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DEVELOPMENT OF PHASE CHANGE SOLUTIONS FOR OPHTHALMIC DRUG DELIVERY BASED ON ION ACTIVATED AND PH INDUCED POLYMERS

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Abstract

The optimal drug concentration required at the site of action for the ocular treatment cannot be attained mainly due to precorneal drug loss; tear turn over, solution drainage by gravity and naso-lachrymal drainage. The purpose of present work was to overcome these problems by developing an in situ gel forming systems of flurbiprofen, based on the ion-activated and pH-induced in situ gelation. In situ gels of flurbiprofen were prepared by simple dispersion method using sodium alginate and carbopol along with HPMC and then evaluated for pH, gelling capacity, rheological, isotonicity, in vitro and in vivo studies. The above mentioned evaluation showed satisfactory results in formulation L_4(2% alginate and 0.4% HPMC) as it showed better gelation, acceptable pH, prolonged in vitro drug release and was found isotonic. In vivo studies with L_4 indicated a noteworthy resistance of PGE_2-prevailed lid closure and PMN migration as compared to flurbiprofen eye drops indicating a better & higher pharmacodynamic effect of in situ gel as compared to eye drop. Formulation L_4 showed promising results, as it increased the precorneal residence time of drug and intensified the ocular bioavailability of flurbiprofen as compared to flurbiprofen eye drops.

Keywords: - Ophthalmic delivery system, in situ gelling, flurbiprofen, control drug delivery system

Introduction

A wide variety of conditions can cause ocular inflammation. Inflammation of the eye may arise as a result of trauma, surgery or infection. Local application of anti-inflammatory medications can decrease inflammation with minimal systemic adverse effects. The main use of NSAIDs is for ophthalmic surgery and effective at reducing inflammation in the cornea and conjunctiva in refractive surgery. During cataract surgery, ophthalmic NSAIDs are utilized to control pain and help to maintain papillary dilatation. Ocular inflammation occurs by arachidonic acid, which is released from phospholipid components of the cell membrane that produces prostaglandins by cyclooxygenase pathway. Prostaglandins are the main mediator of inflammation, which increases the IOP (intraocular pressure) by local vasodilation, lid closure and also prevail the migration of PMN in tears. Presently, these above mentioned ocular inflammatory disorders are treated with NSAIDs [1]. When eye solution is instilled into the eye, the protective mechanisms (production of rears and blinking action of eye) cause the rapid removal of drug solution results in a 10-fold reduction of the drug concentration within few minutes (4-20 minutes) and remaining drug drains out through naso-lachrymal duct into the GI tract, leading to side-effects. Short duration of the therapeutic effect due to rapid elimination of drug, made a frequent dose regimen; necessary. Contrarily, if we make use of the eye gel instead, the contact time increases accordingly, but disadvantages includes difficulties in instillation due to their high viscosity and problems in storage[2]. Ocular therapy can be significantly improved if the precorneal contact time with drug can be increased. Above mention problems can be overcome by the use of in situ gelling systems, a liquid dosage form suitable to be administered by instillation into

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eye, which upon exposure to physiological conditions, changes to the gel phase thus increasing the precorneal residence time of the delivery system and enhancing the ocular bioavailability. It comprises the ease of eye drop instillation and patient compliance as well as sustains release property that is described to intensify ocular bioavailability. The concept of in situ forming gels came into existence in early 80s[3]. Depending on the method employed to cause sol to gel phase transition on the ocular surface, the following three types of systems have been recognized:

- pH-triggered - The polymers used in this system are Pseudolatexes - Carbomer (carbopol), Cellulose acetate phthalate latex (CAP-latex).
- Temperature-dependent - Poloxamers (Pluronic, Tetronics), Cellulose derivatives (MC, HPMC), Xyloglucan.
- Ion-activated induced - Alginates, Gelrite® (Gellan gum) [4].

