Effect of percentage of polyvinyl alcohol on the properties of econazole nitrate polymeric micelles eye drop

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Article Info:

Received Dec 2023
Revised Feb 2024
Accepted Apr 2024
Published Apr 2025
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DOI: https://doi.org/10.32947/ajps.v25i2.1152

Abstract:

Econazole nitrate, a chemically produced triazole drug, is utilized to manage fungal keratitis. It has potent antifungal properties against many species; the readily available formula exhibits inadequate corneal permeability, visual aberrations, excessive tearing, dilution of tears, and leakage via the nasolacrimal duct.

This research aimed to study the effect of polyvinyl alcohol concentration on the properties of econazole nitrate polymeric micelles eye drops. Polymeric micelles loaded with econazole nitrate eye drops were prepared with different polyvinyl alcohol concentrations and evaluated for particle size, polydispersity index, zeta potential, and drug content. Formulations evaluated for ex vivo drug permeation using Franz diffusion cell. The cumulative drug permeation (CDP) percentage of the optimum formulation exhibits a significant variation of 64.4 % which has 2% of PVA as compared to econazole nitrate pure drug suspension 12.69% CDP. The cumulative drug permeation (CDP) percentage of the optimum formulation F3D demonstrated a 5-fold increase in ex vivo permeability through the goat ocular membrane compared to the econazole nitrate suspension may be attributed to the PVA use as a thickening agent. Using econazole nitrate polymeric micelle as eye drop containing 2% PVA led to system that is efficient and superior in overcoming ocular obstacles and facilitating the appropriate administration of lipophilic medicines by increasing contact time at the ocular surface and improving bioavailability.

Keywords: Econazole nitrate, Eye drop, Poloxamer 188, Polymeric Micelles, PVA

تأثير نسبة كحول البولي فينيل على خواص قطرة العين من نترات إيكونازول

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الخلاصة:

تستخدم نترات الايكونانزول، وهو دواء تريازول منتج كيميائيا، لإدارة التهاب القرنية الفطري. لها خصائص مضادة للفطريات قوية ضد العديد من الأنواع. تظهر التركيبة المتاحة بسهولة نفاذية القرنية غير الكافية، والانحرافات البصرية، والتمزق المفرط، وتخفيف الدموع، والتسرب عبر القناة الدمعية الأنفية. هدف هذا البحث الى دراسة تأثير تركيز كحول البولي فينيل على خواص قطرة العين من المذيلات البوليمرية ايكونازول نترات. تم تحضير المذيلات البوليمرية المحملة بقطرات نترات الإيكونازول بتراكيز مختلفة من كحول البولي فينيل وتقييمها لحجم الجسيمات ومؤشر التشتت المتعدد وإمكانات الزيتا والمحتوى الدوائي. تم تقييم التركيبات لدراسة نفاذية الدواء خلال العين باستخدام خلية انتشار فرانز. تظهر نسبة نفاذية الدواء التراكمية للتركيبة المثلى تباينا معنويا بنسبة 64.4٪ والتي تحتوي على 2٪ من بولي فنيل الكحول مقارنة

بمعلق نترات الإيكونازول النقي للدواء 12.69٪. أظهر **F3D** زيادة بمقدار 5 أضعاف في نفاذية خارج الجسم الحي من خلال غشاء العين الماعز مقارنة بتعليق نترات الإيكونازول يمكن أن يعزى إلى استخدام بولي فنيل الكحول كعامل سماكة. استخدام المذيلة البوليمرية نترات إيكونازول كقطرة للعين تحتوي على 2٪ بولي فنيل الكحول أدى إلى نظام فعال ومتفوق في التغلب على عقبات العين، وتسهيل الإدارة المناسبة للأدوية المحبة للدهون عن طريق زيادة وقت الاتصال على سطح العين وتحسين التوافر البيولوجي.

الكلمات المفتاحية: ايكانزول نيرات، مذيلات بوليميرية بولوكسيمير 188,قطرة عينية,بولي فنيل الكحول.

Introduction

The most popular and convenient method of administering medications to the eyes is still topical instillation, which is the recommended course of treatment for numerous ocular conditions. Although low ocular bioavailability and poor corneal permeation, which necessitate multiple daily applications of topically applied drug molecules can limit their efficacy, many drug delivery system (DDS) have been developed in the last few decades to improve drug bioavailability on the ocular surface (1).

