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ORIGINAL ARTICLE / ÖZGÜN MAKALE

PREPARATION AND *IN-VITRO* CHARACTERIZATION OF CONTACT LENSES CONTAINING COENZYME Q10 LOADED MICELLES

KOENZİM Q10 YÜKLÜ MİSEL İÇEREN KONTAKT LENSLERİN HAZIRLANMASI VE İN-VİTRO KARAKTERİZASYONU

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ABSTRACT

Objective: *Coenzyme Q10 (CoQ10) offers potential therapeutic benefits for ocular health, yet faces challenges of poor solubility and bioavailability when applied to the eye. This study aimed to enhance CoQ10 delivery using contact lenses by incorporating CoQ10-loaded polymeric micelles, using Pluronic F127 and solvent evaporation technique.*
Material and Method: *Polymeric micelles encapsulating CoQ10 were produced via solvent evaporation with Pluronic F127. Commercial contact lenses were subsequently loaded with these micelles. Characterization of the loaded lenses included assessments of light transmittance, swelling behavior, and drug release profile under non-sink conditions, simulating the constraints of the ocular surface.*
Result and Discussion: *The unloaded lenses exhibited a light transmittance of 91.78±3.29% and swelling percentage of 47.51±4.45% while micelle-loaded lenses demonstrated high light transmittance levels (95.31±0.80%), ensuring optical clarity. Swelling studies showed a slight increase in size to 48.1±4.4%. The lenses effectively encapsulated 403.6±21.8 µg of CoQ10. In vitro release profile exhibited controlled release over six hours, indicating potential for sustained drug delivery. These results highlight the feasibility of micelle-loaded contact lenses for efficient ocular drug delivery, warranting further exploration into their long-term effectiveness and safety.*
Keywords: *Coenzyme Q10, contact lens, polymeric micelle, solubility enhancement*

ÖZ

Amaç: *Koenzim Q10 (CoQ10), göz sağlığı için potansiyel terapötik faydalar sunmakta, ancak göze uygulandığında düşük çözünürlük ve biyoyararlanım sorunlarıyla karşı karşıya kalmaktadır. Bu çalışma, CoQ10 taşıyan polimerik miselleri Pluronic F127 ve çözücü buharlaştırma tekniği kullanarak kontakt lenslere yükleyerek CoQ10 teslimatını artırmayı amaçlamaktadır*
Gereç ve Yöntem: *Pluronic F127 ile çözücü buharlaştırma yöntemi kullanılarak CoQ10 kapsüllenmiş polimerik miseller üretildi. Ticari kontakt lensler daha sonra bu misellerle yüklendi. Yüklenmiş lenslerin karakterizasyonu, ışık geçirgenliği, şişme davranışı ve göz yüzeyinin kısıtlamalarını taklit eden olmayan emilim koşulları altında ilaç salım profili değerlendirmelerini içermektedir.*
Sonuç ve Tartışma: *Yüklenmemiş lensler %91.78±3.29 ışık geçirgenliği ve %47.51±4.45 şişme oranı sergilerken, misel yüklü lensler yüksek ışık geçirgenliği seviyeleri (%95.31±0.80) göstererek optik berraklığı sağlamıştır. Şişme çalışmaları boyutta hafif bir artışa (%48.1±4.4) işaret*

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etmektedir. Lenslere, etkili bir şekilde 403.6±21.8 µg CoQ10 yüklenmiştir. İn vitro salım profili altı saat boyunca kontrollü salım göstermiş, sürekli ilaç salımı için potansiyel olduğu belirtilmiştir. Bu sonuçlar, etkin oküler ilaç taşıma için misel yüklü kontakt lenslerin uygulanabilirliğini vurgulamakta ve uzun vadeli etkinlik ve güvenliklerinin daha fazla araştırılmasını gerektirmektedir.
Anahtar Kelimeler: *Çözünürlük arttırma, koenzim Q10, kontakt lens, polimerik misel*

INTRODUCTION

Drug-loaded contact lenses represent a novel and promising approach in ocular drug delivery, offering several advantages over conventional eye drops. These specialized contact lenses are designed to provide sustained and controlled release of therapeutics directly to the eye, enhancing drug bioavailability and reducing systemic side effects. The incorporation of drugs into contact lenses can be achieved through various techniques, such as soaking the lenses in drug solutions, embedding drugs within the lens matrix, or attaching drug-loaded nanoparticles to the lens surface. This technology is particularly beneficial for treating chronic eye conditions like glaucoma, dry eye syndrome, and infections, as it maintains a therapeutic level of the drug in the tear film for extended periods, ensuring more effective treatment. Additionally, drug-loaded contact lenses improve patient compliance by reducing the frequency of drug administration and eliminating the discomfort often associated with eye drops [1-3].

