



Research Article

Development and Characterization of a SMEDDS-Based in Situ Ophthalmic Drug Delivery System for Nepafenac

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ABSTRACT

Topical ocular instillation remains the preferred route for treating anterior segment ocular disorders, however, conventional eye drops exhibit notoriously low ocular bioavailability (< 5%) due to stringent physiological barriers, including rapid nasolacrimal drainage, blinking reflex, and the impermeability of the corneal epithelium. This challenge is significantly magnified for Nepafenac, a BCS Class II nonsteroidal anti-inflammatory prodrug whose extremely poor aqueous solubility (0.014 mg/mL) severely limits therapeutic permeation across lipophilic-hydrophilic corneal layers. To overcome these dual physiological and physicochemical bottlenecks, this study developed and evaluated an integrated nanocarrier-hydrogel platform: a Self-Microemulsifying Drug Delivery System (SMEDDS) embedded in an ion-activated *in situ* gelling matrix. The optimized lipid phase comprised Capryol 90 (oil), Cremophor RH 40 (surfactant), and PEG 400 (co-surfactant), which upon aqueous dispersion yielded optical clarity (99.34% transmittance), a mean globule size of 206.1 nm, and an electrostatically stabilizing zeta potential of -17.1 mV. Incorporation into a Gellan gum/HPMC polymeric system facilitated an instantaneous sol-to-gel phase transition (3 seconds) in the presence of simulated tear fluid conditions. Rheological assessment demonstrated a sharp transition from a freely pourable Newtonian sol (48 cps) to a viscoelastic pseudoplastic gel (8190 cps), resisting premature precorneal drainage. *In vitro* permeation profiles exhibited biphasic kinetics characterized by an initial burst release (25–30% within the first hour) followed by sustained diffusion over 6 hours, achieving 99.45% cumulative drug release for the optimized batch F7. Accelerated stability testing (40°C/75% RH for 1 month) confirmed no phase separation and robust chemical integrity with an assay of 95.32%. This dual delivery system presents a clinically promising approach to maximize transcorneal flux, enhance precorneal retention, and minimize dosing frequency.

KEYWORDS: Nepafenac, SMEDDS (Self-Microemulsifying Drug Delivery System), In situ ophthalmic gel, Ion-activated gelation, Gellan gum, Precorneal residence time, Ocular bioavailability, Sustained release.

1. INTRODUCTION AND THEORETICAL BACKGROUND

1.1. Ocular Drug Delivery Challenges and Corneal Barriers

Topical instillation into the conjunctival sac is the primary, non-invasive method for administering therapeutics to the anterior segment of the eye. Despite high patient compliance and direct local targeting, ocular bioavailability from conventional topical formulations (aqueous solutions and suspensions) rarely exceeds 1 – 5%. Upon instillation, a major fraction of the

instilled volume is immediately lost due to the physiological tear turnover rate ($\approx 1 \mu\text{L}/\text{min}$), blink-induced reflex tearing, and rapid nasolacrimal drainage into the systemic circulation, which carries away the instilled drug within 1 to 2 minutes.

Beyond precorneal clearance, the anatomical architecture of the cornea presents a formidable composite barrier:

- **Corneal Epithelium:** Comprising 5-6 layers of stratified, non-keratinized epithelial cells joined by

tight zonula occludens junctions, the epithelium forms a highly lipophilic barrier that strongly restricts the paracellular passage of hydrophilic molecules and large particles.

- **Corneal Stroma:** Directly beneath Bowman's layer lies the stroma, an organized, highly hydrated extracellular matrix made of parallel collagen fibrils and glycosaminoglycans ($\approx 78\text{-}80\%$ water content). It acts as a major physical barrier to poorly soluble, highly lipophilic drugs.
- **Corneal Endothelium:** A single layer of hexagonal cells that maintains corneal transparency through active fluid pumping.

Consequently, optimal transcorneal permeation requires amphiphilic intermediate polarity: sufficient lipophilicity to partition through the superficial epithelium and adequate hydrophilicity to traverse the aqueous stroma.