Polymeric micelles (PMs)is One of the important approaches, PMs are a type of micelles that are created from block copolymers containing both hydrophilic and hydrophobic monomer units. These micelles self-assemble at specific concentrations and temperatures (30°C). PMs are utilized in drug delivery owing to their distinctive characteristics, such as biocompatibility., nano size, core-shell arrangement, morphology, micellar association, high stability, and low toxicity,nano-sized polymeric micelles use led to improved permeation through the cornea of poorly water-soluble drugs and thus decrease application frequency (2).The use of PMsas eye drops gained attention because it combined the advantage of ease of administration of eye drops and the possibility to reduce problems associated with eye drops, particularly if the drug has poor solubility. For example, diclofenac sodium polymeric micelles showed a sustained release pattern and 17–fold increase in ex vivo corneal permeation increase than of that diclofenac sodium phosphate buffer eye drop (3).

Econazole nitrate (ECN(1-[2-[(4-chlorophenyl) methoxy]-2-(2,4-dichlorophenyl) ethyl]imidazole;nitric acid (Figure1) is a imidazole class antifungal drugs that are frequently used as econazole-nitrate salt to treat cutaneous candidiasis, jock itch, ringworm, athlete's foot, tinea, and pityriasis versicolor (7).

Econazole nitrate is class IV according to Biopharmaceutical Classification which has limited solubility and permeability. (8)

Polyvinyl alcohol (PVA) is a synthetic polymer widely used in the medical field with good biocompatibility, chemical resistance, and high water solubility (4). A previous study showed that PVA was used as a thickening agent (5). Adding PVA led to increased viscosity of the solution and improved the dispersion on the ocular surface to enhance the retention of active components on the ocular surface and improve the corneal permeation (6).

For the current research, a polymeric micelle of poorly soluble drug econazole nitrate will be prepared as an eye drop, and the effect of different PVA ratios as viscosity enhancers will be studied.

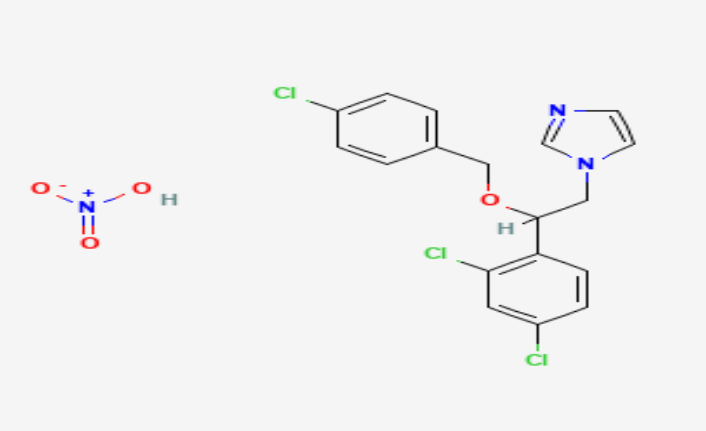


Fig (1) Chemical structure of econazole nitrate (8)

Materials and Methods

Materials

The Iraqi company Safa Pharmaceutical Industries supplied the econazole nitrate pure drug substance. We acquired Poloxamer 188 (Pluronic F68) from Hangzhou Hyper Chemicals in China and Polyvinyl alcohol from Thomas Baker (Chemicals) Pvt. Ltd. – India. The remaining components were all of a chemical grade.

Methods

Preparation of econazole- nitrate loaded polymeric micelle

The rotary evaporation method was used to create optimum polymeric micelles loaded with econazole nitrate formula (9). Methanol, was used to dissolve the drug (100 mg) and poloxamer 188 (6000 mg). The solvent was employed to undergo vacuum evaporation at 45 °C in a revolving evaporator manufactured by Buchi in Switzerland after the solution had been stirred for an hour at room temperature. To hydrate the thin layer, 10 mL of distilled water was used. Following that, the mixture was vigorously shaken at 37°C while rotating at a steady 100 rpm until polymeric micelles containing econazole nitrate were formed. The dispersion was treated to sonication using an ultrasonic homogenizer (Bioland, China) running at a power of 75 W for 30 minutes in order to produce a homogenous micellar dispersion. In an ice bath, the sonication procedure was performed in cycles of three seconds on and six seconds off. To make sure the dispersion reached a homogeneous state, this technique was applied. Using a filter syringe, the unincorporated drug aggregates were successfully removed from the mixture. As a result, ECN polymeric micelles formed into a transparent colloidal dispersion (F1).

