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Formulation and Evaluation of Ion-Responsive in Situ Gel for Ocular Delivery of Lornoxicam: In Vitro and In Vivo Studies

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Abstract

Lornoxicam (LOX) is a potent nonsteroidal anti-inflammatory drug (NSAID) of oxicam class; that can be used to treat ocular inflammation, when applied locally; reducing systemic side effects. LOX has poor water solubility and low dissolution rate. An ion-sensitive in-situ gel for lornoxicam (LOX) solid dispersion was developed using gellan gum, a polymer that gel in response to calcium ions present in physiological fluids. This method allows for the local and continuous release of medication, improving therapeutic efficacy by prolongation of residence time. The aim of this study was to formulate and evaluate lornoxicam solid dispersion loaded in-situ ocular gels to prolong the residence time and enhance the retention of drug on the surface of the eye, thereby good therapeutic efficacy. Different concentrations of gellan gum were tested changed to create various of formulations, and their impact on viscosity and gelation capacity was assessed. Results: In vitro release experiments; showed that the optimized formulation (F8), containing 0.1% (w/w) LOX and 1% (w/w) gellan gum, released 91.7% of the medication within the first 30 minutes and continued to release over six hours In vivo study includes the utilizing of Rattus norvegicus Domestica as animal model, the optimized formulation (F8) demonstrated a significant therapeutic efficacy in reducing ocular irritation within 72 hours Conclusion: The LOX ocular in-situ gel appears to be a promising dosage form that enhances medication retention, reduces drainage, and provides therapeutic benefits.

Keywords: **Lornoxicam, Crospovidone, Ion, Ocular In-situ gel, Gellan gum**

Introduction

LOX is a nonsteroidal anti-inflammatory drug (NSAID) of oxicam class, known for its anti-inflammatory, analgesic, and antipyretic properties [(1)].It is increasingly being used in the treatment of ocular diseases due to its potent anti-inflammatory and analgesic effects [(2)].Prostaglandins, produced through the conversion of arachidonic acid via the COX-1 and COX-2 pathways, play a role in to the development of postoperative macular edema. While the COX-2 pathway is a major contributor to surgical inflammation in the eye, topical NSAIDs like Lornoxicam that inhibit both COX-1 and COX-2 are often used postoperatively to reduce inflammation [(3)]. LOX has poor water solubility and low dissolution rate, which may be a challenge in ocular drug delivery to achieve adequate therapeutic efficacy at the site of action. Surface solid dispersion was chosen to improve the water solubility and dissolution rate of LOX. But the residence time of the therapeutic agent can be hindered by aqueous fluid loss, resulting in only a small portion of the drug reaching the eye [(4)]**.** The "in situ gel" approach has emerged as an effective medication delivery technology that transforms from a solution to a gel [(5)]**.** Its unique "sol to gel" transformation function promotes improved compliance and comfort by removing the need for repeated intraperitoneal injections to treat posterior eye disorders [(6)]**.** In situ gel technology also enable continuous and controlled drug release [(7).] After administration the gel undergoes a sol-gel transition in the conjunctival cul-de-sac in response to external stimuli like pH, temperature, or ions [(8).] In situ gel formation methods can be categorized into chemical and physical mechanism [(9)]**.** Electric fields, and temperature all trigger physical mechanisms. Ion activation and pH changes both promote the chemical process [(10)]. The advantages of in-situ gel (ISG) include reduced nasolacrimal drainage, increased local bioavailability, decreased local side effects and toxicity, ease of administration, prolonged contact time, and reduced dosing frequency [(11)]. Gellan gum (GG), a naturally occurring biopolymer derived from Pseudomonas elodea, GG can undergo a solution-to-gel transition in mono- and divalent cations, Forming a solid gel upon contact with calcium ions in eye fluid [(12)].

Lornoxicam, stands out from other NSAIDS due to its rapid onset of action and superior efficacy in controlling inflammation at potentially lower doses, reducing the risk of systemic side effects. Unlike diclofenac, commonly used NSAID in ocular treatments, lornoxicam offers similar or greater anti-inflammatory effects with a lower incidence of adverse events. The aim of this study is to develop a novel dosage form of lornoxicam that provides several advantages over traditional diclofenac sodium eye drops, including prolonged drug retention, reduced dosing frequency, and minimized systemic absorption [13]. Formulating a 0.1% LOX in situ gel shows promise for treating eye inflammation [14].

