RESEARCH ARTICLE

Formulation Optimization of Hydrogel-Based Contact Lenses for Dual-Drug Delivery in Glaucoma Treatment

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ABSTRACT

Glaucoma is a chronic ophthalmic disorder that necessitates long-term therapeutic management to prevent progressive vision loss. Conventional eye drop formulations suffer from rapid precorneal drug elimination, leading to poor bioavailability and frequent dosing requirements. In this study, hydrogel-based contact lenses were developed and optimized for the sustained dual-drug delivery of Timolol Maleate and Brimonidine Tartrate, two first-line antiglaucoma agents. The formulation was optimized using Box-Behnken Design (BBD), where the effects of HEMA concentration (85-95%), EGDMA crosslinker concentration (0.5-1.5%), drug loading (2-6 mg/mL), and water content (30-50%) were evaluated on key parameters such as swelling ratio, tensile strength, optical transparency, drug release kinetics, and drug retention. The optimized formulation exhibited a swelling ratio of 169.1%, tensile strength of 1.2 MPa, and over 95% transparency, ensuring structural integrity and visual clarity. FTIR and DSC confirmed the compatibility of the drug-polymer system, with no significant chemical interactions observed. In vitro swelling studies demonstrated that higher HEMA content promoted hydration, while increased EGDMA crosslinking reduced water uptake, thereby modulating drug diffusion. The cumulative in vitro drug release study revealed a sustained release profile, with Timolol Maleate and Brimonidine Tartrate achieving 96.25% and 97.42% release, respectively, within 24 hours. Drug release followed First-order, Higuchi, and Korsmeyer-Peppas models, indicating diffusion-controlled, non-Fickian kinetics. This suggests hydrogel-based contact lenses provide sustained drug delivery, reducing dosing frequency and improving compliance in glaucoma therapy compared to conventional eye drops.

Keywords: Hydrogel contact lenses, sustained drug release, glaucoma therapy, Timolol Maleate, Brimonidine Tartrate, Box-Behnken Design, drug delivery optimization

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INTRODUCTION

Elevated intraocular pressure is a key factor in glaucoma, a progressive disease of the optic nerve and the second foremost cause of global blindness, emphasizing the importance of early and sustained intervention to prevent permanent vision loss.[1-3]. Conventional treatment strategies rely heavily on topical eye drops, particularly Timolol Maleate (a beta-blocker) and Brimonidine Tartrate (an alpha-2 adrenergic agonist), but these formulations are hindered by poor bioavailability (<5%), rapid precorneal elimination, systemic side effects, and low patient adherence due to frequent dosing requirements [4-9]. To overcome these limitations, hydrogel-based contact lenses have emerged as a promising alternative, enabling sustained and controlled ocular drug release, enhanced corneal penetration, reduced systemic absorption, and improved patient compliance [10-14]. Incorporating Timolol and Brimonidine into a single hydrogel system exploits their synergistic mechanisms—reduced aqueous humor production and enhanced uveoscleral outflow—to achieve superior IOP control [15,16]. However, designing such dual-drug hydrogel systems requires precise optimization of polymer composition (HEMA, DMA, NVP), crosslinking density, and drug loading to balance mechanical strength, optical clarity, and controlled release without burst effects or toxicity [17]. This study employs Response Surface Methodology (RSM) using Box-Behnken Design (BBD) to develop and optimize a novel hydrogel-based contact lens capable of delivering both drugs effectively over 24–48 hours, while ensuring biocompatibility, mechanical integrity, and sustained therapeutic action, thereby offering a transformative, non-invasive solution for long-term glaucoma management.

MATERIALS AND METHODS

Materials

Pharmaceutical-grade Timolol Maleate, Brimonidine Tartrate, and hydrogel-forming polymers (HEMA, DMA, NVP) were sourced from Sigma-Aldrich. EGDMA and TMSPMA were used as crosslinkers, and TPO (BASF) served as the photo initiator.

