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Original Research Article

FORMULATION AND EVALUATION OF TIMOLOL MALEATE OCULAR IN SITU GEL

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ABSTRACT

The present study was aimed at the formulation and evaluation of an ocular in situ gel of timolol maleate for the effective management of glaucoma. The objective was to enhance ocular residence time and provide sustained drug release while improving patient compliance. In situ gel formulations (F1–F9) were prepared using sodium alginate as a gelling agent. The formulations were evaluated for clarity, pH, drug content, in situ gelling capacity, viscosity, in vitro drug release, release kinetics, and stability. Clarity studies revealed that formulations F1–F8 were clear, whereas F9 showed turbidity. Drug content of all formulations ranged between 96.72% and 99.28%, indicating uniform drug distribution. The pH of all formulations was adjusted to 5.0 ± 0.1 to ensure ocular compatibility. Formulations F4, F5, and F6 exhibited immediate gelation with prolonged gel integrity. Viscosity studies showed low viscosity before administration and a significant increase after gelation, ensuring ease of instillation and prolonged ocular residence. The optimized formulation F5 demonstrated sustained drug release with 98.60% cumulative drug release over 5 hours and followed first-order release kinetics (R^2 = 0.9800). Stability studies confirmed that formulation F5 remained stable over 30 days with no significant changes in drug content or gelling capacity. The study concludes that the developed timolol maleate ocular in situ gel is a promising system for sustained glaucoma therapy.

Keywords: Timolol maleate, Ocular in situ gel, Sodium alginate, Glaucoma, Sustained drug release, Ion-activated gel, Ophthalmic drug delivery.

INTRODUCTION

Glaucoma is a progressive ocular disorder characterized by elevated intraocular pressure (IOP), which can lead to irreversible optic nerve damage and visual field loss if left untreated. Timolol maleate, a non-selective β-adrenergic receptor blocker, is widely prescribed as a first-line antiglaucoma agent due to its proven efficacy in reducing aqueous humor production and lowering IOP.

However, conventional ophthalmic solutions of timolol maleate suffer from rapid precorneal elimination caused by blinking, tear turnover, and nasolacrimal drainage, resulting in low ocular bioavailability and the need for frequent administration, which may reduce patient compliance (Abdelmonem *et al.*, 2025).

Ocular in situ gel drug delivery systems have emerged as a promising approach to overcome these limitations. These systems are instilled as low-viscosity solutions that undergo sol-to-gel transition upon exposure to physiological conditions such as temperature, pH, or ionic strength of the tear fluid (Vigani *et al.*, 2020).

The formed gel increases the residence time of the drug on the ocular surface, thereby enhancing bioavailability, prolonging therapeutic action, and reducing dosing frequency. In situ gels also offer improved patient comfort compared to conventional gels or ointments due to ease of administration and minimal vision interference (Padmasri *et al.,* 2020).

Timolol maleate is an ideal candidate for in situ gel formulation because of its suitable dose, high aqueous solubility, and short biological half-life (Shah *et al.,* 2020). Incorporation of timolol maleate into a polymeric in situ gel matrix using biocompatible and ophthalmically acceptable polymers can provide sustained drug release and improved therapeutic efficacy. Polymers such as gellan gum, sodium alginate, carbopol, and poloxamers are commonly used to achieve ion-activated, pH-sensitive, or thermoresponsive gelation (Sah *et al.,* 2017).

The present research work focuses on the formulation and evaluation of timolol maleate ocular in situ gel with the objective of enhancing ocular residence time, achieving sustained drug release, and improving patient compliance. The developed formulations were evaluated for physicochemical properties, gelation behavior, drug content, in vitro drug release, and stability to assess their suitability as an effective ocular drug delivery system.

MATERIALS AND METHODS

Formulation development of ocular *in-situ* gel

The formulation development of an in-situ gel of Timolol maleate holds significant importance and presents a compelling need for study.

