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

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ABSTRACT

Objective: The aim of this study was to prepare and evaluate a pH sensitive ocular in-situ gel of Nepafenac, to increase the ocular residence time. **Methods:** pH sensitive in situ gel formulations were prepared using different concentrations of Carbomer CB [0.5%, 0.6%, 0.7%] in combination with hydroxypropyl methylcellulose HPMC K40 [0.75%, 1%, 1.5%] or HPMC K100 [0.5%, 0.75%, 1%, 1.5%]. The prepared in situ gels were evaluated for appearance, pH, gelling capacity [sol-to-gel transition/in vitro], tonicity, viscosity, in vitro release studies, release kinetic analysis, and the selected formulas were subjected to rheological studies, and the finally selected formula was subjected to drug content, FT-IR studies, and ocular irritancy tests. **Results:** Increasing the concentration of the carbomer polymer improved the gelling capacity and gelation time, also the higher the viscosity and concentration of the hydrophilic HPMC polymer, the higher the viscosity of the formula, which affected the release, gelation capacity and time. The overall results showed that formula F10 [CB 0.7%, HPMC K100 0.75%] exhibited excellent pH-triggered in-situ gelation time, sustained the release of Nepafenac for 3 h' time with a release rate of more than 90%. **Conclusion:** Ocular in situ gel of Nepafenac offers a potential dosage form to increase the residence time in the ocular cul de sac, decreasing the drug drainage, and increasing the effectiveness of the drug.

KEY WORDS In situ gel, Nepafenac, pH-dependent, Nanosuspension.

INTRODUCTION

Ocular in-situ forming gels are polymeric dispersions of low viscosity, which are liquid upon installation and undergo phase transition; spontaneous coagulation in the ocular cul-de-sac to form visco elastic gels [1], in response to the environmental changes [pH, temperature, ion exchange [2]. In situ ocular gels are superior to conventional ocular dosage forms [solutions and suspensions] in which ocular drainage is the main set back, [3], and even to the new dosage forms [inserts] in which some patients find it difficult to apply [4] in addition to the irritation it may cause [5]. pH-triggered system show sol-gel transformation when the pH is raised by tear fluid to the ocular pH 7.4, most of the pH sensitive polymers are acidic polyanions that are of low viscosity when they are unionized, but as the pH increases to the body pH, the polymer becomes ionized and swells in the presence of water [6]. The pH sensitive polymers are either: cellulose

acetate phthalate latex which is liquid at pH 4.4 and forms a gel at lacrimal fluid pH of 7.2-7.4, or polyacrylic acids PAA; such as carbomers, polycarboxylic, these polymers differ in the degree and type of cross linking and the type of substitution, they gel at pH above their pKa of 6 ± 0.5 , or polyvinyl acetaldethylamino acetate AEA solutions with has a low viscosity at pH 4 and form a hydrogel at neutral pH condition [7]. Although PAA are excellent pH sensitive polymers but the amount required to form a stiff gel upon instillation in the eye is not easily neutralized by the buffering action of tear fluid or may require higher PAA concentration that may irritate the ocular tissue; therefore, combination PAA with a suitable hydrophilic cellulose viscosity-enhancing polymer allows a reduction in the PAA concentration without comprising the in situ gelling properties [8], and will improve mucoadhesion. Nepafenac is a non-steroidal anti-inflammatory drug NSAID propionic acid derivative; which inhibits both Cyclooxygenase

enzymes COX 1 and COX 2 [9], which function is to analgesic and anti-inflammatory activities and when Nepafenac at a concentration of 0.2% [10], is given topically to the eye surface, it is effective in decreasing aqueous levels of proteins and the rate of miosis, and the maintenance of mydriasis during cataract surgery.

Thereby; preventing and controlling ocular inflammation after cataract surgery [11, 12]. The aim of the study was to prepare ocular in-situ gel of Nepafenac using carbomer as a pH sensitive gelling agent with different concentration of a hydrophilic mucoadhesive polymer.