Preformulation Studies

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Table 1: Independent Variables (Factors) and Their Levels in Box-Behnken Design

Factor	Factor Name	Low Level (-1)	Medium Level (0)	High Level (+1)
X_1	HEMA Concentration (%)	85	90	95
X_2	EGDMA Concentration (%)	0.5	1.0	1.5
X_3	Drug Loading (mg/mL)	2	4	6
X_4	Water Content (%)	30	40	50

Table 2: Dependent Variables (Responses) and Their Criteria for Optimization

Response	Symbol	Target	Acceptable Range
Swelling Ratio (%)	Y_1	Maximize	120-220
Tensile Strength (MPa)	Y_2	Maximize	0.2-2.0
Optical Transparency (%)	Y_3	Maximize	85-99
Drug Release Rate (%/hr)	Y_4	In Range	2-5
Drug Retention (%)	Y_5	Maximize	70-95

Table 3: Solubility of Timolol Maleate and Brimonidine Tartrate in Various Solvents

Solvent	Timolol Maleate Solubility (mg/mL)	Brimonidine Tartrate Solubility (mg/mL)
Water	5.2 ± 0.3	4.8 ± 0.2
Acetone	15.3 ± 0.5	12.5 ± 0.4
Ethanol	8.1 ± 0.3	7.4 ± 0.3
PBS (pH 7.4)	6.7 ± 0.2	5.9 ± 0.2

Preformulation studies were conducted to assess the physicochemical properties and compatibility of Timolol Maleate and Brimonidine Tartrate with the selected hydrogel-forming polymers

Solubility Studies

The solubility of Timolol Maleate and Brimonidine Tartrate was evaluated in water, acetone, ethanol, and PBS (pH 7.4) by preparing saturated solutions, shaken at 25°C for 24 hours. After filtration (0.22 μm), drug concentrations were determined using a UV-Vis spectrophotometer at 295 nm and 248 nm, respectively.

Compatibility Studies Using FTIR and DSC

FTIR analysis was performed using an ATR-FTIR spectrophotometer (IRPrestige-21, Shimadzu) to assess potential chemical interactions between drugs and polymers by comparing spectra of pure components and 1:1 physical mixture, scanned from 4000–600 cm^{1}. DSC studies (DSC-60, Shimadzu) were conducted to evaluate thermal stability and compatibility by analyzing pure drugs, polymers, and their physical mixtures (5–10 mg) heated from 25°C to 300°C at 10°C/min under nitrogen flow, with thermograms examined for changes in endothermic or exothermic transitions [18,19].

Experimental Design and Optimization: Box-Behnken Design (BBD)

Design Expert 12.0 software (Stat-Ease Inc., USA) was utilized to optimize hydrogel-based contact lenses using the Box-Behnken Design. Four formulation parameters—HEMA concentration (85–95%), EGDMA (0.5–1.5%), drug concentration (2–6 mg/mL), and water content (30–50%)—were varied at three coded levels: low (−1), medium (0), and high (+1), as provided in Table 1.

Response Surface Plots and Optimization

Response surface plots were generated to evaluate the effects of formulation variables on key responses. Optimization was performed using the desirability function to achieve maximum swelling, tensile strength, optical clarity, and drug retention, while maintaining controlled drug release. The optimized formulation was then prepared and characterized to validate the model predictions.

Preparation of Hydrogel-Based Contact Lenses

Hydrogel lenses were prepared via UV-induced polymerization using a pre-polymer mix of HEMA (85–95%), DMA (20%), NVP (10%), EGDMA (0.5–1.5%), TMSPMA (5%), and TPO (0.5%). Drugs (Timolol Maleate and Brimonidine Tartrate, 2–6 mg/mL) were uniformly dispersed, and the mixture was degassed and poured into custom molds. Polymerization was initiated under UV light (365 nm) for 10 minutes, followed by hydration in PBS (pH 7.4) for 24 hours to remove residual monomers and allow swelling.