Materials and Methods

Materials

Lornoxicam and Crospovidone were obtained from Henan Grange Biotechnology Co.Ltd., Gellan gum was obtained from Hangzhou Hyper Chemicals Limited; in China, Ethanol Tri ethanol amine, and Boric acid were obtained from Hyperchem; The experiment model animals used were Rattus norvegicus domestica (Domestic Norwegian rat).

Methods

Production of Lornoxicam Surface Solid Dispersion (SSD)

Kneading Method

The SSD was prepared using the kneading technique. 200 mg of LOX and 1000 mg of crospovidone were combined in a mortar, and the mixture was mixed for five minutes. Gradually, a small amount of a solvent mixture ethanol, triethanolamine in ratio 1:0.5 was added to the mixture to transform it into a paste after 30 minutes of kneading and left in an oven at 40°C until dry. [15]The material was then pounded into a powder, which was subsequently sieved through a 60-mesh screen. The dried material was then placed in a desiccator with a silica drying agent [16].

In situ gel production

The hot approach was used to prepare the LOX in situ gel 0.1%w/w. This method involved dispersing Gellan gum prefiltered distilled water (using 0.45µm Millipore filter) at 90 °C while stirring constantly for 20 minutes, after complete dispersion it was set aside to cool down, Boric acid and 600mg LOX: Crospovidone (1:5) surface solid dispersion (equivalent to 0.1% LOX) was added. The dispersion was then left overnight at 4°C for complete hydration..[17] Each sample was kept at 4°C.

Table1. Lornoxicam ocular in situ gel formulas composition expressed as %w/w.

Formulation code	LOX (%)	Boric acid (%)	Gellan gum (%)
F1	0.1	0.2	0.3%
F2	0.1	0.2	0.4%
F3	0.1	0.2	0.5%
F4	0.1	0.2	0.6%
F5	0.1	0.2	0.7%
F6	0.1	0.2	0.8
F7	0.1	0.2	0.9
F8	0.1	0.2	1

Preparation of simulated tear fluid

Simulated tear fluid was prepared by mixing 6.7g of NaCl, 2.0 g of $NaHCO_3$, or 0.08 g of $CaCl_2.2H_2O$ was dissolved in 1000 mL of deionized water (pH 7.4), which was kept at 34 °C throughout the testing to create the simulated tear fluid (STF) [18]

Differential Scanning Calorimetry (DSC)

The DSC data were collected using a DSC-60 plus Shimadzu Japan device. Lornoxicam was carefully weighed and placed in sealed aluminum pans. Then placing the drug under a flow of nitrogen gas (100 mL/min) until a stable heat range of 25–300°C was reached [19].

In vitro evaluation of in situ gel

Determination of viscosity

The viscosity of formulations (F4-F8) was measured at room temperature (25±2ºC) using a Brookfield viscometer digital (Brookfield, USP) at 100 rpm with spindle LV-03(63), spindle is allowed in rotate for 2 min before the measurement were taken. [20].

Rheological study

One important indicator of sustainability and ease of administration for ocular in-situ gel compositions is their viscosity for formulations (F4-F8).

The drug's residence time in the eye is mostly determined by the viscosity and rheological properties of in situ-forming drug delivery systems. Viscosity was measured using Brookfield viscometer digital (Brookfield, USP) spindle LV-03(63). The velocity was gradually increased from 12; and 30 rpm to 100 rpm and then decreased again. The viscosity of the formulations was given in centipoise [21].

Gelling capacity

The gelling ability of he made ophthalmic in situ gel compositions was determined by timing the time needed for each formulation to dissolve and gel in freshly simulated tear fluid (STF) at 34°C, which was meant to mimic the ocular media (22).

Osmolality

The formulation's osmolarity was assessed using an osmometer (Osmo Mato 30, Germany). Using a micropipette, 100µl of each ophthalmic preparation (F4-F8) was taken and placed into Eppendorf vials in the osmometer. The freezing point depression was measured [23].

Determining the Drug Content

First, 100 mL of freshly prepared simulated tears fluid (STF) with a pH of 7.4 was added to 1 mL of each formula (F4–F8) to assess the drug concentration. After that, 1 mL was removed and further diluted to make 10 mL using STF. The concentration of LOX was measured using a UV-visible spectrophotometer (Shimadzu, Japan) (22).

