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Preparation and Evaluation of Econazole Nitrate Polymeric Micelle Solution as an Eye Drop

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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 eye drops econazole nitrate 2% exhibits inadequate corneal permeability which require multiple application. This research aimed to develop a polymeric micellar delivery system for econazole nitrate utilizing Poloxamer 407 (Pluronic F127) and Poloxamer 188 (Pluronic F68), with the intention of enhancing its solubility in aqueous environments and improving its penetration through the cornea. First, critical micelle concentration of P407 and P188 was measured using Iodine UV-absorption spectroscopic method. Polymeric micelles loaded with econazole nitrate were prepared using the rotary evaporation process and evaluated for particle size, polydispersity index, zeta potential and entrapment efficiency. Formulations with small particle size and high entrapment efficiency were further evaluated for in vitro drug permeation using Franz diffusion cell and dialysis membrane. The cumulative drug permeation (CDP) percentage exhibited significant variation, ranging from 56% to 83.2%. The optimum formulation F8 containing 1:60 drug: polymer ratio was evaluated for antifungal activity and ex vivo permeation study using Franz diffusion cell and gout cornea. A statistically significant difference in the antifungal activity between the reference standard and F8 was observed. F8 demonstrated a 3.42-fold increase in ex vivo permeability through the goat ocular membrane compared to the econazole nitrate solution. Using econazole nitrate polymeric micelle as a drug delivery system is efficient and superior in overcoming ocular obstacles, and facilitating the appropriate administration of lipophilic medicines.

Keywords: Econazole nitrate, Keratitis, Ocular delivery, Polymeric micelle, Poloxamer

Introduction

Econazole nitrate, a chemically produced triazole drug, is utilized for the management of fungal keratitis with potent antifungal properties against many species [(1)]. ECN have aqueous solubility 800 ucg/ml ,PKa 6.48 ,BCS class IV and LogP 4.37 Shah RM, Eldridge DS, Palombo EA, Harding. Microwave-assisted microemulsion technique for production of miconazole nitrate-and econazole nitrate-loaded solid lipid nanoparticles. European Journal of Pharmaceutics and biopharmaceutics. 2017;117:141-50 [(2)]. The eye drops known as Aurozole®, which are manufactured by Aurolab Pharmaceuticals in India, are widely accessible.

These eye drops are supplied on a regular schedule and are deposited in the corneal layer after being applied topically, the formula also exhibits a correlation with inadequate corneal permeability, visual aberrations, excessive tearing, dilution of tears, leakage via the nasolacrimal duct, and the rate at which tears are replenished which require six time applications per day [(3-5)]. Frequent applications often associated with poor patient consequences [(13, 14)].In general, there are two types of micelles, depending on the weight of the amphiphilic molecules used; low molecular weight surfactant micelles and polymeric micelles [(15)].

adherence and high exposure to preservatives. Enhancing solubility and permeation of the drug can overcome the problems. One approach is polymeric micelles [(6)]. Keratitis is a pathological condition characterized by an inflammatory reaction of the cornea, which is accompanied by corneal edema, migration of cells, and obstruction of the ciliary body [(7)].

This condition may arise from either infectious or non-infectious causes [(8)]. The incidence of keratitis exhibits variability based on the etiology of the illness, including bacterial, fungal, or viral origins [(9)]. Among these options, fungal infection is the most commonly seen. The fungal species often associated with mycotic ulcers of the cornea are Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Candida, and Fusarium [(10, 11)]. The eradication of these illnesses presents a greater level of difficulty [(12)]. The efficacy of antifungal drugs used in the management of keratitis caused by fungus is often associated with limited corneal penetration, stromal permeability, and unfavorable clinical

Surfactant based polymeric micelles

Surfactants are surface-active compounds that can lower surface and interfacial tension at liquid, solid, and gas interfaces, allowing them to blend or diffuse freely in water or other liquids [16]. A surfactant molecule has two parts a hydrophilic head and a hydrophobic tail, thus surfactants are normally amphiphilic molecules and are soluble in both organic solvents and water [17].

Polymeric micelles

Polymeric micelles represent a class of micelles formed from block copolymers consisting of hydrophilic and hydrophobic monomer units that are self-assembled at certain concentration and temperature [18]. PMs are used in drug delivery due to their unique properties, such as biocompatibility, nano size, core- shell arrangement, morphology, micellar association, high stability, and low toxicity [19].Amphiphilic block copolymers possess the propensity to undergo self-assembly into micelles if the critical amount of micelle is surpassed, resulting in the formation of carrier structures at the nanoscale (10–100 nm) with a distinctive core–shell configuration. The presence of a hydrophobic core encased by a hydrophilic shell provides a means of encapsulating hydrophobic drugs, creating a drug reservoir. Simultaneously, the hydrophilic shell acts as a steric barrier, preventing the aggregation of micelles and ensuring their solubility in the presence of water [20-22]. It has been widely used and investigated as ocular drug delivery. For example , Munmun Jaiswal et al., founded that itraconazole polymeric micelle exhibit 6.67 folds increase in transcorneal permeation compared to marketed itraconazole eye drop [23].The objective of this research was to develop a polymeric micellar delivery system for econazole nitrate, with the intention of enhancing its solubility in aqueous environments and therefore improving its penetration through the cornea.