Sodium alginate is a natural hydrophilic sodium salt of alginic acid and forms three dimensional hydrogel matrices with low viscosity, free flowing liquid at concentrations suitable for gel formation in the lachrymal fluid [2]. Alginate changes into stable gel phase due to ionic cross-linking of alginate chains with tear ca^{+2} (divalent cations) (as per egg-box model). To decrease the amount of alginate required for gelation, HPMC was mainly used as viscosity enhancer. Carbopol 934 is a synthetic polyacrylic acid polymer, which shows a sol to gel transition in aqueous solution due to change or increase in their pH and also carbopol offers the advantage of excellent mucoadhesive properties as compared with other polymers e.g. cellulose derivatives[4].

Concept of Sustained drug delivery has become the objective in current fashion of pharmaceutical design and research area has been undertaken in attainment of much better drug product effectiveness, quality and safety [5]. In this regard many polymer combinations were used that endure reversible sol to gel system with physiological conditions; ocular in situ gels of an antibacterial agent Moxifloxacin HCl by using combination of poloxamers with Gellan gum, xanthan gum and sodium alginate were reported [6]. Thermoreversible mucoadhesive ocular in situ gelling systems of fluconazole have been reported by using poloxamers 407, hydroxyl ethyl cellulose, HPMC and PVP [7]. Thus, with this novel drug delivery system, ocular bioavailability can be increased and hence, the frequent drug administration can therefore be decreased resulting in better patient compliance. The objective of the present study was to develop in situ gelling system for flurbiprofen (NSAIDs), which is used as an anti-inflammatory agent. Sodium Alginate and carbopol were used as a vehicle for the formulation of flurbiprofen (0.03%) gel that form gel after administration into the lower **cul-de-sac** of eye and sustained the release of drug during treatment of inflammation.

Materials and Methods

Materials

Flurbiprofen was acquired as a gift from FDC Ltd., Mumbai (India). Sodium alginate, HPMC 15cps and carbopol 934 were purchased from CDH Laboratory Reagent (India). All other regents were of analytical grade.

Preparation of formulations

Table 1 shows the composition of all the formulations. The sodium alginate/HPMC and carbopol/HPMC solutions were prepared by dispersing the required amount in sterile water with continuous stirring by using magnetic stirrer. Benzalkonium chloride (0.01% w/v) solution and sodium chloride (0.9% w/v) was then added to the above solution. Flurbiprofen (0.03% w/v) was dissolved in 0.5ml ethanol and then added to the polymeric solutions under constant stirring to obtain a uniform solution. Sterile water was then added to make the volume up to 100ml. The pH of final solution of L_1-to-L_4 was adjusted to 7.4 using 0.1N NaOH/ 0.1N HCL. The formulations were filled in 10-ml amber colored glass vials, capped with rubber closures and sealed with aluminum caps. In their final pack, all the formulations were terminally sterilized by autoclaving at 121 ºC and 15 Pa for 20 minutes. Sterilized formulations were stored in a refrigerator (4-8 ºC) until use.

Evaluation studies

pH and Gelation studies

The general appearance of formulations was observed which included color and clarity of solution. The pH of the prepared formulations was checked by using pH meter. Gelation studies were carried out in glass test tubes. The studies were carried out using STF of composition (sodium bicarbonate 0.200g, sodium chloride 0.670g, calcium chloride· $2H_2O$ 0.008g and purified water sufficient to make 100 g) [8]. The preparation (100 µl) was carefully placed into the test tube using a micropipette (Handypette Micropipette with fix volume pipettor; Cat. No. 600300) and 2ml of gelation solution (STF) was added slowly. Gelation was assessed by visual examination. The time taken for gel to form and the time taken for it to dissolve was noted.

Assay

The drug content was determined by taking 1ml of the formulation. The vials (n=3) containing formulation properly shaken for 2-3 min. 1ml of the formulation was transferred into volumetric flask with 1ml calibrate pipette. 50ml of simulated tear fluid with pH 7.4 was added. Then the gel was completely crushed with glass rod until the formed gel gets completely dissolve to give clear solution. Final volume was adjusted up to 100ml with STF. Flurbiprofen concentration was determined at 247nm by using UV spectrophotometer [6].