Selection of Vehicle

The in-situ gel formulations of Timolol maleate (F1–F9) were prepared using acetate buffer (pH 5.0) as the selected vehicle, based on solubility studies in various buffers including acetate buffer I.P., citrophosphate buffer B.P., and phosphate buffer USP. For each formulation, 0.5% w/v Timolol maleate was accurately weighed, passed through sieve no. 44, and dissolved in 50 mL of acetate buffer. To the drug solution, the required concentrations of sodium alginate (10–14%) and HPMC 15 cps (0.5–1.0%) were added according to the formulation design. Subsequently, EDTA (0.1%)**,** benzalkonium chloride (0.010%)**,** polyethylene glycol (0.1%) and sodium chloride (q.s. to adjust isotonicity) were incorporated with continuous stirring to ensure uniform mixing. The mixture was stirred for 2–3 hours to allow complete hydration of the polymers and to prevent slug formation. After thorough mixing, the formulations were refrigerated at 4℃ for 24 hours to achieve complete polymer hydration and clarity. The final gels were then subjected to probe sonication to remove entrapped air bubbles and transferred into sterile LDPE dropper bottles. All formulations were stored at 4℃ until further evaluation. The composition of the nine formulations varied systematically in the concentration of sodium alginate and HPMC 15 cps, while other excipients and the drug concentration were kept constant (Varshosaz *et al.,* 2008).

Evaluation of Formulations

Appearance

Clarity is a critical characteristic of ophthalmic preparations, as it ensures the absence of particulate matter and enhances patient compliance. All developed

formulations were evaluated visually for clarity against both black and white backgrounds to detect any turbidity or suspended particles (Saxena and Kushwaha, 2013).

Drug content

The drug content of Timolol maleate in the formulations was quantified using a UV-Visible spectrophotometric method. The concentration of the drug was calculated based on a calibration curve constructed using the regression equation (Y = mx + c), ensuring the accuracy and linearity of the assay (Viram and Lumbhani, 2012).

pH determination

The pH of ophthalmic formulations plays a vital role in drug solubility, stability, and ocular tolerability. Ideally, the pH should lie within the range of 5.0 to 7.4 to avoid discomfort or irritation upon administration. In the case of Timolol maleate in-situ gels, a pH of 5.0 is considered optimal as the drug remains stable within the pH range of 3.5–5.0. A reduction in pH below 5.0 may lead to ocular irritation, while a pH above 5.0 can trigger premature gelation due to the presence of carbopol. The pH of the prepared formulations was measured using a calibrated digital pH meter (Vodithala *et al.,* 2010).

In-situ gelling capacity

The in-situ gelling capacity of the formulations was evaluated by visual observation under simulated physiological conditions. Simulated Tear Fluid (STF) was prepared and preheated to 37°C. The formulations were added to STF in a 1:2 ratio (formulation: STF), and the transformation from sol to gel was visually monitored. This test indicates the ability of the formulation to undergo sol-to-gel transition upon contact with tear fluid (Shankar and Kalikonda, 2014).

Viscosity Study

At pH 5.0 and temperatures below 16℃, the formulations remained in liquid form, exhibiting low viscosity. For viscosity measurement, the pH was adjusted from 5.0 to 7.4 using 0.5 M NaOH, and the temperature was increased to 37℃ to simulate physiological conditions (Mahesh and Manjula, 2012). The viscosity of the resulting gel was measured using a Brookfield Synchrolectric Viscometer (Spindle No. 7) at 50 RPM. To evaluate shear-dependent flow behavior, angular viscosity was recorded at varying RPMs from 10 to 70.

***In-vitro* drug diffusion study**

The in-vitro release profile of the drug from the formulations was studied using a diffusion method through a cellophane membrane. Artificial tear fluid (pH 7.4) served as the dissolution medium. A cellophane membrane, pre-soaked overnight in the medium, was fixed at one end of a glass diffusion cell (5 cm in diameter, open at both ends). One milliliter of the formulation was placed inside the cell, which was then suspended in 50 ml of artificial tear fluid maintained at 37 ± 1℃, ensuring that the membrane just touched the medium. The medium was stirred continuously at 50 rpm using a magnetic stirrer. At hourly intervals, 1 ml samples were withdrawn and replaced with fresh dissolution medium to maintain sink conditions (Costa and Lobo, 2001; Gratieri *et al.,* 2011).