Coenzyme Q10 (CoQ10), often referred to as ubiquinone, is a lipid-soluble compound similar to vitamins, essential for the generation of energy at the cellular level and known for its strong antioxidant capabilities. Although its benefits in cardiovascular and neurological health is widely recognized, CoQ10 has also garnered attention in the field of ophthalmology, particularly for its potential in treating eye conditions such as age-related macular degeneration (AMD) and glaucoma [4,5]. However, the application of CoQ10 in ocular therapies is challenging due to its poor water solubility, high molecular weight, chemical sensitivity, and therefore limited bioavailability [6,7]. The molecule's lipophilic nature hampers its effective absorption and penetration into the eye, necessitating the development of innovative delivery systems. To address these challenges, researches have focused on various formulation strategies, including lipid-based nanocarriers, surfactant-aid solubilization, and liposomes, to enhance the solubility, and ocular bioavailability of CoQ10 [5,8]. These advanced delivery systems aim to improve the penetration of CoQ10 into the eye, thereby maximizing its therapeutic potential. In this study, we encapsulated it into the polymeric micelles to increase the solubility and therapeutic activity.

Polymeric micelles are nanoscopic structures formed by the self-assembly of amphiphilic block copolymers in an aqueous solution. These unique structures, typically in the range of 10 to 100 nm, consist of a hydrophobic core and a hydrophilic shell. The hydrophobic core enables the encapsulation of lipophilic drugs, improving their solubility, and bioavailability, which is a significant advantage in drug delivery applications [9,10]. The hydrophilic shell, usually composed of polyethylene glycol (PEG), imparts stealth characteristics to the micelles, reducing opsonization and prolonging circulation time in the bloodstream. This feature is particularly advantageous in passive targeting of tumors via the enhanced permeability and retention (EPR) effect [11]. Polymeric micelles are also explored for their potential in targeted drug delivery, capable of being functionalized with ligands to recognize and bind to specific cell types. Additionally, stimuli-responsive polymeric micelles, which disassemble or change properties in response to pH, temperature, or enzymatic activity, have shown promise in achieving controlled and site-specific drug release [12,13].

In the micelle preparation, Pluronic F127 copolymer was used. Pluronic F127, a triblock copolymer composed of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) blocks, exhibits unique micellization properties due to its hydrophilic-hydrophobic balance. The physical properties of Pluronic F127, characterized by a higher number of hydrophobic PPO units and a higher ratio of hydrophobic PO to hydrophilic EO units, contribute to its micellization behavior and stability in aqueous solutions[14]. The stability and micellization properties of Pluronic F127 are crucial factors in its potential applications for drug delivery and other biomedical uses [15,16].

In this study, we utilized hydrophobic CoQ10 for its therapeutic potential in ocular applications, acknowledging the challenge posed by its high lipophilicity in drug delivery to the eye. Main formulation strategies are incorporating a significant proportion of surfactants or polymeric micelles, known for their solubility-enhancing ability to enhance solubility and bioavailability. However, given the inherent issue of rapid drainage through the nasolacrimal duct with aqueous micellar dispersions, we innovatively employed contact lenses as a delivery system. This approach not only mitigates the drainage issue but also potentially increases the residence time and bioavailability of CoQ10 on the ocular surface. The study extensively characterizes both the CoQ10-loaded micelles and their integration into contact lenses, offering new insights into the effectiveness of this novel ocular drug delivery system.