Rheological studies

Viscosity of the ocular in situ gels has a great importance in determining the contact time between the drug and ocular tissue. Viscosity of the prepared formulations was determined on a Brookfield viscometer using spindle cp no. 20. Viscosity of sample solutions was measured at different angular velocities at a temperature of 37±1 ºC. A typical run comprised changing of the angular velocity from 2.5 to 100 rpm at a controlled ramp speed. After 6 seconds at 2.5 rpm, velocity was increased to 100 rpm with a similar wait at each speed. The hierarchy of angular velocity was reversed (100 to 2.5rpm) with a similar wait of 6 seconds. The average of two readings was used to calculate the viscosity [8].

Sterility studies

The test for sterility is an important aspect for ophthalmic preparations. The test for sterility is intended for detecting the presence of viable forms of bacteria, fungi and yeast in sterilized preparations. The test must be carried out under conditions designed to avoid accidental contamination of the product during the test. Sterility test was performed according to Indian Pharmacopoeia by using both alternate Thioglycollate and Soya-bean casein digest medium.

Isotonicity studies

Isotonicity is important characteristic of the ophthalmic formulations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. L_4 and L_6 were subjected to isotonicity testing because of different polymer combinations and these exhibited good release characteristics, gelling capacity. Formulations were mixed with few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation (eye drop) containing flurbiprofen. The shape of blood cell (bulging or shrinkage) was compared with standard marketed ophthalmic formulation containing flurbiprofen [9].

In vitro drug release studies

In vitro drug release study was designed using a modified method reported earlier by [10]. 2ml of the test solution were placed in circular plastic cup (2.5cm internal diameter and 1.2cm in depth). This was in turn placed on an inverted USP basket which was kept inside a 250ml beaker. Then, 100ml of simulated tear fluid was added and stirred with a star-headed magnetic bead. Temperature of 37±1 ºC was maintained throughout the study. The aliquots 5ml samples were withdrawn at regular time intervals and replaced by an equal volume of dissolution medium every time. The samples were analyzed spectrophotometerically at 247 nm . Results are shown in Fig.8. The percentage drug release of the all formulations of flurbiprofen ocular in situ gels at different time intervals was fitted to zero order kinetics, first order kinetics and Higuchi model in order to have an idea about the mechanism of drug release.

Interaction studies

To examine any interaction between drug and polymer; interaction studies were carried out using different methods (UV, IR and TLC).

Ultraviolet (UV) Scanning

The sterilized ocular in situ gels were dissolved in STF (simulated tear fluid, pH 7.4). The solutions were filtered through Whatmann filter paper no. 42 and filtered solutions were scanned for UV absorption between 200 and 400nm. UV scan of the pure drug was also run. The spectra recorded were taken as qualitative in order to assay the change in peaks, pattern of curve etc., if any.

Infrared (IR) Spectroscopy

The IR spectra studies were performed on sterilized ocular in situ gels using potassium bromide pellet technique and the spectra were compared with the IR spectra of pure drug. These were done qualitatively in order to assess the pattern of peaks and for comparison purpose.

Thin-Layer Chromatography (TLC) studies

TLC method was carried out using silica gel mixture as the coating substance and mixture of 5 volumes of propan-2-ol and 95 volumes of dichloromethane as the mobile phase. After filtration through Whatmann filter paper no. 42, aliquots (5 µl) of the standard and test solutions were applied on a TLC plate coated with a layer of silica-gel mixture. After removal of plate, allow it to dry in air and examine under ultraviolet light (247 nm).

Ocular Irritation Test (HET-CAM Test)

Ocular irritation study was carried out by HET-CAM (hen's egg chorioallantoic membrane) test [11]. In this test fertilized three hen's eggs for each formulation weighing between 50 and 60 g were selected and candled in order to discard the

defective ones. These eggs were incubated in humidified incubator at a temperature 37±0.5 ºC for 3 days. The trays containing eggs were revolved manually after every 12 h. On day 3, egg albumin (3ml) was taken off by from the sharpened end of the egg using sterile techniques. The hole was sealed by alcohol (70%) sterilized paraffin film with the help of heated spatula. For the development of CAM away from the shell, the eggs were kept in the equatorial position. On the fifth day of incubation, the eggs were candled and non-feasible embryos were removed. On the tenth day, formulations (0.5ml) were instilled through window (2×2 cm) on the equator.A 0.9% Nacl solution was used as a control as it is reported to be practically non-irritant. The scores were recorded according to the scoring schemes as shown in Table 2 and score obtained was given in Table 6 [10].

