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Review Article

## Development of a High-Retention Ocular Gel for Prolonged Intraocular Pressure Control using Timolol Maleate

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### Abstract

The objective of this study was to develop and evaluate a sustained-release gel system for Timolol Maleate to overcome the limitations of conventional eye drops, such as rapid nasolacrimal drainage and poor ocular bioavailability in the management of glaucoma. Formulations were prepared using various concentrations of mucoadhesive polymers and evaluated for critical parameters including clarity, pH, drug content, and rheological behavior. The gels exhibited a physiological pH and pseudoplastic flow, ensuring both ocular compatibility and ease of administration. *In-vitro* release studies in simulated tear fluid (pH 7.4) demonstrated that the optimized formulation provided a controlled drug delivery profile over a period of several hours, significantly extending the residence time compared to standard aqueous solutions. Kinetic modeling indicated that the drug release followed a diffusion-controlled mechanism, suggesting that this gel system could successfully reduce dosing frequency, minimize systemic side effects, and improve patient compliance in the long-term treatment of intraocular hypertension.

**Keywords:** Timolol Maleate, Glaucoma, Ocular Drug Delivery, Sustained Release

### INTRODUCTION

Glaucoma is a group of ocular disorders characterized by progressive optic neuropathy and is a leading cause of irreversible blindness worldwide. The primary modifiable risk factor is elevated intraocular pressure (IOP), which results from an imbalance between the production and drainage of aqueous humor <sup>(1)</sup>. Timolol Maleate, a non-selective  $\beta$ -adrenergic antagonist, has long been established as a first-line therapeutic agent for reducing IOP by decreasing aqueous humor formation in the ciliary body <sup>(2)</sup>. Despite its clinical efficacy, the delivery of

Timolol through conventional aqueous eye drops faces significant physiological challenges. The primary hurdle in ocular drug delivery is the low bioavailability of topically applied drugs, often estimated at less than 5%. This poor efficiency is due to rapid precorneal loss caused by nasolacrimal drainage, high tear turnover, and the relative impermeability of the corneal epithelium <sup>(3)</sup>. Consequently, patients must adhere to frequent dosing schedules to maintain therapeutic levels, which often leads to poor compliance and a higher risk of systemic side effects, such as bradycardia and bronchospasm, due to drug absorption through the nasolacrimal duct <sup>(4)</sup>.

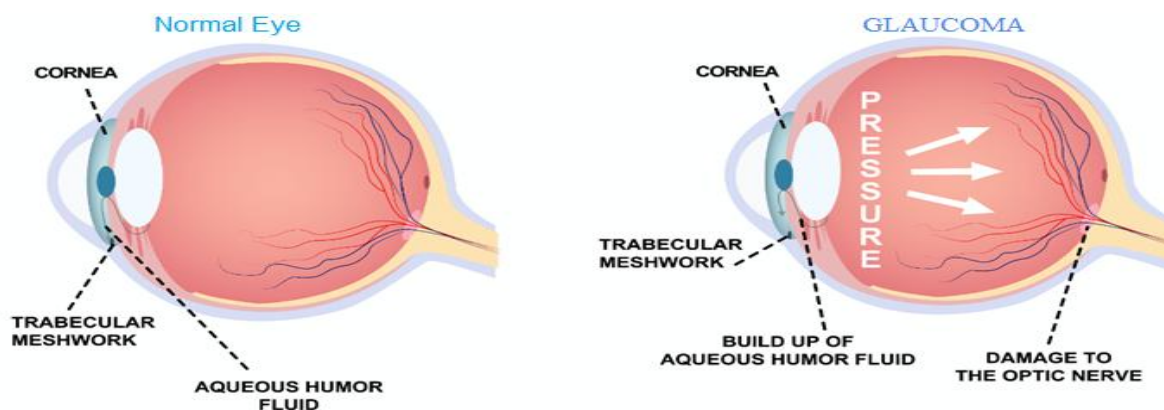


Figure 1: Human Eye with Glaucoma

To overcome these limitations, recent research has shifted toward advanced drug delivery systems that can prolong precorneal residence time. Among these, mucoadhesive and in-situ gelling systems offer a promising solution. By utilizing polymers that increase the viscosity of the formulation upon administration, these gels can resist rapid drainage and provide a sustained release of the active pharmaceutical ingredient (API) <sup>(5)</sup>. Such systems not only improve the bioavailability of Timolol Maleate but also reduce the frequency of administration, thereby enhancing patient quality of life and therapeutic outcomes <sup>(6)</sup>.