In Vitro In Situ Gel Release

Studies on drug release in vitro were carried out using dialysis bags MWCO 14 kDa (sigma /merk) and UK Dissolution apparatus type II (Faithful, China). One dialysis bag's two ends were tightly sealed. The diffusion media was 500 mL of stimulated tears fluid STF (34 ◦C) at 150 r/min. Samples (5 mL) were taken at intervals of 5, 15, 30,60,120,180,240,300and 360 minutes, and equivalent amounts of STF were added to maintain the sink condition. The drug concentration was determined using a UV-visible spectrophotometer (Shimadzu, Japan) detection wavelength of 376 nm. [21].

Fourier Transform Infrared (FT-IR) Studies

FTIR experiments were used to investigate drug-excipient interactions. Using FTIR spectroscopy (Lambda 7600, USP) with KBR pellets, the FTIR graphs of pure Lornoxicam, the physical mixture, and the excipients for the selected formula in situ gel were recorded (24).

In Vitro Draize Test OECD

The objective was to evaluate the ocular therapeutic effect of 0.1% LOX in-situ gel in rats exposed to Xylazine and ketamine, when administered intramuscularly (IM) at high doses to rats, can potentially cause ocular irritation in line with OECD Test Guideline 405;(25).

Materials and methods

Animals:

12 adult albino rats (6 males, 6 females, 200-250g) were used. Both eyes were exposed to xylazine (5-10 mg/kg) and ketamine (50-75 mg/kg) via intramuscular injection to induce irritation.

Groups:

Right Eye (Treatment Group): 0.1 mL of 0.1% LOX gel was applied every 30 minutes for six doses, then every 12 hours for 72 hours.

Left Eye (Control Group): Exposed to the irritant but left untreated.

Scoring System (Draize):

Corneal opacity (0-4), iris condition (0-2), conjunctival redness (0-3), chemosis (0-4), and discharge (0-3) were scored at 1, 24, 48, and 72 hours.

Histopathology:

After 72 hours, eyes were collected for histopathological evaluation of the ciliary processes, iris, and cornea.

Analytical statistic

A similarity factor (f2) was used to analyze the dissolution patterns in order to assess their statistical significance. Quantitative data analysis: A similarity factor (f2) was used in statistical analysis to validate the dissolution profiles. This component has a value between 50 and 100. It is considered that the two dissolution profiles are similar when the f2 > 50 (50-100). However, if the f2< 50, it indicates that the comparison profiles are not similar. f2 values below 50 indicate that the comparative profiles are not similar. P> 0.05 were considered to be non-significant. Using the DD Solver, a significant p<0.05 was significant. The equation was used to define the similarity factor (f2).

$$F2 = 50x\ log\left[1 + \frac{1}{n}\sum_{t=1}^{n}[R_t - T_t]^2\right]^{-0.5} \times 100 \quad (26)$$

(n) is the representation of the total number of dissolution time points. As a percentage at time (t), the test and reference dissolution values are (Rt, Tt), respectively. The remaining results are evaluated using the one way ANOVA (SPSS)(27)

Stability

A stability chamber was used to store an appropriate quantity of ocular formulation in amber-colored vials for three months at accelerated storage temperatures of 40, 25, and 4˚C and a relative humidity of 75 ,60 ,30% ± 5%. Important physicochemical characteristics like pH, drug content, and gelling capability were assessed after the samples were removed at various interval[17]

Ethics Approval

The research was approved by the Protocol Review Committee at the College of Pharmacy at the University of Baghdad, with the reference number REACUBCP352004k. The study adhered to the standards for the Care and Use of Laboratory Animals as outlined in the publication No. 85- 23, amended in 1996, by the US National Institutes of Health (NIH).

Results and Discussion

Differential Scanning Calorimetry (DSC)

The Differential Scanning Calorimetry (DSC) analysis of pure LOX revealed a melting point range between 220°C and 230°C, with a distinct exothermic peak at 228.54°C, confirming its crystalline nature (Figure 1) [19]