In vivo Ocular Anti-inflammatory studies

The PGE_2-induced ocular inflammation in rabbits was used to compare the efficacy of ocular in situ gel with marketed eye drop.

The experimental protocol was designed, and approval of institutional animal ethics committee (IAEC) was taken.

Selection of Animals

White albino rabbits (1-1.5kg) of either sex were selected for the study. Rabbits were divided randomly into the groups of five each. Animals were housed in an institutional animal house under standard conditions with free access to food and tap water.

Methodology

Ocular in situ gel (n=5) was instilled into the left eye of rabbits of Group I and eye drop (n=5) was instilled into the left eye of rabbits of Group II. The right eye of all the rabbits served as the control and was treated with normal saline. After 10 minutes of administration of formulations in respective eyes, 50µl of PGE_2 (1µg/ml in normal saline) (Dinoprostone, Astra Zanacea India Ltd.) was instilled in both eyes of all the rabbits. Then inflammation parameters (i.e., Lid closure and Polymorphonuclear leukocytes (PMN) migration) were evaluated for all the eyes.

Lid closure extent was scored as zero for fully open, one for one-third open, two for two-thirds open and, three for fully closed eye (Table 3). PMN migration was evaluated by counting PMN in tear fluid. Two drops of normal saline were instilled into the lower **cul-de-sac** of the rabbit eye. 50µl of the tear fluid was withdrawn after gentle mixing with the help of micropipette at 1h intervals for 5hrs. Tear fluid so withdrawn was diluted with Turke's fluid in WBC pipette and number of PMN was counted in Neubauer's haemocytometer [1].

Results and Discussion

In situ gel forming systems were prepared using sodium alginate and carbopol 934 at different concentrations along with HPMC, as viscosity enhancing agent. Maximum concentration of sodium alginate used was 2% and carbopol was 0.12% to develop gel systems of flurbiprofen to treat the ocular inflammation. All the formulations contained 0.03% flurbiprofen.

pH and Gelation studies

The prepared ocular in situ gel-forming systems were evaluated for pH measurement; gelling capacity, drug content estimation, rheological study, in vitro release study and in vivo studies. The results of physico-chemical properties of the prepared formulations are shown in Table 4. The formulations from L_1-to-L_4 were light yellow and L_5-to-L_6 was whitish in color. Foreign particles are not the only cause of discomfort in the eye. Irritation or pain may also follow the instillation of solutions of unfavorable osmotic pressure or pH, or solutions that contain certain medicaments or preservatives. The lachrymal fluid is iso-osmotic with blood plasma and, therefore, with 0.9% w/v sodium chloride. Isotonicity study of formulations was done by method reported earlier and pH was adjusted to 7.4 (pH of eye) of L_1-to-L_4 formulations by using 0.1N NaoH/0.1N HCl. The drug content uniformity of drug was calculated for all the formulations and found to be in acceptable range. Percent drug content in all six formulations was in the range of 98.3-103.1% indicating homogeneity of formulations. Viscosity and gelling capacity (speed and extent of gelation) are two main prerequisites of a gelling system. The optimum viscosity of the ocular in situ gelling system allows the easy instillation into the eye as a liquid (drops), and then undergoes rapid sol to gel transition due to ionic interaction and change in pH. Formulations L_3 and L_4 showed instantaneous gelation when came into contact with gelation fluid (STF) due to presence of higher concentration of sodium alginate than in others. However, the mechanism of gel formation depends upon the type of polymer used. Gelation of L_1 to L_4, was due to ionic cross-linking of alginate chains with ca^{2+} (divalent cations) present in tears and L_5 to L_6 due to change or increase in their pH and the gel was completely formed at pH 7.4 (pH of eye). The environment of the conjunctival sac favors the phase transition of sodium alginate and carbopol 934 solutions to the gel form. Drainage from the precorneal area would therefore be considerably reduced. The batch L_1, L_5 and L_6 formulation showed weak gelation, due to the presence of a

