CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION, DEVELOPMENT AND EVALUATION OF OCULAR IN SITU GEL OF NSAIDS DRUG NEPAFENAC

[1]Kundan Singh, [2]Dr. Janki Prasad Rai, [3]Dr.Akhlesh Kumar Singhai,
[4]Ms. Sushma Somkuvar, [5]Dr. Manju Prajapati
[1]Department of Pharmacy, LNCT University, Bhopal (M.P.)

Article Received: May 2022 **Accepted:** June 2022 **Published:** June 2022

Abstract:
In situ gels are systems which are applied as solutions or suspensions and are capable of undergoing rapid sol-to-gel transformation triggered by external stimulus such as temperature, pH etc. on instillation. The aim of the present study was to formulate and evaluate pH responsive in-situ gel for ophthalmic delivery. Ophthalmic nepafenac is used to treat eye pain, redness, and swelling in patients who are recovering from cataract surgery (procedure to treat clouding of the lens in the eye). Nepafenac is in a class of medications called nonsteroidal anti-inflammatory drugs (NSAIDs). It works by stopping the production of certain natural substances that cause pain and swelling. Ophthalmic in situ gelling system of Nepafenac was successfully formulated using polymeric combination of gelling agents Pluronic F127, Carbopol 934 as, temperature sensitive and pH-sensitive respectively along with HPMC 15cps as viscosity enhancing agent. All the formulations except F7, F8 and F9 showed instantaneous gelation when contacted with simulated tear fluid (STF), formulation F6 showed best gelation property amongst all other. Formulation F6 showed sustained drug release for a period of 6 hour. The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order Higuchi and Korsmeyerpeppas release kinetic equation in order to determine the mechanism of drug release.

Key words:*Nepafenac, nonsteroidal anti-inflammatory drugs, Ophthalmic, In situ gel*

Corresponding author:
Kundan Singh
Department of Pharmacy, LNCT University, Bhopal (M.P.)
drxkundan1998@gmail.com

QR code

*Please cite this article in press*Kundan Singhet al,***Formulation, Development And Evaluation Of Ocular In Situ Gel Of Nsaids Drug Nepafenac.,***Indo Am. J. P. Sci, 2022; 09(6).*

INTRODUCTION:

Ophthalmic *in-situ* gels are viscous polymer-based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physicochemical parameter like ionic strength, pH or temperature. Gel dosage forms are successfully used as drug delivery systems considering their ability to prolong the drug release [1]. To prolong the precorneal resident time and improve ocular bioavailability of the drug various polymers system were studied as *in-situ* gelling vehicle for ophthalmic drug delivery system. The *in-situ* formulation exhibited well, viscosity, drug content and sustained drug release. Conventional liquid ophthalmic formulations demonstrate low bioavailability because of a constant lacrimal drainage in the eye. The normal drainage of an instilled drug dose commences immediately upon instillation and is essentially completed within 5 min. typically ophthalmic bioavailability's of only 1–10% are achieved due to the short precorneal residence time of ophthalmic solutions [1-2].

Polymer solution is a free-flowing liquid at ambient temperature and gels at body temperature. Cappello et al. developed novel "protein polymers" ProLastins, which undergo an irreversible sol gel transition. When injected as a solution into the body, the material forms a firm, stable gel within minutes. It remains at the site of injection providing absorption times from less than one week to many months. Such a system would be easy to administer into desired body cavity [3-4].Another formation of *in-situ* gel based on physiologic stimuli is formation of gel is induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH [5].

In situ gelling systems consist of polymer that exhibit sol-to-gel phase transitions in the cul-de-sac which improves patient compliance due to change in specific Physico-chemical parameters like pH, temperature and ionic strength in the environment. The development of in situ gel systems has received considerable attention over the past few years. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort.

Ophthalmic Nepafenac is used to treat eye pain, redness, and swelling in patients who are recovering from cataract surgery (procedure to treat clouding of the lens inthe eye). Nepafenac is in a class of medications called nonsteroidal anti-inflammatory drugs (NSAIDs). It works by stopping the production of certain natural substances that cause pain and swelling. The aim of the study to prepare ocular in-situ gel of Nepafenac using carbomer as a pH sensitive gelling agent with different concentration of a hydrophilic mucoadhesive polymer.

MATERIAL AND METHODS:

Material:

Nepafenac was obtained as gift samples from pharmaceutical Company. PluronicF127 was obtained from Sigma Aldrich, Mumbai. Benzalkonium chloride from Merck Ltd, Mumbai, Sodium chloride from Loba chemicals, Hydroxypropyl methylcellulose (HPMC-15cps) and carbopol-934 from Central Drug House, Mumbai, India. All other chemicals and solvents were of analytical grade and used as received. Distilled water was prepared in laboratory using all glass distillation apparatus.

Methods:

Formulation development of *In-situ* gel:

The preparation of Pluronic F127 based ocular *in-situ* gel all the ingredients were sieved from sieve no 44. Then solution of 0.5% and 0.1% of drugs was prepared in acetate buffer 5.0 I.P. The solution was cooled in an ice bath and pluronic F127 was added slowly with continuous stirring.