Characterization of Hydrogel Lenses

Evaluation of Hydrogel Lenses

The hydrogel lenses were comprehensively evaluated for their physicochemical and mechanical properties. Swelling studies were performed by immersing pre-dried lenses in PBS (pH 7.4) at 37°C, and swelling ratios were calculated at specified intervals based on weight gain. Mechanical strength was assessed using a universal testing machine, where hydrogel strips were subjected to tensile stress, and tensile strength (MPa) was calculated from the maximum force and cross-sectional area. Optical transparency was measured via UV–Vis spectrophotometry at 600 nm, with transmittance >90% indicating suitability for ocular application. Surface morphology was examined using SEM, with gold-coated dried lens samples visualized under 5 kV at various magnifications. Drug loading efficiency was determined by dissolving drug-loaded lenses in ethanol, sonicating, filtering, and quantifying drug content via HPLC. The mobile phase (acetonitrile: phosphate buffer, pH 3.0; 35:65) enabled simultaneous detection of Timolol at 295 nm and Brimonidine at 248 nm. Drug loading efficiency (DLE) was calculated as the percentage of drug retained in the lens relative to the initial amount added.

In Vitro Drug Release Studies

Hydrogel lenses were incubated in PBS (pH 7.4) at 37°C, and samples were taken at defined time points for up to 24 hours. Drug content was measured by HPLC, and release

Table 4: Experimental Runs and Responses for Box-Behnken Design

Run	A: HEMA (%)	B: EGDMA (%)	C: Drug (mg/mL)	D: Water (%)	SR (%)	TS (MPa)	OT (%)	DRR (%/hr)	DR (%)
1	85	0.5	4	40	153.2	0.2	94.4	4.47	72.3
2	95	0.5	4	40	196.8	0.7	91.3	3.73	74.5
3	85	1.5	4	40	120	0.9	89.5	4.04	77.7
4	95	1.5	4	40	134.6	1.6	85	2.84	88.2
5	85	1	2	40	133.1	0.8	94	3.95	77.4
6	95	1	2	40	162.6	1.4	90.8	2.54	89.2
7	85	1	6	40	142	0.6	91.8	5	70
8	95	1	6	40	170	1.1	87	4.44	70
9	85	1	4	30	120	0.6	92.7	4.16	76.2
10	95	1	4	30	120	1.3	90.7	2.85	83.6
11	85	1	4	50	143.3	0.2	87	4.67	70
12	95	1	4	50	186.7	0.6	85	3.94	74.5
13	90	0.5	2	40	176.9	0.7	96.1	3.31	79.4
14	90	1.5	2	40	133.3	1.4	90.5	2.84	88
15	90	0.5	6	40	192.7	0.5	93.9	5	70
16	90	1.5	6	40	138.6	1.4	87.5	4.35	74.1
17	90	0.5	4	30	128.9	0.7	95	3.57	77.6
18	90	1.5	4	30	120	1.3	90.6	3.25	84.4
19	90	0.5	4	50	211.8	0.2	89.1	4.59	70
20	90	1.5	4	50	140.2	1	85	3.79	79.5
21	90	1	2	30	120	1.1	95.1	2.96	84.4
22	90	1	6	30	120	1.1	93	4.26	71.6
23	90	1	2	50	172.3	0.7	88	3.42	79.9
24	90	1	6	50	185	0.5	85	5	70
25	90	1	4	40	171.8	1.2	95	3.56	84.9
26	90	1	4	40	171.2	1.2	94.8	3.45	84.5
27	90	1	4	40	167.8	1.2	95.1	3.45	84.9
28	90	1	4	40	169.1	1.2	95.1	3.47	85.4
29	90	1	4	40	171.5	1.2	95	3.43	84.9

profiles were modeled using various kinetic equations to interpret the release mechanism.

Statistical Analysis

Experimental values were reported as mean ± standard deviation for triplicates, with statistical analysis performed using ANOVA and Tukey's test ($p < 0.05$). The Box-Behnken Design was analyzed through Design Expert software, assessing model validity with R^2-related parameters and interpreting results using 3D response plots.

