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Review Article

FORMULATION, DEVELOPMENT AND EVALUATION OF OPTHALMIC IN SITU FORMULATION OF NAPROXEN

Bhagat B. V.[1], Patare M. B.[1], Pawar B. S.[2], Pawar R. D.[3]

1. Dr. V.V.P. Fs College of Pharmacy, Vilad ghat, Ahmednagar- 414111
2. Dr. V.V.P. Fs College of Pharmacy, Vilad ghat, Ahmednagar- 414111
3. Dr. V.V.P. Fs College of Pharmacy, Vilad ghat, Ahmednagar- 414111

Address for correspondence:

Bhagat B.V., Dr. V.V.P. Fs College of Pharmacy, Vilad ghat, Ahmednagar- 414111

E-mail- babasahebbhagat@gmail.com

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ABSTRACT

Ocular drug delivery was considered a challenging approach for many decades, due to the limitation in the bioavailability in addition to the common drawbacks of the conventional eye preparations represented with blurred vision, pre-corneal elimination and high variability. For this reason ion- induced ocular in-situ gel were formulated using gellan gum in three different concentrations (0.1,0.2 and 0.3%) as ion cross-linking polymers in conjugation with HPMC as viscosity enhancer.

The objective of the present study was to develop an ion activated in situ gelling system for Naproxen, so as to increase the precorneal residence time, reduced dosing frequency and improved patient compliance. The formation of gels depends on factors like temperature modulation, pH change, presence of ions from which the drug gets released in a sustained and controlled manner. In situ gel forming solution of Naproxen was developed using Gellan gum as the gelling agent in combination with Hydroxypropyl Methylcellulose (HPMC) which acted as a viscosity-enhancing agent.

The formulation in gel form showed almost complete release of drug over the period 8 of hours.

Keyword: Gellan gum, ophthalmic in situ gelling, sol-gel transition, Naproxen.

INTRODUCTION:[1-5]

Ocular drugs are mostly applied locally to the surface of the eye as eye drops for treatment of either the external ocular infections such as conjunctivitis, blepharitis, keratitis sicca, or intraocular diseases such as glaucoma, proliferative vitreoretinopathy, endophthalmitis, recurrent uveitis, acute retinal necrosis and cytomegalovirus retinitis etc. However, due to efficient protective mechanisms of the eye (e.g. lachrymal secretion, blinking reflex) and systemic absorption in the conjunctiva, major part of the drug is rapidly eliminated from the ocular surface and only a small fraction of drug is absorbed into the eye, which results in poor bioavailability of the drugs. This needs frequent dosing of eye drops, which causes pulse kinetics of the drugs in the eye.

In situ gelling systems can fulfill these criteria successfully as they can be retained at the ocular surface for longer duration and thus can increase the residence time of the drug at the site of action, resulting in enhanced drug bioavailability and lesser patient incompliance as compared to conventional ocular drug delivery system.7-10 A wide variety of drug molecules and materials of therapeutic advantages such as antibiotics (Ofloxacin, Ciprofloxacin, Gatifloxacin), beta blockers (Timolol, Carteolol), NSAIDs (Ketorolac Tromethamine, Indomethacin), Pilocarpine hydrochloride, Puerarin, Acyclovir has been delivered through in situ gelling systems, which shows the importance of in situ gelling formulations as the future drug delivery systems.

Advantages of in situ gelling ocular drug delivery systems:

- The main advantage of in situ forming gels is sustained and controlled drug delivery and less or no blurred vision as is the case with ointments.
- Other advantages of in situ gelling systems over eye drops and ointments are increased drug bioavailability due to increased precorneal contact, improved patient compliance because of reduced dosing frequency, requirement of lesser concentration of drug, minimal chances of nasolacrimal drainage of drug thus reduced wastage and lesser systemic side effects.
- Further the in-situ gelling systems may be more comfortable than insoluble or soluble insertion.

Classification of In Situ Gelling Polymers

A) According to their origin:

- **Natural**: Examples include chitosan, alginic acid, xyloglucan, gellan gum, sodium hyaluronate, pectin.
- **Synthetic/semi synthetic:** Examples hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), cellulose acetate phthalate (CAP), Carbopol, Pluronics, poly(lactide-co-glycolide) (PLGA).

