RESEARCH ARTICLE

The Development of an Innovative Ophthalmic *In-situ* Gel Containing Posaconazole

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ABSTRACT

The goal of this study was to create and test various *in-situ* gel formulas for administering posaconazole to the eye to treat fungal keratitis. They used an *in-situ* gelling method to help posaconazole stay in the eye mucosa longer, which made it easier for the body to use. To make *in-situ* gel preparations, polymers such as sodium alginate, poloxamer 407, and poloxamer 188 were used in a cold method. Finally, there was 0.2% (w/w) posaconazole in the mixtures. The pH, drug content, viscosity, gelling capacity, and temperature at which the solution turns into a gel were all checked on the recipes. It was between 32 and 34°C when each blend turned into a gel. There was about the same amount of drugs in all of them. It was also worked out how much of the antifungal and *in-vitro* drugs these mixtures would release. Everyone in the drug release study showed signs of long-lasting release. To sum up, *in-situ* gels that contain posaconazole could be a good way to use optical drug delivery to change how fungus diseases act.

Keywords: Ocular delivery, *In-situ* gel, Posaconazole, Corneal toxicity, Irritation testing.

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INTRODUCTION

In-situ gel formation is facilitated by many natural and synthetic polymers, which may find application in oral, vaginal, ophthalmic, rectal, buccal, intraperitoneal, and parenteral drug delivery.[1,2] A lot of research has been done on *in-situ* gels as an eye medication delivery technology to improve bioavailability and ability.[3,4] Many benefits are provided by *in-situ* gel-forming polymeric formulations, such as prolonged and sustained activity that is comparable to that of a conventional drug delivery system.[5,6] The translated version of the Latin expression "*In-situ*" is "in process." Before being dispensed into the body, drugs are distributed via *in-situ* gels, which undergo *in-situ* gelation upon administration to create a gel. It is primarily a drug delivery structure made of polymers.[7,8]

The sclera is the top layer of the eye. The choroid is in the middle, the lens is in the middle, and the retina, which houses the nervous system, is at the bottom. Together, they make up the eye wall. In simple terms, the eye is round. The cornea is the clear front part of the eye that lets light in. The white part inside the eye is protected by a tough, thick, flexible sclera that covers the rest of the eye. The colored iris makes the hazel, green, grey, blue, and brown parts of the eye stand out. On the front of the eye, the choroid layer, which is in the cornea and has many blood vessels.[9–11] takes its place.

Because the eye drops come out of the eyes so quickly when you smear them, they must not be very bioavailable.[12] Because the eye is built in a way that makes it take longer for drug particles to get where they need to go, the most interesting part of a medical scientist's job is moving drugs through the eyes. There are more than 90% eye drops on the market. For some reason, they don't work well in the eye after topical treatment.[13–15] This is because they have a unique cleaning process.

Applying medicine directly to the conjunctiva and cul-de-sac is one way to treat conditions that affect the front part of the eye. Increasing the corneal transparency and lengthening the time that drugs stay in the cul-de-sac can make them more bioavailable in the eye. There are a lot of new and different dose types on the market, like collagen, shield, and *in-situ* gel. Most of the time, this preparation is not appropriate because it blurs vision. This includes gels, suspensions, ointments, and polymeric implants. This problem is meant to be fixed

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Table 1: pH, poloxamers concentration and gelling temperature of the formulation

Codes	*S1*	*S2*	*S3*	*S4*	*S5*	*S6*	*S7*
Poloxamer 188	20	15	10	7.5	10	15	20
Poloxamer 407	5	10	15	25	10	15	20
pH	6.98	6.26	6.24	7.03	7.00	7.64	6.99
Gelling temperature	30–32	42–43	41–42	31–32	28–29	39–40	32–33

by the *in-situ* gel invention for the ocular medication release method.[16–19] It is thought that making a drug layer thicker in the pre-corneal area will increase its solubility because the cornea drains slowly. However, *in-situ* gels must be made of fluids that don't stick together and flow easily so that results can be repeated.[20,21] This *in-situ* gelling arrangement has benefits such as being easy to use, causing less harm locally and generally, and helping with long-term and sustained medication relief. Some of the problems are that bigger doses can't be directed, the automatic strength isn't very high, and biological degradation can make the material unstable without meaning to.[22–24]