minimal amount of polymer concentration; hence, the condition for ophthalmic formulation could not reach the required gel strength, this might result in the removal of the formulation from the **cul-de-sac** by tear and blinking action before gelation could occur. The polymer concentration of 1.5-2% fulfills the criteria for the formation of strong gel within the shorter gelation time upon instillation. Hence the ophthalmic solution with this polymer combination will have longer residence time and will prevent the drainage of formulation from the eyes. The pH of all the six formulations was found satisfactory and all the six formulations passed the test of sterility.

Rheological studies

The viscosities of formulations were in following order – $L_4>L_3>L_2>L_1>L_6>L_5$. The rheological profile of prepared in situ gelling systems of flurbiprofen is shown in Fig. 1. The viscosity increased with increasing concentration of sodium alginate and carbopol. L_4 showed the maximum viscosity at 2.5 rpm, where as the minimum viscosity at 2.5 rpm was shown by L_1; this is due to change in polymer concentration.

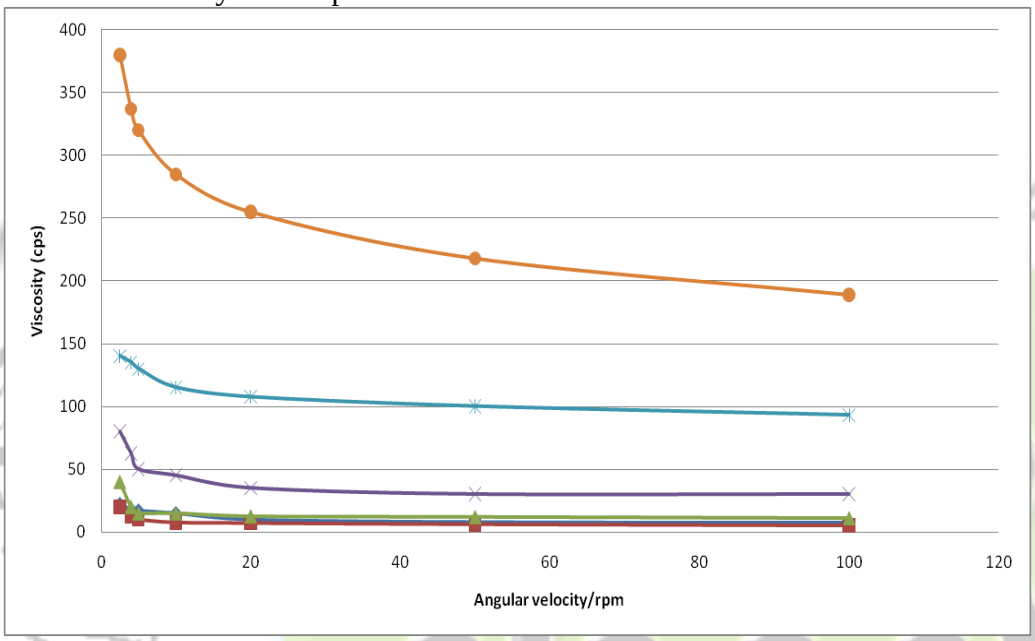

Fig. 1: Rheological profile of *in-situ* gelling systems of flurbiprofen (L_1-L_6)

Formulation L_1 (-▲-); Formulation L_2 (-×-); Formulation L_3 (-*-); Formulation L_4 (-•-); Formulation L_5 (-♦-); Formulation L_6 (-■-)

The formulations exhibited pseudoplastic rheology, as evidenced by shear thinning and a decrease in the viscosity with increased angular velocity. The viscosity was directly dependent on polymeric content of the formulations. The administration of ophthalmic preparations should influence as little as possible the pseudo-plastic character of the pre-corneal film . Since the ocular shear rate is very high, ranging from 0.03 s^{-1} (during inter-blinking) periods to 4250-28500 s^{-1} (during blinking) ; viscoelastic fluids with a viscosity that is high under the low shear rate conditions and low under the high shear rate conditions, which is called pseudoplastic fluid, are often preferred. When shear is applied by blinking action of eye on in situ gels, the contacts begin to break down, the particles become aligned and the flow starts. On being exposed to shearing force, the prepared gel tends to lose its viscosity followed by restoration to its original viscosity when the stress is removed. With the increase in concentration of polymer, the number of interactions between polymer chain increases leading to a three dimensional network structure and hence, exhibit the non Newtonian flow.