1.2. Nepafenac: Pharmacodynamics and Physicochemical Constraints

Nepafenac (2-(2-amino-3-benzoylphenyl) acetamide) is a nonsteroidal anti-inflammatory prodrug indicated for the

prevention and treatment of postoperative pain and inflammation associated with cataract surgery. Unlike conventional topical NSAIDs (such as diclofenac or ketorolac), Nepafenac undergoes rapid intraocular bioactivation: after penetrating the corneal barrier, it is hydrolyzed by intraocular hydrolases in vascular ocular tissues (iris, ciliary body, retina, and choroid) into its active, potent metabolite, **amfenac**. Amfenac potently inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), thereby suppressing prostaglandin biosynthesis and attenuating anterior and posterior segment inflammation.

Despite this prodrug advantage, Nepafenac belongs to **BCS Class II**, characterized by low aqueous solubility (**0.014 mg/mL**) and high membrane permeability. Due to its extreme hydrophobicity, conventional aqueous drops require suspension formulations that often suffer from uneven dosage distribution, variable dissolution rates in precorneal fluid, particulate irritation, and foreign body sensation that triggers reflex lacrimation and rapid elimination.

Marketed Ophthalmic Formulations of Nepafenac

Brand Name	Strength (% w/v)	Formulation Type	Manufacturer
Nevanac	0.1%	Ophthalmic solution/suspension	Alcon Laboratories
Ilevro	0.3%	Ophthalmic solution/suspension	Alcon Laboratories
Nepaflam	0.1%	Ophthalmic solution	Sun Pharma Laboratories
Nepaonce	0.3%	Ophthalmic solution	Entod Pharmaceuticals
Prevanac	0.1%	Ophthalmic solution	Croon Pharma Pvt. Ltd.
Nepalact	0.1%	Ophthalmic solution	Sun Pharmaceutical Industries Ltd.
Nepatop	0.1%	Ophthalmic solution	Entod Pharmaceuticals

1.3. Rational Design: SMEDDS-Loaded In Situ Gelling Platform

To overcome both poor aqueous solubility and rapid precorneal drainage simultaneously, this work establishes a hybrid nanotechnology platform combining a **Self-Microemulsifying Drug Delivery System (SMEDDS)** with a stimulus-triggered *in situ* gelling polymer matrix.

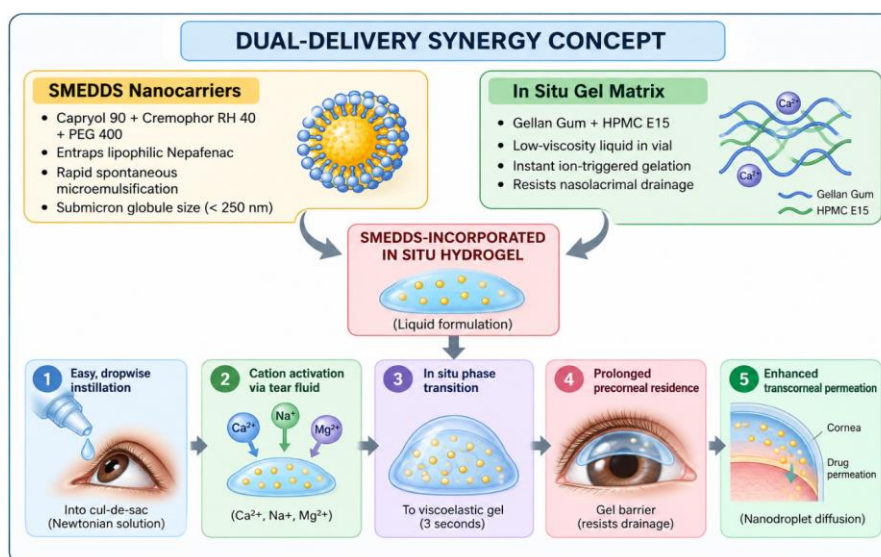


Figure 1: Schematic representation of the dual-delivery strategy of nepafenac-loaded SMEDDS-incorporated in situ hydrogel for enhanced ocular drug delivery.