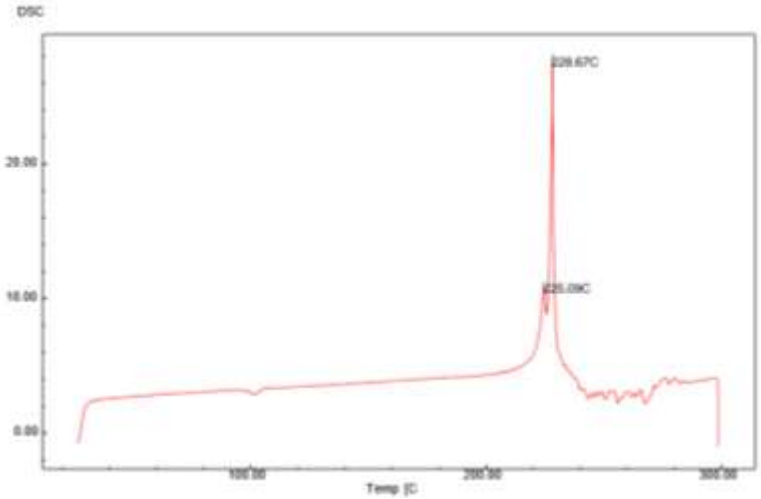

Figure 1. Differential scanning calorimetry of pure Lornoxicam

Fourier Transform Infrared (FTIR)

Spectroscopy was employed to analyze the spectra of pure LOX its physical mixture, and the selected formulation F8. The FTIR spectrum of pure LOX displayed characteristic peaks at 3462.25 cm^{-1} for OH stretching (broad peak), 3100.96 cm^{-1} for NH stretching (amide group), 3066.26 cm^{-1} for CH aromatic stretching, 1645.95 cm^{-1} for C=N stretching (thiazine ring), 1595.84 cm^{-1} for C=O stretching (amide), 1424.17 cm^{-1} for C=C stretching, 1082.83 cm^{-1} for S=O stretching, and 789.71 cm^{-1} for C-Cl stretching. The FTIR spectra of formulation F8 (Figure 2) showed consistent peaks corresponding to these functional groups**.** Fourier Transform Infrared (FTIR) spectroscopy of the final formulation F8 revealed no interaction between the bands of LOX and the gellan gum or Crospovidone (28)·

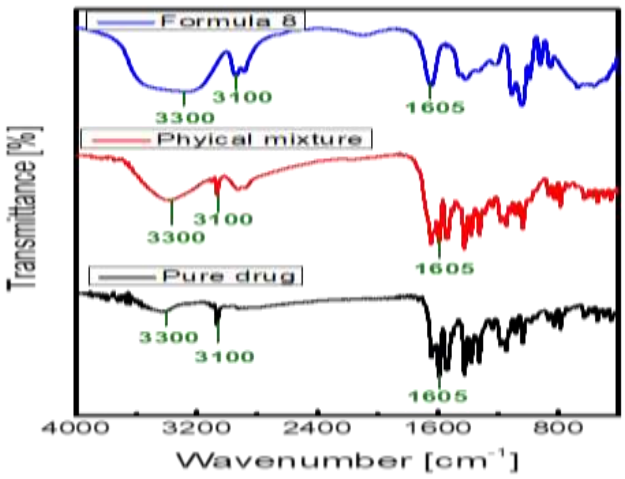

Figure 2. The FTIR spectra of Lornoxicam, the selected formulation F8, and its physical mixture indicate that there is no interaction between Lornoxicam and the other excipients.

Gelation Capacity

Formulations F1, F2, and F3 failed to produce an in-situ gel and were therefore excluded from further analysis. An increase in the concentration of gellan gum was directly correlated with enhanced gelling capacity. Among the tested formulations, F8 exhibited immediate gelation and prolonged duration (Table 2). Among the formulations, F8 proved to be the most effective, showing immediate instantaneous and long-lasting gelation. This performance can be attributed to the hydroxyl and carboxyl groups of gellan gum, which facilitate cross-linking at higher polymer concentrations. This cross-linking forms a rigid polymer matrix, enhancing gelling strength (29).

Viscosity

The viscosity of formulations F4 to F8 exhibited a significant increase following the sol-to-gel transition, with formulation F8 reaching a viscosity of 811 CP. This enhancement in viscosity was directly correlated with the increasing concentration of gellan gum, with formulations containing 0.9% and 1% gellan gum demonstrating optimal gelation properties. Specifically, the increase in gellan gum concentration led to a pronounced rise in apparent viscosity, attributable to enhanced polymer chain interactions. Gellan gum, a widely employed gelling agent in ocular drug delivery systems table2 .[30]

Osmolarity

The osmolality of the formulations ranged from 315 to 378 mOsm/L, falling within the acceptable range for ophthalmic preparations (Table 2). Formulation F8 was identified as the optimal formulation, The osmolarity of all formulations was also within an acceptable range, as solutions with osmolarity below 100 mOsm or above 640 mOsm/L are considered irritants [23]

Drug content

Drug content of 94.2% ± 0.852 in simulated tear fluid (STF), indicating uniform drug distribution within the ophthalmic gel, suggesting proper preparation and uniform drug distribution table 2 [31].

