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Research Article

Formulation and Evaluation of Bilastine Thermosensitive Mucoadhesive Ophthalmic *in situ* Gel

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Abstract

Background: Bilastine is a non-sedating, second-generation antihistamine used to treat urticaria and allergic conjunctivitis. ***Objective***: to formulate and test bilastine as a mucoadhesive ophthalmic *in situ* gel in order to extend its presence at site for longer time and help treat conjunctivitis and allergic rhinitis. ***Methods***: We prepared formulations using different concentrations of poloxamers (Poloxamer 407 (P407) and Poloxamer 188 (P188)) in combination with hydroxypropyl methyl cellulose (HPMC). The prepared formulas were evaluated for their physicochemical properties, sol-gel transition temperature, viscosity, mucoadhesive strength, drug release, and kinetic modeling. ***Results***: The prepared *in situ* gels were clear and transparent, having a pH ranging from 7.4 to 7.5 and a gelation temperature between 29.5 and 34.7 °C. Increasing the concentrations of P-407 and HPMC increased viscosity, gel strength, and mucoadhesion force, but caused a decrease in gelation temperature and drug release. Formula (F 14) containing P 407/P 188/HPMC as 19/4/0.75% w/v, respectively, exhibited favorable characteristics, including optimal gelation temperature (33°C), drug content (93%), gel strength (40 sec), mucoadhesive force (6125 dyne/cm^2), and 91.4% *in vitro* drug release over 5 hours. ***Conclusions***: The bilastine mucoadhesive *in situ* gel formulation is presented as a promising ophthalmic formulation for the treatment of allergic conjunctivitis.

Keywords: Bilastine, HPMC, *In situ* gel, Poloxamer, Thermosensitive.

صياغة وتقييم هلام عيني مخاطي متحسس للحرارة موضعيا للبيلاستين

الخلاصة

الخلفية: بيلاستين هو مضاد هيستامين من الجيل الثاني غير مسبب للنعاس يستخدم لعلاج الشرى والتهاب العين التحسسي. **الهدف**: يركزالبحث الحالي على صياغة وتقييم البيلاستين كهلام عيني لاصق مخاطي موضعي لزيادة وقت البقاء، لعلاج التهاب الملتحمة والتحسس الانفي. **الطرق:** تم تحضير صيغ مختلفة باستخدام تراكيز مختلفة من البولاكسمر (بولكسمر 407 و بولكسمر 188) و هيدروكسي بروبيل مثيل سليلوز. تم اختبار الصيغ من حيث خصائصاها الفيزيائية والكيميائية، ودرجة حرارة التحول من سائل الى هلام, اللزوجة, قوة الالتصاق, تحرر الدواء والنمذجة الحركية. **النتائج:** كان الهلام المعد في الموقع واضحا وشفافا، وذو أس هيدروجيني يتراوح بين 7.4 و7.5 و7.5 ودرجة حرارة تحول للهلام تتراوح بين 29.5 و34.7 درجة مئوية. تسببت زيادة تراكيز بولوكسامير 407 وهيديروكسي بروبيل مثيل سليلوز بزيادة اللزوجة، وقوة الهلام، وقوة الالتصاق بالغشاء المخاطي، ولكنها تسببت في انخفاض في درجة حرارة التحول للهلام وتحرر الدواء. أظهرت الصيغة (F 14) المحتوية على البولكسمر 407 /البولكسمر 188/هيدروكسي بروبيل مثيل سليلوز بنسبة 19/4/ 0.75 % وزن/حجم, على التوالي, خصائص ملائمة، بما في ذلك درجة حرارة التحول من سائل الى هلام (33 درجة مئوية)، والمحتوى من االدواء (93 في المائة)، قوة التماسك (40± 1.1 ثانية) قوة التصاق بالغشاء المخاطي (6125 ± 62 داين/ سم^2) و91.4 % تحرر الدواء على مدى 5 ساعات. **الاستنتاجات:** يعتبر الهلام العيني المخاطي موضعي التكوين للبيلاستين تركيبة واعدة لعلاج التهاب الملتحمة التحسسي.

