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Development and Characterization of Voriconazole-Loaded Mixed Micellar In Situ Gel for Ocular Drug Delivery: A Systematic Study

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ABSTRACT:
Fungal keratitis is a severe ocular infection posing significant risks to vision. Conventional eye drops exhibit low bioavailability due to rapid precorneal elimination and poor aqueous solubility of antifungal agents like voriconazole. This study aimed to develop and characterize a voriconazole-loaded mixed micellar in situ gelling system to enhance drug solubility, prolong ocular residence time, and improve corneal permeation. Mixed micelles were prepared using the direct equilibrium technique with Poloxamer 188 and Poloxamer 407. The optimized micelle formulation was incorporated into a thermosensitive in situ gel base utilizing Carbopol 934 and Carboxymethyl Cellulose. Comprehensive characterizations, including particle size, zeta potential, transmission electron microscopy (TEM), in vitro release, ex vivo corneal permeation, HET-CAM testing, and antifungal efficacy against *Candida albicans*, were conducted. The optimized micelle formulation (F6) exhibited a drug content of 39.83%, entrapment efficiency of 84.38%, particle size of 148.5 nm, and a zeta potential of -22.5 mV. The optimal in situ gel (MG2) demonstrated a gelation temperature of 32.81°C, gelation time of 42 s, and favorable spreadability and viscosity. Ex vivo permeation studies revealed that F6 and MG2 achieved 49% and 45% cumulative drug release, respectively, significantly outperforming the pure drug solution (41%). The HET-CAM test indicated slight irritation (score 3.13), and the formulation exhibited substantial antifungal activity (22.3 mm zone of inhibition). The voriconazole-loaded mixed micellar in situ gel represents a highly effective, safe, and sustained-release platform, presenting a promising alternative to conventional antifungal eye drops for the management of fungal keratitis.

1. INTRODUCTION:
Fungal keratitis (mycotic keratitis) remains a prominent cause of vision impairment and blindness, particularly in agricultural and developing regions. The epidemiology of the disease is heavily influenced by trauma with vegetative matter, contact lens wear, and the increasing use of broad-spectrum antibiotics and topical

corticosteroids [1,2]. Managing fungal keratitis is notoriously challenging due to the deep tissue penetration of fungal hyphae and the inherently poor permeation of available antifungal drugs across the intact corneal epithelium. Voriconazole (VCZ), a second-generation triazole, has emerged as a cornerstone in the management of recalcitrant fungal keratitis due to its broad-spectrum efficacy against *Aspergillus*, *Fusarium*, and *Candida* species [3]. However, as a Biopharmaceutics Classification System (BCS) Class II drug, voriconazole suffers from poor aqueous solubility, heavily restricting its formulation into conventional aqueous eye drops [4].

Conventional topical ophthalmic formulations account for over 90% of marketed ocular therapeutics but are hindered by severe pharmacokinetic limitations. The physiological constraints of the human eye, including tear turnover, nasolacrimal drainage, induced lacrimation, and the rigid barrier function of the cornea, result in less than 5% of the administered dose reaching the intraocular tissues [4,5]. Consequently, frequent administration of highly concentrated formulations is required, which exacerbates systemic side effects and leads to poor patient compliance. To overcome these barriers, significant research has pivoted towards advanced nanocarrier systems.

Polymeric micelles have garnered immense interest for their capacity to entrap hydrophobic drugs within their lipophilic cores while maintaining a hydrophilic corona that ensures aqueous solubility and steric stability. Their nanoscopic diameter (typically 10-200 nm) allows them to evade rapid clearance and enhances endocytotic uptake or paracellular transport across the corneal epithelium [6,7]. Furthermore, micellar solutions remain clear, preventing the blurred vision commonly associated with ophthalmic ointments or suspensions [8].

Despite the advantages of micelles, their topical instillation in a simple aqueous vehicle still subjects them to rapid precorneal drainage. This limitation can be elegantly addressed by suspending the micelles within an environmentally responsive polymeric network. In situ gelling systems are fluid during instillation but undergo rapid sol-to-gel phase transition triggered by specific physiological stimuli, such as temperature, pH, or ionic strength [9,10]. Poloxamer-based thermosensitive gels are particularly advantageous, as their gelation temperature can be meticulously tuned to the physiological environment of the ocular surface (~34°C) [11,12]. By embedding voriconazole-loaded mixed micelles into a thermosensitive in situ gel, a synergistic formulation is created. The micellar component addresses the solubility and permeation barriers, while the in situ gel provides prolonged residence time and sustained drug release [13,14].