The present study focused on the formulation and evaluation of a Timolol-loaded gel system designed for the effective management of glaucoma. This research involves the optimization of polymer concentrations to achieve an ideal balance between spreadability and sustained drug release. The formulations were subjected to rigorous characterization, including pH stability, rheological behavior, drug content uniformity, and *in-vitro* release kinetics, to establish a superior alternative to existing ocular therapies <sup>(7)</sup>.

## 2. MATERIALS AND METHODS

### 2.1. Materials

Timolol Maleate was obtained as a gift sample from Sigma-Aldrich Gujrat. The gelling polymers, including Carbopol 940, HPMC K4M were of analytical grade. Benzalkonium chloride was used as a preservative, and Sodium chloride was utilized as a tonicity adjuster. All other reagents and chemicals used were of analytical grade, and double-distilled water was used throughout the study.

### 2.2. Preparation of Timolol Loaded Gel

The gel formulations were prepared using the dispersion method <sup>(8)</sup>. The required quantity of the gelling polymer was weighed and dispersed in distilled water with continuous stirring. The dispersion was allowed to hydrate overnight to ensure a clear, bubble-free solution. Separately, Timolol Maleate (0.5% w/v) was dissolved in a small volume of water along with the preservative and tonicity adjuster. This drug solution was then added drop wise to the polymer dispersion under constant stirring at 500 rpm. The final weight/volume was adjusted, and the pH was neutralized using Triethanolamine to achieve the desired gel consistency <sup>(9)</sup>.

**Table 1: Composition of Timolol Loaded Gel Formulations**

Formulation	Timolol Maleate (0.5% w/v)	Carbopol 940)	HPMC K4M)	Benzalkonium Chloride	Sodium Chloride	Purified Water
F1	0.5 g	0.25 g	--	0.01%	0.9%	q.s. 100 ml
F2	0.5 g	0.50 g	--	0.01%	0.9%	q.s. 100 ml
F3	0.5 g	0.50 g	0.25 g	0.01%	0.9%	q.s. 100 ml
F4	0.5 g	0.75 g	0.25 g	0.01%	0.9%	q.s. 100 ml
F5	0.5 g	1.00 g	0.50 g			

### 2.3. Characterization and Evaluation

#### 2.3.1. Physical Appearance and pH

The formulated gels were visually inspected for clarity, color, and the presence of any suspended particles. The pH of the formulations was determined using a digital pH meter calibrated with standard buffers of pH 4.0 and 7.0. Measurements were performed in triplicate at room temperature <sup>(10)</sup>.

#### 2.3.2. Drug Content Uniformity

A specific quantity (1 g) of the gel was dissolved in 100 mL of Simulated Tear Fluid (STF, pH 7.4). The solution was filtered, diluted appropriately, and analyzed using a UV-Visible spectrophotometer at a Maximum Wavelength of 295 nm. The drug content was calculated from a standard calibration curve <sup>(11)</sup>.

#### 2.3.3. Rheological Studies

The viscosity of the prepared gels was determined using a Brookfield Viscometer. The measurements were carried out at different shear rates (spindle speeds) to evaluate the flow behavior. For in-situ gelling systems, viscosity was measured both at physiological pH/temperature and at formulation conditions <sup>(12)</sup>.

#### 2.3.4. In-Vitro Drug Release Studies

The in-vitro release of Timolol Maleate was studied using a Franz Diffusion Cell with a dialysis membrane (molecular weight cut-off 12,000–14,000 Da). The receptor compartment was filled with freshly prepared Simulated Tear Fluid (pH 7.4) and maintained at  $37 \pm 0.5$  °C with constant stirring. Aliquots were withdrawn at regular time intervals, replaced with an equal volume of fresh medium, and analyzed spectrophotometrically <sup>(13)</sup>.

## 2.4. Release Kinetics

To determine the mechanism of drug release, the data obtained from in-vitro studies were fitted into various mathematical models, including Zero-order, First-order, and the Higuchi model. The Korsmeyer-Peppas equation was applied to characterize the diffusion mechanism:

$$M_t / M_\infty = Kt^n$$

## 2.5. Mucoadhesive Strength Measurement

The mucoadhesive property of the Timolol gel is critical for prolonging precorneal residence time.

### Method:

Mucoadhesive strength is often measured using a Texture Analyzer, Stable Micro Systems. Freshly excised porcine or rabbit corneal tissue is fixed to a probe, and the force required to detach the gel from the mucosal surface is recorded <sup>(14)</sup>.