Characterization of the Optimum formula

Polymeric Micelles size, polydispersity index and zeta potential

Using Brookhaven Instrument Corp.'s dyn amic light scattering method, the average p article size (average diameter), zeta potenti al (charge on particle surface), and polydis persity index (spectrum of particle sizes) w ere ascertained for the formula. This approach entailed examining the variations in light scattering, which can be ascribed to the random movement of particles in a dispersion of polymeric micelles. A 1 mL sample of the diluted polymeric micelle dispersion was placed in a folded capillary zeta cell and zanalyzed using light scattering at a temperature of 25°C and an angle of 15° (10)(11).

Determination of the drug content

Specifically, a 100 mL volumetric flask was filled with 1 mL of liquid econazole nitrate polymeric micelle. Afterwards, 70 milliliters of methanol were introduced, and following 30 minutes of sample sonication, a transparent solution was acquired. The solution's volume was reduced by adding 100 mL of methanol. After that, it was subjected to centrifugation for 15 minutes at a speed of 3000 rpm. Subsequently, it was filtered using a 0.22µm millipore filter and analyzed by scanning at specific lambda max to determine the drug content (12).

Preparation of econazole-nitrate eye drop

The production of Econazole nitrate 1% op hthalmic drop involved the combination of econazole nitrate polymeric micelles solut ion (F1) with polyvinyl alcohol at three var ying concentrations (1%, 1.4%, and 2% w/ v) for F1D, F2D, and F3D respectively. Po lyvinyl alcohol was used as a thickening a gent, while 0.02% benzalkonium chloride served as a preservative (13).

Formula code	Econazo le nitrate	Poloxamer 188	PVA concentraation	benzalkonium chloride
Puredrug suspension	100mg			
F1	100mg	6000 mg		
F1D	100mg	6000 mg	1%	0.02%
F2D	100mg	6000 mg	1.4%	0.02%
F3D	100mg	6000 mg	2%	0.02%

Characterization of econazole nitrate eye drop

Physicochemical Characterization of Eye Drops

Determination of the Formulations pH

(0.1g) of each formulation was dispersed in 20 mL of distilled water, and a pH meter was used to measure the pH (14)

Determination of the Formulations Viscosity

The viscosities of the prepared eye drops (F1, F1D, F2D, and F3D) were measured using a viscometer (Brookfield-DVE-USA). Measurements were performed in triplicate using suitable spindle number 62 and sheared at a rate of 10,30, 50, and 100 rpm(15).

Ex vivo permeation of econazole nitrate eye drops

A Franz diffusion cell with donor and receptor compartments divided by goat cornea was used for a comparative examination of the ex vivo transcorneal permeation of optimum formula, F1, F1D, F2D, F3D, and a pure drug suspension of econazole nitrate. The eyeball was promptly transported to the laboratory within 1 hour after the animal's sacrifice (ethical approval no 11on 16-6-2023). It was acquired in its entirety, immersed in Ringer's salt solution. The cornea, along with about 2-4 mm of the adjacent scleral tissues, was effectively excised. Subsequently, Ringer's salt solution was used to thoroughly rinse the cornea until the washings showed clarity free of any adherent tissues. Following this, the cornea was carefully transferred into a recently prepared phosphate buffer with a pH value of 7.4. A continually stirred 7 mL of freshly prepared phosphate buffer comprised the receptor medium. The upper compartment of the donor contained a solution containing a concentration of 10 mg/mL of econazole nitrate. The division of the upper and lower compartments was achieved by utilizing a

goat cornea with a surface area of 0.798 cm^2. The epithelial surface of the cornea was oriented towards the donor compartment and a continuous, undamaged connection was maintained with the release medium. To accurately reproduce ocular conditions observed in living organisms, the entire system was maintained at 37 °C and 100 RPM with a 0.5 degree of accuracy (16).

Optimum eye drop selection

Regarding ex vivo trans-corneal permeation, viscosity measurement, and drug content the best eye drop formula was selected.

Isotonicity Test

The aqueous solution is combined with small quantity of blood and scrutinized in comparision to established ophthalmic preparation using a H40 microscope magnification (16,17).