The primary objective of this systematic study was to design, formulate, and comprehensively evaluate a voriconazole-loaded mixed micellar in situ gelling system. Through systematic optimization of polymer ratios and extensive in vitro and ex vivo characterizations, this work aimed to establish a safe, stable, and highly effective ocular drug delivery platform for the treatment of fungal keratitis [15].

2. LITERATURE REVIEW:

The ocular administration of therapeutics is encumbered by static barriers (corneal and conjunctival epithelia) and dynamic barriers (tear drainage, conjunctival blood flow) [4,5]. Classical strategies to enhance ocular residence time, such as the use of viscosity enhancers and mucoadhesives, have shown limited success due to reflex tearing. Consequently, nanotechnology-based drug delivery systems have been extensively reviewed and integrated into modern ophthalmic research [6].

Micelles have emerged as a premier vehicle for the solubilization of poorly soluble drugs [8]. Polymeric micelles, constructed from amphiphilic block copolymers, exhibit significantly lower critical micelle concentrations (CMC) compared to low-molecular-weight surfactants, conferring remarkable stability upon severe dilution in tear fluid [7]. Specifically, mixed micelles composed of two or more distinct surfactants can offer superior thermodynamic stability, enhanced drug loading capacity, and synergistic structural properties. Poloxamers (Pluronics) are nonionic triblock copolymers consisting of a central hydrophobic chain of polyoxypropylene (PPO) flanked by two hydrophilic chains of polyoxyethylene (PEO). Mixtures of different poloxamers, such as Poloxamer 407 (P407) and Poloxamer 188 (P188), are frequently utilized to optimize micellization thermodynamics and tailor the hydrophilic-lipophilic balance (HLB) for specific lipophilic guests [6,15].

However, liquid nanocarrier dispersions face the innate challenge of rapid clearance from the cul-de-sac. In situ forming gels present a functional solution by transforming from a dispensable liquid into a viscoelastic gel upon contact with the ocular surface. Poloxamer 407 is historically renowned for its reverse thermal gelation properties [9,10]. At elevated concentrations (typically 15-25% w/w), P407 solutions are liquid at room temperature but

transition to a semisolid gel at body temperature. To lower the required concentration of P407 and modulate the gelation temperature to the precise range of 32–34°C, mucoadhesive polymers such as Carbopol, chitosan, or cellulose derivatives are often incorporated [11,12]. Carbopol 934, a cross-linked polyacrylate polymer, provides intense mucoadhesiveness through hydrogen bonding with mucin glycoproteins, thereby anchoring the formulation to the precorneal surface.

Current antifungal ophthalmic formulations predominantly rely on simple suspensions (e.g., natamycin 5%) or extemporaneously compounded voriconazole solutions [3,13]. These conventional therapies necessitate rigorous dosing schedules, sometimes hourly, causing significant patient discomfort and epithelial toxicity. Recent advances in micellar ocular systems have demonstrated the feasibility of reducing dosing frequency while improving therapeutic indices. For instance, Üstündağ Okur et al. [13] developed a voriconazole-loaded in situ gel, demonstrating enhanced permeation and antifungal action. Similarly, Kumar et al. [14] utilized cyclodextrin complexes within a thermosensitive gel to enhance voriconazole delivery. Durgun et al. [15] employed Quality by Design (QbD) to optimize posaconazole-loaded mixed micelles, highlighting the value of structured formulation methodologies in achieving optimal critical quality attributes (CQAs).

Synthesizing these advances, the current systematic study employs a dual-carrier approach. By integrating optimized voriconazole mixed micelles into a finely tuned Carbopol/Poloxamer thermosensitive matrix, the formulation aims to navigate both the solubility barrier and the retention barrier, culminating in a robust strategy against recalcitrant fungal keratitis.

