INGF2	0.5	18	0.2
INGF3	0.5	18	0.3
INGF4	0.5	18	0.4
INGF5	0.5	18	0.5

Evaluation of the gel formulations (Paul et al., 2017)

Physicochemical properties of in-situ gel

The formulated gels were evaluated for pH, clarity, drug content, viscosity and gel strength.

Determination of pH

The pH of each formulation was determined by pH meter. Initially, the pH meter was calibrated using standard buffer solutions of pH 4 and pH. 1 mL of

the formulation was diluted with distilled water and the pH of the solution was recorded by dipping the electrode in the solution.

Clarity testing

The clarity was checked visually by viewing the formulation alternately against white and black background and was graded as turbid (+), clear (++) and very clear (+++).

Drug content

Drug content was determined spectrophometrically using UV at 273 nm. 1 mL of the formulation was dissolved in 10 mL PBS 6.8 and suitably diluted. The absorbance of the resulting dilution was recorded on UV spectrophotometer.

Viscosity Determination

Viscosity of *insitu* gel system was determined using Brook field viscometer DV-1. Temperature of 37±0.5ºC was maintained and the spindle was lowered perpendicularly into both *insitu* sol and gel formulations which were placed in a beaker. The viscosity of each formulation was determined by applying 100 rpm speed.

Rheological Studies

The measurement of viscosity of prepared *insitu* gel was done with Brookfield viscometer. The *insitu* formulations were rotated for 2 minutes at different speeds (10-100 rpm) for selected spindle. At each speed the corresponding dial reading was noted. The viscosity of different *insitu* gel formulations was measured at different speeds at room temperature.

Gel Strength

Gel strength was determined by placing a standard weight of 35 g onto 50 g of thermoreversible gel (placed in 100 ml beaker) maintained at gelation temperature using controlled water bath. The time in seconds by the weight to penetrate 5 cm deep into the container was recorded as gel strength.

In-vitro drug release study

Drug release from gel was determined by using Franz diffusion cell. Artificial dialysis membranes were soaked in receptor medium for 2h prior to use. Phosphate buffer saline (12 ml) pH 6.8 was added into the receptor chamber maintained at 34 ± 1°C. Gel equivalent to 2.5 mg of drug was placed into donor compartment and the setup was kept on stirring. Aliquots of 1ml were withdrawn at predetermined time intervals from receptor compartment and replaced with fresh buffer till 12 h. The samples were diluted suitably and analyzed spectrophotometrically at 273 nm and the amount of drug released was determined using calibration curve.

Stability Study

Stability studies of the formulations were carried out at 40 ± 2°C, 75 ± 5% RH at an interval of one month for 3 consecutive months. The results were compared with respect to gelation temperature, pH, viscosity, drug content and drug release to indicate stability for optimized formulation (ICH, 2003).

Results and Discussion

Preformulation Studies

The preformulation studies reveal that the ibuprofen drug was off white colored solid, with no odor, melting at 78-80°C with solubility in 0.1N HCl and organic solvent and practically insoluble in water.

The calibration curve in phosphate buffer pH 6.8 was constructed (figure 1) and the linear equation was used for calculating the concentration of ibuprofen in samples.

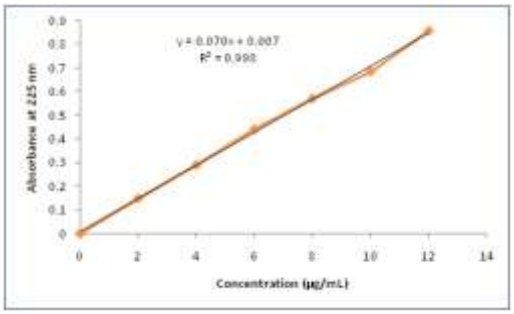

Figure 1 Calibration curve of ibuprofen in pH 6.8 phosphate buffer

No physical or chemical incompatibility was visible from the FTIR spectra of the pure drug and the physical mixture of drug, carbopol and poloxamer.