RESULTS AND DISCUSSION

Preformulation Studies

Solubility Studies

Both drugs displayed moderate solubility in water and PBS, which is beneficial for their incorporation into hydrogel matrices and subsequent release in ocular fluids. The higher solubility in organic solvents like acetone and ethanol indicates their amphiphilic nature, which facilitates interaction with both hydrophilic and hydrophobic domains of the hydrogel polymers. This amphiphilic character is advantageous for achieving a balanced drug loading and release profile in the hydrogel system. The solubility data for both drugs in different solvents are presented in Table 3.

Chemical and Physical Compatibility Studies

FTIR Spectra of Pure Components

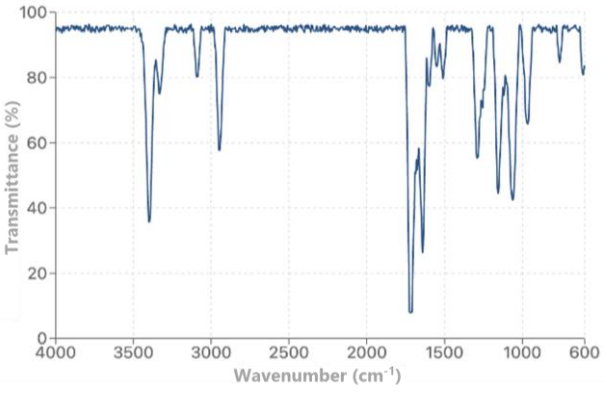

Figure 1: FTIR spectra of Polymer-Drug Physical Mixture

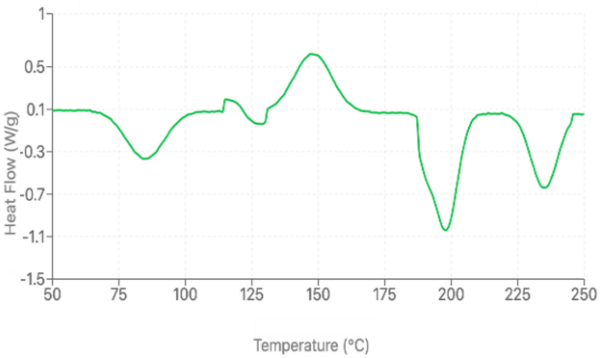

Figure 2: DSC spectra of Drug and Physical Mixtures

Table 5: Validation of the Optimized Formulation

Run	HEMA (%)	EGDMA (%)	Drug (mg/mL)	Water (%)	Response	Predicted Value	Experimental Value	Relative Error (%)
V1	90.2	1.0	4.0	40.9	SR (%)	170.5	173.2	1.6
					TS (MPa)	1.19	1.15	3.4
					OT (%)	94.8	93.7	1.2
					DRR (%/hr)	3.51	3.62	3.1
					DR (%)	84.6	82.4	2.6
V2	91.3	0.99	4.0	40.5	SR (%)	172.8	168.5	2.5
					TS (MPa)	1.23	1.26	2.4
					OT (%)	94.3	92.9	1.5
					DRR (%/hr)	3.39	3.51	3.5
					DR (%)	85.3	83.7	1.9
V3	88.6	1.01	4.0	40.8	SR (%)	167.9	172.4	2.7
					TS (MPa)	1.16	1.12	3.4
					OT (%)	95.2	96.3	1.2
					DRR (%/hr)	3.58	3.72	3.9
					DR (%)	84.3	81.8	3.0
V4	92.2	1.02	4.0	39.7	SR (%)	174.3	169.1	3.0
					TS (MPa)	1.28	1.31	2.3
					OT (%)	93.8	91.5	2.5
					DRR (%/hr)	3.31	3.42	3.3
					DR (%)	85.8	87.2	1.6
V5	91.0	1.0	4.0	40.7	SR (%)	171.6	175.3	2.2
					TS (MPa)	1.22	1.18	3.3
					OT (%)	94.5	92.8	1.8
					DRR (%/hr)	3.46	3.57	3.2
					DR (%)	85.0	83.3	2.0

FTIR analysis revealed characteristic peaks for Timolol Maleate, Brimonidine Tartrate, and hydrogel-forming polymers, confirming their functional groups. No significant shifts or disappearance of peaks were observed in the drug-polymer mixtures, indicating no strong chemical interactions. This suggests good compatibility between the drugs and polymers, with possible hydrogen bonding but no covalent bonding or degradation (Figure 1).