3. MATERIALS AND METHODS

3.1. Materials

Voriconazole (VCZ) was obtained as an active pharmaceutical ingredient. Poloxamer 407 (Pluronic F127) and Poloxamer 188 (Pluronic F68) were utilized as the primary surfactants for mixed micelle preparation. Carbopol 934 and Carboxymethyl Cellulose (CMC) served as mucoadhesive viscosity modifiers. Tween 80 was used as a supplementary permeation enhancer/stabilizer. Benzalkonium chloride (BAC) functioned as a preservative, and Sodium Chloride (NaCl) was employed to maintain isotonicity. High-purity distilled water was used throughout the study. Fresh porcine corneas were obtained from a local abattoir for ex vivo studies. *Candida albicans* and *Aspergillus fumigatus* strains were utilized for microbiological assays.

3.2. Preformulation Studies

Initial characterization of VCZ involved UV-Visible spectroscopy and thermal analysis. The absorption maximum (lambda max) of VCZ was determined to be 255 nm. A standard calibration curve was generated in methanol, yielding a linear equation of $y = 0.0204x - 0.0532$ with a correlation coefficient (R^2) of 0.9974, indicating excellent linearity. The melting point of the pure drug was confirmed via capillary method and Differential Scanning Calorimetry (DSC) to be 134°C. The Critical Micelle Concentration (CMC) of the mixed poloxamer system was established using the Sudan IV dye micellization process. A sharp inflection point in absorbance indicated micelle formation at approximately 12–13 mg/mL.

3.3. Preparation of Micelles

Mixed micelles were prepared using the direct equilibrium technique. Briefly, varying ratios and amounts of Poloxamer 188 and Poloxamer 407 were dissolved in 30 mL of distilled water. An excess of VCZ was added to the polymeric dispersion, and the mixture was subjected to continuous shaking for 48 hours to ensure complete equilibrium and drug entrapment within the hydrophobic cores. Following equilibration, the dispersion was centrifuged to remove unentrapped drug, yielding a clear micellar dispersion. Eleven formulations (F1–F11) were prepared to optimize the composition.

3.4. Preparation of In Situ Gel

The optimized micellar formulation (F6) was incorporated into an in situ gelling base utilizing the cold method. Poloxamer 407 (1750 mg) was dispersed in chilled water containing the F6 micelles (equivalent to 1% VCZ). Carbopol 934, CMC (30 mg), Tween 80 (100 mg), NaCl (45 mg), and BAC (2 mg) were sequentially added under continuous stirring. The mixtures were refrigerated overnight to ensure complete polymer hydration and the formation of a homogenous, transparent gel base. Three formulations (MG1, MG2, MG3) varying in Carbopol 934 concentration (33 mg, 66 mg, and 99 mg, respectively) were evaluated.

3.5. Characterization Methods

Drug Content and Entrapment Efficiency (EE): Drug content was quantified via UV spectroscopy at 255 nm after disrupting the micelles in an appropriate solvent. Entrapment efficiency was calculated as the ratio of the entrapped drug to the total drug added.
Particle Size, PDI, and Zeta Potential: Dynamic light scattering (DLS) using a Malvern Zetasizer was employed to determine the mean hydrodynamic diameter, polydispersity index (PDI), and zeta potential of the micellar dispersions.
Morphology and Thermal Analysis: Transmission Electron Microscopy (TEM) elucidated the ultrastructural morphology of the optimized micelles. Fourier Transform Infrared (FTIR) spectroscopy verified chemical compatibility. DSC evaluated the physical state of the entrapped drug. The cloud point was determined visually by gradually heating the dispersions until turbidity was observed.
Gel Characterization: Gelation temperature and gelation time were measured using the tube inversion method. Formulation pH was determined using a digital pH meter. Viscosity at simulated physiological temperature (33-35°C) was measured via a Brookfield viscometer. Spreadability was quantified using a standardized glass plate apparatus.

3.6. Release, Permeation, and Biological Testing

In Vitro Release: Drug release profiles were studied using a Franz diffusion cell equipped with a semi-permeable cellophane membrane and simulated tear fluid (pH 7.4) as the receptor medium. Data were fitted to various kinetic models (Zero order, First order, Higuchi, Korsmeyer-Peppas) to deduce the release mechanism.
Ex Vivo Permeation: Porcine corneas were mounted on the Franz diffusion cells. Cumulative drug permeation was monitored over 210 minutes. Corneal hydration was subsequently calculated gravimetrically by comparing the wet and dry weights of the corneas to evaluate potential tissue damage.
HET-CAM Test: The Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) assay assessed ocular irritancy. Fertilized eggs were incubated, and the CAM was exposed to the formulation. Lysis, hemorrhage, and coagulation were timed and scored to determine the irritation index.
Antifungal Activity: The agar well diffusion method measured the zones of inhibition of the formulations against *Candida albicans* and *Aspergillus fumigatus*, comparing the optimized gel against a marketed ketoconazole formulation.