MATERIAL AND METHOD

Materials

All solutions in this study were meticulously prepared using reagent grade chemicals and ultra-pure water (18 MΩ cm). The HPLC grade Acetonitrile and Ethanol were procured from Supelco, Germany, and Aklar Kimya, Turkey, respectively. Coenzyme Q10 was sourced from Abcr, Germany. Pluronic F127, used as a surfactant, was obtained from Merck, Germany. Contact lenses were (Dailies Total 1®) were bought from optic market. Dailies Total 1 water gradient contact lenses are designed with a 14.1mm diameter, a base curve of 8.5mm, and a central thickness measuring 0.09mm for a -3.00D prescription. Lenses made from a substance known as delefilcon A, these lenses possess a modulus of 0.7MPa. Delefilcon A is composed of a silicone hydrogel core with a 33% water content and an outer hydrogel layer with an 80% water content. The inorganic salts, sodium chloride (NaCl), sodium bicarbonate ($NaHCO_3$), Calcium chloride ($CaCl_2$), and potassium chloride (KCl), also from Merck, Germany, were used to prepare physiological buffer solution for dissolution test.

Preparation of CoQ10-Loaded Polymeric Micelles

The CoQ10-loaded polymeric micelles were prepared using a reverse-phase evaporation method [10]. Initially, CoQ10 and Pluronic F127 were dissolved in 3 ml of chloroform to form a homogenous solution (Table 1). This solution was then added dropwise to 10 ml of distilled water under continuous stirring. The purpose of this gradual addition was to ensure the formation of micelles with CoQ10 encapsulated in the core surrounded by the Pluronic F127 corona. After the complete addition of the chloroform solution, the mixture was left to stir 700 rpm overnight. This step was critical to facilitate the evaporation of the organic solvent, leading to the self-assembly of micelles. The stirring process was carefully monitored to ensure a gentle and consistent mixing, which is crucial for the formation of uniform micelles. Following the evaporation of chloroform, the micelle suspension was further processed to remove any undissolved active substance. This was achieved by filtering the suspension through a 0.22 µm membrane filter. The filtration process not only removed the undissolved CoQ10 but also helped in obtaining a clear micelle solution, which is essential for subsequent characterization and application. Finally, the obtained micelle suspension was subjected to thorough characterization. The characterization process aimed to assess the size, zeta potential and encapsulation efficiency of CoQ10 of the prepared micelles. This step is crucial to ensure that the micelles meet the required standards for their intended use in drug delivery applications.

Table 1. Formulation components

Components	F1	F2	F3
Pluronic F127 (%)	2.00	2.00	2.00
CoQ10 (%)	0.50	0.75	1.00

Drug Loading onto Contact Lenses

The process of drug loading onto contact lenses was meticulously conducted using commercially

available Dailies Total 1® contact lenses. The procedure initiated with the preparation of the lenses, which were left to dry overnight. This drying step is crucial as it ensures the removal of any moisture that could potentially interfere with the subsequent drug loading process. Once the lenses were adequately dried, they were immersed in the F1 formulation for diffusion-mediated loading. The drug loading process was facilitated by placing the lenses in a shaking water bath set at 37°C with a speed of 75 rpm over the night. This controlled environment, including the temperature and agitation, was meticulously maintained to optimize the drug loading onto the lenses.

Following the incubation, the drug-loaded lenses were carefully retrieved and gently dried using a clean tissue. This step is important to remove any excess formulation from the lens surface, preparing them for subsequent characterization. The final step involved a comprehensive characterization of the drug-loaded lenses. The characterization of the lenses is a crucial phase, as it ensures the suitability and safety of the lenses for ocular use.

Characterization of Polymeric Micelles

In this study, the characterization of micelles was conducted with a focus on analyzing the particle sizes, distributions, and zeta potentials of the micelles. The size, size distribution, and polydispersity index (PDI) of the micelles were determined using Dynamic Light Scattering (DLS) with a Zetasizer Nano ZS (Malvern Instruments, UK). These measurements were performed at 25°C using a He-Ne laser (633 nm) at a scattering angle of 173 degrees (n=4). Disposable Zetasizer cuvettes were employed micelles and each sample was measured four times to ensure accuracy and reproducibility of the data. Additionally, the zeta potential of the micelle formulations was also assessed using the Zetasizer. This involved the use of specific cuvettes designed for zeta potential measurements, with each formulation being measured three times.