Materials and Methods

Materials

The econazole nitrate compound was acquired from Safa Pharmaceutical Industries, a company based in Iraq. Poloxamer 407 (Pluronic F127) and Poloxamer 188 (Pluronic F68) were obtained from Hangzhou Hyper Chemicals, China. All other materials were of chemical grades.

Critical micelle concentration

In order to ascertain the critical micelle concentration (CMC) of P407 and P188, as well as the formation of polymeric micelles (PMs) in deionized water via the combination of copolymer P407 and P188, the dye solubilizing technique was used, namely the Iodine UV-absorption spectroscopic method. A solution of the KI/I_2 standard was prepared by dissolving 0.5 g of iodine and 1 g of potassium iodide in 50 ml of deionized water. Multiple samples of P407 and P188, as well as a combination of copolymer P407 and P188 solution, were created within a concentration range of 0.03% to 0.2% (w/v). For each sample, a volume of 100 µL of KI/I_2 solution was introduced. The mixes underwent incubation for a duration of 12 hours at ambient temperature prior to quantification. The experimental procedure included doing measurements at a wavelength of 366 nm with a UV-Vis spectrometer. A figure was generated to depict the relationship between the absorbance of Iodne and the amounts of copolymers P407 and P188, as well as their combination. This plot was used to determine the critical micelle concentration (CMC). The abrupt decline in absorbance was interpreted as an indication of the concentration of P407 and P188, as well as the combination of copolymer P407 and P188, beyond the critical micelle concentration (CMC) [24, 25].

Econazole nitrate-loaded polymeric micelles

The preparation of polymeric micelles loaded with econazole nitrate was conducted using the rotary evaporation process [26]. The drug and copolymer were dissolved in a nonselective solvent, methanol, in accordance with the formulation design specified in Table 1. The solution was agitated at ambient temperature for a duration of one hour, and afterward, the solvent was subjected to evaporation at a temperature of 45 ◦C under vacuum conditions using a rotating evaporator manufactured by Buchi in Switzerland. The thin layer was hydrated using 50 mL of distilled water that had been heated to 60 ◦C. The mixture was then violently agitated at 37 ◦C with a constant rotation speed of 100 rpm until polymeric micelles containing econazole nitrate were produced. To achieve a uniform micellar dispersion, the dispersion was subjected to sonication using an ultrasonic homogenizer operating at a power of 75 W for a duration of 30 minutes.

The sonication process was carried out in an ice bath, with a cycle of 3 seconds on and 6 seconds off. This method was used to ensure the dispersion attained a homogenous state. The removal of the Unincorporated drug aggregates was achieved by the process of filtering using a filter syringe of 0.45 um. This resulted in the formation of a clear colloidal solution consisting of ECN polymeric micelles [23, 27].

Table 1. Composition of polymeric micelle formulations

Formulation code	Amount of drug (mg)	PF68 (mg)	PF127 (mg)	Drug:Polymer ratio	Pf68: Pf127 ratio
F1	10	10		1:1	
F2	10	50		1:5	
F3	10	100		1:10	
F4	10	200		1:20	
F5	10	300		1:30	
F6	10	400		1:40	
F7	10	500		1:50	
F8	10	600		1:60	
F9	10	700		1:70	
F10	10	500	100	1:60	5:1
F11	10	400	200	1:60	4:2
F12	10	300	300	1:60	3:3
F13	10	200	400	1:60	2:4
F14	10	100	500	1:60	1:5
F15	10		600	1:60	

Entrapment efficiency

In order to assess the entrapment efficiency (EE%) of micellar solutions, every formula (PM1-PM15) underwent centrifugation using the cooling ultracentrifuge at a speed of 14000 revolutions per minute and a temperature of 4°C for a duration of 1 hour to separate the supernatant . Subsequently, the supernatant layer was obtained following filtration and subjected to spectrophotometric analysis at a wavelength of 271 nm after appropriate dilution [28]. The micellar efficiency was determined by using equation (1) to get the percentage [15].

$$EE\% = \frac{amount\ of\ drug\ in\ the\ micelles}{total\ amount\ of\ drug\ initially\ added} 100\% \quad \text{(equation 1)}$$

Micelles size and polydispersity index

The mean particle size (mean diameter), zeta potential (particle surface charge), and polydispersity index (size range of particles) were measured for all formulations using the dynamic light scattering technique provided by particle size analyzer and zeta potential analyzer (Brookhaven) Instrument Corp. This method involved analyzing the fluctuations in light scattering, which can be attributed to the Brownian motion of particles in a polymeric micelles' dispersion. A volume of 1 ml of the diluted dispersion of polymeric micelles was introduced into a folded capillary zeta cell and subjected to light scattering analysis at a temperature of 25°C and an angle of 15° [29] .