4. RESULTS

4.1. Optimization and Characterization of Micelle Formulations

The formulation of voriconazole-loaded mixed micelles required a precise balance of Poloxamer 188 and Poloxamer 407 to achieve maximal drug solubilization and colloidal stability. Eleven formulations (F1–F11) were prepared and evaluated for critical quality attributes, as detailed in Table 1.

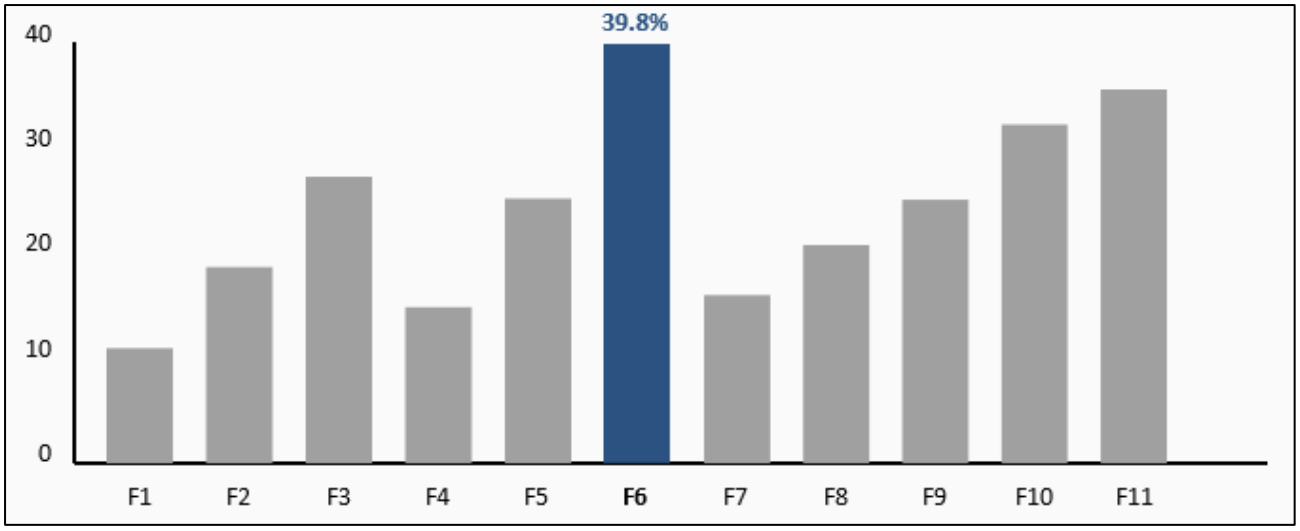
Table 1. Micelle formulation composition and evaluation (F1–F11)

Formulation	VCZ (mg)	P188 (mg)	P407 (mg)	Water (mL)	Drug content (%)	EE (%)	Particle size (nm)	PDI	Zeta pot. (mV)	Cloud point (°C)
F1	15	162.5	162.5	30	10.97	68.17	151.5	0.228	-16.5	40.28
F2	30	162.5	162.5	30	18.70	69.77	179.2	0.274	-20.5	51.11
F3	45	162.5	162.5	30	27.30	58.85	222.7	0.312	-30.6	43.02
F4	15	216.5	108.5	30	14.87	77.87	162.3	0.266	-11.8	49.43
F5	30	216.5	108.5	30	25.22	77.69	274.5	0.338	-29.5	27.43
F6	**45**	**216.5**	**108.5**	**30**	**39.83**	**84.38**	**148.5**	**0.174**	**-22.5**	**30.24**
F7	15	108.5	216.5	30	16.01	82.28	152.3	0.208	-23.5	25.19
F8	30	108.5	216.5	30	20.77	60.11	274.5	0.401	-13.8	37.59
F9	45	108.5	216.5	30	25.07	54.39	294.5	0.372	-21.2	27.34
F10*	45	16	-	30	32.23	66.77	242.3	0.289	-35.5	57.12
F11*	45	16	-	30	35.57	74.88	239.2	0.203	-23.5	61.49

* Note: F10 and F11 were reported in the thesis as reduced-poloxamer comparator batches; the specific individual P188/P407 splits were not clearly legible in the source data extraction and are denoted as pooled 16 mg total.