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INTRODUCTION

Ocular allergy and allergic conjunctivitis are common allergic eye conditions that have become much more common in recent years. They include a group of conditions that affect the lid, conjunctiva, and/or cornea, causing red, watery, swollen, and itchy eyes that are often linked to allergic rhinitis [1]. Generally, management of allergic conditions involves using topical ocular drug delivery systems containing lubricants that help flush the ocular surface of allergens, mast cell stabilizers, and anti-histamines that relieve itching and redness [2]. Bilastine is a second-generation H1-antihistamine that is taken by mouth to treat the symptoms of allergic rhinoconjunctivitis and chronic idiopathic urticaria [3, 4]. An ophthalmic solution in a

concentration of 0.6% has been reported as safe after long-term administration in adults for the symptomatic treatment of allergic conjunctivitis [5]. Ocular drug delivery is difficult because of the unique anatomy and physiology of the eye, which includes physiological ocular barriers, tear turnover, and nasolacrimal drainage, all of which cause drug loss and limited drug absorption [6]. A variety of ocular drug delivery routes are available, but the topical route using eye drops remains the most common route because of its safety, fast onset of action, and direct eye targeting. However, precorneal drainage and therefore short residence time are still problems, leading to low bioavailability and a reduction in therapeutic efficiency [7]. Currently, ophthalmic *in situ* gel represents one of the developed approaches to overcome the limitations of conventional formulation approaches. Ophthalmic *in situ* drug delivery systems are liquid at room temperature, but they transform into a gel after instillation into the eye in response to changes in temperature, pH, or electrolyte composition in the physiological eye environment. Such systems have many advantages, such as a simple method of preparation, the delivery of an accurate dose and the ability to provide a prolonged duration of action [8,9]. Poloxamers are a synthetic amphiphilic triblock copolymers made up of two poly(ethylene oxide) (PEO) units at the ends and a poly(propylene oxide) (PPO) unit in the middle. They represent the most widely used thermosensitive polymers in the formulation of ophthalmic *in situ* gel [10]. Researchers have extensively studied ophthalmic *in situ* gels based on poloxamers, and they prefer a combination of P407 and P188 over P407 because P 188 modifies the gelation temperature to the desired ranges and changes the viscosity of the gels formed [11,12]. However, the use of poloxamers alone typically fails to provide sufficient mucoadhesion, prompting the use of various mucoadhesive polymers to enhance residence in the application site. Hydroxypropyl methyl cellulose (HPMC) has been used by many researchers for ophthalmic formulations due to its safety, rate-control effect, and appropriate physicochemical properties [13,14]. This study aimed to formulate and evaluate thermosensitive, mucoadhesive ophthalmic *in situ* gels of bilastine, combining P407 and P188 with HPMC, for the management of ocular allergies.

METHODS

Materials

Bilastine (Wuhan HSN Pharma Research Co., Ltd., China), Poloxamer 407 (BSAF, USA), Poloxamer 188 (Guangdong Gaoliang Technology Co., Ltd., China), HPMC E50 (Himedia Laboratories Pvt. Ltd., India), and mucin (Shanghai D&B Biological Science and Technology Co., Ltd., China) were purchased from the local market and benzalkonium chloride was provided by Pioneer Co. for Pharmaceutical Industries, Iraq.

Preparation of thermosensitive ophthalmic in situ gels

Bilastine *in-situ* gels were prepared by the cold method [15,16]. We dissolved weighed amounts of Poloxamer 407 (17–19% w/v) and Poloxamer 188 (P 188) (3–4% w/v) in cold deionized water (4 °C) with continuous magnetic stirring for 4 hours. We then stored the dispersions in the refrigerator for 24 hours to achieve complete polymer hydration and dissolution. The required amount of HPMC (0.5–1% w/v) was added slowly and gradually to the poloxamer dispersion at 4 °C with slow continuous stirring (50 rpm) for 30 min to prevent foam formation. Finally, bilastine (0.6% w/v) and benzalkonium chloride (0.01% w/v) as a preservative, are added, stirred for 1 hour to obtain a clear solution, and completed the solution volume. Formulations were stored at 4 °C until further use. Table 1 displays the code and composition of the formulated ocular *in situ* gels.