Table 2. Evaluation parameters of Lornoxicam ophthalmic in situ gel formulations.

Formula code	Gelation capacity	Gelation Time min	Drug content%	Viscosity CP	Osmolality mOsmol/L
F1	-	-	-	-	-
F2	-	-	-	-	-
F3	-	-	90.1±0.849	-	-
F4	+	58.1±6.586	90.8±0.861	322	315.6±23.809
F5	++	110±10.801	90.6±0.853	446.4	367.6±9.463
F6	+++	137.3±5.249	92±0.816	612	343.3±20.138
F7	+++	256.6±6.236	90.1±0.849	706.8	372±10.230
F8	+++	335±4.082	94.2±0.852	811	378±10.614

(Data are expressed as means ± SD, n = 3)

Rheology studies

The formulations displayed shear-thinning behavior , with an increase in shear stress corresponding to increased angular velocity, consistent with pseudoplastic rheology .[32]

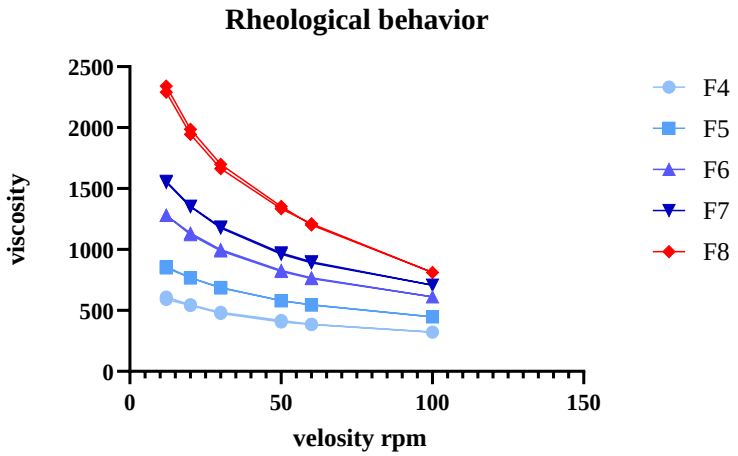

Figure3. Rheological behavior for in situ gel formulations

In vitro drug release

In vitro drug release studies showed that 73% to 91.7% of the drug was released within 6 hours across formulations F5 to F8. Notably, formulation F8 exhibited a similarity factor of less than 50 when compared with other formulations, indicating a distinct release profiles as shown in the table (3). Increasing gellan gum concentration from 0.7-0.9% to 1% enhanced the drug release rate as shown in the Figure 4. The formation and swelling of the gellan gum matrix upon hydration strengthen the gel network. A higher gellan gum concentration results in a more robust gel network, ensuring a more controlled and consistent drug release [10]. Improved gel structure can enhance drug encapsulation and provide better control over medication release. The concentration of gellan gum influences viscosity and gel characteristics. Higher gellan gum concentrations result in more viscous gels, that can expand and potentially form a more porous matrix. This increased porosity facilitates drug diffusion through the gel, enhancing the rate of medication release [33][17]. The presence of additional excipients, such as Crospovidone, also impacts the drug release profile. Crospovidone, a super disintegrant, assists in breaking down the matrix and promoting drug dissolution. Increased gellan gum concentration can enhance the interaction between Crospovidone and the gel matrix, leading to more effective drug release [34]. Statistical analysis, including one-way ANOVA, confirmed that formulation F8 yielded the best results, with a significant p-value (<0.05) and a similarity factor F2<50.