Then the resulting solution was kept in a refrigerator under 4^0C for 24h. This storage was help in dissolving the Pluronic F 127 completely. After 24h carbopol 934 and HPMC 15cps were added slowly along with other excipients with continuous stirring. The stirring should be continued to 2-3 hours for proper mixing and avoid slug formation. The resulting formulation kept on probe Sonicator to remove air bubble. All formulations were stored in LDPE (Low Density Polyethelene) bottles for further use. All the containers stored in refrigerator [6].

Composition of Different formulations of *In-situ* gel:

Table 1: Composition of different formulations of *In-situ* gel

S. No.	Ingredient (%)	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Nepafenac	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2.	Pluronic F127	10	12	14	10	12	14	10	12	14
3.	Carbopol 934	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4
4.	HPMC 15cps	1.0	1.0	1.0	0.75	0.75	0.75	0.5	0.5	0.5
5.	EDTA	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
6.	Benzalkonium Chloride	0.010	0.010	0.010	0.010	0.010	0.010	0.010	0.010	0.010
7.	NaCl	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
8.	Poly ethylene glycol	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
9.	Acetate Buffer (pH 5.0)	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml

Appearance:
Clarity is one of the most important characteristic features of ophthalmic preparations. All developed formulations were evaluated for clarity by visual observation against a black and white background [7].

Drug content:
The assay of drug Nepafenac was performed by UV method. The calculation was based on calibration curve method using regression equation (Y=mx+c) [8].

pH:
pH is one of the most important parameter involved in the ophthalmic formulation. The two areas of critical importance are the effect of pH on solubility and stability. The pH of ophthalmic formulation should be such that the formulation will be stable at that pH and at the same time there would be no irritation to the patient upon administration of the formulation. Ophthalmic formulations should have pH range in between 5 to 7.4. The developed formulations were evaluated for pH by using calibrated digital pH meter[9]. For *In situ* gel pH 5.0 should be optimum because both the drug is stable at pH 3.5-5.0. Lowering the pH from 5.0 can causes irritation to eye and on raise the above 5 will result in gelation of formulation due to presence of carbopol.

***In-situ* gelling capacity:**
In situ gelling capacity determined by visual inspection. The formulation has been exposed to the physiological conditions of temperature and pH. Simulated tear fluid (STF) was prepared and warm up to 37^0C. Formulations were introduce into STF in a ratio of 1:2 Change in consistency of Formulations were visually inspected [10].

Viscosity study:
At pH 5.0 and temperature less than 16^0C the developed formulations were in liquid state and show low viscosity. For viscosity studies the pH of formulations were raised from pH 5.0 to pH 7.4 and the temperature was raised to 37^0C. pH was raised to 7.4 by the addition of 0.5M NaOH[11]. The resulting gel studied for viscosity on Brookfield Synchrolectric Viscometer using Spindle No.7 at 50 RPM for comparative study. The angular viscosity was measured by gradually increase the RPM from 10 to 70.

***In-vitro* drug diffusion study:**
The *in vitro* release of drugs from the formulations was studied through cellophane membrane. The dissolution medium used was artificial tear fluid freshly prepared (pH 7.4). Cellophane membrane, previously soaked overnight in the dissolution

medium, was tied to one end of a specifically designed glass cylinder (open at both ends and of 5 cm diameter). A 1-ml volume of the formulation was accurately pipetted into this assembly. The cylinder was attached to the metallic driveshaft and suspended in 50 ml of dissolution medium maintained at 37±1°C so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at 50 rpm using magnetic stirrer. Methodology Aliquots, each of 1-ml volume, were withdrawn at hourly intervals and replaced by an equal volume of the receptor medium [12-13].

RESULTS AND DISCUSSION:

Ophthalmic *in situ* gelling system of Nepafenac was successfully formulated using polymeric combination of gelling agents Pluronic F127, Carbopol 934 as, temperature sensitive and pH-sensitive respectively along with HPMC 15cps as viscosity enhancing agent. The clarity of the prepared formulations was found satisfactory but precipitate observed in formulation during storage. The pH of all formulations was found 5.0. The drug content of the prepared formulation was within the acceptable range, and ensures dose uniformity. The formulation F6 showed maximum drug content.

All the formulations except F7, F8 and F9 showed instantaneous gelation when contacted with simulated tear fluid (STF), formulation F6 showed best gelation property amongst all other. Formulation F6 showed sustained drug release for a period of 6 hour. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order Higuchi and Korsmeyerpeppas release kinetic equation in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum hence indicating drug release from formulations was found to follow Korsmeyerpeppas release kinetics.