Characterization Studies Micelle-Loaded-Contact Lenses

Light Transmittance: In this study, the light transmittance of micelle loaded and unloaded contact lenses was quantitatively assessed using a UV-Vis spectrophotometer. Each lens type was fully immersed in deionized water and placed optical path of the UV. Transmittance was measured at a wavelength of 480 nm, within the visible light spectrum. An air was used as a blank to calibrate the spectrophotometer for each set of measurements. To ensure reliability, each transmittance measurement was performed in triplicate [17].

Water Retention and Swelling Determination: The dry weight of the lenses (W_{dry}) was initially measured. The lenses were then immersed in water and incubated for 24 hours. Subsequently, the surface water was blotted off with a tissue, and the final weights of the swollen lenses ($W_{swollen}$) were recorded. The percentage of swelling was calculated using the following equation:

Swelling Percentage = $[(W_{swollen} - W_{dry}) / W_{dry}] \times 100$ [17].

The encapsulation efficiency of CoQ10 within the polymeric micelles was quantitatively analyzed using a UV spectrophotometer. A 100 µl aliquot of the micelle solution was first diluted with 1 ml of acetonitrile to ensure the proper dissolution of CoQ10 for analysis. This step was done to disrupt the micellar structure, releasing the encapsulated CoQ10 into the acetonitrile. The diluted samples were then subjected to UV analysis following a validated method specific for CoQ10 quantification at 274 nm [18]. The encapsulation efficiency was calculated using Equation 1 [16].

$$\text{E. E. (\%)} = \frac{\text{Loaded CoQ10 in micelles}}{\text{Total CoQ10 weight}} \times 100 \quad (1)$$

***In Vitro* CoQ10 Release Study from Contact Lenses**

The study focused on determining the release profile of the active substance from contact lenses loaded with CoQ10 micelle formulations. After successfully loading the micelles onto the contact lenses, the lenses were subjected to active substance release studies conducted in a shaking water bath. The

release studies were performed at 37°C with a shaking speed of 75 rpm, using 20 ml of simulated tear fluid as the dissolution medium. The simulated tear fluid was prepared by dissolving 0.68 g of NaCl, 0.22 g of $NaHCO_3$, 0.008 g of $CaCl_2$, and 0.14 g of KCl in 1000 ml of water, mimicking the natural ocular environment [19]. The dissolution studies were carried out under non-sink conditions to closely replicate physiological conditions.

At predetermined time points – specifically at 0.5, 1, 2, 3, 4, and 6 hours – aliquots of 0.5 ml were withdrawn from the dissolution medium. These samples were then diluted with acetonitrile and analyzed using UV spectrophotometry to determine the concentration of the released active substance at 274 nm ($\lambda_{acetonitrile}$). To maintain the volume consistency in the dissolution medium, an equivalent volume of fresh simulated tear fluid was added back after each sampling. The entire process was replicated thrice (n=3) for each formulation to ensure the reliability and reproducibility of the results.

Statistical Analysis

Statistical evaluations were carried out using a one-way analysis of variance (ANOVA) using Stat-Ease's Design Expert software version 13.0.5.0 (Minneapolis, MN, USA). Differences between formulations were deemed statistically significant at a p-value threshold of less than 0.05.

RESULT AND DISCUSSION

Preparation of Polymeric Micelles

In our study, polymeric micelles were formulated using Pluronic F127 polymer. Pluronic F127 is a triblock copolymer that is well-recognized for its thermoresponsive properties and its ability to form stable micelles with a hydrophobic core and hydrophilic shell in aqueous solutions. The core provides a reservoir for hydrophobic drugs, like CoQ10, enhancing their solubility and stability within biological systems [16,20]. The solvent evaporation technique is particularly advantageous for encapsulating hydrophobic drugs. This method involves dissolving both the drug and the polymer in a common volatile organic solvent, followed by the gradual removal of the solvent, leading to the self-assembly of the polymer into micelles with the drug encapsulated within the core [21]. This approach allows for the fine-tuning of micelle size and drug loading, crucial for ensuring efficient drug delivery and release kinetics [22].