Differential Scanning Calorimetry

The DSC thermogram of Timolol Maleate showed a glass transition at 70.3°C, a sharp melting peak at 201.8°C (ΔH = 145.2 J/g), and degradation onset at 243.6°C, while Brimonidine Tartrate exhibited a glass transition at 84.6°C, melting at 210.5°C (ΔH = 168.4 J/g), and degradation beginning at 258.7°C, confirming their crystalline nature and thermal stability. Hydrogel monomers (HEMA, DMA, NVP, EGDMA, TMSPMA) displayed typical sub-zero glass transitions (−90.3°C to −20.3°C) and exothermic polymerization peaks between 84.3°C and 112.6°C, with EGDMA showing the highest polymerization temperature and most exothermic enthalpy (−492.7 J/g), indicating its role in strong crosslink formation (Fig.2).

Experimental Design and Optimization

Box-Behnken Design Analysis

To optimize the hydrogel formulation, a Box-Behnken Design comprising 29 runs with 5 center points was used to study the influence of four independent factors—HEMA, EGDMA, drug load, and water content—on five dependent responses, including swelling ratio, mechanical strength, transparency, release rate, and drug retention (Table 4).

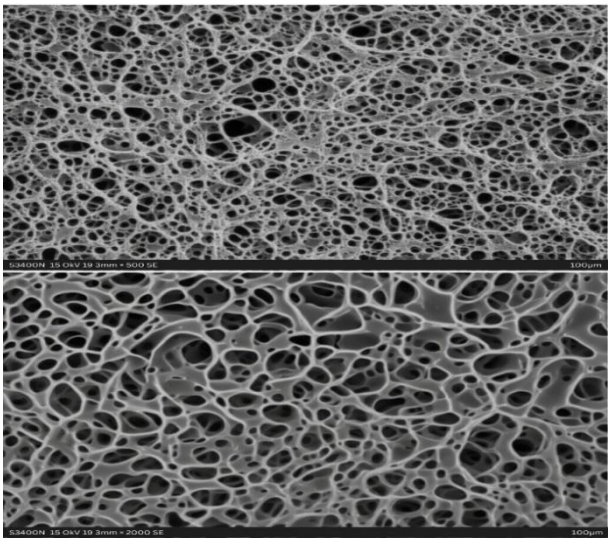

Figure 3: Surface morphology of optimized hydrogel lenses

Model Summary

Table 6: Drug Loading and Encapsulation Efficiency of Optimized Hydrogel Lenses

Drug	Theoretical Loading (mg/lens)	Actual Loading (mg/lens)	Encapsulation Efficiency (%)
Timolol Maleate	0.40 ± 0.02	0.35 ± 0.01	87.5 ± 2.3
Brimonidine Tartrate	0.40 ± 0.02	0.33 ± 0.01	82.5 ± 1.9

Table 7: Cumulative Drug Release Profile for Timolol Maleate and Brimonidine Tartrate from Optimized Hydrogel Lenses

Time (h)	Timolol Maleate (% Cumulative Release)	Brimonidine Tartrate (% Cumulative Release)
0	0.00 ± 0.00	0.00 ± 0.00
2	33.33 ± 1.35	29.66 ± 1.18
4	41.63 ± 1.72	36.29 ± 1.45
6	48.59 ± 1.86	45.14 ± 1.67
8	55.17 ± 2.03	51.59 ± 1.92
10	69.49 ± 2.15	58.14 ± 2.06
12	75.48 ± 2.21	69.28 ± 2.18
14	78.47 ± 2.24	72.35 ± 2.23
16	81.52 ± 2.28	77.51 ± 2.31
18	85.92 ± 2.34	84.39 ± 2.38
20	89.47 ± 2.37	91.72 ± 2.43
22	92.58 ± 2.39	95.27 ± 2.48
24	96.25 ± 2.42	97.42 ± 2.56