Stability studies

The optimized sterile formulation was subjected to accelerated stability testing. It was filled in sterile glass vials, sealed with gray butyl rubber stoppers and aluminum

caps. The vials were stored in a stability chamber maintained at 40 ± 2°C and 75 ± 5% RH for one month. Samples were withdrawn weekly and analyzed for drug content and in-situ gelling capacity to evaluate formulation stability (Nayak *et al.,* 2012).

RESULTS AND DISCUSSION

The in situ gel formulations of timolol maleate (F1–F9) were successfully prepared using acetate buffer (pH 5.0) as the vehicle, selected based on solubility studies. The composition of formulations varied systematically in the concentrations of sodium alginate and HPMC 15 cps, while the drug and other excipients were kept constant, as shown in Table 1. This design enabled evaluation of the effect of polymer concentration on physicochemical properties, gelation behavior, viscosity, and drug release.

Clarity is an essential requirement for ophthalmic formulations to ensure patient comfort and acceptability. As presented in Table 2, formulations F1–F8 were found to be clear, indicating proper solubilization of timolol maleate and uniform polymer dispersion. However, formulation F9 exhibited turbidity, which may be attributed to the higher concentration of sodium alginate (14%) combined with lower HPMC content, leading to polymer aggregation or incomplete hydration. Hence, F9 was considered less suitable for ocular application.

Drug content analysis revealed that all formulations showed drug content in the range of 96.72% to 99.28%, confirming uniform distribution of timolol maleate within the formulations (Table 3). Among all formulations, F5 exhibited the highest drug content (99.28 ± 0.82%), suggesting better formulation homogeneity and minimal drug loss during preparation.

The pH of ophthalmic formulations must be compatible with ocular tissues to minimize irritation. Initially, all formulations exhibited acidic pH values ranging from 4.4 to 4.9, which were adjusted to 5.0 ± 0.1 using acetate buffer. As shown in Table 4, all formulations met the acceptable pH range for ocular administration, ensuring patient comfort and drug stability.

The in situ gelling capacity of the formulations is a critical parameter that determines the ability of the formulation to undergo sol-to-gel transition upon contact with tear fluid. As shown in Table 5, formulations F4, F5, and F6 exhibited immediate gelation and remained intact for an extended period of up to 8 hours ("+++"). This behavior can be attributed to the optimal combination of sodium alginate and HPMC concentrations, which enhances ionic cross-linking with tear fluid calcium ions and strengthens the gel matrix. Other formulations showed moderate gelation ("++"), remaining for a few hours.

Viscosity studies play an important role in assessing ease of instillation and ocular residence time. As shown in Table 6, all formulations exhibited relatively low viscosity in solution form (622–685 cps), facilitating easy administration as eye drops. Upon gelation, viscosity increased significantly (2350–2755 cps), indicating successful in situ gel formation. Formulation F5 showed an optimal balance between solution viscosity and gel viscosity, ensuring ease of instillation along with prolonged ocular retention.

The in vitro drug release profile of the optimized formulation F5 is presented in Table 7. An initial release of 10.85% within 0.5 hours was observed, which may be attributed to surface-associated drug. This was followed by a sustained and controlled release pattern, achieving 98.60% cumulative drug release over 5 hours. The sustained release behavior confirms the ability of the sodium alginate–HPMC gel matrix to regulate drug diffusion effectively.

Release kinetic analysis was carried out to determine the mechanism of drug release. As shown in Table 8, formulation F5 exhibited a higher correlation coefficient for the first-order model (R^2 = 0.9800) compared to the zero-order model (R^2 = 0.8207), indicating that the release of timolol maleate followed concentration-dependent kinetics, predominantly governed by diffusion through the hydrated gel matrix.

Stability studies of the optimized formulation F5 were conducted for 30 days, and the results are summarized in Table 9. The formulation showed negligible changes in drug content, which remained above 98%, and retained its in situ gelling capacity throughout the study period. These results indicate good physical and chemical stability of the formulation under refrigerated storage conditions.