Poloxamers are used *in-situ* forming devices for optical drug delivery because they are biocompatible, easy to sterilize, and change shape based on temperature. Poloxamer is bendable, sticks to mucus, and changes shape in response to temperature. It is a poloxamer that controls the long-term release of both small and big drug particles. Poloxamer 407 can't be made bigger for oral use because it can change lipid profiles and could be harmful to the kidneys. The way poloxamer 407 is made says that it can better dissolve medicines that don't dissolve well in water and have a longer release profile in many galenic uses.

Poloxamers are artificial triblock copolymers having a mass ratio of 4:24 and a core hydrophobic polyoxypropylene sequence surrounded by two hydrophobic series and two water-soluble polyoxyethylene chains.[25–28] Poloxamer 188 (P188), a non-ionic direct copolymer, FLOCOR, PLURONIC F68, and RheothRx, has a mean molecular weight of 8400 Daltons. P188 has an 18-hour half-life and is safe for 72 hours. P188 should repair cell membranes.[29,30]

Like ravuconazole, albaconazole, voriconazole, and azaconazole, posaconazole is a member of the second generation of triazole groups. It works better than the first drugs in this group at killing germs that cause wounds.[31,32] It was chosen as an active helper because it does a lot of different things. The drug has been through phase III tests and has been approved by regulators to treat and stop fungal infections that are getting in the way. Zingomycetes, *Aspergillus*, *Candida*, and *Cryptococcus neoformans* are some of the molds that are affected. It is made up of the same building blocks as itraconazole.[33–35]

Fungal keratitis is a corneal disease that can be caused by problems with the immune system or by yeast, bacteria, viruses, fungi, or amoebas getting into the eye.[36] When people use steroids and broad-spectrum antibiotics, plant and dirt debris can get into corneal ulcers, people who wear contact lenses, and eye injuries are all things that can make fungal keratitis spread.[37] If you want to escape complications and losing your sight, you need to treat fungal keratitis as soon as possible.[38]

MATERIALS AND METHODS

Materials

Pomaconazole was a gift from Honour Labs Ltd. in Telangana, India, and sodium alginate was bought from Nice Chemicals in Ahmedabad, India. Loba chemistry in Mumbai, India, was where the benzalkonium chloride was bought. Poloxamers 407 and 188 were kindly given to us by BASF in Turkey. We bought a Spectrum spectra/pro 4 rc dialysis membrane (12-14 kDa mw, 23.8 mm diameter, flat width-33.12 mm, 4.45 mL/cm capacity) from Himedia Laboratories Pvt. Ltd. in Mumbai, India.

Method

Preparation of in-situ gel

We use gelling agents like poloxamer Analogus in the cold way of *in-situ* gel formation. The *in-situ* gel's polymeric solution is made up of poloxamer 407(25) and poloxamer 188 (7.5). These were mixed with cold water and a magnetic mixer for two hours or until the mixture was completely dissolved. A dispersed polymeric solution is made, and it is then put in the fridge for 48 hours to make a clear solution.

Determination of solution gel temperature-

There was water in a clear beaker that had 10 mL of polymeric solution in it. The setup was put on a magnetic mixer that turned at least 200 times per minute. The temperature of the water bath was slowly raised to a maximum of 2°C while it was being stirred all the time. A thermometer was put into the sample fluid to keep track of the evaluation as it went on. The gelation temperature is when the magnetic bar stops moving and gels. Table 1 shows pH, poloxamers concentration and gelling temperature of the formulation.