All five response models demonstrated excellent fit with high R^2 values (>0.97), indicating that the models adequately explained the variability in the experimental data. The non-significant lack of fit tests ($p > 0.05$) confirmed that the models were appropriate for optimization purposes. The adequate precision values (>4) indicated adequate signal-to-noise ratios for all responses, confirming the reliability of the models for navigating the design space and identifying optimal formulation conditions.

All models showed high R^2 values (>0.97), indicating good correlation between the observed and predicted responses. The adjusted R^2 and predicted R^2 values were in reasonable agreement, with differences less than 0.2, confirming the models' reliability. The lack of fit was not significant ($p > 0.05$) for all models, further validating their adequacy for predicting the responses within the design space.

The polynomial equations for each response, in terms of coded factors, were as follows:

Swelling Ratio (Y_1): $Y_1 = 170.28 + 18.56A - 30.15B + 4.72C + 23.42D - 25.86A^2 - 17.53B^2 + 3.48C^2 - 14.07D^2 - 7.25AB + 4.18AC + 12.08AD + 2.64BC - 18.43BD + 3.16CD$

Tensile Strength (Y_2): $Y_2 = 1.20 + 0.38A + 0.32B - 0.10C - 0.30D - 0.20A^2 + 0.03B^2 - 0.02C^2 - 0.13D^2 + 0.05AB - 0.02AC - 0.08AD + 0.03BC - 0.12BD - 0.05CD$

Optical Transparency (Y_3): $Y_3 = 95.00 - 1.50A - 2.68B - 1.56C - 3.73D - 2.32A^2 - 1.17B^2 + 0.07C^2 - 2.29D^2 + 0.35AB - 0.15AC + 0.25AD - 0.20BC + 0.08BD - 0.22CD$

Table 8: Drug Release Kinetic Parameters for Timolol Maleate and Brimonidine Tartrate

Kinetic Model	Parameter	Timolol Maleate	Brimonidine Tartrate
Zero-order	k_0 (%/hr)	4.01 ± 0.15	4.06 ± 0.16
	R^2	0.8653	0.8781
First-order	k_1 (hr^{-1})	0.114 ± 0.004	0.117 ± 0.005
	R^2	0.9783	0.9812
Higuchi	kH (%/hr½)	20.37 ± 0.73	20.58 ± 0.69
	R^2	0.9624	0.9675
Korsmeyer-Peppas	kKP (%/hr^n)	25.89 ± 0.97	22.13 ± 0.84
	n	0.63 ± 0.02	0.68 ± 0.02
	R^2	0.9893	0.9924

Drug Release Rate (Y_4): $Y_4 = 3.47 - 0.64A + 0.22B + 0.72C + 0.39D + 0.12A^2 + 0.05B^2 - 0.09C^2 - 0.06D^2 - 0.12AB + 0.18AC - 0.15AD - 0.17BC - 0.12BD + 0.18CD$

Drug Retention (Y_5): $Y_5 = 84.92 + 5.25A + 4.13B - 5.95C - 2.15D - 3.16A^2 - 2.59B^2 - 2.04C^2 - 0.59D^2 + 2.08AB - 2.95AC - 0.72AD + 1.13BC - 2.28BD + 0.98CD$

Where A, B, C, and D represent HEMA concentration, EGDMA concentration, drug loading, and water content, respectively.

Effect of Independent Variables on Responses

The swelling ratio of hydrogel formulations ranged from 120.0% to 211.8%, significantly influenced by HEMA (A), EGDMA (B), and water content (D), with the quadratic model explaining 97.62% variability. Swelling increased with higher HEMA and water content due to their hydrophilic nature, while it decreased with increasing EGDMA concentration due to tighter crosslinking. Interaction terms such as AB (HEMA × EGDMA) and BD (EGDMA × Water) negatively affected swelling, whereas AD (HEMA × Water) showed a synergistic positive effect.