- 1. Self-Microemulsifying Drug Delivery Systems (SMEDDS):** SMEDDS are isotropic, thermodynamically stable mixtures of natural or synthetic oils, solid or liquid non-ionic surfactants, and co-surfactants. Upon gentle agitation and aqueous exposure to precorneal fluid, these systems spontaneously assemble into fine oil-in-water (o/w) microemulsions with submicron droplet diameters (< 250 nm). By encapsulating Nepafenac inside the oil core, the drug remains in a solubilized state, preventing precipitation, maximizing concentration gradients across the corneal surface, and facilitating endocytic or paracellular lipid transport across lipophilic epithelial membranes.
- 2. Ion-Activated in Situ Hydrogels:** Traditional pre-formed ophthalmic hydrogels suffer from poor patient adherence due to blurred vision and difficulty in precise drop instillation. *In situ* gelling systems resolve this by maintaining a low-viscosity liquid state during storage and instillation, transitioning instantaneously into a semi-solid viscoelastic hydrogel upon exposure to physiological ocular stimuli.

Gellan Gum (Gelrite): An anionic microbial exopolysaccharide composed of a repeating tetrasaccharide unit (β -D-glucose, β -D-glucuronic acid, and α -L-rhamnose). In aqueous media, it forms

random coils at room temperature, upon contact with mono- and divalent cations (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) present in simulated tear fluid, gellan molecules cross-link into ordered double helices, forming a three-dimensional gel network.

Hydroxypropyl Methylcellulose (HPMC): A semi-synthetic hydrophilic cellulose ether incorporated as a secondary viscosity-enhancing and mucoadhesive polymer. It reinforces the mechanical stability of the gellan network, retards burst diffusion, and prolongs corneal retention via non-covalent hydrogen bonding with ocular mucin layers.

2. MATERIALS AND METHODS

2.1. Materials and Equipment

- Active Pharmaceutical Ingredient (API):** Nepafenac (gift sample provided by Sun Pharma).
- Polymers and Functional Excipients:** Gellan gum, HPMC K100, HPMC E15, (Oxford Lab Fine Chem LLP, Palghar), Benzalkonium chloride (ARIES Chemicals, Vadodara), Capryol 90 (Gattefossé, Ahmedabad), Polyethylene glycol 400 (PEG 400) and PEG 4000, Methanol (Starcoin Chem., Ahmedabad), Carbopol (934P), General analytical reagents (Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat).

Sr. No.	Equipment	Model / Manufacturer
1	Precision Electronic Balance	Scaletec, SAB-203E
2	Double-Beam UV-Vis Spectrophotometer	UV-1800, Shimadzu Corporation, Kyoto, Japan
3	Magnetic Stirrer with Hotplate	MS500, Remi Instruments Ltd., Mumbai, India
4	Digital pH Meter	Orion Star A216, Cole-Parmer, India
5	Rotational Viscometer	Brookfield DV-II+ Pro, Brookfield Engineering Inc., USA
6	Ultrasonic Bath Sonicator	Frontline Sonicator, India / Sabar Scientific, Ahmedabad
7	Franz Diffusion Cell Apparatus	TDT 06-T, Electrolab Ltd., Mumbai, India
8	FTIR Spectrophotometer	IR Spirit, LabSolutions IR Software (v2.24), Shimadzu