Formulation of posaconazole loaded in-situ gel

It was possible to put *in-situ* gels into groups based on their chemical makeup, gelling temperature, and pH levels. It was decided that S4, which had 25% P407 and 7.5% P188, was the best formulation for planning an ophthalmic formulation. Three different concentrations of sodium alginate were found to have the best *in-situ* gel alignments. The same amount of posaconazole was added to the liquid poloxamers for each preparation, and the mixture was mixed continuously until the posaconazole was evenly spread. It was made better to use benzalkonium chloride (0.02% w/w) as a stabilizer in the

Table 2: Formulation batches of *in-situ* gel

Ingredients	*F*	*F1*	*F2*	*F3*	*F4*
Posaconazole	-	0.2	0.2	0.2	0.2
Poloxamer 188	7.5	7.5	7.5	7.5	7.5
Poloxamer 407	25	25	25	25	25
Sodium chloride	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02
Sodium alginate	-	-	0.2	0.4	0.6
Distilled water Q.S.	100	100	100	100	100

mixes. To maintain isotonicity, sodium chloride (0.9% w/w) was added. It was also determined how medicine and other mixture additives affected gelling temperature. Table 2 gives formulation batches of in-situ gel.

Characterization of in-situ gel

The developed ophthalmic formulation underwent various characterizations, including measurements of pH, gelling temperature, clarity, viscosity, drug content, and clarity.

pH

With the use of a standardized pH meter, the pH of gel was determined.

Gelling capacity

At 32 to 34ºC in a beaker, a drop of ready formulation was located for determination of gelling capacity. Gelling time was visually noticed.

+ gel after few minutes the gel get quickly dissolved
++ For few minutes, instantaneous gelation retains.
+++ For approximately an hour the fast gelation rest

Drug content

To measure the medicine concentration of the posaconazole *in-situ* gelling combination, 100 mL of pH 7.4 simulated tear fluid and 1-mL of precisely weighed *in-situ* gel were mixed. Shaking for two to three minutes clarified and broke up the mixture. Posaconazole was 260 nm on the UV-visible spectrophotometer.

Viscosity

At 25 to 37ºC with the help of Brookfield viscometer having spindle RV^2 and 100 rpm, by this method viscosity of the gel was examined.

Clarity

Below the white and black background with optical examination, the clarity of made solution was concluded. Turbid, +, clear, ++, and very clear +++.

Isotonicity

Keeping isotonicity high is crucial for ophthalmic products to avoid tissue damage and eye irritation. Salts exert osmotic pressure on water solutions. Osmometers measure tonicity. The ocular product's osmotic pressure should be 290 to 310 mOsmol/kg.

HPLC analysis

The HPLC setup had an Agilent 1100 UV detector and a gradient pump. A 4.6 x 150 mm, 5 µm C18 column from GL Sciences in Japan was used. The tests used a flow rate of 1-mL/min at 262 nm and 25°C. It was 70:30 methanol to acetonitrile in the mobile phase. The medicine was kept for two and a half minutes. The procedure's LoQ, linearity, LoD, stability, selection, accuracy, and precision were all checked and found to be valid. Figure 1 shows HPLC chromatogram of Posaconazole.

In-vitro drug release study

For the *in-vitro* drug release study (Figure 2), the dialysis bag method was used. For the *in-situ* gel versions, they were tested for release in stirred tear fluid with a pH of 7.4 at 50 rpm. The temperature was kept between 32 and 34ºC to mimic the temperature of the eye's surface. A dialysis layer (Spectra/Pro, with a molecular weight of 12–14 kDa) was used to remove 5 g of the preparation from the discharge media. The preparation was then wrapped in ends. The sheath was cooked in bidistilled water at 33 ± 1°C for 30 minutes before it was used. At set times every 1 to 8 hours, 0.5 mL of the test were taken out and replaced with the same amount of fresh medium. Three times, the tests were seen.

Stability of the in-situ gel

Physical stability reports say that posaconazole overflows *in-situ* gels were kept for three months in stability cabinets at 25 ± 2°C and 40 ± C and in the fridge at 5 ± 1°C. After three months of loading, the posaconazol substance, optical presence, pH, gelation time, and *in-situ* gel quality were all checked. Three sets of trials were carried out.