Determination of gelation temperature

Gelation temperature of gel formulations suggests that Poloxamer in the concentration of 18% w/v showed best results for phase transition at 32-34°C. As the concentration of poloxamer increased from 18 to 20 %, transition temperature decreased from 34 to 25 °C. *In situ* intranasal gels must transform to gel form at nasal temperature and exist in solution form when stored at room temperature. If the gelation temperature of is lower than 25°C, a gel may be formed at room temperature whereas when the gelation temperature is higher than 34°C, solution form will not show phase transition at the nasal temperature resulting in the nasal clearance of the administered drugs at an early stage.

The addition of carbopol 934 also affected the gelation behaviour of the formulations. The effect of varying concentration of carbopol 934 on gelation temperature revealed that all the formulations were able to transform to gel form at temperature from 25-32°C (figure 2). Increasing the concentration of carbopol 934 led to a decrease in gelation temperature of the formulations. A concentration of 0.4% and higher of carbopol 934 decreased the gelation temperature to 25°C making the concentrations unsuitable for *in situ* intranasal gel delivery.

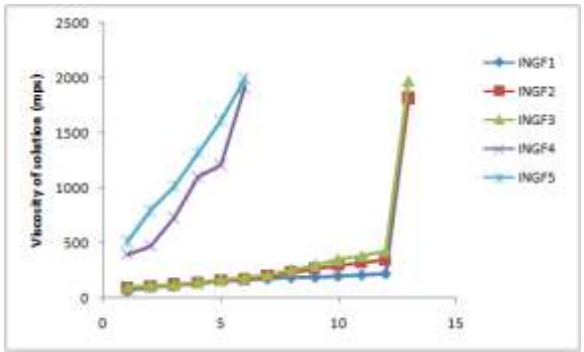

Figure 2 Effect of carbopol 934 on gelation temperature

Evaluation of the gel formulations

The pH of all the formulations was found to be between 5.9 to 6.3 which is lies in the range of nasal

pH (5.5 to 6.5). This ascertains that all the formulations are compatible with nasal mucosa. The formulations INGF1, INGF2 and INGF3 were found to be clear while INGF4 and INGF5 were turbidity appearance revealing that clarity of the gel is inversely proportional to the concentration of Carbopol. The results of pH, clarity, drug content, viscosity, gelling time and gel strength are presented in table 2.

Table 2 Physicochemical properties of the *in situ* gel formulations

Formulation code	pH	Clarity	Drug content (%)	Viscosity (cps)		Gel Strength (g)	Gelling time (sec)
				Sol	Gel		
INGF1	5.9	+++	91.3	27	108	4.7	12
INGF2	6.1	++	94.1	34	120	5.4	10
INGF3	6.1	++	93.9	45	161	6.2	8
INGF4	6.2	+	94.7	56	178	6.9	6
INGF5	6.3	+	95.6	77	201	7.7	4

The most important feature for intranasal *in situ* gel is viscosity of the formulation. A formulation suitable for application to the nasal cavity should ideally have a low viscosity when applied and after administration should have a high viscosity in order to stay at the application site. All the formulations exhibited a carbopol 934 concentration dependent increase in viscosity. Viscosity of the both *insitu* sol and *insitu* gel was examined at 100 rpm. INGF5 formulation was having maximum viscosity. The viscosity of INGF3 (45 in sol to 161 in gel) was taken as optimum. Viscosity of the sol formulation ranged between 27 to 77 cps while that of the *insitu* gel ranged between 108 to 201 cps.

Rheological Studies

Rheological behaviour study is an important parameter for the *in situ* gels. The viscosity of formulations should be in an optimum range which improves its ease of administration. The flow curve (viscosity against speed / rpm) of the formulations indicated that for the all the polymer concentrations, the formulations exhbited the properties of pseudoplastic systems with shear thinning. The prepared formulations tend to thin when being exposed to shearing force and therefore tend to be easily syringeable and spreadable (table 3).