In vitro drug permeation

The research employed a Franz diffusion cell, which comprised of two compartments - the donor and receptor compartments. These compartments were separated by a dialysis membrane that had been pre-soaked. The dialysis membrane had a hole size of 0.22 um(Mol. Wt. cut off 12–16 kDa) . The donor compartment was filled with a formulation containing 10 mg/mL of econazole nitrate-loaded polymeric micelles (2ml) (F3-F5-F8-F11F-13 and pure drug suspension). The receptor compartment was filled with 7 ml Phosphate Buffer containing 1% sodium lauryl sulfate, with a pH of 7.4. The system was stirred at a speed of 100 rpm, and the temperature was maintained at 37± 0.5 °C. At regular time intervals, a 1 mL sample was extracted and then substituted with an equivalent amount of new medium. The drug concentration of each sample was quantified, and graphs depicting the percentage of cumulative drug permeation were generated as an estimate of time [23].

Selection of optimized micellar formulation

The selection of the optimum formulation was based on three criteria: the maximum percentage of entrapment efficiency, the percentage of cumulative drug penetrated with tiny particle size, and the smallest PDI values. Additionally, the composition was analyzed using Scanning Electron Microscopy (SEM) [19, 30].

Scanning Electron Microscopy

The optimized sample (F8) was subjected to negative staining and afterward air dried at room temperature. A scanning electron microscopy (SEM) picture was then acquired.

In vitro antifungal activity

Candida Albicans, which was obtained from the culture collection of the microbiology department at Iskandaryia hospital, was introduced onto potato dextrose agar. The procedure for the production of potato dextrose agar (PDA). The media was made by suspending 39g of PDA in 1L of distilled water, followed by sterilization using an autoclave at an operating pressure of 15 Ibs at a temperature of 121°C for a duration of 15 minutes. The media cooled and poured into the petri dishes [18].

A 0.5% v/v concentration of Candida albicans microbial inoculum was evenly distributed over the nutrient agar substrate inside the petri dish. Following the solidification of the agar plate, a circular well with a diameter of 5 mm was created. One mL of the drug solution in its pure form and the polymeric micelle known as econazole nitrate were introduced into the wells using a sterile syringe. Following a 72-hour incubation period, the radius of the zone of inhibition was assessed and compared between the two preparations [31, 32].

Ex vivo transcorneal permeation

A comparative analysis was conducted to assess the ex vivo transcorneal permeation of F8 and a pure drug suspension of econazole nitrate, employing a Franz diffusion cell consisting of donor and receptor compartments that were separated by goat cornea. The eyeball was promptly transported to the laboratory within a span of one hour after the animal's sacrifice. 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, the cornea was subjected to a thorough rinsing process using Ringer's salt solution until the washings exhibited clarity devoid of any attached tissues. Following this, the cornea was carefully transferred into a recently prepared phosphate buffer with a pH value of 7.4. The receptor medium consisted of 7ml mL of freshly prepared phosphate buffer, which was continuously agitated.

The donor upper compartment comprised of 2ml formulation with a concentration of 10 mg/mL of econazole nitrate. The upper and lower compartments were partitioned using a goat cornea with an area of 0.815 cm2. The cornea was positioned in a such that its epithelial surface was oriented towards the donor compartment and maintained a continuous and undamaged connection with the release medium.In order to replicate ocular circumstances that occur in living organisms, the complete system was maintained at a temperature of 37 °C with a precision of 0.5 [33].

Stability study

The stability assessment of micelles included both qualitative observation and quantitative analysis of drug content. The F8 samples were maintained in a container that was put at a temperature of 25 ◦C ± 2 ◦C for a duration of 3 months [34]. The samples were retrieved at the end of a 3-month period, and the drug content was assessed by comparing it to the first measurement, along with a visual examination. Particle size also measured.

Statistical analysis

The results of the experiments were analyzed using the one-way analysis of variance (ANOVA) test at the level of ($P \leq 0.05$) and presented as a mean of three samples standard deviation. The results would be significant if $P \leq 0.05$, and the results would be non-significant if $P > 0.05$.

Results and Discussion

Critical micelle concentration

Iodine (I_2) was used as a hydrophobic probe for the purpose of monitoring the formation of polymeric micelles. Initially, when the concentrations of P407, P188, and the combination of P407 and P188 were raised, there was a little drop in the absorbance of iodine. However, above a certain threshold, a rapid and considerable reduction in absorbance was seen. This threshold is often referred to as the critical micelle concentration (CMC) point. Iodine exhibits hydrophobic properties, making it more inclined to reside in the hydrophobic core of pluronics. Consequently, it was hypothesized that I-3 is transformed into I_2 as a result of an excess of KI in the solution. This transformation occurs due to the solubilization of I_2, which is more hydrophobic, by the hydrophobic core of the polymeric micelle. This process enables the maintenance of the saturation concentration of I_2 in water [35]. The concentration of P407, P188, and a combination of P407 and P188 (% w/v) was plotted against the absorbance intensity of I2 in order to determine the critical micelle concentration (CMC).