Microbiological Studies

Sterility studies

The gel formation continued in a Haier HR40-IIA2 cabinet with laminar airflow, with or without posaconazole. The visual recipes were examined for sterility regulators to prevent reproduction. A clean environment sterility analysis of the *in-situ* gel with or without posaconazole authorized the universal pharmacopeia. Soybean casein abstract media was employed for aerobic bacteria and fungi. A liquid thioglycollate container held anaerobic bacteria. Each medium received 1-mL of formulation mixtures daily for 14 days. Fungi were kept at 25°C and bacteria at 35. The advancement test determined how effectively standard testing fluids dissolved in the sterility research. For the aerobe, anaerobe, and yeast growth elevation test, fluid thioglycollate carriers were filled with 100 CFU of *Clostridium sporogenes* ATCC 19404, *Staphylococcus aureus* ATCC 6538, and *Candida albicans* ATCC 10231. Microbes received different media quantities. For 48 hours, the procedures were maintained at 35ºC.

Determination of MIC of posaconazole

The broth micro reduction assay followed CLSI standards for fungi and filamentous yeasts. Phosaconazole was combined with dimethyl sulfoxide at a final concentration of 500 to

Table 3: pH, gelling capacity, drug content, viscosity and clarity of *in-situ* gel

Formulations	*F*	*F1*	*F2*	*F3*	*F4*
Ph	6.26 ± 0.02	6.99 ± 0.01	7.00 ± 0.01	7.03 ± 0.02	7.64 ± 0.01
Gelling capacity	+++	+++	+++	+++	+++
Drug content	-	84.24 ± 0.26	83.18 ± 0.34	81.21 ± 1.05	93.47 ± 0.49
Viscosity	338 ± 2.1	354 ± 3.6	378 ± 9.27	414 ± 11.35	457 ± 8.56
Clarity	++	+++	++	+++	+++

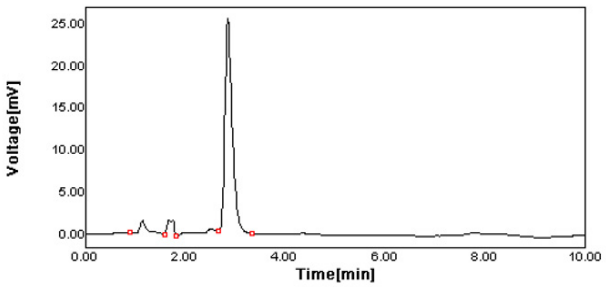

Figure 1: HPLC chromatograph of posaconazole

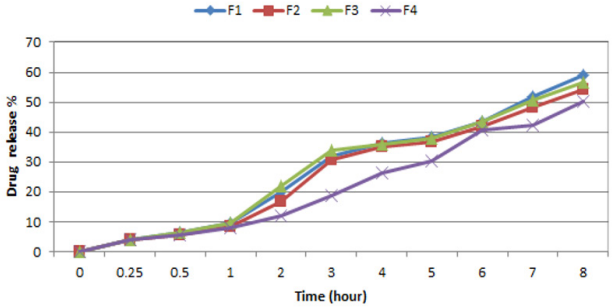

Figure 2: Posaconazole release study from *in-situ* gel

0.125 µg/mL. 0.0165M MOPS buffer (3-(N-morpholino) propane sulfonic acid) raised the RPMI 1640 intermediate buffer pH to 7.0. Spectrophotometric inoculum production involved 0.4 to 5×10^4 spores/mL for molds and 1.5 (± 1.0) × 103 cells/mL for yeasts. MOPS-buffering RPMI 1640 was employed. The proposed mixture was examined for its antifungal effectiveness against fungal keratitis-causing *A. flavus* (ATCC 204304 and 204305), *C. tropicalis* (RSKK 2421), and *C. albicans* (ATCC 1031). Each microdilution plate received 0.1 mL inoculum to strengthen it. Developable MICs were repaired after 48 hours. The same-rate well expansion rattled the plates. Each well's development was compared to the posaconazole-free control well using an interpretive mirror. The MIC endpoints were calculated using the final medication dose that inhibited control well growth by 50%.