MATERIALS AND METHODS

Materials

Nepafenac, hydroxypropyl methylcellulose K40 (HPMC K40), hydroxypropyl methylcellulose K100 (HPMC K1000), were obtained from Hangzhou Hyper Chemicals Limited, China and Carbomer (CB) Carbopol 940 was purchased from HiMedia lab., Pvt Ltd, Mumbai, India.

METHODS

Characterization of Nepafenac

1-Differential scanning calorimetry DS

Thermal characterization of pure drug was performed with DSC [Shimadzu, Japan]. Samples were weighed (2.00 ± 0.5 mg) and placed in sealed aluminum pans. The equipment was calibrated with indium. The samples were scanned at 200 °C/min from 250 °C to 300 °C.

2-Solubility measurement of Nepafenac

Excess amount of Nepafenac was sonicated for 10 min with different solvents; water, phosphate buffer pH 7.2 and simulated tear fluid STF pH 7.4 (sodium chloride 0.6 gm, bicarbonate sodium 0.20 gm, calcium chloride 2H₂O 0.008g, one drop of HCL, distilled water to 100 ml) [13]. These solutions were incubated in a water bath shaker (Mettler, Germany) at room temperature for 72 h. The samples were then filtered and examined after suitable dilution, spectrophotometrically at the maximum wavelength of 330 nm [14].

Preparation of Nepafenac in situ gel

pH sensitive Nepafenac in situ gel formulations were prepared according to table 1 using different concentration of HPMC K40 or HPMC K100 [0.5%, 0.75%, 1%, 1.5%) by heating 70 ml water to 70 °C, then HPMC was added slowly with continuous stirring on a hot plate [15] Stuart, UK, after complete addition of HPMC, the solution was allowed to cool in a refrigerator overnight, to obtain a clear fully hydrated dispersion. Then CB (0.5%, 0.6%, 0.7%) was sprinkled [16] on the HPMC dispersion slowly with continuous stirring on the magnetic stirrer with heating to approximately 70 °C, until the CB was fully dispersed. The desired amount of Nepafenac was dissolved in about 30

promote prostaglandin production; hence, providing both ml of phosphate buffer 7.2 using the sonicator, until a clear drug solution was obtained, this solution was finally added to the polymer dispersion with continuous stirring after polymer solution cooled and the final volume was made up 100 ml with water. The formulation was filtered by passage through a sterile membrane filter of pore size of 0.22 µm (Millipore type) into previously sterilized final containers which are then sealed to exclude microorganism. Preservatives were excluded to avoid interaction with the formula ingredients and to avoid irritation to the ocular membranes

Evaluation parameters of the formulated in-situ gels

Appearance

The formulations were observed for general appearance i.e. color, and for the presence of suspended particulate matter. The clarity of the preparation was checked using against black and white background [16, 17].

pH

The pH of the formulations was measured using a digital pH meter (ATC China). The pH meter probe was immersed in the formulation for 5 min. and then the readings were taken [18].

Gelling capacity [sol-to-gel transition/in vitro]

All prepared formulations were evaluated for gelling capacity, time and viscosity in order to identify the compositions suitable for use as in-situ gelling systems. The gelling capacity was determined by placing a drop of the formula in a vial containing 2 ml of freshly prepared simulated tear fluid and visually assessing the gel formation and recording the time for gelation and the time taken for the gel formed to dissolve [19, 20].

Osmolality evaluation

0µl of ophthalmic preparation was taken using a micropipette and placed in Eppendorf vials and placed in the osmometer Osmomato 30, Germany and the depression in freezing point was recorded in comparison with standard NaCl 1%W/V solution of 300mOsmol [21].

Rheological studies

Viscosity and rheological properties of in situ forming drug delivery systems is an important factor in determining residence time of the drug in the eye [22]. Viscosity determination was carried NDJ-5S using spindle 1. The angular velocity was increased gradually from 6, 12, 30, to 60 rpm and then decreased backward. The viscosity of the formulations was measured in mPa. s.

