Research Article

Formulation and Evaluation of Naphazoline *In Situ* Gel for the Treatment of Nasal Congestion

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ABSTRACT

Nasal *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 nasal *in situ* gel of Naphazoline hydrochloride. Nasal *in situ* gel of Naphazoline hydrochloride was prepared by cold method. In the present study four different formulations were prepared using different concentration of poloxamer 407 as a polymer. The formulations were evaluated for physical parameters like clarity, pH, drug content, gelation, rheological studies, *in vitro* drug release studies. All the formulation were light white and clear. The drug content of all the formulations were ranged between 85.52-92.10% and cumulative drug release was ranged between 58.09 to 78.09%. Among the four formulations, F3 was identified as the potential candidate due to its immediate gelation at nasal temperature, optimum pH and increased cumulative drug release.

Keywords: *In situ* gel, Naphazoline hydrochloride, Poloxamer 407, cold method.

INTRODUCTION

Nasal congestion is a key component of rhinitis. Rhinitis is defined as an inflammation of the lining of the nose that is characterized by nasal congestion, rhinorrhea, sneezing, and/or itching. The pathophysiology of nasal congestion includes mucosal inflammation, often involving increased venous engorgement, increased nasal secretions, and tissue swelling. Inflammation associated with allergic rhinitis and rhinosinusitis can reduce the physical size of the nasal passages by inducing vasodilation, increasing blood flow, and increasing vascular permeability. The result is engorgement of nasal venous sinusoids, swelling of the anterior and inferior turbinates and obstruction of nasal airflow, ultimately contributing to nasal congestion.[1,2]

Decongestants generally serve as the first-line treatment for nasal congestion. They are marketed as topical and oral formulations. Topical vasoconstrictors are divided into two categories: the sympathomimetic amines and their imidazoline derivatives. Both categories of drugs produce local vasoconstriction by stimulating the adrenergic receptors on the lamina propria of vessels.[2]

The only drugs specifically used to relieve vascular nasal obstruction are the α-adrenoceptor agonist sympathomimetic agents because of their vasoconstrictor action, which opposes mucosal engorgement in the highly vascular nasal mucosa.[3]

Naphazoline belongs to the sympathetic adrenomimetics, α2-adrenoreceptors stimulators, imidazole derivatives product group. The drug administration leads to vasoconstrictor and decongestive effects.[4]

The major problems that persist with nasal solutions are that they are cleared off rapidly from nasal cavity. The half-life of clearance for both liquid and powder formulations that are not mucoadhesive is in the order of 15–20 min. Therefore, another possible strategy is to decrease the mucocilliary clearance using mucoadhesive gel formulations to prolong the residence time at the nasal absorption site and thereby facilitate the uptake of the drug. Approach to enhance the nasal bioavailability is to aim at prolonging the contact time with the nasal surface by using viscosity-enhancing or *in situ* gelling polymers. An *in situ* gel is drug delivery system that exhibits sol-to-gel phase transition due to change in specific physicochemical parameters such as ionic, temperature or pH.[5]

The principal advantage of *in situ* gels is that they can be easily administered with accurate and reproducible dose compared to that of ordinary gels, have an advantage over ordinary gels that they can be easily instilled in liquid form and are capable of prolonging the residence time of the formulation on the surface of the nasal cavity due to gelling.[5]

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]

MATERIALS AND METHODS

Materials

Naphazoline hydrochloride, Poloxamer 407, HPMC K4M, PEG 400, Methyl Paraben and distilled water were used in the preparation of nasal *in situ* gels. All the ingredients were 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]

To prepare *in situ* gel, poloxamer was dissolved in small quantity of water in cold conditions. Then the required quantity of HPMC was dissolved in the above solution. Later, the drug, PEG 400 and methyl paraben were incorporated and stirred until a clear solution was obtained. Finally, the volume was adjusted to 100 ml with distilled water and kept overnight at freezing conditions (4 - 10 °C).