2.2. Drug Identification and Compatibility Studies

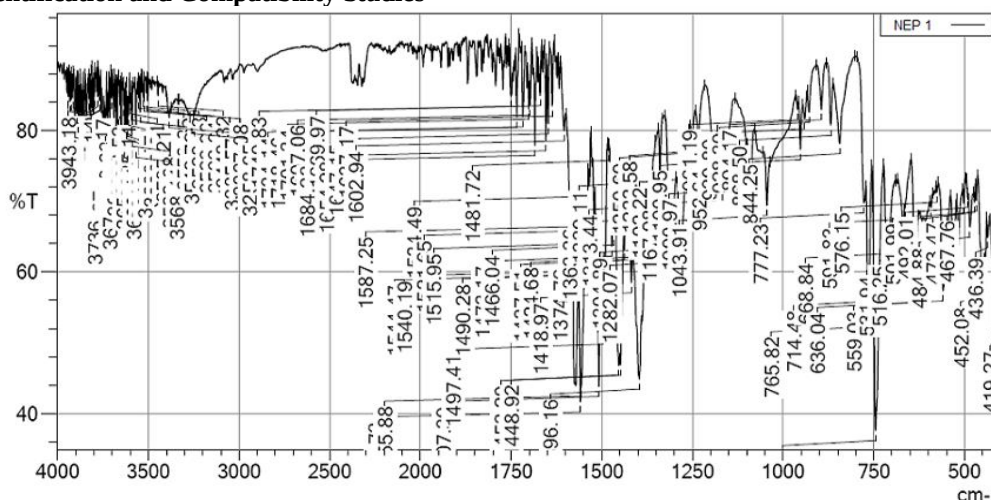


Figure 2: Fourier Transform Infrared (FTIR) Spectrum of Pure Nepafenac displaying characteristic functional vibrations (primary amine N-H and aromatic carbonyl C=O stretching bands).

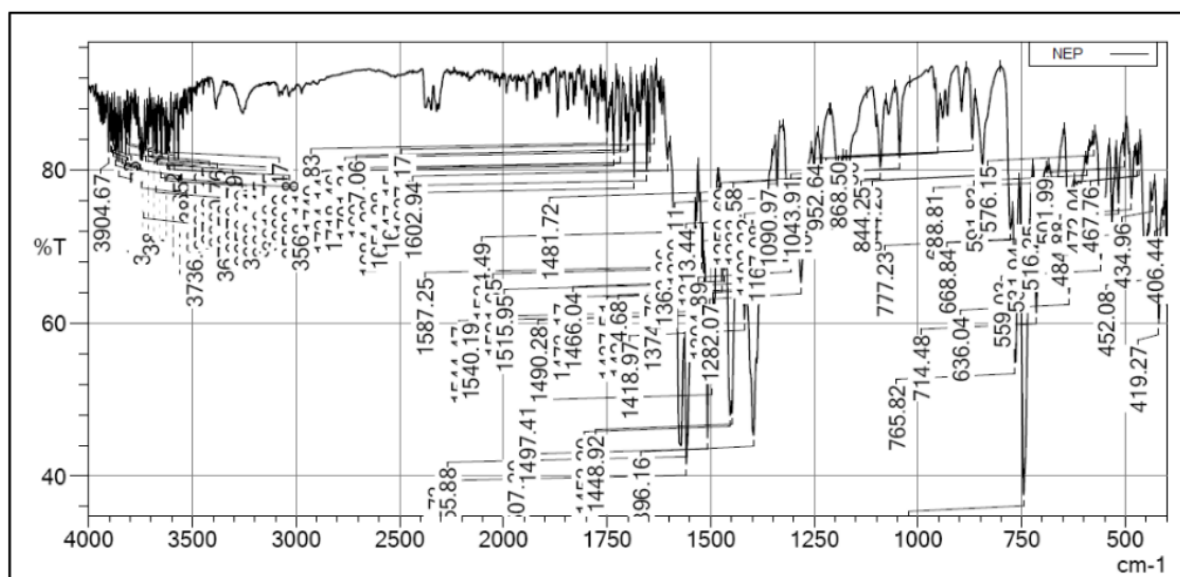


Figure 3: FTIR Spectrum of Nepafenac physical mixture demonstrating absence of significant band shifts, confirming chemical compatibility with matrix excipients.

2.3. Analytical Method: UV-Visible Spectrophotometry

Standard stock solutions of Nepafenac were prepared in methanol and diluted serially to establish a calibration range between **6-18 $\mu\text{g/mL}$** . Absorbance values were

recorded against a methanol blank. The resulting linear regression equation was:

$$y = 0.0428x - 0.0026, \quad (R^2 = 0.9998)$$

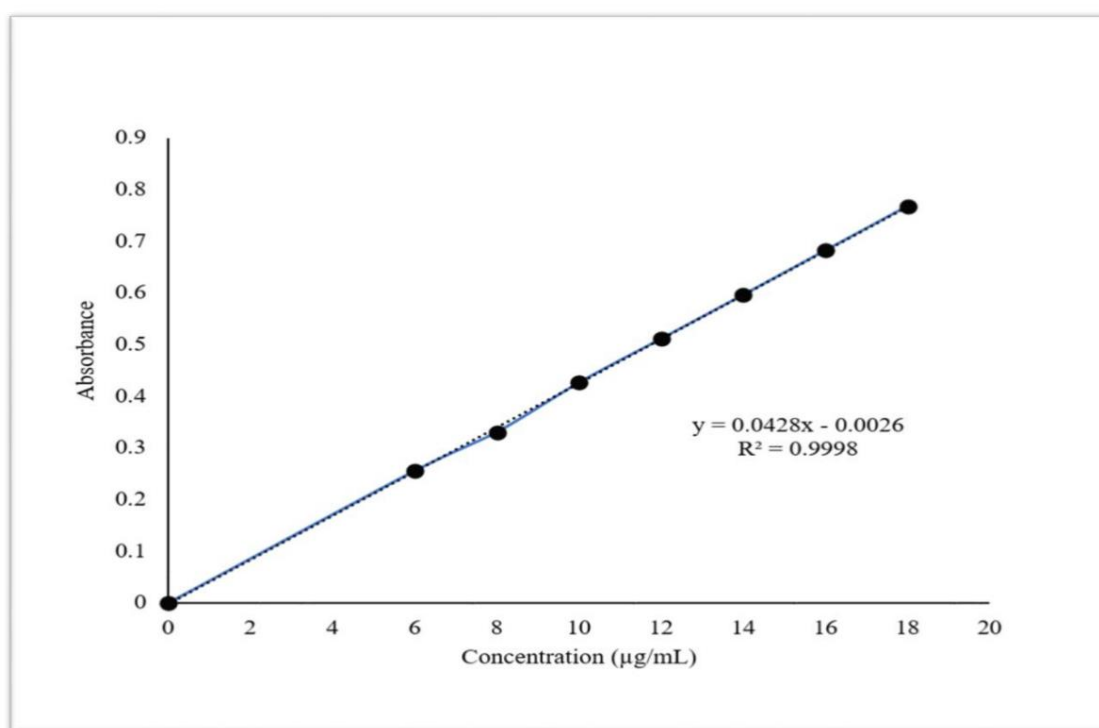


Figure 4: UV Calibration Curve of Nepafenac in Methanol. Concentration versus absorbance relationship (**6 to 18 $\mu\text{g/mL}$**) with linear fit equation $y = 0.0428x - 0.0026$ and regression coefficient $R^2 = 0.9998$.

2.4. Excipient Screening and Solubility Studies

Solubility was evaluated by adding an excess of Nepafenac into individual oils, surfactants, and co-

surfactants. Mixtures were equilibrated under continuous agitation at ambient temperature for 48 hours, followed

by centrifugation and quantification. The highest solubility values were achieved with:

- **Lipid Phase:** Capryol 90 (78.54 ± 2.45 mg/mL)
- **Surfactant Phase:** Cremophor RH 40 (65.23 ± 1.84 mg/mL)
- **Co-surfactant Phase:** PEG 400 (54.12 ± 2.11 mg/mL)

2.5. Optimization via Factorial Design

A 3^2 Full Factorial Design was employed to model and optimize the gel matrix:

- **Independent Variables:** Concentration of Gellan gum (X_1) and Concentration of HPMC E15 (X_2).

- **Dependent Responses:** Gelation time (Y_1), Viscosity (Y_2), and Cumulative Drug Release (%CDR) at 6 hours (Y_3).

3. RESULTS AND DISCUSSION

3.1. Pseudo-Ternary Phase Behavior

Pseudo-ternary phase diagrams constructed with Capryol 90, Cremophor RH 40, and PEG 400 across surfactant-to-co-surfactant (S_{mix}) weight ratios of 1:1, 2:1, and 3:1 delineated clear self-Microemulsifying regions. The S_{mix} ratio of 2:1 generated the largest microemulsion domain, confirming adequate packing geometry of the mixed interfacial surfactant film to yield spontaneous nano-dispersion upon contact with aqueous media.