Sterility studies

There was no appearance of turbidity and hence no evidence of microbial growth; when all six formulations were incubated for not less than 14 days at 30-35 Cº in case of fluid thioglycollate medium and 20-25 ºC in the case of soya-bean casein digest medium. The preparations examined; therefore, passed the test for sterility.

Isotonicity studies

The optimized formulations were subjected to isotonicity study. Isotonicity testing of L_4 and L_6 formulation exhibited no change in the shape of blood cells (bulging or shrinkage), which reveals the isotonic nature of the formulation and compared with that of standard marketed ophthalmic eye drop of flurbiprofen. Fig. 2, 3, 4 and 5 showed the comparative isotonicity results between prepared formulations and marketed eye drop.

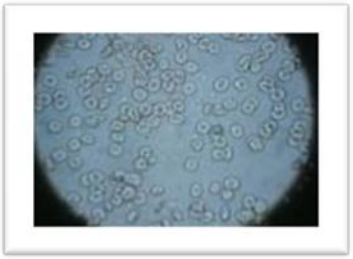

Fig. 2: Blood cells with flurbiprofen as standard marketed eye drop

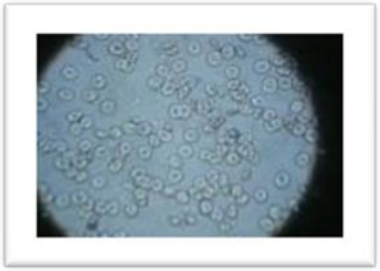

Fig. 3: Blood cells with isotonic sodium alginate formulation L_4

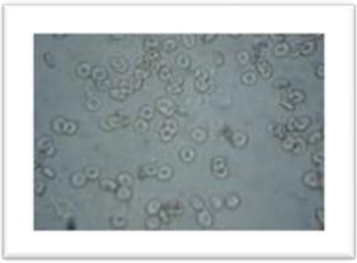

Fig. 4: Blood cells with isotonic carbopol 934 formulation L_6

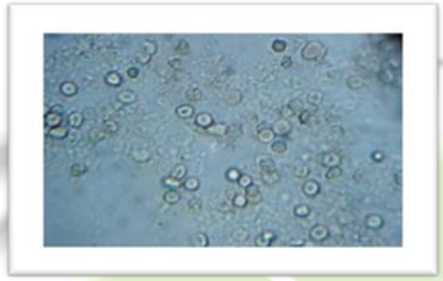

Fig. 5: Blood cells without maintained isotonicity of formulation L_4

In vitro drug release studies

Gelation studies showed satisfactory gelation of formulations with STF. In vitro release profile of the formulation was determined in simulated tear fluid (pH 7.4) and the formulations demonstrate a slow-release rate. Drug content was determined with the help of standard curve and% cumulative drug release was calculated. The release rate constant for zero order, first order and higuchi release was calculated for ocular sol-to-gel systems. The results of in vitro release showed that the amount of drug release decreased with increase in polymer concentration and this trend continued for the entire duration of the study.