The CMC value for the polymeric micellar solution of P407 was found to be 0.1% (w/v), as depicted in Figures 1-3. This value is not significantly different from the previously reported CMC value obtained through the pyrene probe method ($6.9 \times 10\text{-}5$ M or 0.0869% w/v) [34, 36]. The augmentation in the concentration of P407 throughout the preparation procedure beyond the critical micelle concentration (CMC) value results in an enhancement in the static and dynamic stability of polymeric micelles [37].

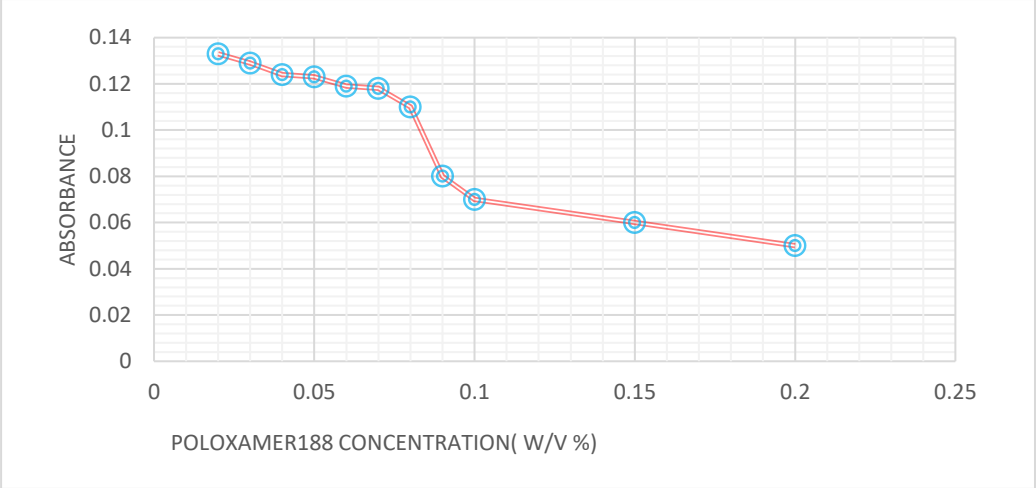

Figure 1. CMC determination for P188 using the iodine probe method.

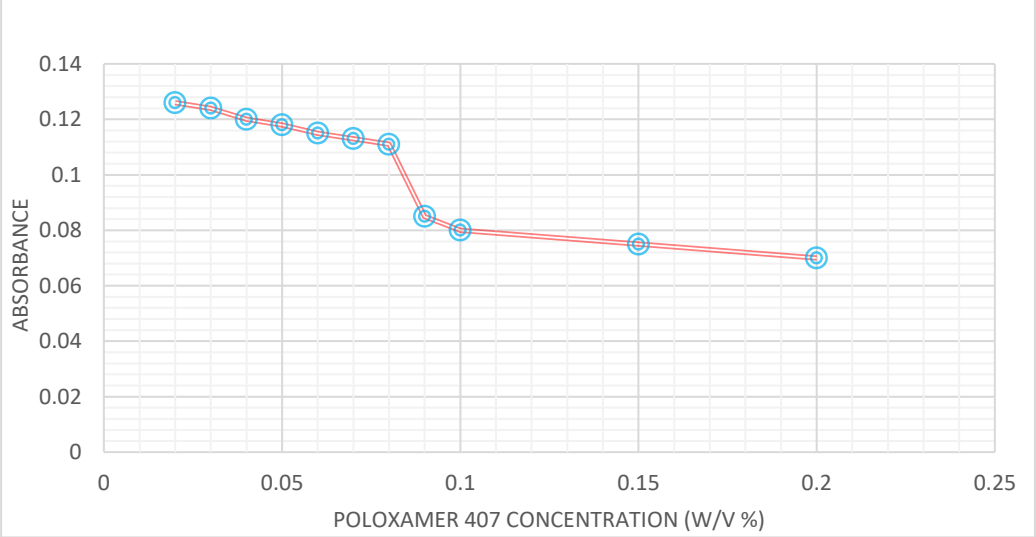

Figure 2. CMC determination for Poloxamer P407 using the iodine probe method.

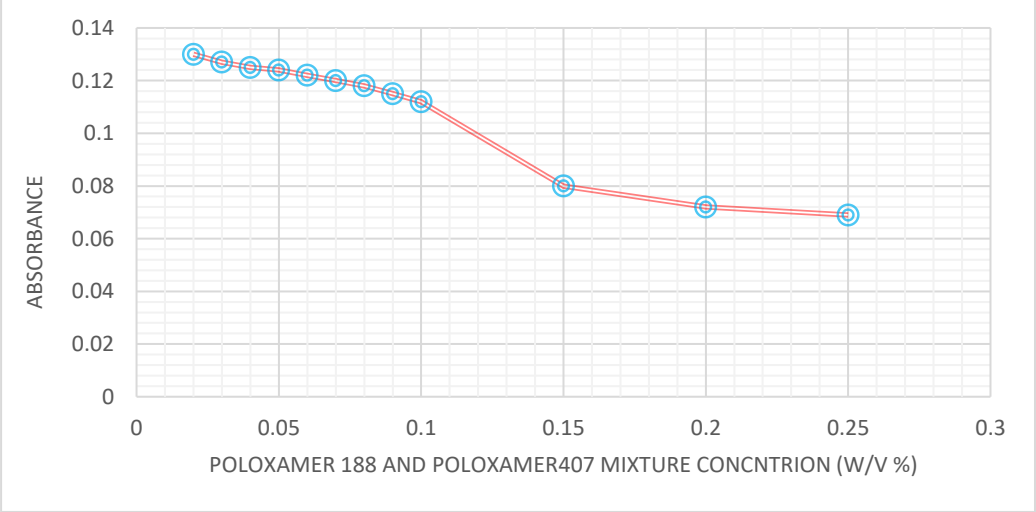

Figure 3. CMC determination for P188 and P407 mixture using the iodine probe method.