In vitro release studies

In vitro release study of in situ gel solution is carried out by using dissolution apparatus type II paddle type, Copley UK. The formulation was placed in dialysis

membrane 0.08 μm pore size, which was previously soaked in STF overnight. The dialysis membrane is tied to the paddle shaft and immersed in 300 ml [15] of STF pH7.4 [23] as a dissolution medium and it was rotated at 50 rpm [16], maintained at a temperature of 37 ± 0.5 °C [24,25]. Samples of 10 ml were withdrawn at regular intervals and replaced with an equal volume of fresh medium. The test was done in triplets and the mean result was plotted against time.

Release kinetic analysis

The release data were subjected to different mathematical models such as first order, Higuchi's model, and Korsmeyer-Peppas model to evaluate the release mechanism of the drug from the gel, [26, 27] the criteria for selecting the most appropriate model was based on a goodness-of-fit test, according to the equations:

$$\text{First order } D[M]/dt = K_1[M] \quad \text{Eq. [1]}$$

$D[M]/dt$ Concentration of drug released per time K_1 First order rate constant concentration of the drug

$$M = KHt^{1/2} \quad \text{Eq [2]}$$

M Amount of Drug released KH Higuchi rate constant t time for release

$$M_t/M_\infty = Kk_{\text{p}}t^n \quad \text{Eq. [3]}$$

Fraction of drug released at time t Korsmeyer Peppas rate constant n release exponent

Determination of drug content

The drug content was determined by diluting 1 ml of the selected formula to 100 ml with freshly prepared STF pH 7.4. Samples were taken from different sites of the container. Then 1 ml was withdrawn and further diluted to 10 ml with STF. Nepafenac concentration was then determined at the maximum wavelength using a UV-Visible spectrophotometer Cary, win UV Varian Australia.

FT-IR studies

The possibility of drug-excipients interactions was investigated by FTIR studies. The FTIR graph of pure drug and the excipients for selected formula were recorded using KBR pellets. [28] The in-situ gel formula was placed in a petri dish and allowed to dry and then studied.

Ocular irritancy studies

The modified Draize technique was designed for the ocular irritation potential of the ophthalmic product. [24] Ocular irritation studies of the filtered selected formula [by a Milli-pore-filter] were performed on three male rabbits weighing 1-2 kg. According to Draize test, an eye drop of 50 μl of the selected formula, which was filtered with a 0.22 μ Millipore filter, was placed in the lower cul-de-sac and irritancy was tested at the time interval of 1 hr., 24 h, 48 h, and 72 h after administration. The rabbits were observed periodically for redness, swelling and watering of the eye [21].

Table 1: Nepafenac ocular in situ gel formulas composition expressed as % W/V

Formulation code	Nepafenac	Carbomer CB	HPMCK 40	HPMCK 100
F1	0.2	0.5	0.75	
F2	0.2	0.5	1	
F3	0.2	0.5	1.5	
F4	0.2	0.6	0.75	
F5	0.2	0.6	1	
F6	0.2	0.6	1.5	
F7	0.2	0.7	0.75	
F8	0.2	0.7	1	
F9	0.2	0.7	1.5	
F10	0.2	0.7		0.75
F11	0.2	0.7		1
F12	0.2	0.7		1.5
F13	0.2	0.7		0.5

Table 2: pH Values and physical appearance and gelation capacity and sol-gel transition time of Nepafenac ocular in-situ gel

Formulation	pH	Physical appearance	Gelation time[min]	Gelling capacity*
F1	5.1 \pm 0.12	Thin Transparent Liquid	1.5 \pm 0.5	-
F2	6.0 \pm 0.03	Transparent liquid	2.5 \pm 0.5	+
F3	6.0 \pm 0.04	Transparent Gel	9 \pm 0.1	+++
F4	5.8 \pm 0.11	Transparent Liquid	4.5 \pm 0.5	++
F5	4.9 \pm 0.21	Opaque Liquid	11 \pm 0.5	++
F6	5.8 \pm 0.03	Translucent dispersion	23 \pm 1.0	+++