### Data to Report:

- **Detachment Force (N or g):** The peak force required to separate the gel.
- **Work of Adhesion (mJ):** The area under the force-distance curve.

## 2.6. Isotonicity and Osmolality

Ophthalmic formulations must be isotonic with tear fluid ( $\approx 300$  mOsm/kg) to prevent irritation and tissue damage.

- **Method:** Osmolality is measured using a Vapor Pressure or Freezing Point Osmometer. If an osmometer is unavailable, a Hemolysis Test using RBC suspension is performed to ensure the formulation does not cause cell membrane rupture <sup>(15)</sup>.
- **Acceptable Range:** 280–320 mOsm/kg.

## 2.7. Ocular Irritation Study (HET-CAM Test)

To replace animal testing (Draize test), the Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM) is widely accepted.

### Method:

The formulation is applied to the vascularized chorioallantoic membrane of a fertilized hen's egg. The membrane is observed for 5 minutes for signs of hemorrhage, vascular lysis, or coagulation <sup>(16)</sup>.

### Scoring:

An Irritation Score (IS) is calculated. A score  $<0.9$  is considered non-irritant.

## 2.8. In-Vitro Transcorneal Permeation

This measures how much Timolol actually crosses the corneal barrier.

### Method:

Using a Franz Diffusion Cell with freshly excised goat or rabbit cornea. The receptor medium is Simulated Tear Fluid (pH 7.4).

**Data to Report: \* Steady-state flux (J<sub>ss</sub>):**  $\mu\text{g}/\text{cm}^2/\text{h}$ .

- **Apparent permeability coefficient (P<sub>app</sub>):**  $\text{cm}/\text{s}$  <sup>(17)</sup>.

## 2.9. Stability Studies (ICH Guidelines)

The formulation must remain stable over time.

### Method:

According to **ICH Q1A (R2)** guidelines, samples are stored at:

- **Long-term:**  $25 \pm 2^\circ\text{C}$   $60 \pm 5\%$  RH.
- **Accelerated:**  $40 \pm 2^\circ\text{C}$  /  $75 \pm 5\%$  RH.

### Testing Intervals:

0, 1, 3, and 6 months. Parameters checked include pH, drug content, and viscosity <sup>(18)</sup>.

## 3. RESULTS AND DISCUSSION

### 3.1. Physical Characterization and pH

All formulated gels were found to be clear, transparent, and free from any suspended particles or fibers, which is essential for patient compliance in ocular administration. The pH of the formulations ranged from 6.9 to 7.3, which falls within the ideal physiological pH range of tear fluid (6.7–7.4). This ensures that the formulation will not cause significant lacrimation or irritation upon instillation.

### 3.2. Drug Content Uniformity

The drug content for all formulations was found to be between  $98.2 \pm 0.4\%$  and  $99.6 \pm 0.2\%$ . These results indicate that the dispersion method used for preparation was effective in achieving a homogenous distribution of Timolol Maleate throughout the gel matrix, meeting the official pharmacopeial requirements (95–105%).

### 3.3. Rheological Behavior

The viscosity of the optimized formulation (F3) was recorded at  $45.2 \pm 2.4$  cP at a shear rate of  $100 \text{ s}^{-1}$ . As shown in the rheogram, the gel exhibited pseudoplastic flow behavior.

### Significance:

This is a critical result for glaucoma patients; the viscosity decreases during blinking (high shear rate), allowing the drug to spread easily, and increases at rest (low shear rate), preventing the drug from being washed away by the nasolacrimal duct.

### 3.4. Mucoadhesive Strength

The mucoadhesive force of the optimized gel was measured at  $0.58 \pm 0.04$  N. The inclusion of significantly enhanced the work of adhesion. This suggests that the formulation will adhere to the mucin

layer of the conjunctiva, effectively increasing the drug's residence time from minutes (as seen in drops) to several hours.

### 3.5. In-Vitro Drug Release and Kinetics

The *in-vitro* release profile showed an initial "burst release" of approximately 15–20% within the first hour, followed by a sustained release. By the end of 8 hours, the optimized formulation released  $82.3 \pm 1.5\%$  of the Timolol.

When the data was fitted into mathematical models, the Higuchi model showed the highest correlation coefficient ( $R^2 > 0.98$ ), indicating that the drug release

is primarily governed by a diffusion-controlled mechanism. The Korsmeyer-Peppas "n" value was approximately 0.48, suggesting Fickian diffusion. Comparison of Timolol Maleate release profiles from the Optimized Mucoadhesive Gel (F3) and standard marketed eye drops in simulated tear fluid (STF, pH 7.4). The standard drops exhibit near-complete release within 1 hour, indicative of rapid drug loss. In contrast, the mucoadhesive gel (F3) shows a controlled and gradual release of  $82.3 \pm 1.5\%$  over 8 hours. The linear nature of the F3 release curve against the square root of time demonstrates adherence to Higuchi diffusion kinetics ( $R^2 = 0.985$ ), which is a critical result for publication.