Table 1: Composition of different formulations of *In-situ* gel

S. No.	Ingredient (%)	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Timolol maleate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
2.	Sodium Alginate	10	12	14	10	12	14	10	12	14
3.	HPMC 15cps	1.0	1.0	1.0	0.75	0.75	0.75	0.5	0.5	0.5
4.	EDTA	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
5.	Benzalkonium Chloride	0.010%	0.010%	0.010%	0.010%	0.010%	0.010%	0.010%	0.010%	0.010%
6.	NaCl	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
7.	Poly ethylene glycol	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
8.	Acetate Buffer (pH 5.0)	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml

Table 2: Clarity test of *in situ* gel formulations

S. No.	Formulation code	Clarity
1	F1	Clear
2	F2	Clear
3	F3	Clear
4	F4	Clear
5	F5	Clear
6	F6	Clear
7	F7	Clear
8	F8	Clear
9	F9	Turbid

Table 3: Drug content analysis

S. No.	Formulation	Drug Content (%)
1	F1	98.12±0.25
2	F2	96.78±0.36
3	F3	97.62±0.25
4	F4	96.95±0.11
5	F5	99.28±0.82
6	F6	97.48±0.32
7	F7	96.72±0.25
8	F8	97.91±0.41
9	F9	98.34±0.98

Table 4: pH Determination

Formulation	Initial pH	Adjusted to
F1	4.4	5.0 ± 0.1
F2	4.6	5.0 ± 0.1
F3	4.9	5.0 ± 0.1
F4	4.7	5.0 ± 0.1
F5	4.8	5.0 ± 0.1
F6	4.6	5.0 ± 0.1
F7	4.4	5.0 ± 0.1
F8	4.8	5.0 ± 0.1
F9	4.6	5.0 ± 0.1

Table 5: *In situ* gelling capacity of *In situ* gel formations

Formulation code	*In situ* gelling capacity
F1	"++"
F2	"++"
F3	"++"
F4	"+++"
F5	"+++"
F6	"+++"
F7	"++"
F8	"++"
F9	"++"

"+" gelation after five minutes and dissolves rapidly

"++" gelation immediate, remains for few hours

"+++" gelation immediate, remains for extended period 8 hours

Table 6: Comparative viscosity of *In situ* formulation

Formulation Code	% of Sodium Alginate	Viscosity of Solution (cps)	Viscosity After Gelation (cps)
F1	10	628	2480
F2	12	645	2620
F3	14	662	2755
F4	10	635	2425
F5	12	668	2575
F6	14	685	2688
F7	10	622	2350
F8	12	640	2460
F9	14	658	2545

*Spindle no.7 rpm 50

Table 7: *In vitro* drug release profile of Timolol maleate from *in situ* Formulation F5

Time (h)	√Time $(h)^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	−0.301	10.85	1.035	89.15	1.950
1	1.000	0.000	28.40	1.453	71.60	1.855
1.5	1.225	0.176	46.20	1.665	53.80	1.731
2	1.414	0.301	72.90	1.863	27.10	1.433
2.5	1.581	0.398	84.10	1.925	15.90	1.201
3	1.732	0.477	91.35	1.961	8.65	0.937
4	2.000	0.602	97.85	1.991	2.15	0.333
5	2.236	0.699	98.60	1.994	1.40	0.146

Table 8: Comparative study of regression coefficient for selection of optimize Formulation F5

Drug	Zero order	First order
Timolol maleate	$R^2 = 0.8207$	$R^2 = 0.9800$

Table 8: Stability data sheet

F. Code	7 Days		15 Days		30 Days	
	Drug content (%)	In-situ gelling capacity	Drug content (%)	In-situ gelling capacity	Drug content (%)	In-situ gelling capacity
F5	99.05	++	98.62	++	98.20	++

CONCLUSION

The study successfully developed a timolol maleate ocular in situ gel using sodium alginate that exhibited good clarity, suitable pH, uniform drug content, and efficient in situ gelation. The optimized formulation F5 demonstrated appropriate viscosity, sustained drug release, and good stability, indicating enhanced ocular residence time and improved therapeutic efficacy. The developed in situ gel system represents a promising and patient-friendly approach for the effective management of glaucoma.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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