Polymeric micelles

The rotary evaporation technique was chosen for its appropriateness in the production of micelles intended for ocular administration [38]. This approach yields formulations with a notable capacity for drug loading, while also allowing for the practical removal of the organic solvent used during preparation. The formulations were developed in order to investigate the impact of polymeric surfactants on many metrics, including entrapment efficiency, particle size distribution, and in vitro permeation. This was done with the aim of identifying the optimal formulation.

Characterization

Micelle size and polydispersity index

Table 2 presents data on the dimensions of polymeric micelles loaded with econazole nitrate, denoted as F1-F15. The sizes of these micelles ranged from 27.9 to 135.8 nm, while the polydispersity index (PDI) values varied from 0.127 to 0.544. 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 potential as effective drug carriers for the purpose of ocular administration [39]. Smaller PDI values are indicative of a particle size distribution that is extremely homogeneous, while higher PDI values suggest a broader particle size distribution [40]. The observed PDI values for the tested formulations were consistently below 1.0, suggesting a uniform and tightly distributed particle size. Increasing Pf68 to drug ratio reduced the particle size below 100 in F3 to F9. Combination of Pf127 with Pf68 in F10 to F14 also showed low particle size with low PDI.

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. These findings are shown in Table 2, which displays the results for formulations F1-F15. The zeta potential values for all formulations were observed to be below -10 mV, suggesting the favorable durability of polymeric micelles. Comparable findings were seen in earlier investigations [41, 42].

Table 2. Formulation and characterization of econazole-nitrate polymeric micelles carrier system (N = 3)

Formulation code	Micelle size (nm)±SD	Polydispersity index ±SD	Zeta potential±SD	EE%±SD	In-vitro CDP % at 6th h ±SD
F1	113.6±2.5	0.33±0.035	-44.98±(-1.03)	٧١±0.53	
F2	131.4±0.81	0.544±0.22	-61.76±(-2.1)	٧١.4±0.87	
F3	78.4±0.5	0.304±0.008	-19.56±(-1.89	73. 2±1.1	66.8±1.43
F4	78.1±0.77	0.334±0.010	-13.2±(-0.5	74.5±0.9	
F5	75.3±0.37	0.373±0.021	-45.48±(-0.65	76.4±0.55	63±2.11
F6	74±1.3	0.467±0.025	-64.29±(-1.3	78.6±0.46	
F7	64.5±0.85	0.354±0.017	-13.06±(-0.8	80.8±1.3	
F8	86.3±1.1	0.127±0.003	-22.67±(-0.54	82.6±2.1	83.2±1.8
F9	34.8±1.49	0.403±0.01	-13.22±(-0.77	83±1.65	
F10	30.5±1.15	0.464±0.021	-55±(-1.11	82.1±0.62	
F11	110.1±2.27	0.432±0.016	-22.9±(-0.99	78.1±0.73	56±1.45
F12	27.9±2.1	0.425±0.026	-4.84±(0.85	79.4±0.39	
F13	49.5±2.1	0.409±0.02	-38.8±(-0.32	80±0.76	71.5±1.78
F14	30.8±1.9	0.373±0.018	0±0	75±1.56	
F15	135.8±1.67	0.377±0.012	-51±(-1.43)	79±2.4	

Entrapment efficiency

Table 2 presents the entrapment efficiency (EE) of polymeric micelles loaded with ECN prepared. The experimental findings from F1 to F9 indicate that an elevated concentration of copolymer (PF68) is associated with an increase in entrapment efficiency. This observation is consistent with the results obtained from formulae F10 to F15, which align with earlier research [35]. An increased entrapment effectiveness leads to enhanced solubility of hydrophobic drugs.

In vitro permeation

From the 15 prepared formulations F3, F5, F8, F11, and F13 were chosen for further evaluation. These formulations had the highest EE% with lowest particle size and PDI. The in vitro drug permeation characteristics, as shown in Figure 4, and Table 3 were used to ascertain the percentage of cumulative drug permeation (CDP)

at the 6th hour for the selected formulations in comparison with the pure drug solution. CDP for all formulations exhibited significant difference in the amount of drug permeated ($p<0.05$) ranging from 56% to 83.2% after 6 hr. compared to drug suspension which was around 20% at the same period.