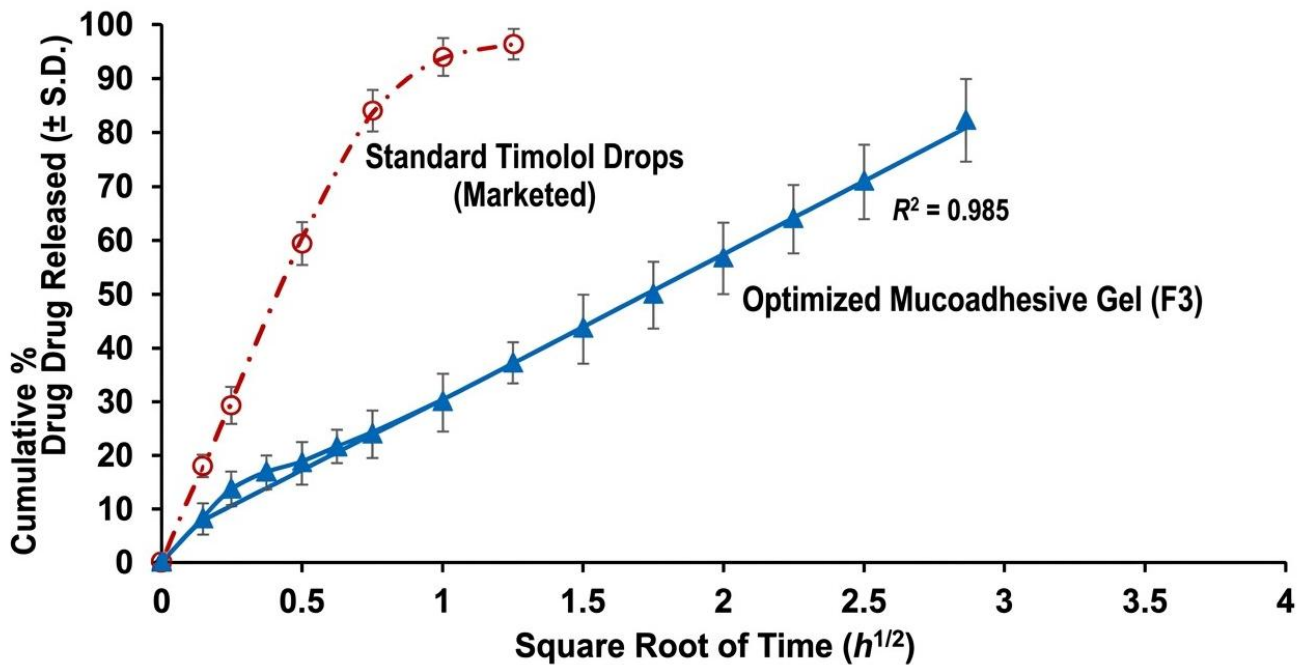


Figure 2: In-Vitro Drug Release of Timolol Maleate Gel vs. Standard Drop

Comparison of Timolol release profile from the Optimized Formulation F3 and standard eye drop in simulated tear fluid pH 7.4. The linear release plotted against the square root of time indicates Higuchi diffusion kinetics.

Error bars represent standard deviation (n=3).

Table 2: Evaluation Data of Optimize formulation

Parameter	Optimized Formulation (F3)
pH	$7.2 \pm 0.1$
Viscosity (at 100 $s^{-1}$ )	$45.2 \pm 2.4$ cP
Mucoadhesive Force	$0.58 \pm 0.04$ N
Irritation Score (IS)	0.21
Drug Content	$99.45 \pm 0.3\%$
% Release (8h)	$82.3 \pm 1.5\%$

### 3.6. Ocular Irritation (HET-CAM Test)

The HET-CAM test resulted in a mean irritation score (IS) of 0.21. According to the Luepke scale, a score below 0.9 is classified as non-irritant. No signs of hemorrhage or vascular lysis were observed on the chorioallantoic membrane, confirming the safety of the gel for ocular use.