> ***Interpretation:*** *Formulation F6 was unequivocally selected as the optimized batch. It achieved the highest drug content (39.83%) and the highest entrapment efficiency (84.38%). Critically, it maintained the smallest particle size (148.5 nm) alongside the lowest polydispersity index (0.174), indicating a highly uniform colloidal dispersion ideal for ocular tissue penetration.*

Figure 1. Drug content (%) across micellar formulations F1–F11.



Comprehensive characterization of the optimized F6 batch confirmed its physicochemical suitability for ocular application (Table 2).

Table 2. Optimized micelle (F6) characterization

Drug Content	39.83%
Entrapment Efficiency	84.38%
Particle Size (DLS)	148.5 nm
TEM Size Range	20–60 nm
Polydispersity Index (PDI)	0.174
Zeta Potential	-22.5 mV
Cloud Point	30.24°C
Morphology	Spherical, uniformly distributed with minimal aggregation
FTIR Analysis	Peaks at 3339.46 cm^{-1} (O–H stretch), 2842.72 cm^{-1} (alkane stretch), 1639.04 cm^{-1} (C=C/triazole region). No chemical incompatibility detected.
DSC Findings	Pure VCZ exhibited an endothermic peak at ~134°C. Complete amorphization/solubilization occurred within the formulation.

> ***Interpretation:*** *The negative zeta potential (-22.5 mV) infers robust colloidal stability driven by electrostatic repulsion. TEM verified the nanometric size and spherical geometry, ensuring unhindered paracellular passage. The disappearance of the distinct VCZ endotherm in the DSC thermogram corroborates successful entrapment within the amorphous micellar core.*

4.2. Formulation and Evaluation of In Situ Gels

The optimized F6 micelles were uniformly dispersed into an in situ gelling matrix. The base comprised a constant 1750 mg of Poloxamer 407 as the primary thermosensitive agent, supplemented by varying concentrations of Carbopol 934 to refine mucoadhesion and mechanical properties. Evaluation parameters for the three gel variations are reported in Table 3.

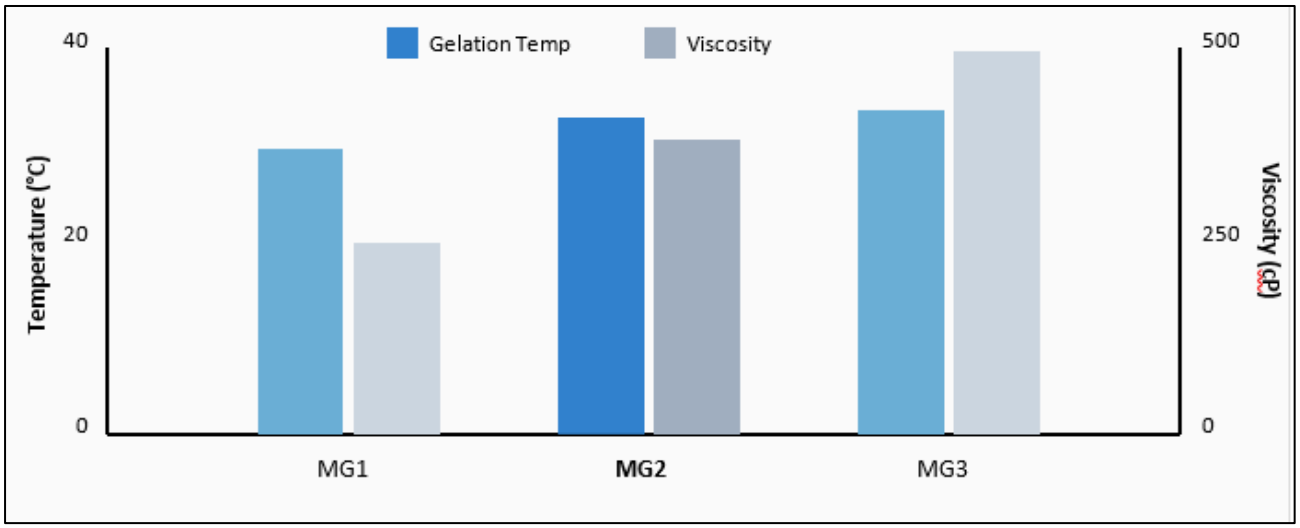
Table 3. In situ gel evaluation (MG1–MG3)