All ophthalmic preparations must maintain isotonicity in order to prevent irritation of the eye and tissue (18). The isotonic solution will preserve the inte grity of the blood cells.

In contrast the cells undergo contraction when the solution attains hypertonicity and enlargement when the solution falls below hypotonicity (16).

Irritation Test

A test for ocular irritation was performed in order to determine the optimal effective formulation. The study employed a cohort of six white albino rabbits, which were approximately 1.5 kilograms in weight and ranging in age from 5 to 10 months. The animal house of the Iraqi Centre for Cancer Research and Medical Inheritance authorized the use of these rabbits, which were also provided by the ethical council for animal experimentation at Musyansiriya University's College of Pharmacy(ethical approval no 11on 16-6-2023). A solitary drop of econazole nitrate eye solution was applied to the inner eye of each rabbit, with the right eye serving as a control. We conducted a diligent observation of the eyes for indications of discharge, edema, irritation, and inflammation. The monitoring period interval commences at the moment of installation and is recorded at intervals of 1, 24, and 48 hours. Furthermore, the documented time intervals consist of 18 and 19 hours. The assessment of the experiment was performed following the grading scheme that is detailed in Table 1 (20,21).

Table 1. The scales employed in the assessment of the irritation test

Score	Description of irritation
0	The absence of any inflammatory symptoms, including redness, excessive tear production, or edema.
1	There is moderate inflammation and redness, accompanied by a few tears.
2	Moderate inflammation and redness accompanied by severe tearing
3	Severe redness, inflammation, and tearing

Results and Discussion

Polymeric micelle Preparation and Characterization

The optimum polymeric micelle of ECN formula was successfully prepared and their dispersion was evaluated to be used as eye drops (22).

Micelle size, polydispersity index and zeta potential

The size of the micelle was 86.3±1.1nm, while the polydispersity index (PDI) value

was 0.127 as in Fig 2. The first value indicates the appropriateness for ocular use, while the second parameter signifies the uniformity of the preparation. It has been proposed that formulations with particle sizes below 100 nm have the potential as effective drug carriers for ocular administration (23). Smaller PDI values are indicative of a particle size distribution that is extremely homogeneous, while higher PDI values suggest a broader particle size distribution (24). The observed PDI values for the tested formula were consistently below 1.0, suggesting a uniform and tightly distributed particle size (24).

The assessment of zeta potential, a measure of surface charge, is crucial in evaluating the durability of formulations including polymeric micelles. The obtained results from the conducted experiments indicate that the incorporation of econazole nitrate into copolymers led to the manifestation of negative zeta potential values. The zeta potential values for the optimum formulation were observed to be (-22.67 mV) as seen in Fig 3, suggesting the favorable durability of polymeric micelles through electrostatic repulsion or attraction between the micelles. When the zeta potential is high and either positive or negative, it creates a repulsive force between micelles, preventing them from aggregating or flocculating. This electrostatic repulsion helps to maintain the stability of the micellar dispersion over time (24). Comparable findings were seen in earlier investigations (25, 26).