B) According to physiological mechanisms causing gelation of polymers by :

- pH triggered

- Temperature triggered
- Ion Activation

pH triggered:

pH triggered in situ gelling systems are solutions, which upon exposure to the pH of the lachrymal fluid converts into the gel phase e.g., such as cellulose acetate phthalate and Carbopol.

Temperature triggered:

Temperature triggered in situ gelling polymers remains liquid at room temperature (20-25°C) and undergoes gelation at physiological temperature (35- 37°C).

Ion Activation:

These include polymers whose solution viscosity increases upon exposure to ionic concentration of the tear fluids. Example: Gellan gum.

Gallen Gum:

Gellan gum is commercially known as Gelrite. Deacetylated gellan gum is an anionic extracellular polysaccharide secreted by Pseudomonas elodea. When formulated in aqueous solution, it forms clear gels in the presence of the mono or divalent cations present in the lachrymal fluids. It is one of the most commonly used in situ gelling polymers. It has been approved as pharmaceutical excipient. Various mechanisms have been suggested to explain the gelation of gellan gum. In the solution Gelrite molecules remains weakly associated with each other by Vander Waals bonds and forms double helices at room temperature. When Gelrite solution comes in contact with the cations, some of the helices forms aggregates mediated by cations, resulting in cross linking of the polymer.

MATERIAL:

Table no. 1: List of material and supplier

Sr. no.	Chemicals	Supplier
1	Naproxen	Chempure Private Limited Bangalore, India
2	Gellan gum	Suvidhinath Laboratories, Barodara, Gujrat
3	HPMC	Dr. V.V.P.F's College of pharmacy, Vilad ghat, Ahmednagar.
4	Distilled water	Dr. V.V. P. F's College of pharmacy, Vilad ghat, Ahmednagar.

Table no.2: List of Instruments used

Sr. No.	Instrument	Manufacturer
1.	Electronic balance	Shimadzu
2.	UV spectrophotometer	Jasco (V 630)
3.	Magnetic Stirrer	Remi Instruments Ltd.
4.	FT-IR spectrophotometer	Jasco (IR 4500)

METHOD:

Preparation of In-situ ophthalmic Formulation of Naproxen: Gellan was dissolved in hot phosphate buffer pH 7.4 (prepared from potassium di hydrogen ortho phosphate and sodium hydroxide in fresh water for injection at 70 °C under laminar flow), by continuous stirring at 40 °C. The quantity of naproxen required to give a final drug concentration of 0.1% (m/V) was added to the polymeric solution and stirred until dissolved. The formulations were filled in 10 ml amber coloured glass vials, capped with rubber bungs and sealed with aluminium caps. In their final pack, the formulations terminally sterilized by autoclaving at 121 °C and 15 Pa for 20 minutes. Sterilized formulations were as to stored in a refrigerator (4–8 °C).

Table no. 3: In-situ Opthalmic formulation of Naproxen

Sr. No.	Ingredients	Concentration %		
		F1	F2	F3
1.	Naproxen	0.1	0.1	0.1
2.	Gellan gum	0.1	0.2	0.3
3.	HPMC	0.1	0.1	0.1
4.	Benzalkonium chloride	0.001	0.001	0.001
5.	Deionized water	Up to 10ml	Up to 10ml	Up to 10ml

Pre-formulation Studies

1. **Organoleptic characteristics of drug and excipient:** The characteristic of drug and excipient are carried out by observing physical nature of drug and excipients.
2. **Solubility studies**: Solubility of drug is defined as the amount of solute (drug) that dissolves into a given solvent (solution) to obtain saturated solution of drug at constant temperature and constant pressure. Such knowledge is important for the formulator, as it gives the information about the

selection of best solvent medium for drug substance, recognize and overcome the challenges that occur in the formulation process of pharmaceutical solutions. Solubility of Naproxen was tested in various solvents distilled water, methanol, Chloroform.