F7	5.9±0.07	Thin Opaque Dispersion	11±0.5	++
F8	5.6±0.01	Opaque Dispersion	8±0.5	++
F9	4.9±0.10	Opaque pourable dispersion	20.5±0.5	+++
F10	5.6±0.02	Translucent dispersion	40±3.0	+++
F11	5.6±0.05	Translucent gel	26±2.0	+++
F12	6.2±0.03	Very Thick gel	35±1.0	++++

* Where: - No gelation, + Gel after few minutes, dissolve rapidly, ++ Immediate gelation, remain for few min, +++ Immediate gelation but for few extended periods, ** the results are expressed in mean ±SD (n=3)

Table 3: Osmolality of Nepafenac ocular in-situ gel

Formula	DepressioninfreezingpointΔ°C	Osmolality[mOsmol]
1%NaCl	0.54	300
F1	6.7±0.01	3526.32±5.263
F2	6.4±0.02	3368.42±10.526
F3	6.2±0.05	3263.16±26.316
F4	6.3±0.05	3315.79±26.316
F5	6.6±0.02	3473.68±10.526
F6	6.1±0.04	3210.53±21.053
F7	6.5±0.02	3421.05±10.526
F8	6.4±0.03	3368.42±15.789
F9	6.4±0.01	3368.42±5.263
F10	6.4±0.02	3368.42±10.526
F11	6.9±0.03	3631.58±15.789
F12	6.5±0.05	3421.05±26.316
F13	6.7±0.035	3526.32±18.421

The results are expressed in mean±SD (n=3)

Table 4: The release kinetic analysis of Nepafenac ocular in-situ gel

Formulation	First Order		Higuchi		Korsmeyer-peppas			
	K1	R ²	KH	R ²	K1	R ²	n	
F1	0.025	0.9235	8.408	0.8436	19.561	0.9494	0.314	Fickian
F2	0.013	0.7954	6.577	0.9038	13.842	0.9824	0.336	Fickian
F3	0.026	0.9689	8.782	0.9224	17.337	0.9853	0.350	Fickian
F4	0.021	0.9166	8.021	0.8778	17.046	0.9573	0.334	Fickian
F5	0.012	0.8847	6.345	0.9594	9.760	0.9808	0.405	Fickian
F6	0.040	0.9744	9.391	0.7096	29.987	0.9618	0.224	Fickian
F7	0.014	0.9595	7.339	0.9586	3.840	0.9846	0.641	Non-Fickian
F8	0.911	0.9242	6.658	0.9334	2.746	0.9794	0.692	Non-Fickian
F9	0.013	0.9439	6.882	0.9900	8.311	0.9935	0.459	Non-Fickian
F10	0.021	0.9789	8.073	0.9151	13.702	0.9895	0.384	Fickian
F11	0.023	0.9041	8.992	0.8791	8.084	0.9833	0.523	Non-Fickian

Figure 1a: The viscosity of Nepafenac ocular in-situ gel formulas at 0.75% of the hydrophilic polymer, in relation to the angular velocity at room temperature (n=3)

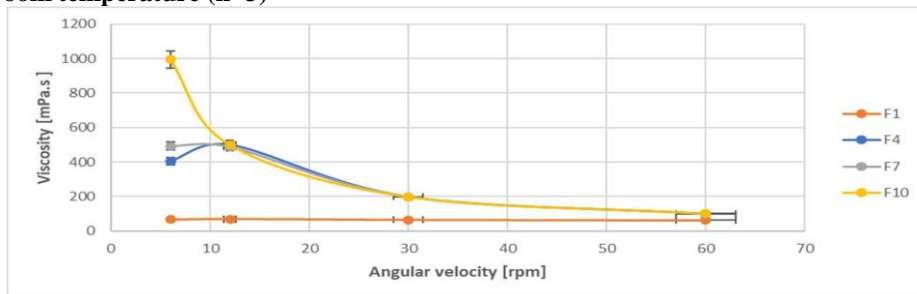


Figure 1b: The viscosity of Nepafenac ocular in-situ gel formulas at 1% of the hydrophilic polymer, in relation to the angular velocity at room temperature (n=3)