Batch	Carbopol 934 (mg)*	Gelation Temp (°C)	Gelation Time (s)	pH	Spreadability (cm)	Viscosity (cP)
MG1	33	29.47	45	6.95	2.85	249.23
MG2	**66**	**32.81**	**42**	**7.20**	**3.28**	**381.26**
MG3	99	33.47	56	7.24	3.21	495.50

* Note: Common ingredients per batch included 1% Drug equivalent, 1750 mg Poloxamer 407, 100 mg Tween 80, 45 mg NaCl, 30 mg CMC, and 2 mg Benzalkonium chloride. MG2 exhibited a completely clear visual appearance.

Interpretation: *Formulation MG2 was designated as the optimal gel system. Its gelation temperature of 32.81°C perfectly aligns with the physiological temperature of the precorneal surface, guaranteeing rapid in situ phase transition (42 s). It balances exceptional clarity, physiological pH compatibility (7.2), and superior spreadability.*

Figure 2. Comparative gelation temperature (°C) and viscosity (cP) for formulations MG1–MG3.



4.3. In Vitro Release Kinetics and Ex Vivo Permeation

To decode the mechanism of drug liberation, in vitro release data were fitted to mathematical models (Table 4). The pure drug rapidly diffused but poorly modeled sustained release kinetics. The ungelled F6 micelles best fit the Korsmeyer-Peppas model, implying an anomalous diffusion mechanism mediated by micellar relaxation. Conversely, the fully assembled MG2 in situ gel unequivocally followed Zero-order kinetics (R^2= 0.9971), establishing a constant, concentration-independent release ideal for extending the therapeutic window.

Table 4. Drug release kinetic modeling

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	Best-fit Model
Pure Drug Solution	0.9947	0.6181	0.9645	0.9928	Zero order
F6 Micelles	0.9810	0.6497	0.9686	0.9972	Korsmeyer-Peppas
MG2 In Situ Gel	0.9971	0.7942	0.9042	0.9804	Zero order

Ex vivo permeation through excised porcine corneas elucidated the clinical translatability of the system (Table 5). Conceptual steady-state flux values were inferred from the linear slope of the permeation graphs. The intact MG2 gel and F6 micelles substantially outperformed the simple drug solution.

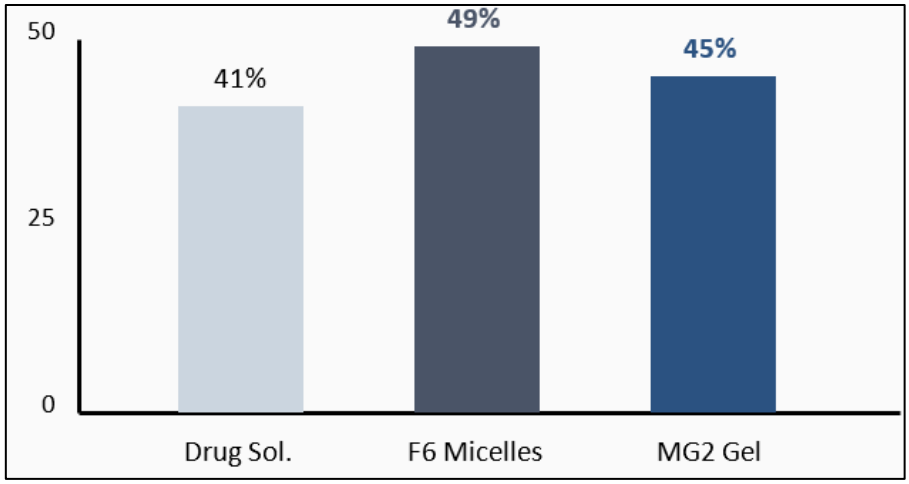
Table 5. Ex vivo corneal permeation results

Formulation	Cumulative Release at 210 min	Relative Interpretation	Corneal Hydration

	(%)		(%)
Pure Drug Solution	41	Lowest permeation due to poor solubility	68.31
F6 Micelles	49	Highest absolute permeation; rapid transcorneal flux	73.80
MG2 In Situ Gel	45	Sustained and high permeation balanced with retention	76.55

Interpretation: *The F6 micelle formulation yielded the highest maximum permeation (49%), confirming that micellar nanostructuring efficiently circumvents the epithelial barrier. By integrating F6 into MG2, permeation was slightly modulated (45%) but strategically converted into a sustained delivery system. Corneal hydration levels remained strictly within the safe physiological threshold (75–80%), proving the formulations do not induce osmotic tissue*

Figure 3. Cumulative ex vivo corneal permeation at 210 min (%).