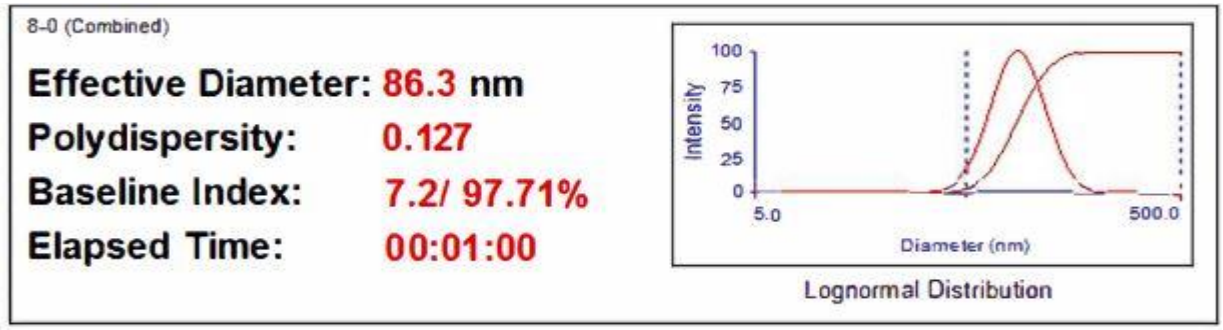


Fig 2 Particle size and polydispersity measurement of the optimum formulation

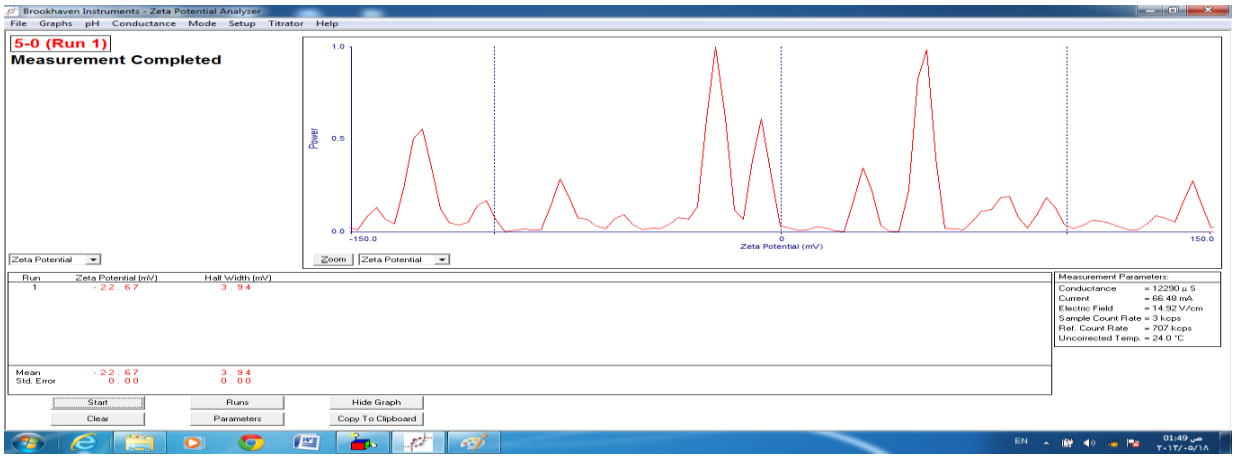


Fig 3 Zeta potential measurement of the optimum formula

Drug Content

The drug content results of the optimum formula were (91.3% ± 0.92%) which complies with the pharmacopeial limits ranging from 90 to 110% of the label claim (27).

Characterization of econazole nitrate eye drop

Determination of the Formulation's pH

The findings indicated that the prepared eye drops exhibited pH values ranging from 6.1±0.95 to 7.3±0.98, a range that is known to be ocularly tolerable, devoid of any discomfort or irritation(27).

Determination of the Formulations Viscosity

The results of the viscosity measurements indicated that an increase in the concentration of polyvinyl alcohol resulted in a corresponding rise in the viscosity of the econazole nitrate eye drop as shown in Fig 3. This, in turn, caused the solution to become thicker and the dispersion to improve on the ocular surface, thereby enhancing the drug's retention on the ocular surface. Consequently, these factors contributed to improved corneal permeation and a reduced dosage frequency of the formulation.(28)(29)