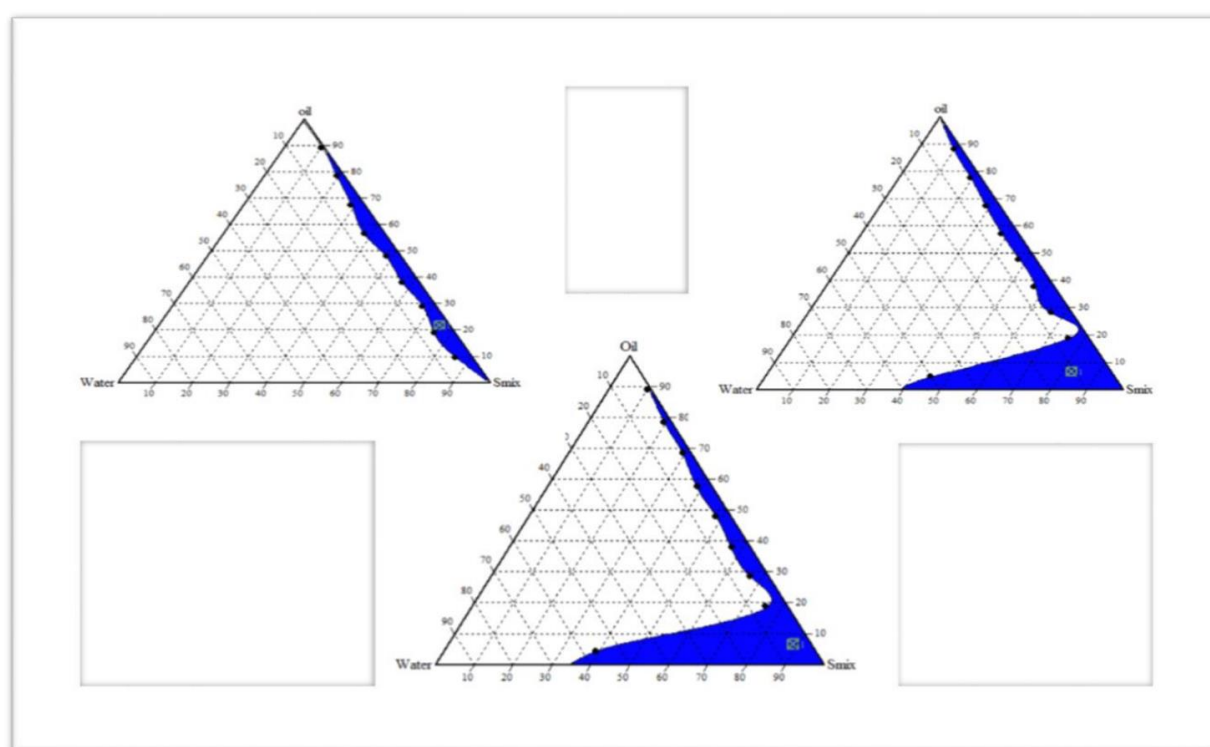


Figure 5: Pseudo-Ternary Phase Diagrams. Phase boundary diagrams constructed at S_{mix} ratios of 1:1, 2:1, and 3:1 illustrating the microemulsion region.

3.2. Physicochemical Characterization of SMEDDS

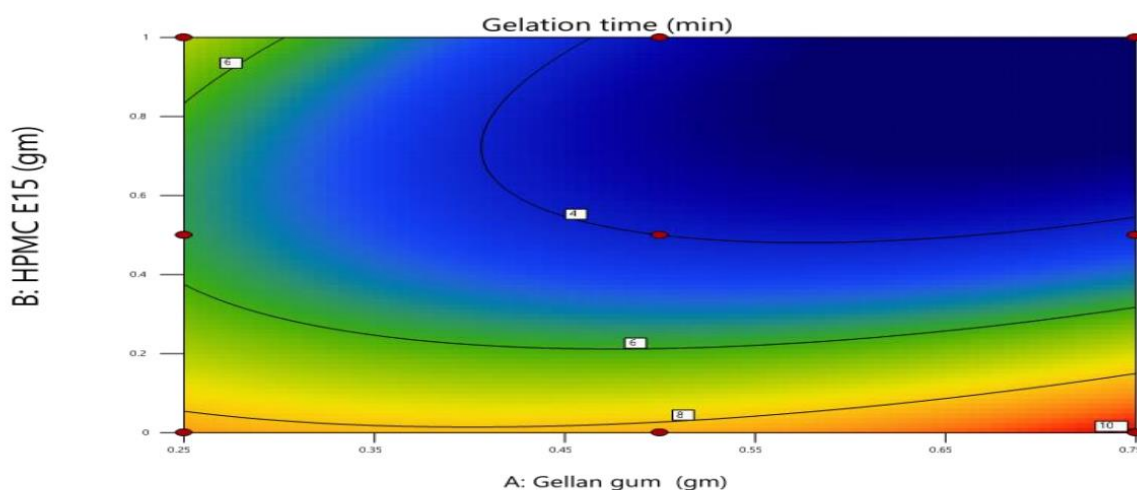
- **Optical Transmittance:** 99.34%, reflecting an optically isotropic nanodispersion.
- **Mean Droplet Diameter:** 206.1 nm, favorable for uniform corneal distribution and cellular uptake.
- **Zeta Potential:** -17.1 mV, providing electrostatic repulsion to prevent droplet coalescence.