RESULT AND DISCUSSION

Several concentrations of poloxomers, which are made by polymers, were used to keep an eye on preliminary tests. The *in-situ* gelling organization is made up of different pH components, such as poloxamer 407, poloxamer 188, and sodium alginate. Poloxamer 407 and poloxamer 188 are very heat-sensitive, which helps make heat-sensitive *in-situ* gels by using the cold method. Ethylene oxide and propylene oxide gel too easily when heated too much, but poloxamer 407 can make drugs that don't dissolve well in water dissolve better.

Determining appropriate gelling temperature both poloxamer 407 and poloxamer 188, sodium alginate, sodium chloride, and posaconazole are to be combined together at various concentrations. Table 3 displays various terms, including pH, concentration and gelling temperature of poloxamer.

Description of *In-situ* Gel

When describing thermosensitive *in-situ* gel formation, things like clarity, pH, viscosity, drug amount, gelling temperature, and gelling capacity are all taken into account.

pH

This pH is compatible with eyes and would not induce irritation inside the eye. The pH of the prepared polymeric solution is displayed in Table 3. The pH of the prepared polymeric solution ranges between 6.2 to 7.6.

Gelation Temperature and Gelling Capacity

The created thermo-sensitive *in-situ* gel formulation has the right viscosity, making it easy to instill as a liquid drop in the eye and enabling the formulations to dissolve quickly into the *in-situ* gel. If the concentration of gelling agent increases then gelling capacity will go on increasing.

Gelling capacity based on which type of polymers were added with their different concentration gelation temperature of prepared polymeric solution ranging between 31 to 34ºC. Sodium alginate is accountable (responsible) for reducing gelation temperature.

Drug Content

It was ensured that the medication content in the produced formulation was within permissible limits and that the dose was uniform. The produced formulation's drug content ranged from 81.21 to 93.47%.

Viscosity

Table 3 shows the viscosity of the produced polymeric solution. When *in-situ* gel is injected into a conjunctival decubitus, its viscosity changes to a gel-forming state because the eye's bioavailability is reduced. The produced polymeric solution of *in-situ* gel has a specified viscosity.

Clarity

In-situ gels are simultaneously subjected to visual inspection before and after gelling against a white or black backdrop in

order to obtain a clan solution free of undesirable particles or opalescence. At temperature ranges of 4 to 25°C, ideal *in-situ* gels with transparent properties create clear solutions.

Isotonicity

The osmometer is used to measure tonicity. The measured tonicity of 0.298 or 298 mOsmol/kg, is within permissible bounds.

HPLC

In-vitro drug release study

Posaconazole gelling products F1 through F4 were put through *in-vitro* release tests. The release vehicle was simulated tear fluid with a pH of 7.4. Posaconazole formulations showed constant drug release for 8 hours. The amount of posaconazole released *in-vitro* from formulations F1, F2, and F3 was found to be 68, 62, and 64%, respectively, after 8 hours ($p > 0.05$). In contrast to the other formulations, the F4 one showed a delayed release. This could be an attempt to get more sodium alginate into the formulas that are being made.

Stability

Stability cabinets were used for the three-month stability investigations, which were conducted at 5 to 25ºC. The samples' visual appearance, clarity, and gelation time were all confirmed to be unchanged by the monthly periodic analysis.

Studies on microbiology

The superior *in-situ* gels accepted the purity test since the liquid thioglycollate medium at 35°C for 14 days and the soya bean casein digest medium at 20 to 25°C showed no turbidity growth or bacterium growth. To ensure the growth promotion test and sterility test media worked, both species of bacteria had to be present in all mediums.