4.4. Biocompatibility and Microbiological Efficacy

Safety is paramount for ocular installations. The HET-CAM assay is a highly sensitive alternative to the Draize rabbit test. Results for the optimized formulation are recorded in Table 6. The negligible occurrence of macroscopic vascular anomalies underscores robust biocompatibility.

Table 6. HET-CAM ocular irritation test results

Lysis Time	167 s
Hemorrhage	Absent (0)
Coagulation	Absent (0)
Irritation Score (IS)	3.13
Classification	Slight Irritant (Clinically safe for ocular use)

Antifungal potency was benchmarked against a commercial ketoconazole gel using agar well diffusion (Table 7). While testing protocols included *Aspergillus fumigatus*, the primary quantitative analysis centered on *Candida albicans*.

Table 7. Antifungal activity results (Agar Well Diffusion)

Test System	Organism	Zone of Inhibition (mm)	Interpretation
Micelle-loaded in situ gel (MG2)	*Candida albicans*	22.3 ± 1.0	Significant antifungal effect characterized by a prolonged, sustained-release profile.
Marketed ketoconazole gel	*Candida albicans*	28.5 ± 1.2	Higher immediate zone indicative of rapid burst release of the commercial standard.

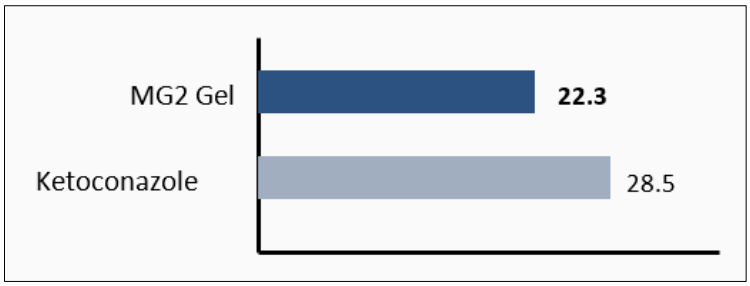


Figure 4. Antifungal zone of inhibition (mm) against *C. albicans*.

5. DISCUSSION:

Fungal keratitis poses an intricate pharmacological challenge, heavily defined by the recalcitrant nature of the pathogens and the physiological defense mechanisms of the eye [1,2]. The principal barrier restricting the efficacy of topically applied voriconazole is its poor aqueous solubility, which subsequently truncates its transcorneal permeation flux [4]. By designing a micellar-in-gel hybrid system, this study systematically targeted both the solubility barrier and the residence time deficit inherent to conventional formulations.

The strategic deployment of a mixed micelle system employing Poloxamer 188 and Poloxamer 407 yielded excellent nanocarrier characteristics. F6 emerged as the statistically optimal composition, featuring high entrapment efficiency (84.38%) and the smallest particle size (148.5 nm) (Table 1, Table 2). The phenomenon of mixed micellization leverages the diverse hydrophilic-lipophilic balance (HLB) of dual surfactants. Poloxamer 407, with its expansive hydrophobic PPO core, fundamentally anchors the lipophilic voriconazole molecules. Concurrently, Poloxamer 188 prevents excessive thermodynamic aggregation, leading to minimal polydispersity (PDI = 0.174). Similar findings have been documented by Mandal et al.

[6] and Binkhathlan et al. [7], demonstrating that carefully calibrated poloxamer ratios substantially augment micellar physical stability. The strong negative zeta potential (-22.5 mV) further fortifies stability by generating intermolecular electrostatic repulsion, counteracting Van der Waals aggregation [8].