The observed variability may be attributed to differences in particle size and PDI across all five formulations. Formulations F3, F5, and F11 demonstrated incomplete cumulative drug permeation, which may likely be attributed to poor entrapment efficiency and high PDI value which results in particle aggregates and larger particle size, which is known to influence the homogeneity and uniform distribution of particles inside the formulation. The measure of how well a substance or material is able to capture or retain another substance inside its structure. The observed CDP percentage of 71% in sample F11 may be attributed to the presence of a high PDI, which is known to influence the homogeneity and uniform distribution of particles inside the formulation. The selection of F8 as the optimal formulation, which exhibited the greatest percentage of cumulative drug release (83.2%), might potentially be attributed to its appropriate particle size, lowest PDI, and higher entrapment efficiency [43-45].

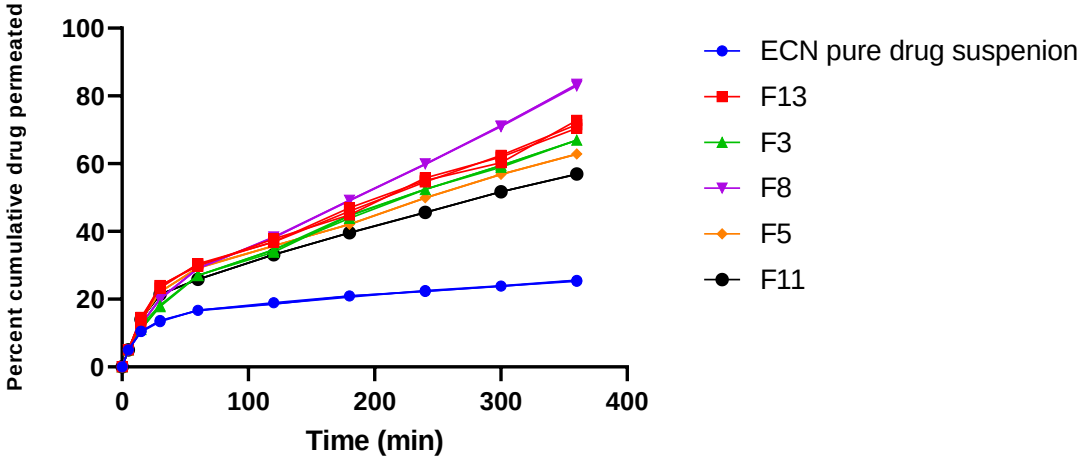

Figure 4. Comparative in vitro drug permeation profiles of econazole nitrate from prepared polymeric micelles and pure drug suspension in Phosphate Buffer, pH 7.4 using Franz diffusion cell (n = 3).

Table 3. Calculation of In vitro drug permeation parameters

Parameter	PD	F3	F5	F8	F11	F13
Steady flux ucg/cm/min	0.0282	0.1385	0.1384	0.1816	0.1139	0.11033
Lag time(min)	16	22	19	17	23	22.45
Permeation coefficient	0.00282	0.01385	0.01384	0.01816	0.01139	0.01033
Enhancement ratio		4.9	4.9	6.4	4	3.6

Optimum formula selection

The PDI value of 0.127, which is the lowest value observed, indicates that the polymeric micelles are homogenous. This suggests that there is a strong interaction between the drug and polymer from the structures there is probability to form hydrogen and covalent bonding between the drug and the polymer which mean there is good interaction between them, and we can use software structural data base to predict this interaction, resulting in the formation of more regular polymeric micelles with a size of 86.3 nm. Therefore, the formulation denoted as F8 was chosen as the most favorable option due to its optimal size range of polymeric micelle particles for ocular administration. This formulation had a low PDI, suggesting a uniform and consistent particle size distribution. Additionally, F8 demonstrated a high capacity for encapsulating the drug and exhibited the greatest level of in vitro drug permeation

Scanning electron microscopy

The scanning electron microscopy (SEM) picture of F8 reveals the presence of spherical particles with a limited size distribution, as seen in Figure 5. Particles with a size less than 100 nm are especially well-suited for ocular administration. The optimal formula for loading econazole nitrate was chosen as F8.