MIC of posaconazole

The MIC values for the final medication concentration that slowed control well progress by 90 and 50% were discovered. Posaconazole has MIC90 values of 1, 2, 0.5, and 0.5 µg/mL against *C. tropicalis, C. albicans, A. flavus,* and *A. fumigatus*, in order. The MIC50 values for all species were 0.25 µg/mL. The MIC values for *A. flavus* and *A. fumigatus* from outdoor strains and clinical isolates matched our investigation. *Asperigillus* sp. has a 1-mg/L MIC90. Both bacteria had MICs between 0.2 and 5 µg/mL. For *A. flavus* detachments, the range was 0.125 to 1-µg/mL and 0.25 to 1-µg/mL. *Candida* species with CLSI M27-A3 MIC values ≤1-µg/mL are considered liable, 2 µg/mL requires susceptibility, and 4 µg/mL or higher is challenging.

CONCLUSION

We chose to use poloxamer 407 because it is an important part of making *in-situ* gel and has great qualities, such as being a thermo-sensitive copolymer. Poloxamer 188 and poloxamer 407, on the other hand, are used together in a polymeric solution mixture. The *in-situ* glue is successfully made using the cold method. Many measurements were taken, such as pH, viscosity, clarity, gelation, temperature, medication content, stability, and study that was done in a lab. Based on this study, the developed *in-situ* gel product might be able to deliver posaconazole to the eyes.

REFERENCES

1. Kouchak M. In Situ Gelling Systems for Drug Delivery. Jundishapur J Nat Pharm Prod. 2014;1;9(3):20126. https://doi.org/10.17795/jjnpp-20126
2. Madan M, Bajaj A, Lewis S, Udupa N, Baig J. In situforming polymeric drug delivery systems. Indian J Pharm Sci. 2009;71(3):242. https://doi.org/10.4103/0250-474X.56015
3. Nair AB, Shah J, Jacob S, Al-Dhubiab BE, Sreeharsha N, Morsy MA, et al. Experimental design, formulation and in vivo evaluation of a novel topical in situ gel system to treat ocular infections. PLoS ONE. 2021;19;16(3):e0248857. https://doi.org/10.1371/journal.pone.0248857
4. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020 Mar 20;24(1). https://doi.org/10.1186/s40824-020-0184-8
5. Madan M, Bajaj A, Lewis S, Udupa N, Baig J. In situforming polymeric drug delivery systems. Indian J Pharm Sci. 2009;71(3):242. https://doi.org/10.4103/0250-474X.56015
6. Cao S, Ren X, Zhang Q, Chen E, Xu F, Chen J, et al. In situ gel based on gellan gum as new carrier for nasal administration of mometasone furoate. International Journal of Pharmaceutics. 2009;5;365(1-2):109-15.. https://doi.org/10.1016/j.ijpharm.2008.08.042
7. Chaudhary B, Verma S. Preparation and Evaluation of NovelIn SituGels Containing Acyclovir for the Treatment of Oral Herpes Simplex Virus Infections. The Scientific World Journal. 2014;2014:1-7. https://doi.org/10.1155/2014/280928
8. Tamara Perchyonok V, Zhang S, Oberholzer T. Chitosan and Gelatin based Prototype Delivery Systems for the Treatment of Oral Mucositis: from Material to Performance in vitro. CDD. 2013;1;10(1):144-50. https://doi. org/10.2174/1567201811310010020
9. Majeed A, & Khan NA. Ocular in-situ gel: An overview. Journal of Drug Delivery and Therapeutics, 2019;9(1):337-347. https://doi.org/10.22270/jddt.v9i1.
10. Wang L, Zhou MB, Zhang H. The Emerging Role of Topical Ocular Drugs to Target the Posterior Eye. Ophthalmol Ther. 2021;10(3):465-94. https://doi.org/10.1007/s40123-021- 00365-y
11. Gupta, B., Mishra, V., Gharat, S., Momin, M., & Omri, A. (2021). Cellulosic Polymers for Enhancing Drug Bioavailability in Ocular Drug Delivery Systems. Pharmaceuticals (Basel, Switzerland), 14(11), 1201. https://doi.org/10.3390/ph14111201
12. Makwana S, Patel V, Parmar S. Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride. Results in Pharma Sciences. 2016;6:1-6.https://doi.org/10.1016/j.rinphs.2015.06.001
13. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, et al. Research progress of in-situ gelling ophthalmic drug delivery system. Asian Journal of Pharmaceutical Sciences. 2019;14(1):1-15. https://doi.org/10.1016/j. ajps.2018.04.008
14. Bisht R, Mandal A, Jaiswal JK, Rupenthal ID. Nanocarrier mediated retinal drug delivery: overcoming ocular barriers to treat posterior eye diseases. WIREs Nanomed Nanobiotechnol. 2018;10(2).https://doi.org/10.1002/wnan.1473
15. Joseph RR, Venkatraman SS. Drug Delivery to the Eye: What Benefits do Nanocarriers offer? Nanomedicine (Lond). 2017;12(6):683-702. https://doi.org/10.2217/nnm-2016-0379