Table 1: Formulation table for the preparation of nasal *in situ* gels

Ingredients	Formulation Code			
	F1	F2	F3	F4
Naphazoline Hydrochloride (g)	0.015	0.015	0.015	0.015
Poloxamer 407 (g)	15%	16%	17%	18%
HPMC K4M (g)	0.106	0.106	0.106	0.106
PEG 400(ml)	0.05	0.05	0.05	0.05
Methyl paraben(g)	0.05	0.05	0.05	0.05
Distilled water (q.s to)	30	30	30	30

EVALUATION OF *IN SITU* GELS:

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

Clarity:

The developed formulations were inspected visually for clarity, colour and presence of any particulate matter in solution and gel form against white background.[7]

pH:

One ml of the prepared gels was transferred to a 10 ml volumetric flask, and the solution was diluted with distilled water. The pH of resulting solution was determined using a digital pH meter.[8]

Viscosity:

The viscosity of the *in situ* gel was determined by using Brookfield viscometer. The measurements were made at 4°C and 35°C using spindle no. 27 and 64 respectively at a shear rate ranging from 0.3 to 20 rpm. The formulation under study was placed in the sample holder and then the spindle was inserted perpendicular into the sample. The spindle rotated at constant optimum speed. The viscosity determinations of formulation were carried out before(4°C) and after(35°C) the formation of gel.[9]

Gelation temperature:

The gelation temperatures of formulations were determined using a modified "Visual Tube Inversion Method". Approximately 4g of *in situ* gel was transferred to vials and incubated in a thermostatic water bath with an increasing rate of 1˚C/min; an equilibration period of 5 min was applied after each temperature rise. Observation of the gel surfaces was taken at every temperature point by tilting the vials to the horizontal position, the temperatures at which the surfaces remained immobile within 30 sec were measured by an inserted thermometer and were recognized as the gelation temperatures.[10]

Drug content analysis:

Drug contents of formulations were determined by using double beam UV visible spectrophotometer. One milliliter of formulation was taken in capacity of 10 ml volumetric flask, diluted with phosphate buffer of pH 6.4 and volume adjusted to 10 ml. One milliliter quantity from this solution was again diluted with 10 ml of phosphate buffer of pH 6.4. Another one milliliter was again taken from this solution and diluted in 10ml of phosphate buffer of pH 6.4. Finally, the absorbance of the prepared solution was measured using a double beam UV visible spectrophotometer.[5]

***In vitro* drug diffusion studies:**

The drug release of the Naphazoline hydrochloride *in situ* gel was measured using Franz diffusion cell. Assembly was set and the temperature was maintained at 37±0.5°C, then 1 ml of nasal *in situ* gel of Naphazoline hydrochloride was applied in the donor compartment, which was separated by the receptor compartment with the cellophane membrane. 5ml aliquots of samples were withdrawn at regular time intervals and replaced with an equal volume of phosphate buffer as fresh receptor medium. The samples were appropriately diluted with Phosphate buffer and analyzed spectrophotometrically (Double beam UV-visible spectrophotometer).[11,12]

RESULTS AND DISCUSSIONS

In the current study, a total of 4 formulations of *in situ* nasal gels of Naphazoline were developed and evaluated for gelling temperature, gel melting point, viscosity, drug content, pH, and *in vitro* drug release.

The results obtained for the experiments conducted on the *in situ* gels are as follows;

Clarity:

Clarity of the formulation plays an important role in the point of view of appearance and pharmaceutical elegance. The clarity of all the formulations were observed under ambient lighting with black and then white background. There were no foreign particles present in the formulation. The observations in the Table No.02 shows that all the formulations were found to be clear.

pH:

The pH of the formulation should be such that it should not cause any irritation to the nasal mucosa after the administration of the dosage form. pH of the *in situ* gel was determined by using digital pH meter. From the results (Table No.02) it was found that pH value of all formulations was within the range of nasal secretions.

Table 2: Clarity and pH readings of *in situ* gels

Formulation code	Clarity	pH (±SD) *
F1	Clear	6.78±0.005
F2	Clear	6.87±0.011
F3	Clear	7.01±0.005
F4	Clear	6.97±0.011

*Data expressed as mean ± SD, n=3

Viscosity:

Viscosity is the deciding factor for ease of application of formulation in nasal cavity. The viscosity of all the formulations before and after formation of gel was measured by using Brookfield viscometer. The value of viscosity was found to be between 16700 to 18200cps as shown in Table No.03. From the observed results it was found that as the concentration of poloxamer 407 was increased, the viscosity of the gel also increased.

Gelation temperature:

Gelation temperature is the temperature at which liquid phase gets converted into gel phase at a particular temperature. Data given in Table No.03 clearly revealed that all formulation exhibited gelation at 31-37°C which is in the range of nasal physiological temperature. (30-37°C).