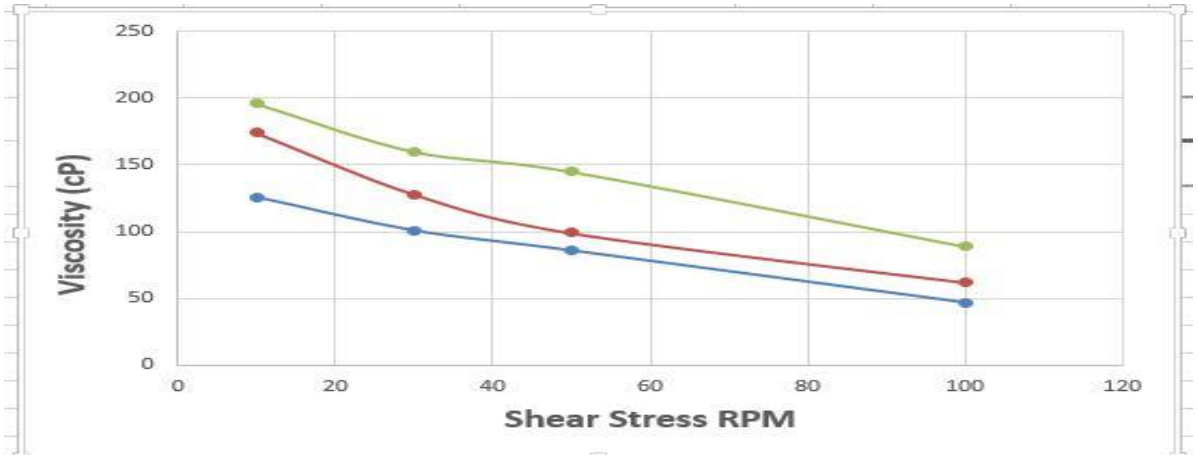


Fig 4 Viscosity measurement of F3D (Green), F2D (Red), and F1D (Blue).

Ex vivo permeation of econazole nitrate eye drops

The ex vivo trans-corneal permeation profile of F1 and (F1D-F3D) was compared to the profiles of a pure drug suspension of econazole nitrate to assess the impact of micelles and polyvinyl alcohol concentration on increasing corneal permeation through the cornea (30). The findings indicate that the permeation characteristics of F3D differ significantly ($P < 0.05$) from those seen with econazole nitrate suspension (PD), F1, F1D, and F2D with corresponding values of 64.4%, 12.69%, 43.45%, 49.8%, and 56.2% CDP respectively as showed Fig 4. In comparison to the econazole nitrate suspension (PD), F3D demonstrated a 5-fold increase in ex vivo permeability through the goat ocular membrane. This increase was found to be substantially larger ($P < 0.05$), indicating the enhanced efficiency of polymeric micelles. In contrast to the epithelium, the hydrophilic stroma acts as a hindrance to lipophilic compounds, consequently, the pure drug suspension was incapable of traversing the stromal layer, while F3D have much higher permeation than that (F1, F1D, and F2D) may be attributed to the polyvinyl alcohol increased concentration that led to enhance contact time on the ocular surface and improve corneal permeation (31). The limited amount of tear fluid present in the cul-de-sac is inadequate to dilute polymeric micelles below their critical micelle concentration (CMC), hence ensuring the stability of the polymeric micelles carrier

system(31). The durability of polymeric micelles is anticipated to be sustained until they reach the aqueous humor, mostly owing to the low critical micelle concentration (CMC) value of poloxamer 188.