Table 2: results of evaluation of Clarity, Drug Content, pH and *In situ* gelling capacity

Formulation code	Clarity	Drug Content (%)*	pH	pH Adjusted	*In situ* gelling capacity
F1	Turbid	98.85±0.45	4.8	5.0±0.1	"+"
F2	Clear	98.78±0.23	4.7	5.0±0.1	"++"
F3	Clear	98.65±0.25	4.9	5.0±0.1	"++"
F4	Clear	98.78±0.15	4.6	5.0±0.1	"+++"
F5	Clear	97.45±0.63	4.7	5.0±0.1	"+++"
F6	Clear	99.45±0.27	4.5	5.0±0.1	"+++"
F7	Turbid	98.78±0.15	4.3	5.0±0.1	"+"
F8	Turbid	97.85±0.35	4.5	5.0±0.1	"+"
F9	Turbid	97.85±0.14	4.6	5.0±0.1	"+"

*Average of three determinations (n=3)
"+" gelation after five minutes and dissolves rapidly
"++" gelation immediate remains for few hours
"+++" gelation immediate, remains for extended period 8 hours

Table 3: Comparative viscosity of *In situ* formulation

Formulation code	% of Pluronic F 127	Viscosity of solution (in cps)	Viscosity after galation
F1	10	658	2250
F2	12	698	2310
F3	14	756	2345
F4	10	674	2145
F5	12	712	2236
F6	14	798	2374
F7	10	690	2245
F8	12	723	2340
F9	14	769	2389

*Spindle no.7 rpm 50

Table 4: *In vitro* drug release profile of Nepafenac from *in situ* Formulation F6

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	11.45	1.059	88.55	1.947
1	1	0	26.65	1.426	73.35	1.865
1.5	1.225	0.176	42.23	1.626	57.77	1.762
2	1.414	0.301	65.58	1.817	34.42	1.537
2.5	1.581	0.398	73.32	1.865	26.68	1.426
3	1.732	0.477	84.45	1.927	15.55	1.192
4	2	0.602	93.32	1.970	6.68	0.825
5	2.236	0.699	98.45	1.993	1.55	0.190

Table 5: Comparative study of regression coefficient for selection of optimize Formulation F6

	Zero order	First order	Higuchi	Korsmeyerpeppas
F6	R^2 = 0.881	R^2 = 0.955	R^2 = 0.965	R^2 =0.967

CONCLUSION:

In Conclusion, Evaluation of in situ gel is determined to ensure that the prepared preparation meets the standard and is safe. In the chemical evaluation in situ gel determined the diffusion of the active substance of a compound by measuring its concentration. In microbiology evaluation determine if the preparations is contaminated or not, also be effective and safe.

REFERENCES:

1. Patel Nisha, Shinde Gajanan, Rajesh KS. Ophthalmic In situ gel, A genesis journal Pharmagene, 2(4), 2014, 29-33.
2. F. Suisha, N. Kawasaki, S. Miyazaki, M. Shirakawa, K. Yamatoya, M. Sasaki, D. Attwood, Xyloglucan gels as sustained release vehicles for the intraperitoneal administration of mitomycin C. Int. J. Pharm., 172, 1998, 27–32
3. Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanabe H, Attwood D. Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations. Drug Dev Ind. Pharm., 29(2), 2003, 113-9.
4. Nerkar Tushar, GujarathiNayan A, Rane Bhushan R, Bakliwal Sunil R, Pawar S.P. In situ gel: Novel Approch in sustained and controlled

drug delivery system. International Journal of Pharmaceutical sciences, 4(4), 2013, 1-18.
5. Saraswat R., Bhan C. S., Gaur A. A Review on Polymers Used In In-Situ Gel Drug Delivery Systems, 1(2), May-Jun 2011.
6. Varshosaz J, Tabbakhian M, Salmani Z. Designing of a Thermosensitive Chitosan/Poloxamer insitu Gel for Ocular Delivery of Ciprofloxacin. The Open Drug Delivery Journal. 2008; 2(1):61-70.
7. Saxena P, Kushwaha SK. Temperature sensitive ophthalmic hydrogels of levofloxacin hemihydrate with enhanced solubility and prolonged retention time. International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(3):77-883.
8. Viram P, Lumbhani AN. Development and evaluation of ion-dependent insitu nasal gelling systems of metoclopramide hydrochloride as an antimigraine model drug. International Journal of Latest Research in Science and Technology. 2012; 1(2):80-9.
9. Vodithala S, Khatry S, Shastri N, Sadanandam M. Development and evaluation of Thermoreversible Ocular Gels of ketorolac tromethamine. International Journal of Biopharmaceutics. 2010; 1(1):39-45.
10. Shankar SJ, Kalikonda A. pH induced insitu gel formulation of Lomefloxacin HCl. Universal Journal of Pharmacy. 2014; 3(1): 38-43.
11. Mahesh NS, Manjula BP. Study of an Alginate /HPMC based in situ gelling opthalmic delivery system for levofloxacin hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences. 2012; 4(3):655-8.
12. Costa P, Lobo JMS. Modelling and comparison of dissolution profiles. European Journal of Pharmaceutical Science. 2001; 13:123-33.
13. Gratieri T, Martins G, Freitas O De, Melani E. Enhancing and sustaining the topical ocular delivery of fluconazole using chitosan solution and poloxamer/chitosan insitu forming gel. European Journal of Pharmaceutics and Biopharmaceutics. 2011; 79:320-27.