Table 1: Composition of bilastine ophthalmic *in situ* gel formulations*

Code	Poloxamer 407 (% w/v)	Poloxamer 188 (% w/v)	HPMC (% w/v)
F1	17	3	0.5
F2	17	3	0.75
F3	17	3	1
F4	18	3	0.5
F5	18	3	0.75
F6	18	3	1
F7	18	4	0.5
F8	18	4	0.75
F9	18	4	1
F10	19	3	0.5
F11	19	3	0.75
F12	19	3	1
F13	19	4	0.5
F14	19	4	0.75
F15	19	4	1

*Each formula contained bilastine (6 mg/ml) and 0.05% w/v of benzalkonium chloride.

Determination of physicochemical properties and gelation temperature

The physical appearance of *in situ* gels was examined by visual observation. The pH of the formulation was determined using a calibrated pH meter (Hanna, Italy) [17]. The drug content was determined by diluting 1 mL of the formulation in 3 mL of methanol with manual shaking for 2–3 minutes to mix and dissolve the contents, then the volume was made up to 10 mL in a volumetric flask using phosphate buffer (pH 7.4). Appropriate dilutions were made using phosphate buffer (pH 7.4), and samples were analyzed at 274 nm using a UV-visible spectrophotometer [18]. Measurements were conducted in triplicate. The gelation temperature of the *in situ* gels was determined by the magnetic stirrer method, reported in the literature [19]. A beaker containing 10 mL of cold formulation and a magnetic bar was placed on a temperature-controlled hot plate magnetic stirrer. A thermometer was immersed in the formulation for constant temperature monitoring. The solution was heated at a rate of 2 °C/min with continuous stirring at 50 rpm. The temperature at which the magnetic bar stopped moving was recorded as the

gelation temperature. Each measurement was performed in triplicate. The osmotic pressure of 50 µL of bubble-free formulation was determined using an osmometer (5004 Micro-Osmette, Precision Systems Inc., USA) at room temperature. Measurements were conducted in triplicate [20]. Gel strength was measured by placing 5 g of formulation in a 10 mL measuring cylinder. The samples were equilibrated at 34 °C using a temperature-controlled water bath. A weight of 3.5 g was applied to the surface of the gelled samples. The time taken for the weight to penetrate 0.5 cm through the gel was recorded as the gel strength [21]. Measurements were conducted in triplicate. The spreadability was measured by placing 0.5 g of gelled formulation in the center of a 2 cm-diameter circle pre-marked on a glass plate (10 cm × 10 cm), which was then covered by a second glass plate of the same size. A weight of 500 g was placed on the upper glass plate for 5 minutes. Upon weight removal, the diameter of the circle in centimeters formed after spreading the gel was determined [22].

Determination of viscosity and rheological studies

The viscosity of the developed formulations was determined using a MYR digital rheometer (Model VR 3000, Spain). The spindles were selected based on the viscosity range and torque. Initially, before gelation (25 °C), samples were subjected to shear at a constant rate of 50 rpm using spindle type R3. After gelation (35 °C), the rheological properties of the gelled formulations were determined by measuring viscosity at different rotational speeds ranging from 10 to 200 rpm using spindle type R6. Each sample underwent shearing for 2 minutes before the measurements were recorded. All the measurements were performed in triplicate [23].

Determination of mucoadhesive strength

The mucoadhesive force of formulations was determined using the previously reported two-pan balance method [24]. Mucin discs were prepared by compressing 100 mg of crude mucin using a manual tablet press (Hangzhou Shengde Machinery Co., China). On the left side of the balance, a glass bottle with a screw-type lid is attached through its lid, while an empty plastic beaker is positioned on the right-side pan and equilibrated it with weights on the left-side pan. To conduct the test, we attached a mucin disc to the bottom of the bottle using double-sided adhesive tape. Before conducting the mucoadhesion test, we hydrated each disc with approximately 3 drops of distilled water. We placed about three drops of formulation on the left side pan and exposed it to a heat source to allow the formula to gel; we positioned this below the suspended vial containing the mucin disc. We destroyed the equilibrium state between the two sides of the balance by removing the equilibrating weights from the right-side pan. We then added a load of 10 g to the vial on the left side, maintaining contact between the mucin disc and the gel beneath it for approximately 1 minute to facilitate the formation of an adhesive bond. Using a pipette, we added water drop by drop into the plastic beaker on the right-side pan after the preload time was complete. The process was continued until the mucin disc detached from the tested sample. The weight of water required to detach the tested sample from the mucin disc was recorded and used to calculate the detachment force using the following equation [25]:

$$\text{Detachment force} = m.g/A$$

We define m as the weight of water in grams, g as the acceleration due to gravity (980 cm/sec^2), and A as the contact area in cm^2.

