CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.6645164

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

FORMULATION DEVELOPMENT AND EVALUATION OF OCULAR IN SITU GEL OF NSAIDS DRUG FOR EFFECTIVE TREATMENT OF EYE DISEASE

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Article Received: April 2022 **Accepted:** May2022 **Published:** June 2022

Abstract:

Ophthalmic in situ gelling system of Suprofen was successfully formulated using polymeric combination of gelling agents Sodium Alginate, HPMC E 50 LV, HPMC K4 M 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. 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 Korsmeyer peppas 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 Korsmeyer peppas release kinetics. 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.

Hey words: *Suprofen, Sodium Alginate, HPMC E 50 LV, HPMC K4 M*

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Please cite this article in press Umesh Kumar et al, ***Formulation Development And Evaluation Of Ocular In Situ Gel Of NSAIDS Drug For Effective Treatment Of Eye Disease.,*** *Indo Am. J. P. Sci, 2022; 09(6).*

INTRODUCTION:

The formation of gels depends on factors like change in a specific physico-chemical parameter (pH, temperature, ion-sensitive) by which the drug gets released in a sustained and controlled manner. There are various novel dosage forms like insitu gel, nanosuspension, nanoparticulate system, liposomes, niosomes, dendrimers, ocular iontophoresis, collagen shield, minidisc, ocular film, implants, ocuserts etc [1].

Development of ocular drug delivery systems has always been challenging because of the draw backs with ocular route like non-productive absorption, impermeability of drugs to cornea, drainage, induced lachrymation and tear turn over. Topical application of drugs to the eye is the well-established route of administration for the treatment of various ocular diseases like dryness, conjunctivitis, keratitis, eye flu etc. New approaches have been investigated for delivery of drugs to the eye by making use of polymers that pays a key role in delivery of drugs to the pre and intra ocular tissues [2].

Such persistent attempts have resulted into achieving the increase in bioavailability and extending the duration of therapeutic action of ocular drug. Smart polymeric systems have proved to be promising means of delivering the drugs. These polymers undergo sol-gel transition after administered. They are in solution phase before administration, but gels under physiological condition. The ocular bioavailability of the drugs can be improved by prolonging their residence time in the cul-de-sac and by increasing their corneal permeability [3].

The general process of drug absorption into the eye from the precorneal area (dose site) following topical ocular administration is quite complex. The classical sequence of events involves drug instillation, dilution in tear fluid, diffusion through mucin layer, corneal penetration (epithelium, stroma, endothelium), and transfer from cornea to aqueous humor. Following absorption, drug distributes to the site of action (e.g., iris-ciliary body).

Parallel absorption via the conjuctiva/sclera provides an additional pathway to eye tissues but, for most drugs, is minor compared with corneal absorption. Also, nonproductive, competing, and parallel pathways (e.g., nasolacrimal drainage or systemic absorption via the conjuctiva) work to carry drug away from the eye and limit the time allowed for the absorption process. Moreover, in some species, such as the rabbit, non-productive absorption into the nictitating membrane can occur [4].

In situ gel forming systems are drug delivery systems that are in solution form before administration in the body but once administered, undergo gelation in situ, to form a gel triggered by external stimulus such as temperature, pH etc and release the drug in sustained or controlled manner. This novel concept of producing in situ gel was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or non-covalent bond formation (physical cross-linking). In situ gel-forming systems can be described as low viscosity solutions that undergo phase transition in the conjunctival cul-de-sac to form viscoelastic gels due to conformational changes of polymersin response to the physiological environment. The rate of in situ gel formation is important because between instillation in the eye and before a strong gel is formed, the solution or weak gel is produced by the fluid mechanism of the eye [5]. Both natural as well as synthetic polymers can be used for the fabrication of in situgels [6]. An Suprofen type anti-inflammatory analgesic and antipyretic. It inhibits prostaglandin synthesis and has been proposed as an anti-arthritic. The aim of present work to develop and characterize in ocular situ gel of Suprofen for effective treatment of inflammation of eyes.

MATERIAL AND METHODS:

Formulation development of *In-situ* gel:

The polymeric solution was prepared by dispersing required quantity of sodium alginate as main polymer and HPMC- E 50 LV, HPMC- K4M as co-polymers in water using a magnetic stirrer until the polymers completely dissolve. Aqueous solution of Suprofen was added in to the polymeric solution with continuous stirring. Buffering and osmolality agents were added to the resulting solution along with benzalkonium chloride. The pH of the solution was adjusted to 6.5 using 0.1 N NaoH/0.1 N HCl [7]. The *in situ* gel formulations are depicted in Table 1.

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

S. No.	Ingredient (%)	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Suprofen	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2.	Sodium Alginate	5	10	15	5	10	15	5	10	15
3.	HPMC E 50 LV	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4
4.	HPMC K4 M	1.0	1.0	1.0	0.75	0.75	0.75	0.5	0.5	0.5
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.	Distilled Water	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml

Drug content:
The assay of drug Suprofen 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 parameters 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. 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 [9].

***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 370C. Formulations were introduce into STF in a ratio of 1:2 Change in consistency of Formulations were visually inspected.

Viscosity study:
At pH 5.0 and temperature less than 160C 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 370C. pH was raised to 7.4 by the addition of 0.5M NaOH.

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[10].

RESULTS:

Ophthalmic *in situ* gelling system of Suprofen was successfully formulated using polymeric combination of gelling agents Sodium Alginate, HPMC E 50 LV, HPMC K4 M 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. 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 Korsmeyer peppas 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 Korsmeyer peppas release kinetics.

Table 2: Drug content analysis

Formulation	Drug Content (%)*	pH	In situ gelling capacity	Viscosity after galation
F1	98.85±0.45	4.8	"+"	2250
F2	98.78±0.23	4.7	"++"	2310
F3	98.65±0.25	4.9	"++"	2345
F4	98.78±0.15	4.6	"+++"	2145
F5	97.45±0.63	4.7	"+++"	2236
F6	99.45±0.27	4.5	"+++"	2374
F7	98.78±0.15	4.3	"+"	2245
F8	97.85±0.35	4.5	"+"	2340
F9	97.85±0.14	4.6	"+"	2389

Table 3: *In vitro* drug release profile of Suprofen 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

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 evaluation determine if the preparations is contaminated or not, also be effective and safe.

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