Table 3 Rheological behaviour of the gel formulations

Formulation code	Viscosity (cps)					
	10 rpm	20 rpm	40 rpm	60 rpm	80 rpm	100 rpm
INGF 1	148	136	112	88	65	47
INGF 2	153	141	120	92	81	63
INGF 3	161	152	131	108	93	77
INGF 4	172	164	140	125	101	89
INGF 5	181	172	149	136	118	101

In vitro drug release from in situ gel

The *in vitro* release studies of different formulations of drug loaded *in situ* gels were carried out for 20 min in PBS pH 6.8. PBS of pH6.8 was selected as medium for drug absorbance since it resembles nasal pH. Throughout thestudy the pH and temperature

were kept constant. The maximum release was found to be for INGF2 and INGF3 with respective release of 96.8 and 95.3%. The polymer concentration plays a key role in release pattern of drug.

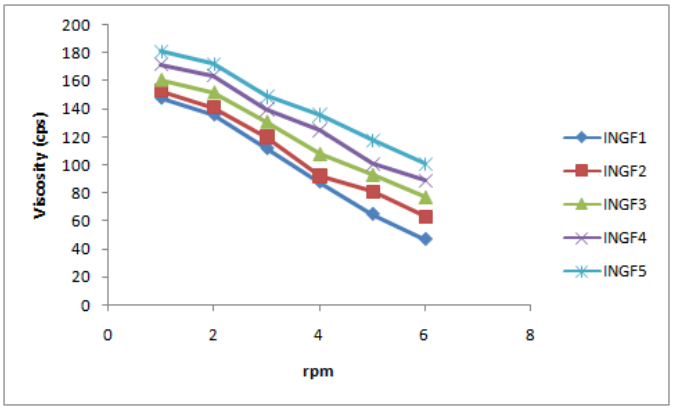

Figure 3 Rheological behaviour of *in situ* gel

The release of drug mainly depends on the polymer concentration. Polymer concentration was proportional to release to some extent. It was seen that very low concentration of carbopol 934 resulted in very quick release of the drug from the formulation making it unpleasant for administration. Also, it was observed that too high concentration of the polymer can adversely affect the *in vitro* release as in formulation INGF4 and INGF5. The G3 formulation was showing highest percentage release and was regarded as the optimised formulation (figure 4).

Stability study

Stability studies (ICH guideline Q1A (R2)) of gel formulations were performed with respect to determining factors like gelation temperature, pH, viscosity, drug content and drug release. Sample analysis after 1, 2 and 3 months exhibited no significant change in all determining factors suggesting stability of gel formulations.

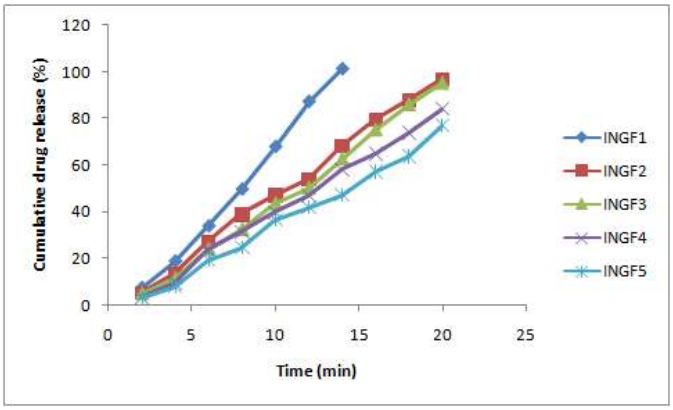

Figure 4 Comparative drug release profile from the formulations

Conclusion

The present study represents formulation of *in situ* intranasal gel for ibuprofen using poloxamer 407 and carbopol 934. Formulation (INGF3) was found to be optimized due to its desirable gelation temperature, gelling time and gel strength. *In-vitro* release studies suggests that carbopol not only acts as mucoadhesive agent but also as an penetration enhancer where as poloxamer acts as thermoreversible polymer leading to sustained release of drug for longer time. In conclusion, intranasal gel of ibuprofen could be better alternative to existing conventional dosage form to improve drug bioavailability and patient compliance.

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