16. Kotreka UK, Davis VL, Adeyeye MC. Development of topical ophthalmic In Situ gel-forming estradiol delivery system intended for the prevention of age-related cataracts. PLoS ONE. 2017;21;12(2):e0172306. https://doi.org/10.1371/journal.pone.0172306
17. Destruel P, Zeng N, Seguin J, Douat S, Rosa F, Brignole-Baudouin F, et al. Novel in situ gelling ophthalmic drug delivery system based on gellan gum and hydroxyethylcellulose: Innovative rheological characterization, in vitro and in vivo evidence of a sustained precorneal retention time. International Journal of Pharmaceutics. 2020;574:118734. https://doi.org/10.1016/j.ijpharm.2019.118734
18. Destruel P, Zeng N, Maury M, Mignet N, Boudy V. In vitro and in vivo evaluation of in situ gelling systems for sustained topical ophthalmic delivery: state of the art and beyond. Drug Discovery Today. 2017;22(4):638-51. https://doi. org/10.1016/j.drudis.2016.12.008
19. Gratieri T, Gelfuso GM, de Freitas O, Rocha EM, Lopez RF. Enhancing and sustaining the topical ocular delivery of fluconazole using chitosan solution and poloxamer/chitosan in situ forming gel. European Journal of Pharmaceutics and Biopharmaceutics. 2011;79(2):320-7. https:// doi.org/10.1016/j.ejpb.2011.05.006
20. Sheshala R, Kok Y, Ng J, Thakur R, Dua K. In Situ Gelling Ophthalmic Drug Delivery System: An Overview and Its Applications. DDF. 2015;14;9(3):242-53. https://doi.org/10.2174/187221130 9666150724101227
21. Kubo W, Konno Y, Miyazaki S, Attwood D. In Situ Gelling Pectin Formulations for Oral Sustained Delivery of Paracetamol. Drug Development and Industrial Pharmacy. 2004;30(6):593-9. https://doi.org/10.1081/ddc-120037490
22. Konatham M, gorle MT, et al. In situ gel polymers: a review. Int J App Pharm. 2021;13(1):86-90. https://doi.org/10.22159/ijap.2021v13i1.39504
23. Prasanthi S, Vidyavathi M. Formulation and Optimization Of Buoyant In Situ Gelling System of Valsartan Using Natural Polymer. Int J Pharm Pharm Sci. 2017 Oct 2;9(10):128. https://doi. org/10.22159/ijpps.2017v9i10.20809
24. Nandgude TD. Emulgel: A Comprehensive Review for Topical Delivery of Hydrophobic Drugs. Asian Journal of Pharmaceutics. 2018;12(02). https://doi.org/10.22377/ajp. v12i02.2366
25. Soliman KA, Ullah K, Shah A, Jones DS, Singh TR. Poloxamer-based in situ gelling thermoresponsive systems for ocular drug delivery applications. Drug Discovery Today. 2019;24(8):1575-86. https://doi.org/10.1016/j.drudis.2019.05.036
26. Fakhari A, Corcoran M, Schwarz A. Thermogelling properties of purified poloxamer 407. Heliyon. 2017;3(8):e00390. https://doi.org/10.1016/j.heliyon.2017.e00390