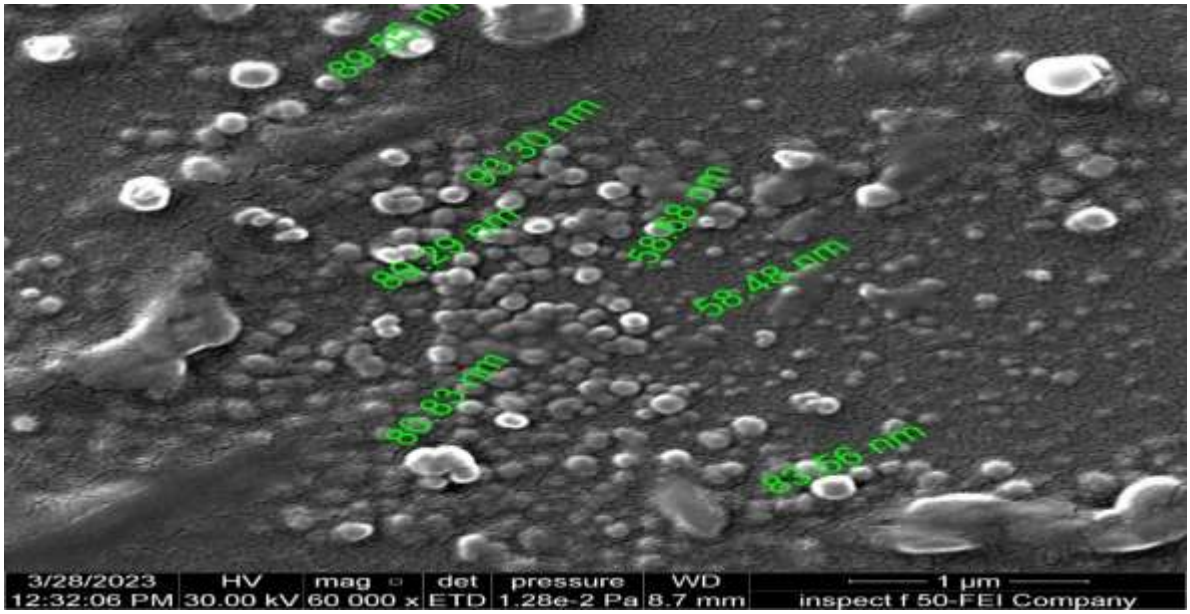

Figure 5. Scanning electron microscopic images of optimized econazole-nitrate loaded polymeric micelles (F8).

In vitro antifungal activity

The diameter of the zone of inhibition caused by F8 was found to be 19 mm ± 1.46 mm, which was greater than the zone of inhibition (14.1 ± 1.96 mm) generated by the pure drug solution (reference standard). A statistically significant difference in the antifungal activity between the reference standard and F8 was discovered after conducting a student's t-test at a significance level of $P < 0.05$ and a confidence range of 95%. Therefore, it can be concluded that the use of polymeric micelles loaded with econazole nitrate exhibits superior efficacy compared to the administration of the pure drug suspension, as seen in Figure 6.

Figure 6. The inhibition zone of econazole nitrate polymeric micelle and for pure drug solution.

Ex vivo transcorneal permeation

The ex vivo transcorneal permeation profile of F8 was compared to the profiles of a pure drug suspension of econazole nitrate in order to assess the impact of micelles on increasing penetration through the cornea [46]. The findings indicate that the permeation characteristics of F8 differ significantly from those seen with econazole nitrate suspension, with corresponding values of 12.69% and 43.45% CDP. In comparison with the econazole nitrate suspension, F8 demonstrated a 3.42-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 Figure 7, and Table 4. Consequently, the pure drug solution was incapable of traversing the stromal layer, while F8 followed the transcellular pathway [47]. 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. 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.

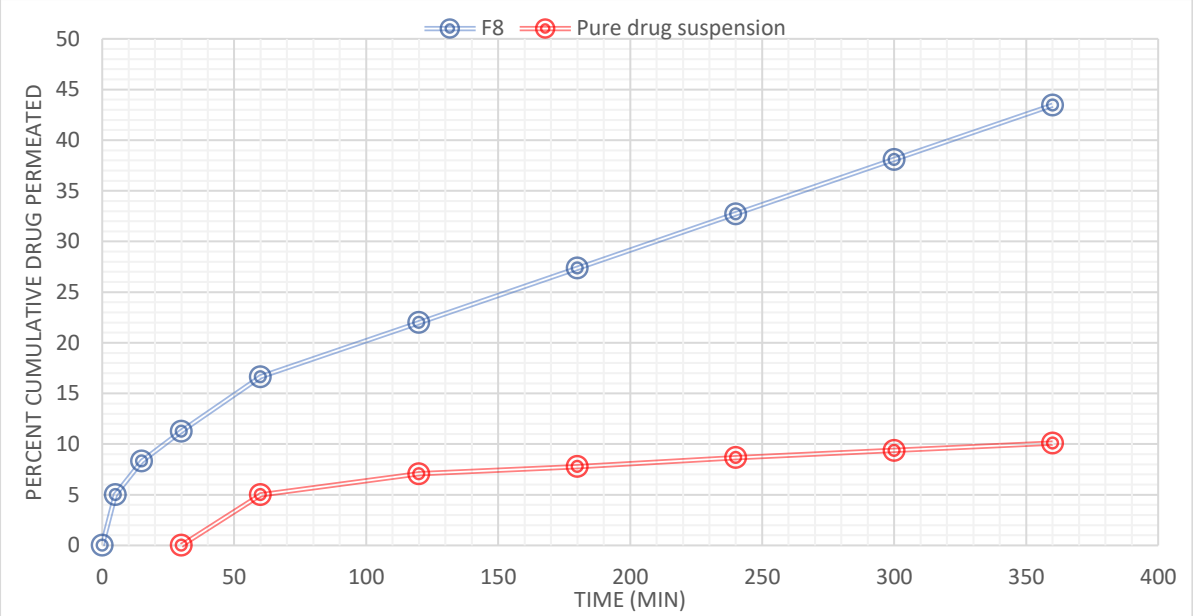

Figure 7. The ex vivo transcorneal permeation profile of F8 was compared to the profiles of a pure drug

Table 4. Calculations of ex vivo transcorneal permeation parameters

Parameter	PD	F8
Steady flux ucg/cm/min	0.0231	0.1091
lag time(min)	15.42	17
permeation coeffcient	0.00282	0.01816
enhancement ratio		4.72

Stability

The results indicate that there was no significant variation in drug content between the formulation F8 at zero months (91.3% ± 0.92%) and at 3 months (88.25% ± 3.60%). This suggests that there was no occurrence of chemical degradation. Furthermore, the presence of visual sedimentation and phase separation was not observable. measurement of particle size (58.8 nm) also supports stability study.