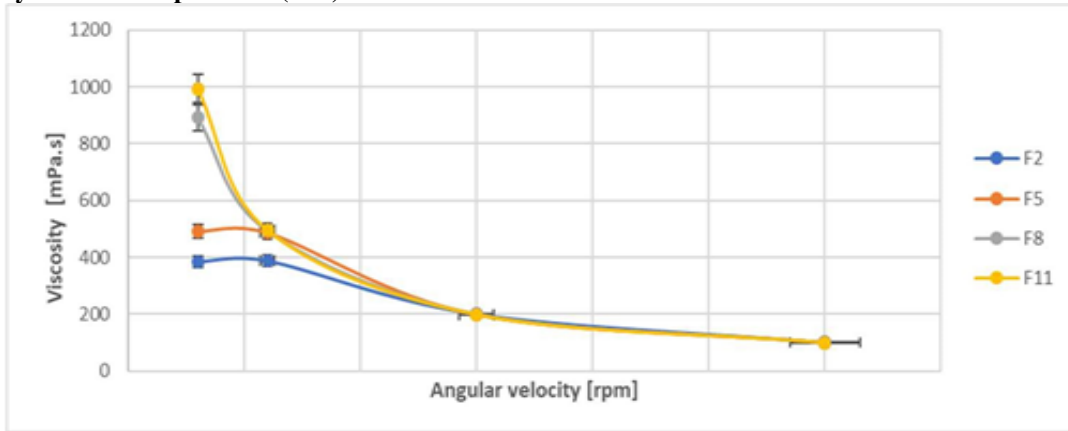


Fig. 2: The viscosity versus angular velocity for F7 (HPMC K40) and F10(HPMC K100) for the same concentration of CB (0.7%) at room temperature (n=3)

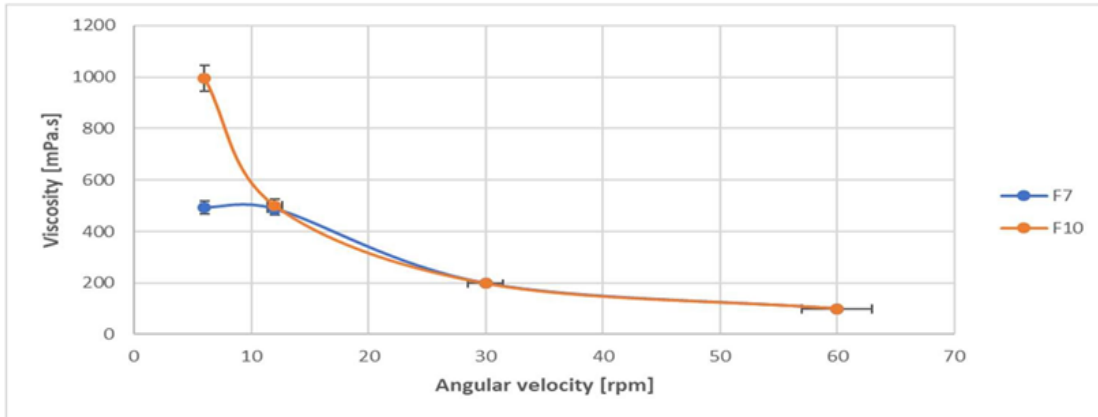


Figure 3: The release profile of Nepafenac ocular in-situ gel formulas F1-F9 containing HPMC K40 in STF at 37 °C (n=3)