The results presented in Table 2 suggest that components influence on the characteristics of CoQ10 loaded polymeric micelles. Across the three formulations, F1, F2, and F3, with increasing concentrations of CoQ10 from 0.50% to 1.00%, a trend of increasing particle size is observed ($p<0.05$). Specifically, the average size of the micelles ranges from 93.62 nm in F1 to 110.52 nm in F3, with corresponding standard errors, indicating a measure of consistency in particle size distribution within each formulation batch.

The PDI values for all formulations are relatively low, with a range of 0.146 to 0.214, suggesting a uniform size distribution among the micelle populations (Figure 1). Uniformity in micelle size is desirable in drug delivery systems for predictable bio-distribution, and drug release profiles.

Zeta potential values, which provide insight into the surface charge and colloidal stability of the micelles, are relatively similar across all formulations, hovering around -15 mV. This negative surface charge is indicative of the stability of the micelle in suspension, as particles with zeta potentials beyond ±30 mV typically exhibit strong electrostatic repulsion, preventing aggregation [23].

Encapsulation efficiency, an important parameter indicating the proportion of CoQ10 successfully incorporated into the micelles, appears to decrease with increasing CoQ10 concentration. F1 shows the highest encapsulation efficiency at 86.02%, while F3, with double the CoQ10 content, shows a reduced efficiency of 54.79%. This trend might suggest a saturation point in the micelle's capacity to encapsulate CoQ10, highlighting the need for a balance between drug load and micellar stability.

These findings provide valuable insights for optimizing CoQ10-loaded polymeric micelle formulations. According to results, F1 formulation was selected in terms of size and encapsulation efficiency.

Table 2. Characterization results of micelles

Formül	Pluronic F127 (%)	CoQ10 (%)	Size±SE (nm) (n=4)	PDI±SE (n=4)	Zeta Potential±SE (mV) (n=4)	Encapsulation Efficiency %±SE (n=3)
F1	2	0.50	93.62±0.44	0.214±0.01	-15.4±0.30	86.02±1.94
F2	2	0.75	103.7±2.11	0.198±0.01	-16.0±0.07	68.41±2.31
F3	2	1.00	110.5±2.70	0.146±0.01	-15.1±0.45	54.79±0.09