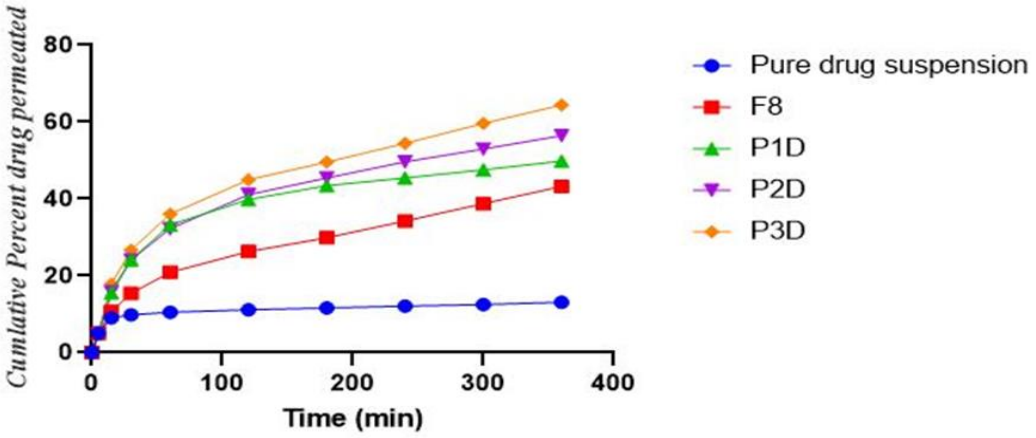


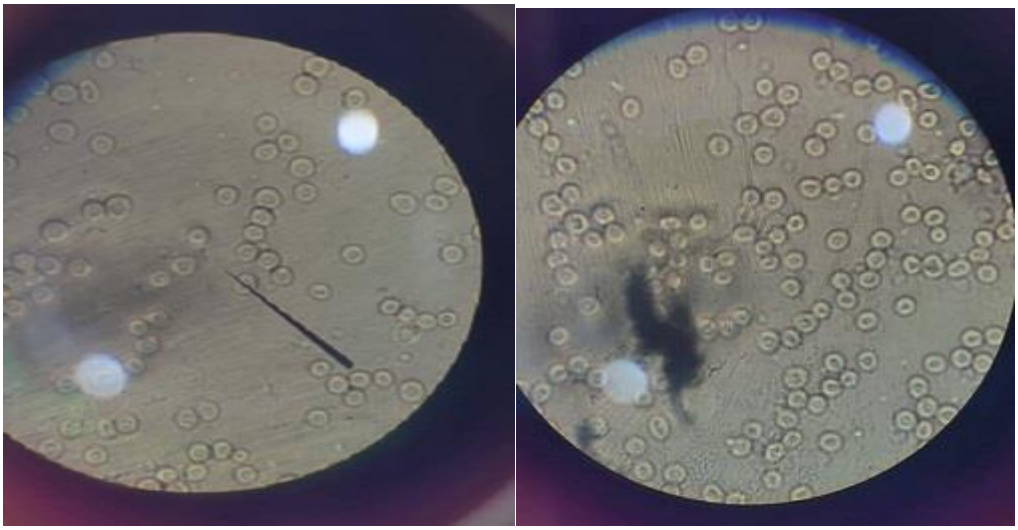
Fig 5 . Ex-vivo transcornel permeation results

Optimum eye drop selection

According to ex vivo, trans-corneal permeation, viscosity measurement, and drug content the best eye drop formula (F3D) was selected.

Isotonicity Evaluation of optimum formula

There is no change in the shape of red blood cells shown in the Fig 6 indicate that the pure drug suspension and optimum eye drop solutions are isotonic (32).



A-pure drug suspension **B-optimum eye drop formulation (F3D)**

Fig 6. Isotonicity test evaluation

Irritation Test of Optimum formula

Irritation of ocular tissues is an important factor to be considered because the eye is a sensitive organ and any foreign material placed in contact with ocular tissues may cause excessive blinking, severe tearing, redness, and discharge. Rabbits were used for the irritation test Fig7 for F3D eye drop formulation demonstrated that no irritation signs (redness, tearing, swelling) were observed even after 48 hr of administration compared to the control(score zero).

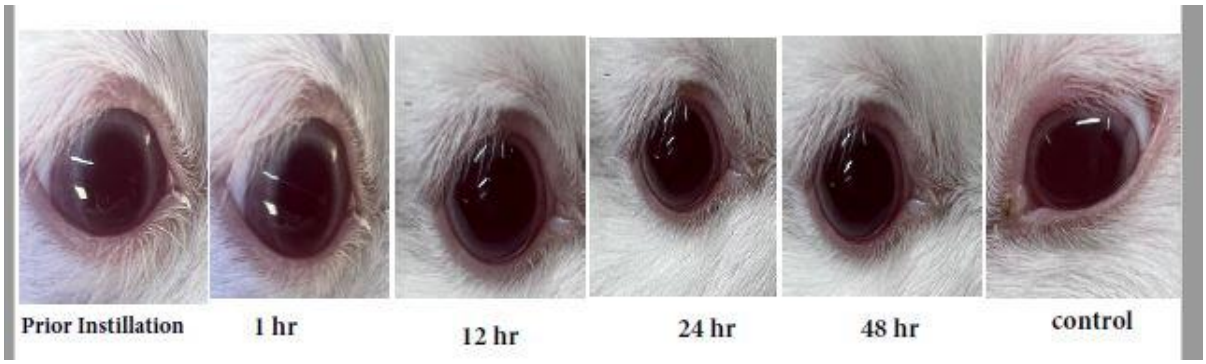


Fig7.Irritation Test results of Rabbit eye

Conclusion

It has been demonstrated that the econazole nitrate polymeric micelle is an exceptionally effective and superior drug delivery system for circumventing ocular obstacles, thereby facilitating the proper administration of lipophilic medications. It has been demonstrated that the permeability of the system is greater than that of a suspension of purified econazole nitrate. In addition, topical administration may facilitate the transportation of the medication to the anterior portion of the eye. Poloxamer 188 micelles were shown to be effective vehicles for delivering a hydrophobic medication to the anterior segment of the eye and the use with PVA as viscosity enhancer result in an increase by a fivefold in the ex vivo trans-corneal permeation without inducing ocular irritation.

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