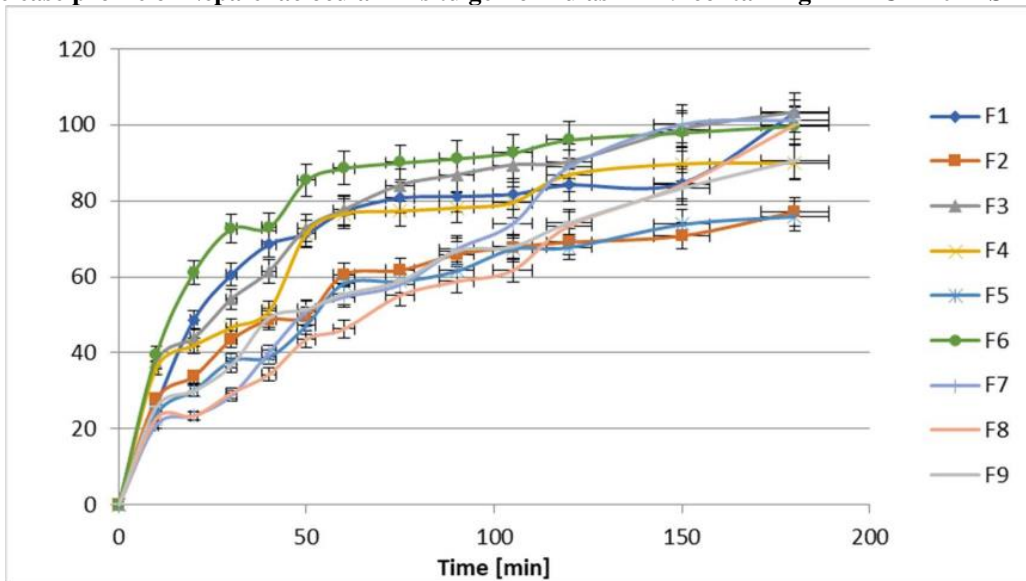
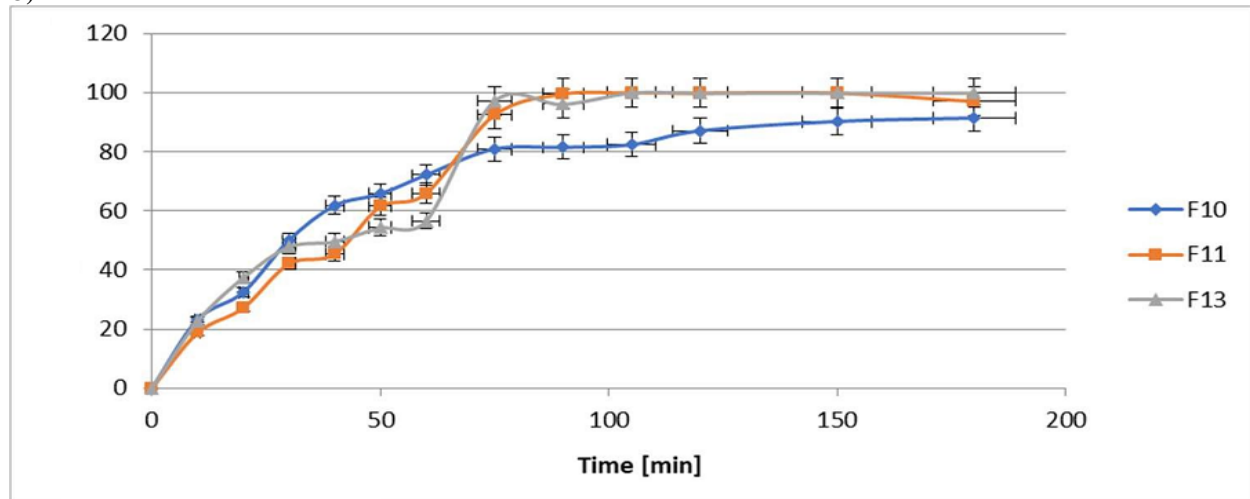