3. **Melting point determination:** Melting point determination of Naproxen was carried out by using melting point apparatus. Readings were recorded in triplicates.
4. **FT-IR spectroscopy analysis:** Infrared spectra of pure water free Naproxen sample is recorded by using FT-IR spectrophotometer (Jasco IR 4500) by suitably diluting with potassium bromide (KBr) at ambient temperature Spectrum were recorded for purity analysis of Naproxen at scanning range 400 to 4000 cm

Evaluation of in-situ ophthalmic formulation:[7-9]:

1. **pH:** The pH of the formulations was measured by using pH meter.
2. **Appearance:** The appearance was determined visually.
3. **Clarity**: Check by observing formulation against clarity test apparatus.
4. **Gelation studies:** Gelation studies were carried out in specially fabricated gelation cells. The cells were cylindrical reservoirs capable of holding 3 mL of solution STF (simulated tear fluid) . Within the cells at the bottom, a 250 L transparent plastic cup was located to hold the gel sample in place after its formation. The studies were carried out using STF of composition 1 (sodium chloride 0.670 g, sodium bicarbonate 0.200 g, calcium chloride dehydrate 0.008 g and purified water sufficient to make 100 g) , which simulated the divalent cation content..
5. **Rheological studies:** Viscosity values were measured using programmable digital viscometer for solutions and gels. Guard leg was mounted on the viscometer. Heli path spindle was used for measurement of low viscosity of solution. (Range3.0-12.0). Helipath spindle was inserted in the test material until fluid level was at the immersion groove on the spindle. The spindle was attached to the lower shaft of the viscometer. The shaft was lifted slightly; holding it firmly with one hand while screwing the spindle. The spindle code 04 was used for measurement of the viscosity of solution and spindle code S 92 was used for measurement of the viscosity of gel. The motor was turn on and spindle was rotated. The value of viscosity was recorded from display window.
6. **In vitro drug release studies**: The Franz diffusion cell was used for in vitro study is placed on magnetic stirrer. The receiving fluid, STF (Simulated tear fluid) was placed in to the diffusion cell. The sterile cellophane membrane was placed on the diffusion cell along with test solution (1 ml) after formation of gel with STF. Temperature of 37 ± 1 °C was maintained throughout the study. Samples (1 mL) were withdrawn at regular time intervals and replaced with an equal volume of pre warmed medium. The sample was withdrawn after 1 hour regularly for 8 hours.

RESULTS AND DISCUSSION:

Pre-formulation Studies:

1. **Organoleptic characteristics of drug and excipient :**

Table no. 4: Organoleptic characteristics of drug and excipient:

Drug and Excipient	Organoleptic characteristics		
	Colour	Odour	Taste
Naproxen	White	Odourless	Bitter
Gellan Gum	White	Odourless	Tasteless
HPMC	Creamy White	Odourless	Tasteless

2. **Solubility studies:** Naproxen is highly soluble in Chloroform and methanol.
3. **Melting point determination:** Melting point determination of Naproxen was carried out by using melting point apparatus**.** Melting point of Naproxen is 154ºC(Standard -153ºC)
4. **FT-IR spectroscopy analysis:**