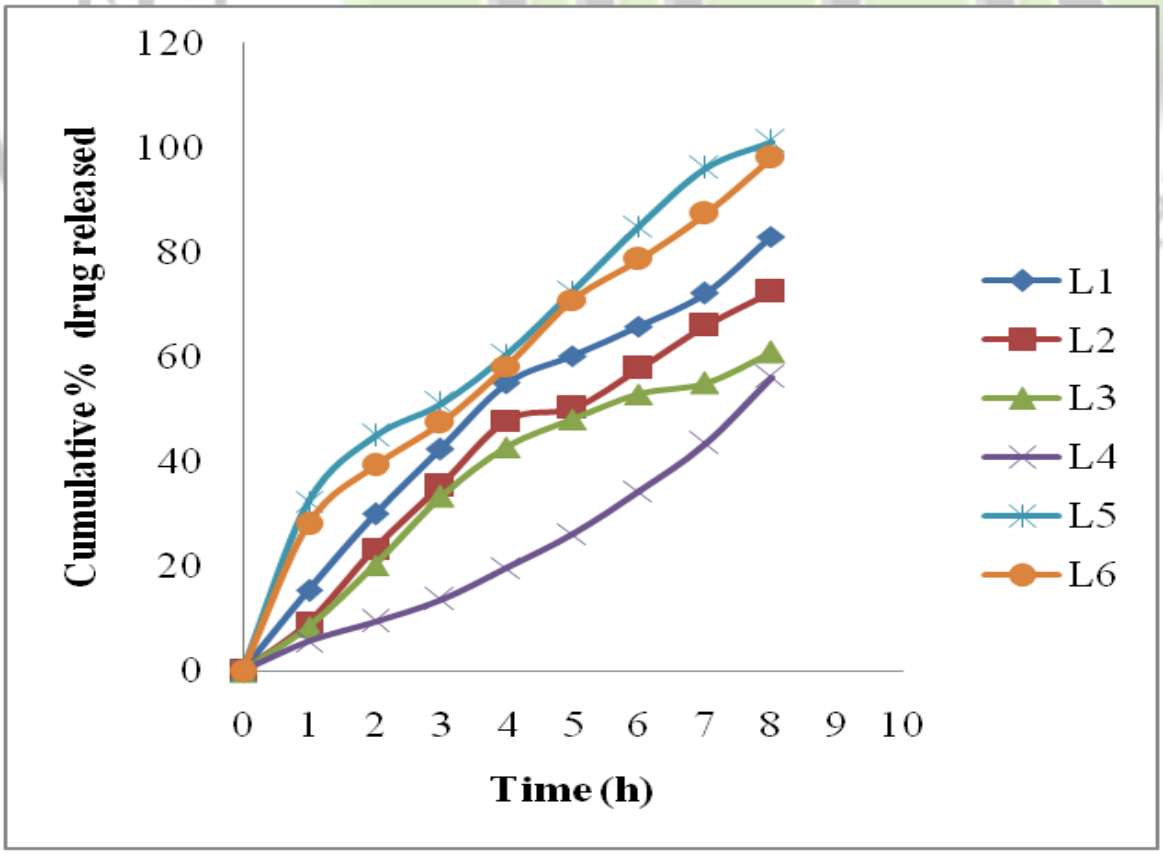

Fig. 6: Plot of *in vitro* release of flurbiprofen for formulations L_1-L_6 from *in situ* gelling systems.

The % cumulative release of flurbiprofen from polymeric gels is shown in Fig. 6. Developed formulations L_5 and L_6 shows 72.63% and 70.96% cumulative drug release after 5 h; this is due to less amount of carbopol 934 present in the formulation; hence these formulations could not be considered as an optimized "once a day" formulation. Flurbiprofen release from the batches with lower polymer concentrations was higher (L_1, L_2, L_5 & L_6) than those with higher polymer concentration (L_3 & L_4). Formulation L_3 (1.5% sodium alginate/0.4% HPMC) and L_4 (2% sodium alginate/0.4% HPMC) sustained the drug release 60.98% and 56.23% in 8 h; it obviously exhibited prolonged release effects, because of presence of maximum polymer concentration; hence these formulations could be considered as an optimized formulation. Moreover; batch L_1 showed high burst release (15% of loaded drug within 1 h) and the batches L_3 & L_4 showed fast gelling property. It is assumed that the dissolution of gels in **cul-de-sac** does get slower than in vitro because of the lower residence volume of lachrymal fluid in eye (7.5-10 µl). Consequently, the in vitro drug release from these systems could occur by diffusion over a long duration of time. The data obtained from in vitro studies of all six formulations were subjected for kinetic treatment in order to know the order of release. Regression coefficient values obtained for each formulation were compared to understand the release kinetics. Comparison of R^2 values obtained by Zero order, First order, and Higuchi kinetic equation revealed that in vitro drug release followed square root of time (Higuchi release) kinetics as the R^2 values obtained by Higuchi kinetic equation were nearer to unity. It can be interpreted from the in vitro drug release kinetics that diffusion was the primary mechanism of drug release from given formulations. The release from the batches followed zero-order kinetics' predominantly, which followed Higuchi type release kinetics, as evidenced by the R^2 value shown in Table 5.