Table 3.f2 similarity factor as compared the formula 8

Formula code	f2 similarity factor value
F5 & F8	44.56
F6 &F8	48.68
F7&F8	48.6

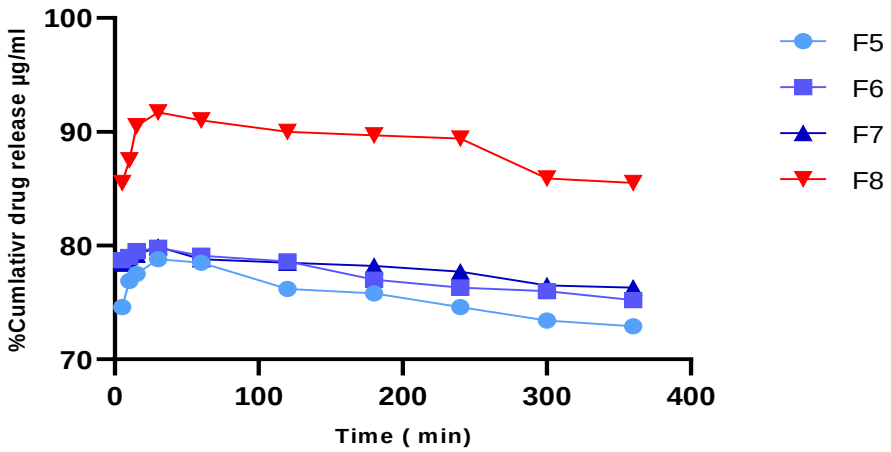

Figure 4. In-vitro release of LOX in-situ gel formulations in pH 7.4 (STF) at 150 rpm and 34°C

Draize test results

1 Hour:

Both groups (right and left eye) showed conjunctival redness (2-3) and slight chemosis (1-2). The treatment group showed no corneal opacity or iris damage.

24 Hours:

The treatment right eye exhibited reduced redness (1-2) and minimal swelling (chemosis 1), suggesting a therapeutic anti-inflammatory effect, while the control left eye still showed mild irritation.

48 Hours:

The treatment right eye had minimal redness and no swelling or discharge, while the control showed slower recovery.

72 Hours:

The treatment right eye fully recovered, with no redness or swelling, while the control left eye still had mild redness and irritation. The statistical analysis of the Draize test results for the 12 rats treated with 0.1% lornoxicam in situ gel over a 72-hour period demonstrated a significant improvement in the treated group compared to the control. Median redness scores in the treated right eye decreased from 2 (IQR 1-2) at 1 hour to 0 (IQR 0-1) at 72 hours, while the control left eye showed slower recovery, with redness decreasing from 3 (IQR 2-3) to 1 (IQR 1-2).[35]

Histopathological findings

Control Left eye

Showed congestion and mild to moderate edema in the ciliary processes.

Treated right eye:

Demonstrated normal histology of the ciliary processes, cornea, and iris, with no signs of inflammation.[4]

Result section (A) of the left eye (irritant) after 72 hr. shows: moderate to severe thickening of ciliary processes with congestion (arrows). H&E stain.100x section(A1) of the left eye (irritant) after 72hr. shows: moderate thickening of ciliary processes (Arrows) with congestion of ciliary vessels (V). H&E stain.400x. section(B) of the right eye (treated) shows: the normal appearance of ciliary processes (Arrows), Iris & cornea (C,). H&E stain.100x: section (B1) of the right eye (treated) shows: the normal appearance of ciliary epithelial processes (Arrows), &blood vessels (V) after 72 hr. .H&E stain.100x Figure 5.

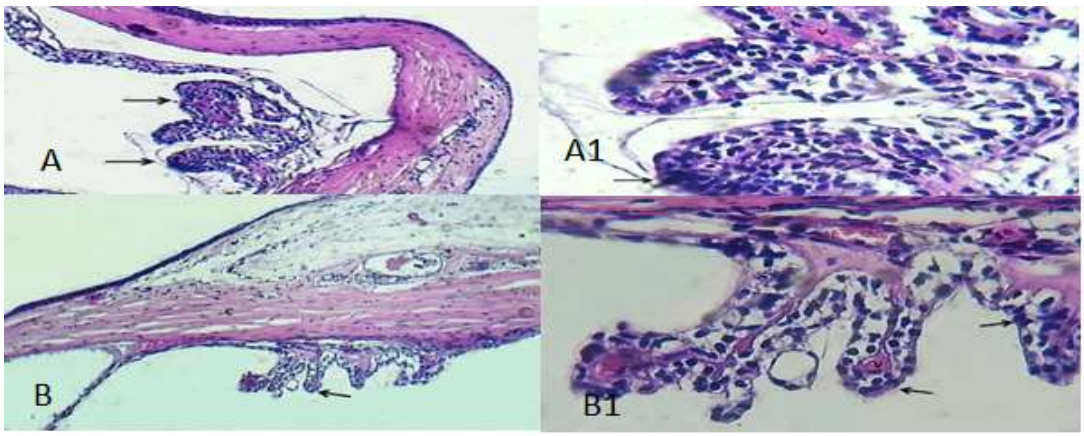

Figure 5. Histopathological examination of rat eye after 72 hours of treatment with in situ gel.1