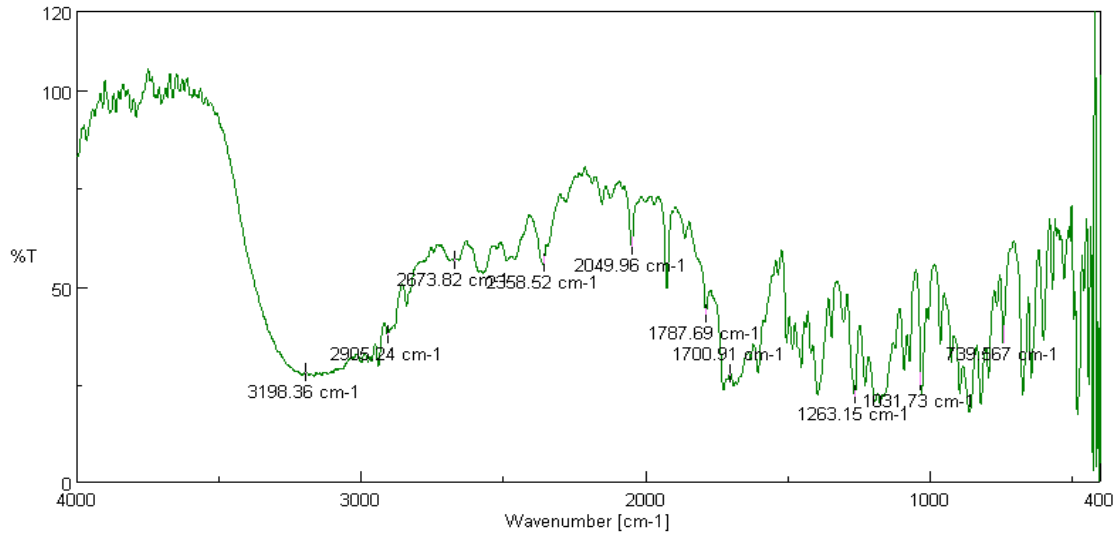

Figure 1. FT-IR of Naproxen

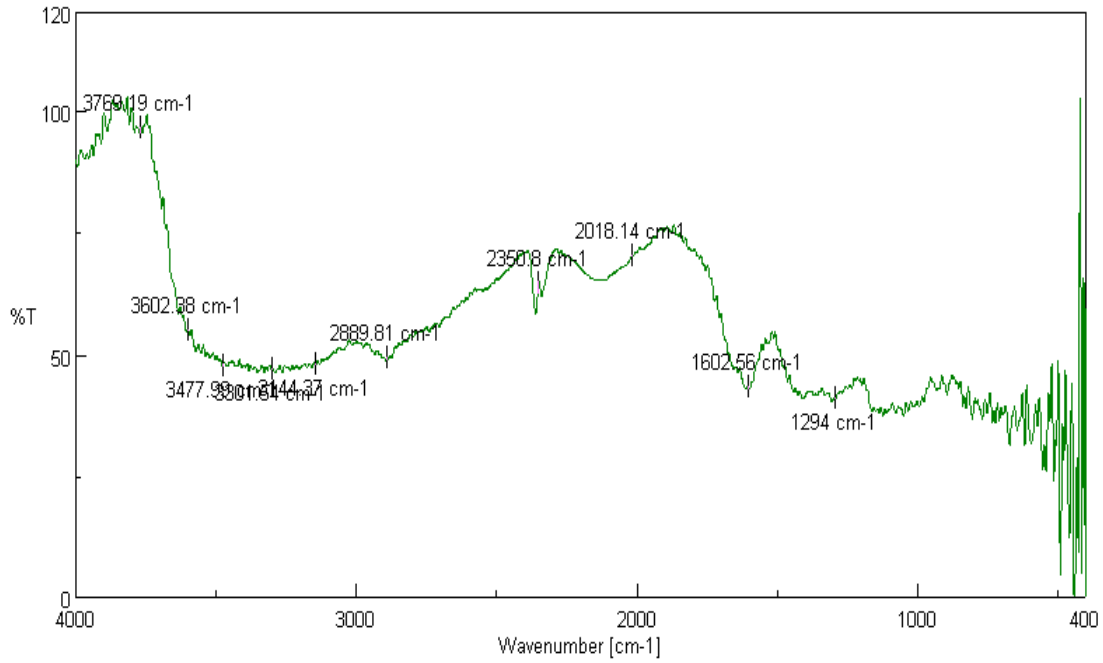

Figure 2. FT-IR of Gellan Gum

5. **Evaluation of in-situ ophthalmic formulation:** Three formulations of Naproxen in situ gelling systems were prepared by using various concentrations of Gellan Gum along with different concentration of hydroxy propyl methyl cellulose as given in Table 3. All the formulations had fixed drug concentration of (0.1%w/v) Naproxen.
6. **Appearance, clarity, pH:** The appearances of all formulations were Transperant in colour and were clear. Terminal sterilization by autoclaving had no effect on the formulations. The haziness observed during autoclaving due to precipitation of HPMC at elevated temperature was found to disappear and the clarity was regained after overnight standing. The pH of all the formulations was found to be within the range of 6.9 to 7.4, which is desirable for the ophthalmic formulations.

Table no 5: Appearance, clarity, pH

Formulation code	Visual appearance	Clarity	pH
F1	Transparent	Clear	6.9
F2	Transparent	Clear	7.1
F3	Transparent	Clear	7.4

7. **Gelling capacity:** The viscosity and gelling capacity plays important role for in situ gelling system. The formulation should have an optimum viscosity for easy instillation into the eye as a liquid which

undergo sol-to-gel transition. Prepared in situ gelling systems were evaluated for the in vitro gelation capacity. All the formulations gave satisfactory results.