Interaction studies

The UV absorption spectra for pure drug and formulations were quantitatively similar, with similar λmax at 247nm and the main peaks of the dosage form were similar to those of the pure drug in the IR spectra. The Rf value 0.86 obtained in TLC studies was the same as that of the pure drug. It could thus be concluded that there was no any interaction between drug and polymer in formulations.

Ocular Irritation Test (HET-CAM Test)

Ocular irritation of the developed formulation was checked by hen's egg chorioallantoic membrane test which is a rapid, sensitive, and inexpensive test. Testing with an incubated egg is a borderline case between in vivo and in vitro systems and does not conflict with the ethical and legal obligations. The chorioallantoic membrane of the chick embryo is a complete tissue including veins, arteries, and capillaries and is technically very easy to study. It responds to injury with a complete inflammatory process, a process similar to that induced in the conjunctival tissue of the rabbit eyes. Developed formulation was tested by this method and the result was compared with those obtained using normal saline, which was used as control that is supposed to be practically non-irritant. A means score of 0 was obtained for normal saline. Carbopol/HPMC-based formulation was non-irritant up to 12 h (mean score 0) while the mean score was found to be 0.33 up to 24 h for the formulation L_4 (Table 6). The study shows that the formulation is non-irritant to mild irritant and could be regarded as well tolerated.

In vivo Ocular Anti-inflammatory studies

Ophthalmically instillation of prostaglandins induces the inflammation and polymorphonuclear leukocytes (PMN) migration in tear fluid in the rabbit's eye. Hence PGE_2-induced lid closure and PMN migration in rabbits were used to evaluate anti-inflammatory effect of ocular in situ gel of flurbiprofen. On the basis of drug release data, formulation L_4 was select for the in vivo evaluation (Lid closure and PMN migration). Table 7 shows lid closure scores and Fig. 7 draws a comparison of PMN count in tears of rabbits. The results show that lid closure scores and PMN count was less in all the eyes treated with flurbiprofen in situ gel as compared to Controls and flurbiprofen eye drop. The lid closure scores in the eyes treated with ocular gel were much less as compared to eyes treated with eye drops that indicates the higher inhibitory effect of flurbiprofen in situ gel over the eye drops against the PGE_2-induced ocular inflammation. Ocular in situ gel showed a statistically significant difference ($P<0.05$) in both lid closure and PMN results with respect to eye drops. The PMN migration results indicate that the inhibitory effect of ocular in situ gel produced more prominent and longer effect rather than eye drop. The results of the in vivo study conclusively indicate effectiveness of gel in sustaining the release of the drug. The eye drops show less effect because of rapid pre-corneal losses of drug. Other, a statistically significantly lowering ($P<0.05$) in PMN count was noted with respect to eye drops. The results of in vivo indicate that ocular in situ gel give better potential over the eye drops in anti-inflammatory studies.

Conclusion

Flurbiprofen (Anti-inflammatory agent) was successfully formulated as ion-activated and pH-induced in situ gel-forming eye drop. The methodology adopted for preparation of in situ gel solution was very simple and cost effective. It is newer approach to improve residence time, bioavailability and to prolong drug release. Considering its features, the formulation can be seen as an alternative to conventional eye drops resulting in decreased frequency of administration and better patient acceptance. The developed formulation is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain the drug release and also the ease of its administration afforded and decreased frequency of administration resulting in better patient acceptance. It could be concluded that polymer combination 2% alginate / 0.4% HPMC showed better potential for sustained topical drug delivery to eyes for rational drug therapy as supported by in vivo test studies.

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