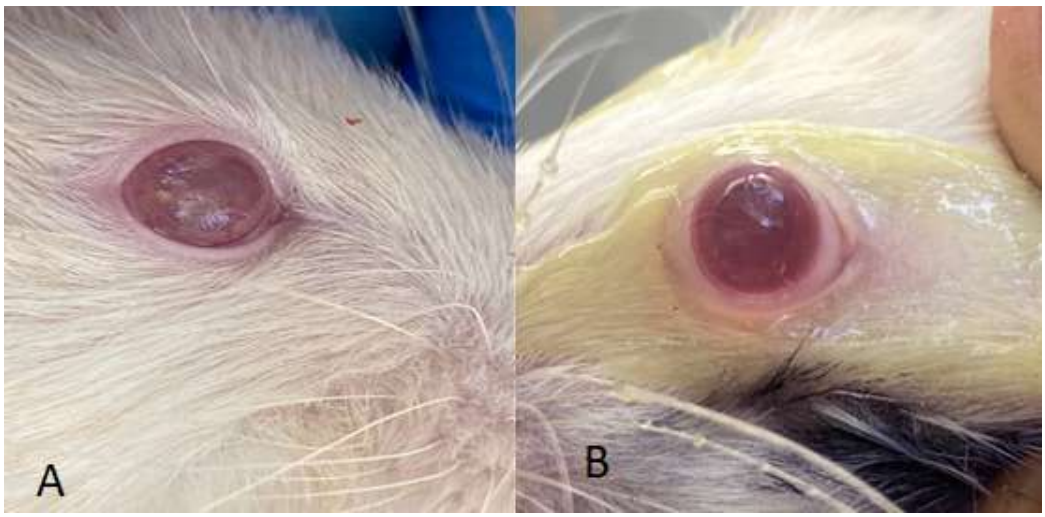

Figure 6. A Left eye of the rat untreated B right eye treated

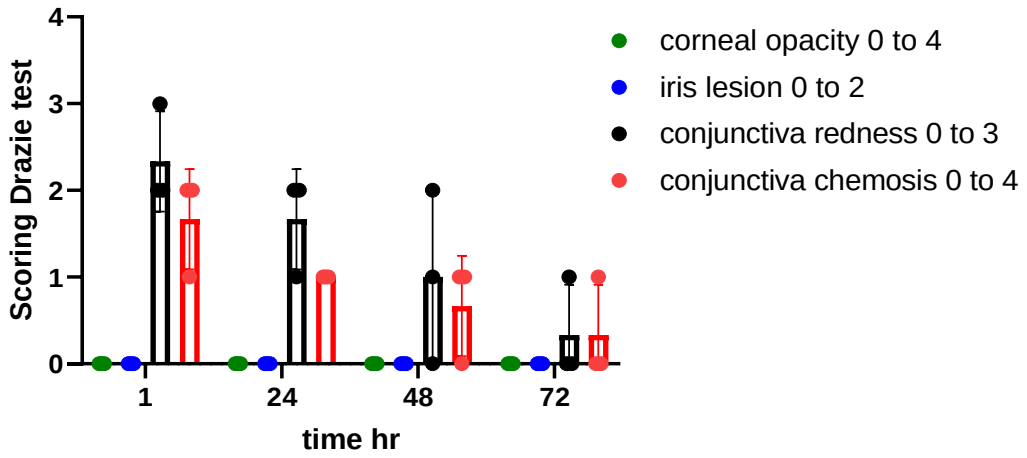

Figure 7. Ocular Response Over 72 Hours: Draize Test Scoring for Corneal Opacity, Iris Lesions, Conjunctival Redness, and Chemosis Following 0.1% Lornoxicam Gel Application

Stability study

The in-situ gel (ISG) stored at refrigeration temperature (4°C) or at room temperature showed physical stability, with minimal changes in pH and drug content for formulation F8. Therefore, refrigeration at 4 °C or room temperature is recommended for storage to prevent aggregation and maintain the stability of the formulation $p>0.05$[17].