3.3. Gelation Kinetics and Rheological Behavior

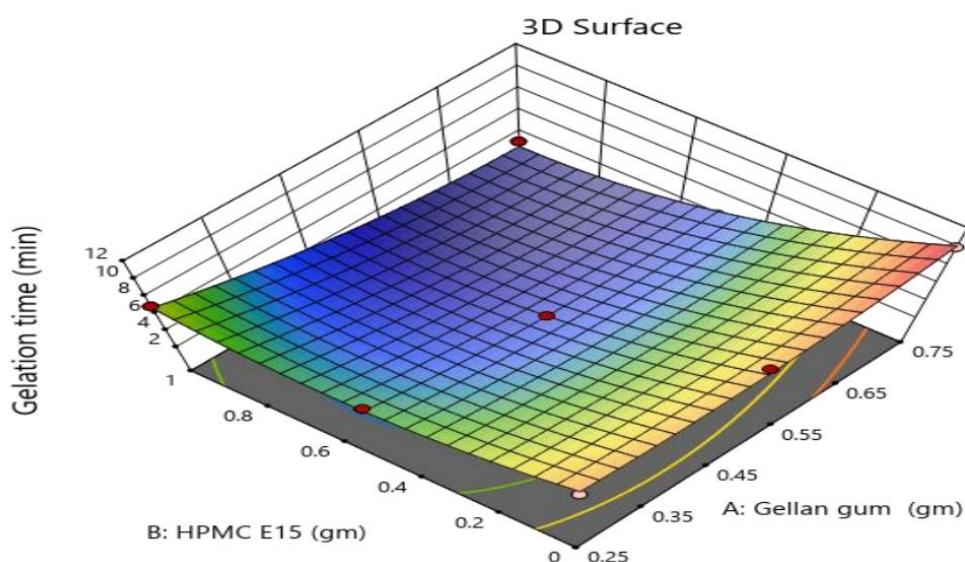
Prior to ion activation, the formulation displayed low-viscosity Newtonian flow, facilitating dropwise instillation. Addition of simulated tear fluid containing

physiological electrolytes induced instantaneous cross-linking into a non-flowing pseudoplastic hydrogel:

- **Viscosity Transition (Optimized Batch F7):** Transitioned from 48 cps (sol) to 8190 cps (gel state).
- **Gelation Time:** Phase transition occurred in 3 seconds.



Contour plot of Gelation time



3D surface plot of Gelation time

Figure 6: Influence of Gellan gum (X1) and HPMC E15 (X2) concentrations on gelation time: (A) 2D contour response surface plot, (B) 3D response surface plot.

3.4. In Vitro Drug Release Kinetics

In vitro release via Franz diffusion cells followed a biphasic dissolution profile:

- **Initial Burst Phase:** 25-30% drug released within the first 60 minutes, attributed to the fast diffusion of Nepafenac located near the surface of the microemulsion droplets.
- **Sustained Matrix Release:** Prolonged diffusion governed by the swollen Gellan gum/HPMC hydrogel network across 6 hours.
- **Comparative Evaluation:** Optimized batch F7 delivered 99.45% cumulative release at 6 hours. In contrast, batch F9 with higher polymer density reached 92%, demonstrating that excessive cross-

linking density restricts the aqueous diffusion pathway. Factorial design center points confirmed values of 11.31% at 1 hour, 34.63% at 3 hours, and 68.22% at 6 hours ($X_1 = 0.5$, $X_2 = 0.5$).