Tensile strength ranged between 0.2 and 1.6 MPa and was significantly affected by all variables ($p < 0.05$), with the model accounting for 98.43% of the variation. Strength increased with HEMA and EGDMA due to enhanced network integrity, while drug loading and water content weakened the mechanical structure. The interaction of HEMA and EGDMA (AB) further enhanced strength, while higher water content reduced this effect (AD, BD).

Optical transparency varied from 85.0% to 96.1%, with the model explaining 98.71% variability. Transparency decreased with increasing levels of all factors, particularly HEMA and EGDMA, due to increased matrix density and light scattering. Drug loading and excessive water further reduced clarity. Negative quadratic terms confirmed that transparency peaked at optimal mid-range levels of the variables.

Drug release rate ranged from 2.54 to 5.00%/h, influenced significantly by all factors ($R^2 = 97.35\%$). It decreased with higher HEMA (due to denser polymer network) and increased with EGDMA, drug loading, and water content, which facilitated faster diffusion. Interaction AB showed

that EGDMA's enhancing effect on release was reduced at high HEMA levels.

Drug retention ranged from 70.0% to 89.2%, with 98.29% variability explained by the model. Retention improved with HEMA and EGDMA due to denser, crosslinked matrices limiting diffusion. In contrast, increased drug loading and water content reduced retention by accelerating drug leaching. The interaction of HEMA and EGDMA positively influenced retention, while HEMA's effect was dampened by higher drug loading (AC).

Optimization and Validation

Based on the desirability function approach, the optimal formulation was identified using the following criteria: maximizing swelling ratio, tensile strength, optical transparency, and drug retention, while maintaining the drug release rate within the acceptable range (2-5%/hr). The desirability function combined these multiple responses into a single composite function, which was maximized to identify the optimal formulation conditions.

The optimization process yielded an optimal formulation with HEMA concentration of 90%, EGDMA concentration of 1.0%, drug loading of 4 mg/mL, and water content of 40%. The predicted responses for this formulation were: swelling ratio of 170.3%, tensile strength of 1.2 MPa, optical transparency of 95.0%, drug release rate of 3.47%/hr, and drug retention of 84.9%. The overall desirability value was 0.89, indicating a high level of satisfaction with the optimized formulation.

To validate the optimization results, five additional formulations (V1-V5) with slight variations in the optimal parameters were prepared and characterized. The predicted and experimental values for these validation points are presented in Table 5.

The experimental values were in close agreement with the predicted values, with relative errors less than 4% for all responses, confirming the reliability and predictive capability of the developed models. The validation results demonstrated that the optimized formulation with HEMA (90%), EGDMA (1%), drug loading (4 mg/mL), and water content (40%) provided the best balance of properties for the dual-drug-loaded hydrogel contact lenses.

Characterization of Optimized Hydrogel Lenses

Swelling Studies

The optimized hydrogel lenses demonstrated a biphasic swelling profile, reaching 169.1 ± 4.8% after 24 hours, which corresponds to approximately 62.8% water content—within the range for commercial soft lenses. The rapid initial hydration was followed by equilibrium swelling, influenced by the hydrophilic HEMA (90%) and moderate crosslinking with EGDMA (1%), thereby ensuring ideal hydration, dimensional stability, and suitability for sustained drug release.

Mechanical Properties

The lenses exhibited tensile strength of 1.2 ± 0.08 MPa, elongation at break of 175.4 ± 12.3%, and elastic modulus of 0.48 ± 0.04 MPa, all within acceptable limits for soft contact lenses. The formulation provided a balance between strength and flexibility, critical for handling, comfort, and sustained ocular wear.