Figure 4: The release profile of Nepafenac ocular in-situ gel formulas F10-F11 F13 containing HPMC K100 in STF at 37 °C (n=3)



RESULTS AND DISCUSSION

Physical evaluation parameters

Appearance

The prepared formulas were translucent, to clear dispersions. The haziness observed during preparation due to precipitation of HPMC at elevated temperature was found to disappear and the clarity was regained after overnight standing.

pH

The pH values of all formulations were found to be satisfactory in the range (4.9-6.2) as shown in table 2. The appropriate pH for NSAID ophthalmic drug preparation is between 6-8 to ensure solubility of the drug, [11] while pH dependent ocular in-situ gel must be lower than the ocular pH of 7.4 for sol to gel transformation due to the buffering action of the tear fluid. Also, non-neutralized CB gels are acidic in nature, therefore the pH of the formulas was around 6 which are considered within the acceptable range for ocular formulation ranging between 5 and 7.4. [1]. The pH of the formulas was significantly dependent on the CB concentration ($p < 0.01$).

Gelling capacity measurement of the sol-gel transition

The gradings for gelling capacity are shown in table 2. Formulations containing HPMC K40 [1.5%] showed excellent gelation [F3-F6-F9] and increasing the concentration of CB significantly improved the gelation time ($p < 0.01$), while changing the HPMC grade to K100 for the same CB concentration greatly improved gelation capacity and time as compared to the K40 grade. F10, F11 and F12. This may be due to an increase in molecular weight of the HPMC and also increasing the density of the hydrophobic methyl group in the higher molecular weight HPMC [29].

Osmolality evaluation

The prepared formulas showed depression of freezing point, 10 folds that of isotonic solutions as seen in table 3. This helps the formulation, since, the colloidal osmolality of tears is twenty-fold less than that of the corneal stroma. Therefore; formulation with a high colloidal osmolality; oncotic pressure, [30] may be of value for damaged corneal epithelial cell, due to Donnan effect, to reduce corneal swelling [deturgescence occurs], leading to a return of normal cell physiology [31]; in conjunction with the NSAID, leading to a return of normal cell physiology [32].

Rheological study

The fluids having high viscosity under low shear rates and low viscosity under high shear rates are called as pseudo-plastic fluids; these are often preferred in ophthalmic preparations [33]. Since the ocular shear rate is very high, the mean blink rate at rest is 17 blinks/min which increases during conversation to 26 blinks/min [34]. Also, during blinking the shearing force on the preparation is large. The higher the viscosity of the preparation, then more shear rate is needed (blinking), this will result in irritation. On the other hand, if the viscosity is too low it will give rise to excessive drainage. Fig. 1a and 1b shows the effect of increasing angular velocity on the viscosity for formulas (F1, F4, F7 and F100) at 0.75% w/v of the hydrophilic polymer and for formulas (F2, F5, F8 and F11) at 1% w/v of the hydrophilic polymer, respectively with increasing concentration of CB. All the formulas showed shear thinning behaviour; characteristic of pseudo-plastic fluids, with no thixotropy. The pseudo-plastic property of the formulation is in favor of sustaining the drainage of the drug from the conjunctival sac of the eye [34]. The viscosity was dependent on the type and concentration polymer used [35], changing the type of HPMC grade affected the viscosity as

seen in fig. 2. The viscosity significantly affected the gelation time ($p < 0.01$).

In vitro release studies

The incorporation of the hydrophilic polymer (HPMC K40 or HPMC K100) with the acidic anionic polymer CB enhanced the consistency and modified the release [24] of Nepafenac. From fig. 3 it is obvious that formulas containing HPMC K40 (F1-F9) showed fast drug release that may be attributed to the lower viscosity of the polymer in comparison with HPMC K100 polymer. Also, the initial fast release of drug can be explained by the fact that eye drops are formulated in water and hence the polymer was completely hydrated, when they meet the simulated tear fluid and gelation occurs, a pre-hydrated matrix is formed in which hydration and water penetration no longer limit drug release leading to an apparent diffusion-controlled release [36].