27. Al Khateb K, Ozhmukhametova EK, Mussin MN, Seilkhanov SK, Rakhypbekov TK, Lau WM, et al. In situ gelling systems based on Pluronic F127/Pluronic F68 formulations for ocular drug delivery. International Journal of Pharmaceutics. 2016 ;502(1-2):70-9. https://doi.org/10.1016/j.ijpharm.2016.02.027
28. Krtalić I, Radošević S, Hafner A, Grassi M, Nenadić M, Cetina-Čižmek B, et al. D-Optimal Design in the Development of Rheologically Improved In Situ Forming Ophthalmic Gel. Journal of Pharmaceutical Sciences. 2018 Jun;107(6):1562-71. https:// doi.org/10.1016/j.xphs.2018.01.019
29. Moloughney GJ, Weisleder N. Poloxamer 188 (P188) as a Membrane Resealing Reagent in Biomedical Applications. BIOT.2012;6(3):200-11. https://doi.org/10.2174/1872208311206030200
30. Waddell LB, Lemckert FA, Zheng XF, Tran J, Evesson FJ, Hawkes JM, et al. Dysferlin, Annexin A1, and Mitsugumin 53 Are Upregulated in Muscular Dystrophy and Localize to Longitudinal Tubules of the T-System With Stretch. J Neuropathol Exp Neurol. 2011;70(4):302-13. https://doi.org/10.1097/NEN.0b013e31821350b0
31. Aykaç K, Yenilmez E, et al.. Posaconazole loaded ocular inserts for antifungal activity. Journal of Pharmaceutical Technology. 2020;1(1):1-6.
32. Chaudhari P, Ghate VM, Lewis SA. Supramolecular cyclodextrin complex: Diversity, safety, and applications in ocular therapeutics. Experimental Eye Research. 2019;189:107829. https://doi.org/10.1016/j. exer.2019.107829
33. Franca JR, Foureaux G, Fuscaldi LL, Ribeiro TG, Castilho RO, Yoshida MI, et al. Chitosan/hydroxyethyl cellulose inserts for sustained-release of dorzolamide for glaucoma treatment: In vitro and in vivo evaluation. International Journal of Pharmaceutics. 2019;570:118662. https://doi.org/10.1016/j.ijpharm.2019.118662
34. Mohammed BS, Al-Gawhari FJ. Preparation of Posaconazole Nanosponges for Improved Topical Delivery System. International Journal of Drug Delivery Technology. 2022;12(1):8-14.
35. Greer ND. Posaconazole (Noxafil): A New Triazole Antifungal Agent. Baylor University Medical Center Proceedings. 2007;20(2):188-96. https://doi.org/10.1080/08998280.2007.11928283
36. Nasser ST, Abdulrassol AA, Ghareeb MM. Design, Preparation, and In-vitro Evaluation of Novel Ocular Antifungal Nanoemulsion Using Posaconazole as a Model Drug. International Journal of Drug Delivery Technology. 2021;11(3):1058-1064.
37. Sengupta J, Saha S, Banerjee D, Khetan A. Epidemiological profile of fungal keratitis in urban population of West Bengal, India. Oman J Ophthalmol. 2009;2(3):114. https://doi.org/10.4103/0974-620X.57310
38. Klont RR, Eggink CA, Rijs AJMM, Wesseling P, Verweij PE. Successful Treatment ofFusarium Keratitis with Cornea Transplantation and Topical and Systemic Voriconazole. Clinical Infectious Diseases. 2005;40(12):e110-e112. https:// doi.org/10.1086/430062