In vitro drug release study

We conducted an *in vitro* drug release study of bilastine-loaded *in situ* gels using the dialysis bag method. The diffusion medium was 100 mL of freshly prepared simulated tear fluid (STF: pH 7.4) maintained at (35±0.5) °C. We soaked a dialysis membrane (molecular weight cut off 8000–14000 kDa) in the diffusion medium overnight and tied it from both ends to form a bag, into which we accurately pipetted 1 mL of formulation, equivalent to 6 mg of bilastine per mL. The dialysis bag, tied at both ends, was suspended inside the beaker containing the diffusion medium. This assembly was kept on a magnetic stirrer at 50 rpm [26]. Samples of 1 mL were withdrawn at specified time intervals and replaced by equal volumes of fresh media at the same temperature to maintain sink conditions. The aliquots were filtered using a 0.45-µm syringe filter, diluted properly with diffusion medium and analyzed by UV spectrophotometer at 274 nm using STF as a blank. We calculated and plotted the percentage of drugs released against different time intervals.

Kinetics analysis of drug release

To describe the kinetics of drug release from selected formulations, different mathematical models are used, namely the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models [27]. We performed model fitting using a DDSolver Excel Microsoft add-in program. The model with the highest correlation (R^2) value was chosen as the best-fit model.

Statistical analysis

The experimental data were analyzed using Prism software (version 8.0). A one-way analysis of variance (ANOVA) test was applied, and (p<0.05) was considered statistically significant (n = 3).

RESULTS

Table 2 displays the physicochemical properties of the prepared formulations (F1–F15). All of the formulations

were clear, colorless, and transparent liquids at 25 °C and when they were chilled. They had a pH between 7.4 and 7.5, a drug content of 93±0.2 to 100±0.31%, and an osmolarity between 393 and 519 mOsm/L. All formulations transformed into gels at temperatures above room temperature, with different sol-gel transition temperatures ranging from 29.5±0.37 to 34.7±0.39 °C (Table 2). The obtained results of gelation temperature suggest that increasing the concentration of P-407 from 17 to 19 % caused a significant reduction (p<0.05) in gelation temperature.

Table 2: Evaluation parameters of bilastine ophthalmic *in situ* gel formulations (Data are expressed as means ± SD, n = 3)

Code	Gelation Temp (°C)	Drug content (%)	Osmolarity (mOsm/l)	Gel strength (sec)	Mucoadhesion strength (dynes/cm^2)	Spreadability (cm)
F1	34.7± 0.39	/	/	/	/	/
F2	32.7±0.47	95.3±0.37	435±5	33±0.8	4287.5±45	4.1±0.02
F3	32±0.87	100±0.31	455±5	36±0.55	4746.875±67	3.8±0.01
F4	32.4±0.46	95.4±0.21	420±10	30±0.3	4134.375±57	4.5±0.02
F5	31.5±0.51	/	/	/	/	/
F6	30.8±0.75	/	/	/	/	/
F7	34±0.40	96±0.31	468±6.55	32±0.9	4440.62 ±76	3.9±0.02
F8	33±0.66	96±0.10	470±10	36±0.6	5206.25±47	3.4±0.01
F9	32±0.52	97±0.50	484±1.53	38±0.8	5971.875±59	3.3±0.01
F10	31.4±0.65	/	/	/	/	/
F11	30.8±0.60	/	/	/	/	/
F12	29.5±0.37	/	/	/	/	/
F13	33.8±0.71	95±0.32	512±6	37±0.87	5053.125± 73	4±0.02
F14	33±0.4583	93±0.20	515±13.23	40±1.1	6125±62	3.6 0.01
F15	30.4±0.3606	95.4±0.24	519 ± 3.60	42±1.3	7196.875±56	3.2±0.01