Optical Transparency

Transmittance exceeded 90% across the visible range, with 95.1 ± 0.5% at 600 nm, confirming excellent optical clarity. The transparency was maintained despite drug incorporation, owing to uniform polymer distribution and absence of aggregation or phase separation, ensuring suitability for both therapeutic and vision correction use.

Surface Morphology

SEM analysis revealed a smooth, uniform surface with well-distributed micropores (2–5 μm), indicating consistent polymerization and drug dispersion. The porous architecture supports hydration, oxygen permeability, and controlled drug diffusion, while preserving structural integrity and optical performance (Fig.3).

Drug Loading and Encapsulation Efficiency

The drug loading and encapsulation efficiency values indicate efficient incorporation of both drugs into the contact lenses. Timolol Maleate showed a slightly higher encapsulation efficiency (87.5 ± 2.3%) compared to Brimonidine Tartrate (82.5 ± 1.9%), with actual loadings closely approaching their theoretical values. The results are presented in Table 6.

In Vitro Drug Release Studies

The optimized hydrogel lenses demonstrated sustained, biphasic release of Timolol Maleate and Brimonidine Tartrate over 24 hours. An initial burst was observed within the first 2 hours (33.33 ± 1.35% for Timolol; 29.66 ± 1.18% for Brimonidine), followed by a controlled release phase, reaching 96.25 ± 2.42% and 97.42 ± 2.56%, respectively, by 24 hours. The initial burst is attributed to surface-bound drug, while the slower phase reflects diffusion from the hydrogel matrix. Timolol's slightly faster release is due to its higher hydrophilicity and lower molecular weight. Both drugs maintained average release rates around 4%/h, ideal for sustained therapeutic levels. Compared to conventional eye drops, the hydrogel lenses significantly prolong drug residence time, potentially improving compliance and therapeutic efficacy (Table 7)

Drug Release Kinetics

Drug release kinetics for both Timolol Maleate and Brimonidine Tartrate followed the Korsmeyer-Peppas model with the highest R^2 values (0.9893 and 0.9924), indicating anomalous (non-Fickian) transport. The release exponents (n = 0.63 and 0.68) confirmed that drug release was governed by both diffusion and polymer relaxation. First-order and Higuchi models also showed good fits, supporting a sustained release profile. The correlation coefficients (R^2) and model parameters for each drug are presented in Table 8.

CONCLUSION

This study successfully developed and optimized dual-drug-loaded hydrogel-based contact lenses for sustained ocular delivery of Timolol Maleate and Brimonidine Tartrate in glaucoma therapy. Using a systematic Box-Behnken Design approach, the effects of HEMA concentration, EGDMA crosslinking density, drug loading, and water content on key performance parameters were evaluated, leading to an optimized formulation with balanced properties: swelling ratio (169.1%), tensile strength (1.2 MPa), optical transparency (95.1%), drug

release rate (3.47% / h), and drug retention (85.4%). The FTIR and DSC analyses confirmed the compatibility of the drug-polymer system, with evidence of hydrogen bonding interactions but no chemical incompatibilities. The hydrogel lenses exhibited high encapsulation efficiencies for both drugs (>82.5%) and provided sustained release over 24 hours, with cumulative release percentages exceeding 96%. The release kinetics followed non-Fickian (anomalous) transport mechanisms, influenced by both drug diffusion and polymer chain relaxation. The optimized hydrogel lenses offer several advantages over conventional eye drops: (1) sustained drug release, reducing dosing frequency from 4-6 times daily to potentially once daily; (2) enhanced bioavailability by bypassing precorneal clearance mechanisms; (3) synergistic delivery of two complementary drugs from a single platform; and (4) dual functionality of vision correction and drug delivery, improving patient convenience and potentially enhancing adherence. The findings of this study demonstrate that hydrogel-based contact lenses can serve as an effective platform for sustained ocular drug delivery, addressing the limitations of traditional eye drops in glaucoma management. The optimization methodology and characterization techniques employed provide valuable insights for the rational design of drug-eluting contact lenses, contributing to the advancement of ocular drug delivery technologies.

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