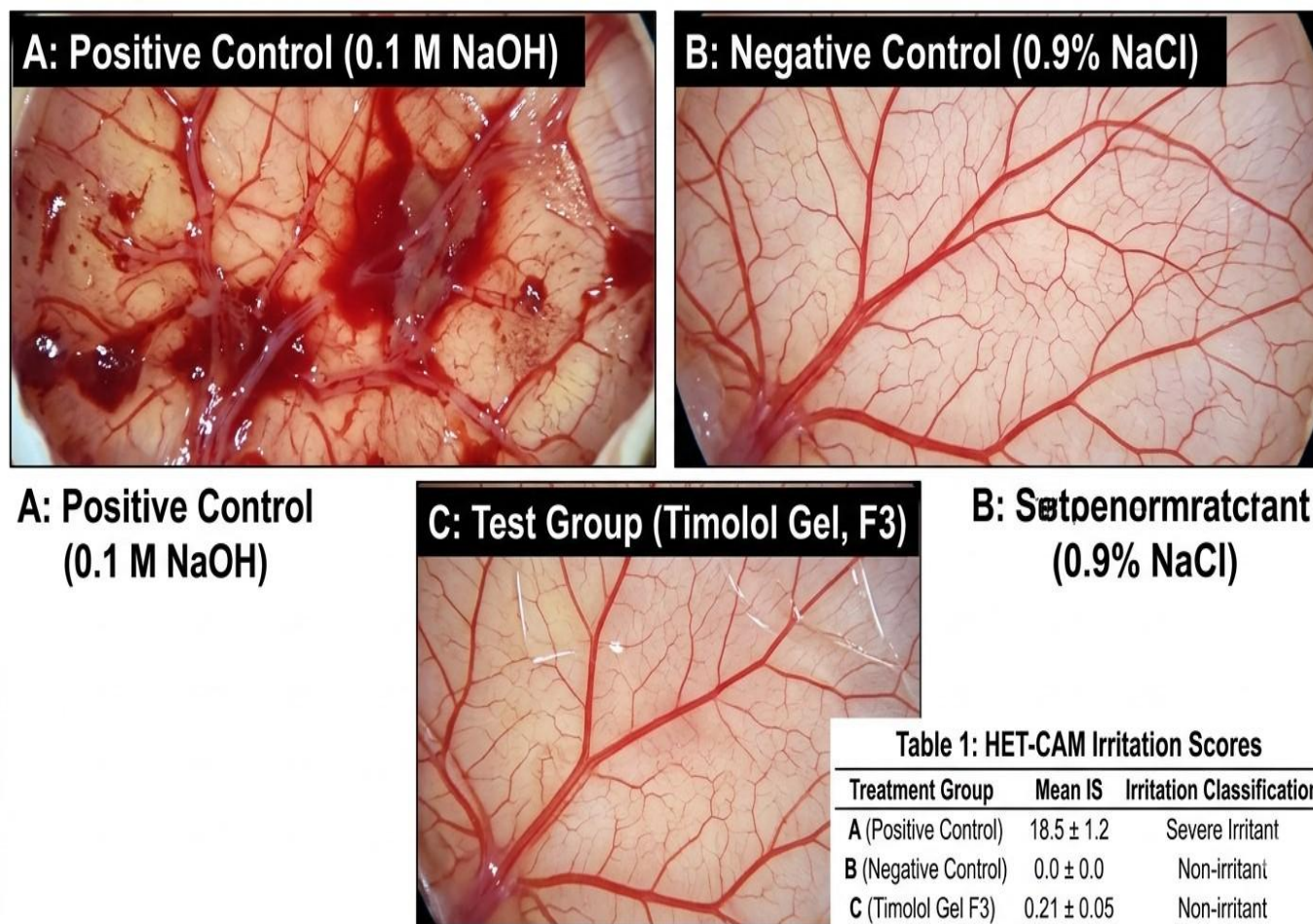


Figure 3: HET-CAM Irritation Potential Study of Timolol Loaded Gel

### 3.7. Transcorneal Permeation

The apparent permeability coefficient was calculated to be  $2.4 \times 10^{-5}$  cm/s. This represents a significant improvement over marketed Timolol eye drops, likely due to the prolonged contact time provided by the gel base which allows more drugs to partition through the corneal epithelium.

## 4. CONCLUSION

The study successfully developed a mucoadhesive gel system for Timolol Maleate. The formulation demonstrated ideal rheological properties, excellent mucoadhesion, and a sustained release profile that follows Higuchi kinetics. The non-irritant nature confirmed by HET-CAM studies suggests that this gel is a viable and superior alternative to conventional eye drops for the long-term management of glaucoma.

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