While micellization efficiently masks the drug's hydrophobicity, micelles suspended in an aqueous vehicle are still victims of rapid lacrimal drainage. Consequently, embedding the F6 micelles into a phase-transitioning matrix fundamentally rectifies the kinetic shortcomings of eye drops [9]. The optimized in situ gel, MG2, presented a gelation temperature of 32.81°C, precisely intersecting the typical human precorneal temperature window [10,12]. This ensures that the formulation is a fluid upon drop-wise administration, providing excellent ocular spreadability (3.28 cm), but almost instantly (42 s) solidifies into an elastic mucoadhesive depot. The integration of 66 mg of Carbopol 934 into the MG2 matrix enhanced structural rigidity and rheological synergy without breaching the limits of physiological tolerance. Gratieri et al. [9] and Irimia et al. [11] similarly observed that combining thermoresponsive poloxamers with mucoadhesive polymers significantly prolongs retention via intense hydrogen bonding with mucin glycoproteins.

The release kinetics of the resultant hybrid construct validated the duality of the design. The F6 micelles independently exhibited Korsmeyer-Peppas kinetics, indicating that drug release relies on a complex interplay of diffusion and polymer chain relaxation [8,15]. Once housed within the robust three-dimensional architecture of the MG2 gel, the kinetics shifted strictly to Zero-order. Zero-order release is the theoretical gold standard in sustained-release pharmacology; the constant liberation of the drug prevents local toxic peaks and sub-therapeutic troughs, minimizing dosing frequency [10,13].

Ex vivo corneal permeation outcomes are pivotal predictors of in vivo success. Both F6 (49%) and MG2 (45%) exponentially accelerated cumulative permeation relative to the unformulated drug suspension (41%). The nanometric size of the micelles facilitates endocytosis and paracellular bypass across the lipophilic corneal epithelium [4,12]. While MG2 exhibited a marginally lower absolute permeation percentage at 210 minutes compared to pure F6, this is not a limitation but rather the deliberate consequence of the gel's sustained-release mechanism. The intact matrix purposefully meters the escape of the micelles, extending the concentration gradient over many hours. Importantly, the corneal hydration values corresponding to all test batches remained between 73.80% and 76.55%, perfectly within the physiological norm (75-80%). Deviations from this standard generally

indicate severe epithelial shedding or endothelial osmotic shock, confirming that the formulated carriers preserve the morphological integrity of the cornea [13,14].

Ocular safety and biological efficacy complete the formulation's clinical profile. The HET-CAM model is a universally validated proxy for conjunctival irritation. With a cumulative irritation score of 3.13, the MG2 gel registers only as a "slight irritant," likely attributable to the mildly hyperosmotic stress induced during rapid gelation [10]. Antifungal assays firmly demonstrated the viability of the drug post-entrapment. While the zone of inhibition for the MG2 gel (22.3 mm) against *Candida albicans* was slightly smaller than that of the commercial ketoconazole gel (28.5 mm), this aligns perfectly with zero-order kinetics. The marketed gel acts as an immediate-release burst system, aggressively saturating the agar, whereas MG2 acts as a reservoir, continually leaching active voriconazole. Sustained localized dosing is ultimately preferred to rapidly depleted bolus doses in treating deep-seated mycotic ulcers [2,3].

Limitations of this study inherently relate to the boundaries of ex vivo and in vitro modeling. The absence of active tear fluid turnover and immune response mechanisms in the Franz cell apparatus necessitates that future research pivots to comprehensive in vivo pharmacokinetic tracking in rabbit models. Nonetheless, the meticulously optimized physicochemical properties of the MG2 formulation offer a highly translatable blueprint.

6. CONCLUSION:

The successful formulation and characterization of a voriconazole-loaded mixed micellar in situ gel establish a highly effective paradigm for combating fungal keratitis. This systematic study confirms that the combination of Poloxamer 188 and 407 produces highly stable, nanometric mixed micelles capable of drastically increasing the apparent solubility and corneal permeation of voriconazole. The subsequent incorporation of these micelles into a finely tuned Carbopol/Poloxamer thermosensitive gel matrix fundamentally transforms the release profile to desired Zero-order kinetics.

The optimized MG2 formulation reacts dynamically to the precorneal temperature, ensuring ease of administration accompanied by immediate phase transition to a resilient mucoadhesive depot. Backed by excellent biocompatibility indices in HET-CAM testing and robust antifungal efficacy against clinical pathogens, the hybrid micelle-gel system actively overcomes the profound limitations associated with conventional topical ophthalmic suspensions. Future directions encompass extended in vivo efficacy trials and advanced ocular pharmacokinetic profiling. Ultimately, this nanotechnological intervention holds profound clinical promise to reduce dosing frequency, elevate patient compliance, and improve therapeutic outcomes in vision-threatening mycotic keratitis.

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