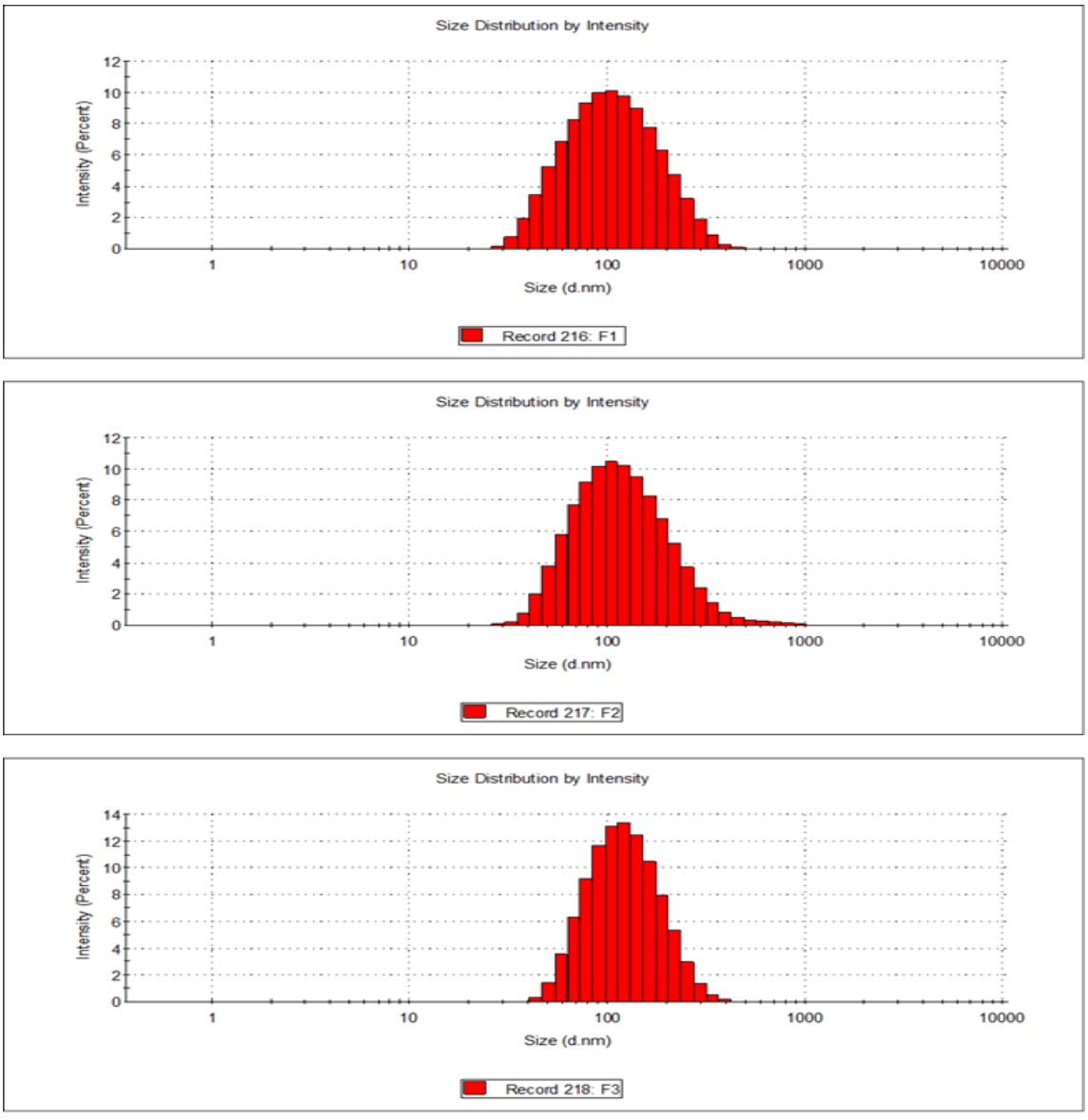

Figure 1. Particle size distribution of micelles

Characterization of Contact Lenses

Characterization studies in contact lenses involve a range of physical characterization techniques to assess their properties. These techniques include transparency, oxygen permeability, mechanical investigation, glass transition temperature, wettability, and water content [24-26]. Furthermore, the release of active pharmaceutical ingredients from drug-eluting contact lenses can be studied using techniques such as UV-Vis spectroscopy to evaluate drug release kinetics. Biocompatibility studies involving cell culture and tissue interaction assays are also essential to assess the safety and

compatibility of contact lenses with ocular tissues [27-29]. These physical characterization techniques provide comprehensive insights into the properties of contact lenses, ensuring their suitability for ophthalmic applications. However, we have used two of them transmittance (transparency) and water content (swelling) like the vast majority studies [25,30,31].

In the characterization studies performed on contact lenses, the F1 formulation was incubated with dried contact lenses to facilitate the loading of the formulation. The study presents an investigation into the loading efficiency and optical clarity of a drug formulation designated as F1 on contact lenses. The incubation of the dried lenses with the F1 formulation resulted in a substantial uptake of the drug, quantified at 403.6±21.8 µg per lens, showcasing the potential of these lenses as a medium for drug delivery.

The pure contact lens showed a swelling percentage of 47.51±4.45%. After loading with CoQ10 micelles, this increased marginally to 48.1±4.4%. This small increase suggests that the incorporation of the micelles into the lens matrix slightly enhances its ability to absorb and retain moisture. The change is relatively minimal and not significant statistically.

There is a more noticeable improvement in light transmittance from 91.78±3.29% in the pure lenses to 95.31±0.80% in the micelle-loaded lenses. This increase in light transmittance suggests that the incorporation of CoQ10 micelles improves the clarity of the lenses. Higher light transmittance in contact lenses is generally desirable as it implies better visibility for the wearer (Figure 2).

Figure 2. Contact lenses containing CoQ10-loaded polymeric micelles

The increase in light transmittance observed in the micelle-loaded contact lenses may be attributed to the unique properties of the micelles. This can be explained that micelles might have a refractive index that is closer to the contact lens material compared to the air or moisture in the pores of the pure lens. This closer match can reduce the scattering of light, allowing more light to pass through the lens, thus increasing its transmittance. This results were in concordance with previous study conducted by Mun et al. [32].