This is evident in formulations (F1-F3) as compared to formulations (F4-F6) and (F10-F12), which contain 17, 18, and 19% P407, respectively. Conversely, a significant increase (p<0.05) in gelation temperature was observed when the concentration of P 188 was increased. This is evident when comparing formulations (F4-F6) to formulations (F7-F9) that contain 18% P407 and 3.4% P 188, respectively, or when comparing formulations (F10-F12) to formulations (F13-F15) that contain 19% P407 and 3.4% P 188, respectively. When HPMC was used as a mucoadhesive polymer for all the P407/P188 polymeric combinations that were studied, the gelation temperature dropped significantly (p<0.05) as the concentration went from 0.5 to 1. Formulations (F2-F4, F7-F9, F13 and F14) showing gelation temperatures in the range of 32–35 °C were considered optimum and formulations outside this range were excluded from further evaluations. The obtained gel strength varied from 30±0.3 to 42±0.13 sec and spreadability ranged from 3.2±0.01 to 4.5±0.02 cm. As illustrated in Figure 1, the viscosity of the selected formulations determined at 50 rpm in sol and gel states varied dramatically, ranging from 120 to 240 mPa.s. before gelation at 25 °C and 2700 to 6770 mPa.s. after gelation at 35 °C.

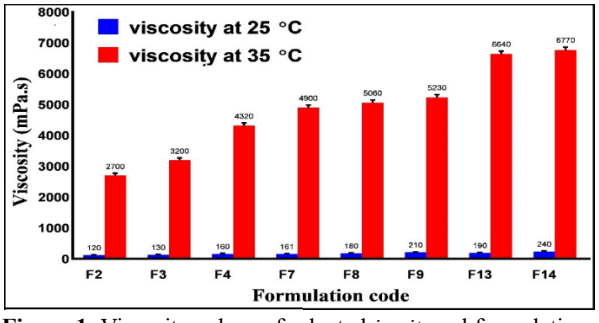

Figure 1: Viscosity values of selected *in situ* gel formulations Bilastine before gelation at 25 °C, and after gelation at 35 °C.

A rheological study of gelled formulations at 35 °C conducted at different rotational speeds indicates that formulations exhibit shear-thinning behavior (Figure 2).

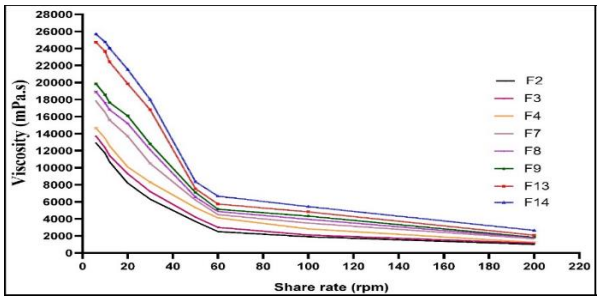

Figure 2: Viscosity profiles of selected *in situ* gel formulations of Bilastine at 35 °C.

Regarding mucoadhesive strength, the obtained values were within the range of 4287.5 to 7196.875 dynes/cm^2 and increased with increasing concentrations of mucoadhesive polymers. The *in vitro* drug release profiles of selected bilastine mucoadhesive *in situ* gel formulations are shown in Figure 3.

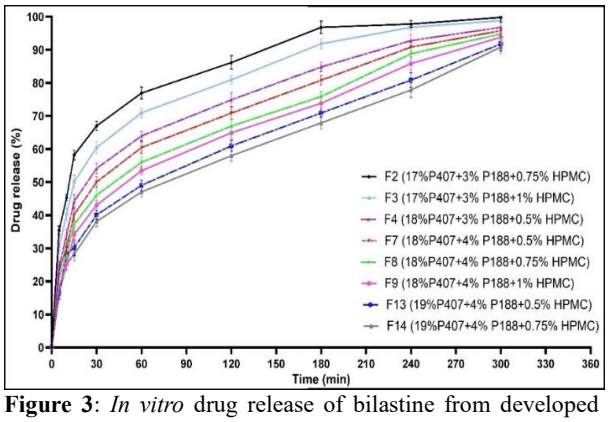

Figure 3: *In vitro* drug release of bilastine from developed formulations. (Mean±SD, n =3).

An initial burst release phase ranging from 57.04 to 74.84% was observed over 1 hour, followed by a slower release phase for 5 hours ranging from 91.82 to 98.80%. As the concentration of poloxamer and mucoadhesive polymer increased, the release of bilastine decreased. Among the studied *in-situ* gel formulations, F14 showed the slowest release after 5 hours, where 91.82% of the initially loaded drug was released.