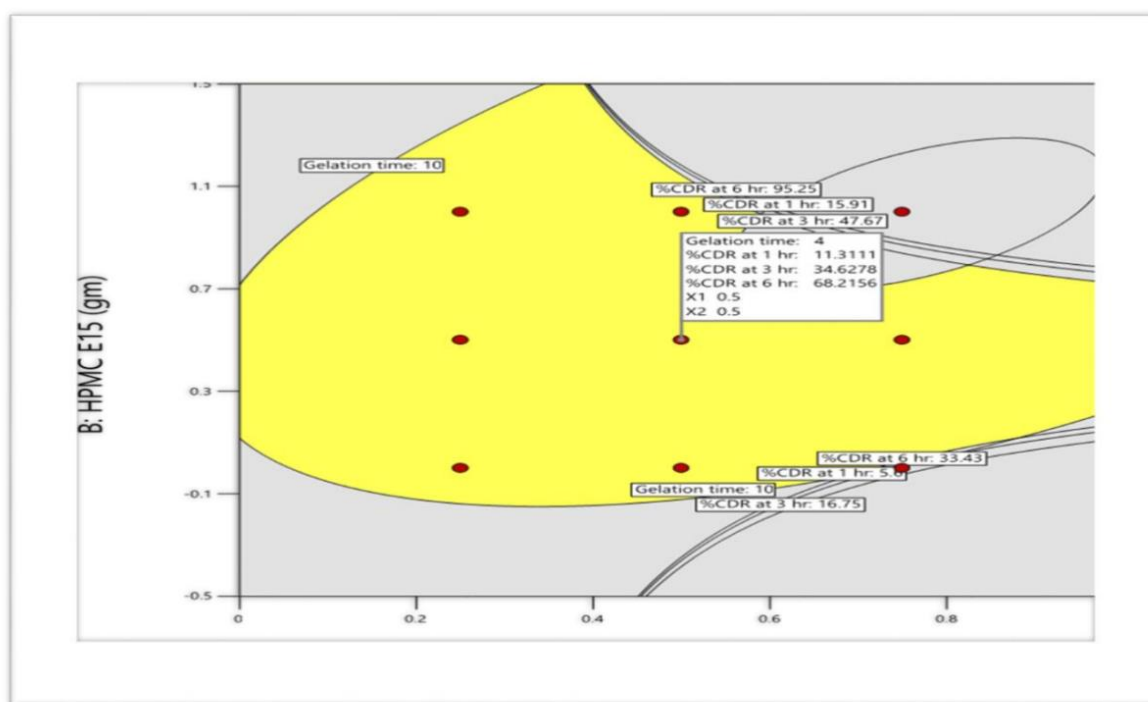


Figure 7: Factorial Optimization Overlay Plot. Graphical overlay plot illustrating the design space for combined responses (Y_1 to Y_5) as a function of polymer concentrations (X_1 and X_2).

3.5. Drug Stability and Compatibility

- **FTIR Compatibility:** Distinct characteristic peaks representing the amide and carbonyl groups of Nepafenac remained intact in the presence of the polymer matrix, confirming chemical stability and absence of drug-excipient degradation.
- **Accelerated Stability Testing (40°C/75% RH, 1 month):** The formulation maintained physical homogeneity without phase separation or precipitation, retaining an assay of **95.32%**.

4. CONCLUSION

Integrating an optimized Capryol 90/Cremophor RH 40/PEG 400 SMEDDS into an ion-responsive Gellan gum/HPMC *in situ* gel successfully addressed the primary barriers of ocular delivery for Nepafenac. The platform combines nanocarrier-enhanced drug solubilization with an instantaneous ion-activated sol-to-gel transition (**3 seconds**), providing sustained transcorneal drug release over **6 hours (99.45%** for batch F7) and physical stability. This dual delivery system presents an effective strategy to prolong precorneal retention, enhance ocular bioavailability, and reduce administration frequency in post-surgical ophthalmic therapy.

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