Table no 6: Gelling capacity

Formulation	Gelling capacity
F1	+
F2	+
F3	+++

+ Gelation immediate (60-90 sec.), remains stable for a 1hrs , + Gelation immediate (60-90 sec), remains stable for a2 to 3 hrs , +++ Gelation immediate (60-90 sec.), which remains for extended periods 7 to 8 hrs .

8. **Rheological studies:** The rheological study of the formulations exhibited decrease in viscosity on increase in shear rate because of the pseudo plastic behavior of the formulations. Moreover, the pseudo plastic property of these formulations may be in favor of sustaining the release of drug in the conjunctival sac of the eye.
9. **In vitro drug release studies:** The drug release profile of the formulations shown in Figure 3. The results indicated that the formulation F-3 showed better sustaining effect amongst all formulations. This may be due to the presence of higher concentration of Gellan gum along with HPMC in the formulation F-3. Results indicated that, the drug release was significantly prolonged by using the in-situ gelling system due to the addition of the polymers Gellan gum and HPMC.

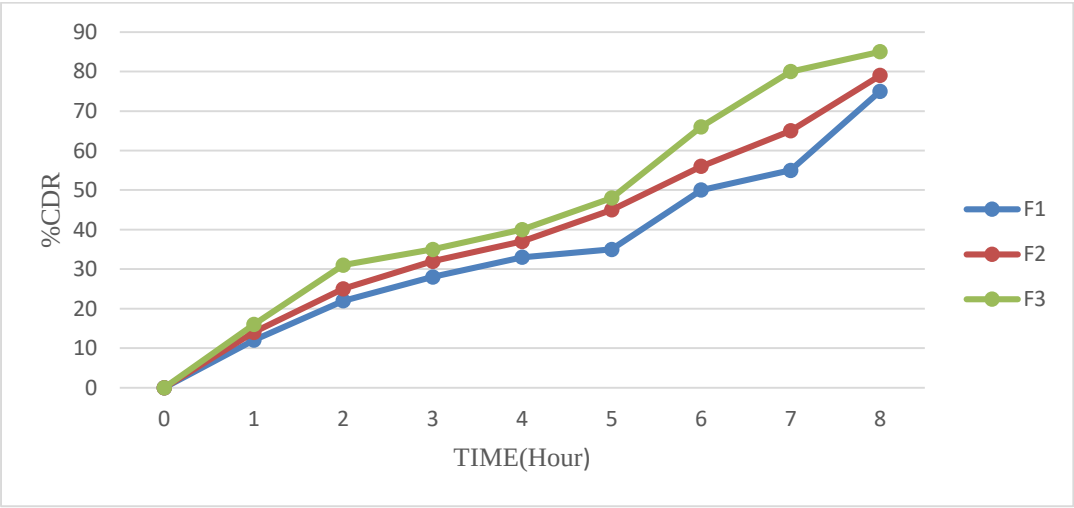

Figure 3: In vitro drug release study

Table no 7: Invitro Drug release studies

Time	%CDR		
	F1	F2	F3
0	0	0	0
1	12	14	16
2	22	25	31
3	28	32	35
4	33	37	40
5	35	45	48
6	50	56	66
7	55	65	80
8	75	79	85

CONCLUSION:

Naproxen is Non steroidal anti-inflammatory use in reduce the pain, inflammation and it was successfully formulated as ion activation in situ gelling system the formulation were liquid at the formulated pH and underwent rapid gelation of in contact with simulated tear fluid (STF) due to ionic interaction. The formulated system provided sustained release of the drug over 8 hour in vitro and develop formulation reduces their side effect on the ocular tissue. Out of 3 different batches prepared only one batch was shoeing optimum results. Optimized formulation F3 were liquid in consistency before in contact with ion(salt) and underwent rapid gelation upon contact with ions(salt) the formulation was found to be clear, translucent having good in situ gelling capacity. The pH of the formulation was found to be within the range of 6.9 to 7.4 , which is desirable for the ophthalmic formulation.

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