DISCUSSION

An important step in the formulation of *in situ* gels is the choice of polymers and their concentrations. The present study utilized two types of thermosensitive polymers, poloxamer 407 and poloxamer 188, at different concentrations to promote *in situ* gelation. Numerous studies have documented the effectiveness of poloxamers as solubilizers [28,29], demonstrating this effect in bilastine-containing formulations that yielded clear and transparent formulations due to the complete dissolution of all components. The drug content of formulations was within desirable limits, ensuring adequacy in the method of preparation and reflecting uniform drug distribution. All formulations had a pH that was suitable and non-irritant, since the eye can tolerate pH values between 4 and 9 [30]. The osmolarity of all formulations was acceptable according to the literature, and solutions with an osmolarity lower than 100 mOsm or higher than 640 mOsm are considered irritants [31]. For ophthalmic *in situ* gels, the gelation temperature is considered a critical parameter. The literature has previously reported a decrease in the gelation temperature as the concentration of P407 increases [32,33]. This decrease is due to a change in the ratio of polyethylene oxide to polypropylene oxide, which leads to the formation of more micelles and facilitates gelation at a lower temperature. On the other hand, the gelation temperature rises when using higher concentrations of P188. This is because the higher polyethylene oxide content of P 188 disrupts the hydration of P 407 molecules, raises the critical micelle temperature, and decreases the likelihood of micelle formation [34,35]. Apart from the change in P407/P 188 concentrations, higher concentrations of HPMC resulted in a reduction in gelation temperature, which may be due to its binding to poloxamer chains, an increase in hydrogen bonding, and the entanglement of adjacent molecules [36]. Gel strength and spreadability of formulations were in accordance with the values of viscosities obtained: gel strength increased, whereas spreadability decreased with increasing viscosity of formulations. Similar observations were reported in the literature [37,38]. The increase in viscosity with temperature observed in all formulations confirms gel formation. An increase in micelle size and number, an increase in micellar interaction, and a higher number of hydrogen bonds formed between the poloxamer ether oxygen atom and the hydroxyl groups of HPMC may explain the higher viscosities observed at higher concentrations of polymers [39]. The shear thinning behavior observed in all formulations is preferred since it will cause better distribution of formulation over the eye surface during blinking [40]. The mucoadhesive strength of formulations depends on the polymer bonding with the membrane; therefore, it increases with the concentration of mucoadhesive polymers and is consistent with observations reported in the literature [41,42]. The concentration of both thermosensitive and mucoadhesive polymers determined the *in vitro* drug release. Initially, there was a fast release, which may be attributed to incomplete gel formation. The reduction in release rate seen later and mainly at higher concentrations of polymers can be attributed to complete gel formation and increased formulation viscosity, which will slow the drug's diffusion into the receptor medium [43,44]. Regarding drug release kinetics, the results shown in Table 3 indicate that the Peppas model was the best. The mechanism of drug release was mainly the Fickian drug release mechanism ($n < 0.45$), suggesting a diffusion mechanism for the release of dissolved drugs.

Table 3: Results of drug release data curve fitting for selected ophthalmic *in situ* gel formulations using several models*

Code	Kinetic models				
	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	Regression coefficient (R^2)				Diffusional exponent *(n)*
F2	0.2853	0.8625	0.8886	0.9919	0.305
F3	0.0975	0.8527	0.9044	0.9923	0.318
F4	0.0406	0.8602	0.9261	0.9923	0.339
F7	0.1751	0.8542	0.8894	0.9909	0.307
F8	0.2090	0.8765	0.9381	0.9863	0.360
F9	0.2623	0.9164	0.9569	0.9811	0.397
F13	0.3908	0.8876	0.9552	0.9867	0.383
F14	0.4049	0.9218	0.9727	0.9804	0.439
F15	0.6973	0.8501	0.9808	0.9933	0.423

*Bold areas represent best fit values

Conclusion

We prepared a promising bilastine-loaded, mucoadhesive thermosensitive ophthalmic *in situ* gel, using the thermosensitive polymers P407/P188 and the mucoadhesive polymer HPMC. Formulation F 14, composed of P 407/P 188/HPMC at 19/4/0.75%, was found to be optimal in terms of physicochemical

properties, with prolonged release over 5 hours, and can be considered promising for the management of ocular conjunctivitis.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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