Table5. Stability study

	Refrigerator Condition 4 ℃ RH 30% ± 5%			**Room Condition 25℃ RH 60% ± 5%**		**Accelerated 40℃ RH 75% ± 5%**	
Parameter	Day 0	Day30	Day 90	Day30	Day90	Day 30	Day 90
Appearance	Opaque	Opaque	Opaque	Opaque	Opaque	opaque	Opaque
Drug content%	94.2±0.852	94.06±0.047	93.3±0.249	94.03±0.0471	92.9±0.205	91.1±0.235	90.03±0.713
PH	6.4±0.294	6.26±0.0471	6.13±0.0942	6.2±0.047	6.03±0.0471	5.9±0.0471	5.3±0.0471
Viscosity	811	811	812	811	807	801	789

(Data are expressed as means ± SD, n = 3)

Conclusions

The use of LOX in an ion-sensitive in situ gel offers several advantages for ophthalmic drug delivery. The formulation utilizes gellan gum, which, upon contact with ions, transitions from a sol to a gel state, enhancing the viscosity and stability of the gel. This transition supports effective drug encapsulation and controlled release, improving therapeutic outcomes. The addition of excipients like Crospovidone further optimizes drug release by aiding in matrix disintegration and dissolution. Formulation F8 demonstrates superior performance in terms of viscosity, drug release rate, and stability, as confirmed by statistical analysis, in vivo study and stability

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Author Contributions

Study conceptualization and design: Riyam Sadiq Jaffer and Hanan Jalal Kassab. Experimental work: Riyam Sadiq Jaffer Data analysis: Riyam Sadiq Jaffer and Hanan Jalal Kassab. Manuscript writing and revisions: Riyam Sadiq Jaffer and Hanan Jalal Kassab.

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Conflict of Interest:

The authors declare they have no conflicts of interest during this work.

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تحضيروتقييم هلام في الموقع استجابة للأيونات لتوصيل لورنكسوكام العيني: دراسات في المختبر وفي الجسم الحي

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الخلاصة

اللورنوكسكام هو دواء مضاد للالتهابات غير ستيرويدي ينتمي إلى فئة الأوكسيمات، ويُستخدم بشكل موضعي لعلاج الالتهابات العينية. يُعتبر تطبيقه الموضعي على العين وسيلة فعّالة لتقليل الآثار الجانبية الجهازية التي قد تنتج عن استخدامه عن طريق الفم أو الحقن. ولكن، أحد التحديات الرئيسية التي تواجه استخدامه موضعياً هو التخلص السريع للدواء عبر الدموع تم تطوير هلال موضعي موضعي حساس لايونات من لورنكسكام باستخدام صمغ الجيلان وهو بوليمر يتفاعل مع ايونات الكالسيوم في السوائل الفسيولوجية مما يسمح بالافراج المستمر والمحلي للدواء يهدف هذا الأسلوب الى تعزيز فعالية العلاج بشكل افضل في هذه الدراسة تم تحضير و تقييم فعالية الجل العيني المحمل بالورنوكسكام تم تحضير تشتت صلب سطحي من لورنوكسكام وكروسبوفدون ، وتم دمجه مع الجل العيني المستجيب للأيونات، القائم على صمغ الجيلان تم اختبار تركيزات مختلفة من صمغ الجيلان لتكوين صيغ مختلفة، وتم تقييم تأثيرها على اللزوجة وقدرة التجلد التي تحتوي على ٠,١٪ (وزن/حجم) من الورنوكسكام و١ % (وزن/ حجم) صمغ الجيلان، أفرجت عن ٩١,٧٪ من الدواء في أول ٣٠ دقيقة، واستمر الإفراز لمدة ست ساعات في النموذج الحيواني باستخدام الجذران أظهرت الصيغة فعالية ف ٨ أظهرت نتائج في التجارب في المختبر في الصيغة المحسنة علاجية كبيرة في تقليل التهيج العيني خلال ٧٢ ساعه من التجربة الحية الاستنتاج: يبدو أن الجل العيني المحمل بالورنوكسوكام هو شكل جرعة واعد يساعد في تحسين احتباس الدواء في الموقع مما يقلل من التصريف السريع ويوفر فوائد علاجية محسّنة .

الكلمات المفتاحية: لورنكسوكام، كروس بوفدون ،جل عيني في الموقع، ايون ، صمغ الجيلان