Another factor that has an influence on the rate of drug release is the molecular weight of the polymer in the formulation. Since HPMC K100 molecular weight is higher than HPMC K40; therefore, the release is slower in these formulas F10, F11 and F13 as seen in fig. 4.

The formulas which displayed the best gelation capacity [F9-F10- F11] release are shown in fig. 5, F10 sustained the release of Nepafenac more than F9, and less than F11, this result may be potentiated by the rheological studies where the rate of drug release decrease when the viscosity increase, the pseudo-plastic property of these formulations may be in favor of sustaining the release of drug in the conjunctival sac of the eye. The results indicated that the formulation F-10 showed better release amongst all formulations. This may be due to the presence of a higher concentration of CB along with the appropriate concentration of HPMC K100.

Release kinetic analysis

The in vitro release profiles were fitted to various kinetic models [table 4] to find the mechanism of drug release. Formulas [1-6], and F10 had a $[n]$ value of less than 0.45; suggesting Fickian, first-order diffusion release. The release of drug from swelling matrices HPMC showed that the rate and amount of drug released was dependent on the active substance dissolution and diffusion rates, and but also from the "drug particle translocation" process. In the case of low solubility drugs, the solid particles of active substance were transported from the swelling front of the matrices to the eroding front of the gel layer. The particle displacement process was explained as a result of the spring-like action of macromolecular chains upon transition from glassy to the

rubbery state of the polymer. The expansion of the polymer chains by relaxation led to movement of dissolved drug. The release mechanism continued to be a diffusion-controlled after the glassy core of the hydrated layer disappeared, as the dissolved drug was already in the system [37]. While F7-F9 and F11; exhibited a $[n]$ value more than 0.45 meaning non Fickian diffusion [38]. In formulas F7-F9 the time needed for polymer swelling is longer than time needed for drug diffusion, due to the fact the higher concentration of CD in comparison with formulas F [1-6] for the same HPMC grade K40, and F11 for HPMC K100.

Drug content

The drug content of formula F10 [the selected formula] was found to $100\% \pm 2\%$ in STF, F10 showed a uniform distribution of the drug in the ophthalmic formulations, according to USP dosage form criteria [39]

FTIR study

FT-IR spectrum of pure Nepafenac, the selected formula F10 and polymers used in the formula are shown in fig. 6. The spectral study showed that there was no significant change in the peaks of pure drug and the selected formula F10. Hence, no specific interaction was observed between the drug and the polymers used in the formulations. Infrared Nepafenac spectrum showed principal peaks at wavenumbers: 3217 cm^{-1} $[\text{OH}]$, 1720 cm^{-1} $[\text{C}=\text{O}]$ of carboxylic acid group, $1610, 1493, 1454 \text{ cm}^{-1}$ are due to ν $[\text{C}=\text{C}]$ polycyclic aromatic structure, $1393, 675 \text{ cm}^{-1}$ are due $[\text{OH}]$ bending [40], also $1180, 1082 \text{ cm}^{-1}$ due ν $[\text{C}-\text{O}]$ of the ether group [28]. The same bands appear in the selected formula F10 [$1724, 1606, 1392, 1113, 1063, 679 \text{ cm}^{-1}$] It reveals there is no drug-excipient interaction.

Ocular irritancy test

In vivo eye irritation testing was carried out using F10. The formulations were found to be non-irritating with no ocular damage or abnormal clinical signs to the cornea, iris or conjunctivae observed. Hence the formulation was suitable for the eye installation [41].

CONCLUSION

The primary requirement of a successful controlled release product focuses on increasing patient compliance, which the in-situ gels offer. Exploitation of polymeric in situ gels for controlled release of drug provides several advantages over conventional dosage forms. Use of biodegradable and hydrophilic polymers for the in-situ gel formulations can make them more acceptable and excellent drug delivery systems.

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