This balance between drug loading capacity and the retention of optical properties underscores the potential of the F1-loaded contact lenses as a promising platform for ocular drug delivery [33].

The release profile of the F1 formulation from contact lenses demonstrates a biphasic drug release over a six-hour period (Figure 3). An initial burst release occurs within the first hour, with approximately 40% of the drug being released, which is typical for systems where the drug is near the surface or readily diffusible. Subsequently, the release rate reaches a plateau between the first and fourth hours, indicating a transition to a more controlled release phase. This suggests that the remaining drug is being released more slowly, likely from deeper within the contact lens matrix. Towards the sixth hour, there is a notable increase in drug release, possibly due to increased hydrogel matrix swelling, enhancing the diffusion of the drug. The standard deviation represented by the error bars implies some variability but overall consistency in the release mechanism, indicating a reproducible drug release system. Such a profile is advantageous for providing sustained therapeutic levels of medication in ocular applications.

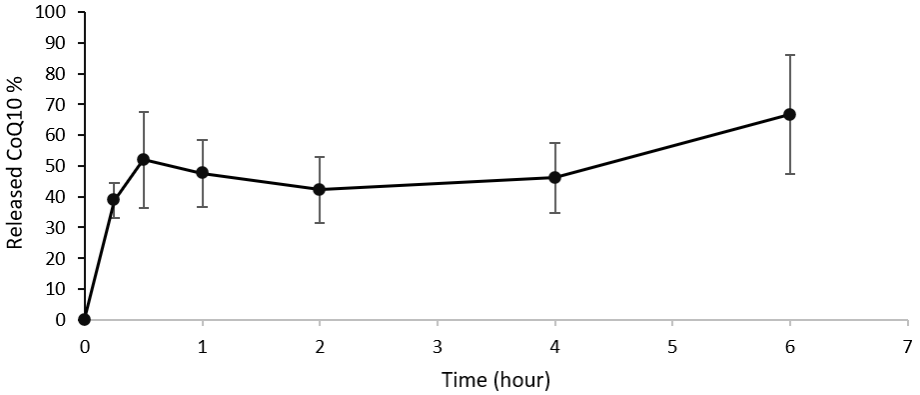

Figure 3. CoQ10 release from contact lenses

In vitro release study was performed with only CoQ10 micelle-loaded contact lenses. Because of the highly lipophilicity and using non-sink condition, pure CoQ10 can not dissolve. The release profile observed from the F1 formulation-laden contact lenses under non-sink conditions in this study are crucial for ocular drug delivery systems, providing insights into the *in vivo* behavior of sustained-release formulations. The non-sink conditions, characterized by the limited volume and dynamic nature of the ocular fluid, lead to a significant initial burst release, which may offer an immediate therapeutic effect upon administration [34]. This is followed by a plateau phase, indicative of a controlled release that could maintain therapeutic drug levels over an extended period. The final uptick in release at later hours could suggest a secondary release mechanism, possibly influenced by lens swelling within the tear film.

As a conclusion, this study successfully demonstrates the potential of contact lenses as a novel delivery system for CoQ10, utilizing polymeric micelles to overcome the challenges associated with its hydrophobic nature. The formulation of CoQ10 within Pluronic F127-based micelles, prepared through the solvent evaporation technique, effectively enhanced its solubility. The subsequent loading of these micelles onto contact lenses resulted in a promising delivery platform, as evidenced by the controlled and sustained release profile observed under non-sink conditions. The swelling behavior of the lenses also indicated a moderate increase in size, which is crucial for comfort and functionality. Overall, these findings highlight the viability of using CoQ10-loaded micelle contact lenses for ocular drug delivery, presenting an innovative approach that could potentially improve therapeutic outcomes in eye-related treatments.

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AUTHOR CONTRIBUTIONS

Concept: A.D.E.; Design: A.D.E.; Control: A.D.E.; Sources: A.D.E.; Materials: A.D.E.; Data Collection and/or Processing: A.D.E.; Analysis and/or Interpretation: A.D.E.; Literature Review: A.D.E.; Manuscript Writing: A.D.E.; Critical Review: A.D.E.; Other: A.D.E.

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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