Conclusion

The use of econazole nitrate polymeric micelle as a drug delivery system has been shown to be very efficient and superior in overcoming ocular obstacles, hence facilitating the appropriate administration of lipophilic medicines. The system has been shown to exhibit superior permeability compared to a suspension of pure econazole nitrate. Additionally, it has the potential to transport the medication to the anterior portion of the eye by topical administration as Polymeric micelles increases aqueous solubility which the main barrier to deliver lipophilic drugs through cornea and consequently the corneal permeation increased significantly. The study demonstrated that poloxamer 188 micelles are efficient vehicles for delivering a hydrophobic medication to the front part of the eye, effectively treating fungal keratitis.

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Mustansiriyah university/college of pharmacy

Competing interests

The authors have no conflicts of interest to declare.

Grant information

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Ethics Statements

The ethics committee of the College of Pharmacy at Mustansiriyah University, Iraq, formally approved the research methodology (Research number 11, Approval number 11, Reference number 83, approved on 16/6/2023).

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Ali Hameed, Athmar Dh. H. Al-Shohani; data collection: Ali Hameed, analysis and interpretation of results: Ali Hameed, Athmar Dh. H. Al-Shohani; draft manuscript preparation: Ali Hameed. All authors reviewed the results and approved the final version of the manuscript.

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تحضير وتقييم مذيلة نترات إيكونازول البوليمرية للتسليم العيني

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الخلاصة

نترات الايكونازول، هو دواء من مجموعة ترايازول منتج كيميائيًا، يستخدم لعلاج التهاب القرنية الفطري. له خصائص قوية مضادة للفطريات ضد العديد من الأنواع. تُظهر المستحضرات المتوفرة منه نفاذية غير كافية للقرنية ، وتسبب مشاكل مثل الزيغ البصري ، والتمزق المفرط ، وتمييع الدموع ، والتسرب عبر القناة الأنفية الدمعية. يهدف هذا البحث إلى تطوير نظام توصيل ميسيلار بوليمري لنترات الايكونازول ، بهدف تعزيز قابليته للذوبان في البيئات المائية وتحسين تغلغلها عبر القرنية. تم الحصول على مركب نترات إيكونازول من شركة الصفا للصناعات الدوائية ، وهي شركة مقرها العراق ،. تم الحصول على بولوكسامير ٤٠٧ (F127) و بولوكسامير ١٨٨ (F68) من شركة هنغازو الصينية . للتأكد من تركيز الميسيل الحرج (CMC) لـ P407 وP188 ، وكذلك تكوين مذيلات البوليمر (PMs) في الماء منزوع الأيونات عن طريق مزيج من البوليمر المشترك P407 وP188 ، تم استخدام تقنية تذويب الصبغة ، وهي امتصاص اليود للأشعة فوق البنفسجية طريقة التحليل الطيفي. تم تحضير مذيلات بوليمرية محملة بنترات إيكونازول باستخدام عملية التبخير الدوراني. استخدم البحث خلية انتشار فرانز تتكون من جزأين - مقصورات المانح والمستقبل. أظهرت نسبة نفاذ الدواء التراكمية (CDP) تباينًا كبيرًا تراوحت بين ٥٦٪ إلى ٨٣,٢٪. تم تقييم الفعالية المضادة للفطريات للميسيل البوليمرية نترات إيكونازول باستخدام تقنية منطقة التثبيط ضد المبيضات البيضاء. تم اكتشاف فروق ذات دلالة إحصائية في النشاط المضاد للفطريات بين المعيار المرجعي و .F8 أظهر F8 زيادة بمقدار ٣,٤٢ ضعفًا في نفاذية خارج الجسم الحي من خلال غشاء عين الماعز مقارنة بمحلول نترات إيكونازول. يعد استخدام مذيلة بوليمر نترات إيكونازول كنظام لتوصيل الأدوية فعالاً ومتفوقًا في التغلب على عقبات العين ، وتسهيل الإدارة المناسبة للأدوية المحبة للدهون. لقد ثبت أن النظام يُظهر نفاذية ممتازة مقارنة بتعليق نترات إيكونازول النقية. بالإضافة إلى ذلك، يمكن للإدارة الموضعية أن تنقل الدواء إلى الجزء الأمامي من العين.

الكلمات المفتاحية: نترات الايكونازول، التهاب القرنية، التوصيل العيني، المذيلة البوليمرية، بولوكسامير