Figure 1: Gelation at 35°C (F3)

Table 3: Viscosity and gelation temperature readings of *in situ* gels

Formulation code	Viscosity		Gelation temperature (°C±SD) *
	Solution (cP±SD) *	Gel (cP±SD) *	
F1	145±0.577	16700±0.577	30±1.732
F2	134±0.577	16740±0.577	33±0.577
F3	117±0.577	17800±0.577	35±0.577
F4	125±0.577	18200±0.577	38±1.732

*Data expressed as mean ± SD, n=3

Drug content studies:

The drug content in all the formulations was found to be in the range of 85.52 to 92.10%. The highest drug content was observed in the formulation F3 i.e., 92.10% followed by 91.4% in F4 as given in Table No.04.

Table 4: Drug content of prepared formulations

Formulation code	Drug content (%±SD)*
F1	88.81±0.011
F2	85.52±0.005
F3	92.10±0.005
F4	91.4±0.173

*Data expressed as mean ± SD, n=3

***In vitro* drug diffusion studies:**

All the formulations were subjected to diffusion studies using Franz diffusion cell in PBS 6.4 as diffusion medium. The percentage cumulative drug release after 6 h of study was found to be 60.42%, 55.09%, 78.2% and 72.23% for formulations F1, F2, F3 and F4 respectively, as shown in figure 02. The maximum cumulative drug release was shown by formulation F3 followed by F4.

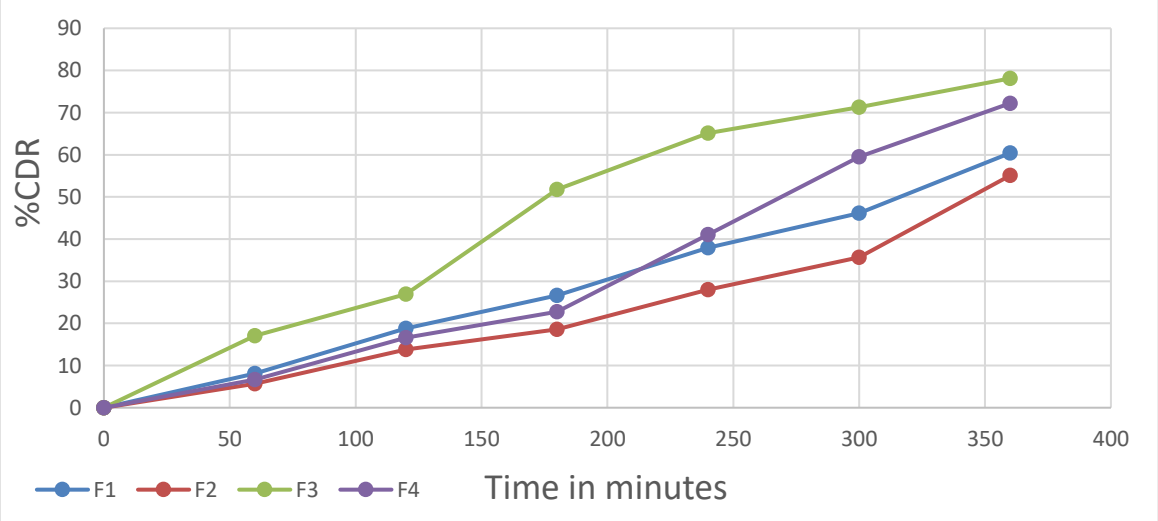

Figure 2: *In vitro* drug diffusion profile of formulations (F1-F4)

CONCLUSION

Nasal *in situ* gel can provide controlled and prolonged therapeutic effect. This reduces the dosing frequency and hence improves the patient compliance. In the present study nasal *in situ* gel of Naphazoline HCl for the treatment of congestion was successfully formulated.

All the prepared *in situ* gels were subjected to various evaluation parameters. The formulations were found to possess pH values ideal for the nasal mucosa, ensuring it caused no irritation. All formulations were found to be clear. All formulations exhibited gelation at 31-37°C which is in the range of nasal physiological temperature. (30-37°C).

The value of viscosity of gel was found to be between 16700 to 18200cps. The drug content was found to be in the range of 85.52% to 92.10%. The percentage cumulative drug release of all the formulations in 6hrs was ranged between 58.09% to 78.09%.

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