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Original Research Article

Formulation & Evaluation of Timolol Loaded Ointment Gel for Glaucoma Therapy

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Abstract: Glaucoma is a major cause of irreversible blindness worldwide and requires effective long-term management. The present study aimed to formulate and evaluate a Timolol-loaded ophthalmic ointment gel to enhance ocular retention, improve bioavailability, and provide sustained drug release. The formulation was prepared using Timolol Maleate, Carbopol 934P, HPMC K15M, Poloxamer 407, and suitable ophthalmic excipients. The optimized formulation was evaluated for physicochemical properties, drug content, viscosity, spreadability, in vitro drug release, ocular irritation, sterility, and stability. The formulation exhibited satisfactory pH (7.2 ± 0.12), drug content (98.45 ± 0.56%), viscosity (4580 ± 45 cP), and spreadability (12.65 ± 0.32 g·cm/sec). In vitro release studies showed sustained drug release with 99.20 ± 1.26% release over 10 hours. The formulation was non-irritating, sterile, and remained stable during storage studies. The results indicate that the developed Timolol-loaded ointment gel is a promising ophthalmic delivery system for glaucoma therapy, offering prolonged drug action, improved patient compliance, and enhanced therapeutic effectiveness.

Keywords: Timolol Maleate, Glaucoma, Ophthalmic Ointment Gel, Sustained Release, Ocular Drug Delivery, Stability Study.

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INTRODUCTION

Glaucoma is a multifactorial and progressive optic neuropathy characterized by degeneration of retinal ganglion cells and damage to the optic nerve, ultimately leading to irreversible visual impairment and blindness. It is recognized as one of the most prevalent causes of permanent r blindness worldwide and represents a major public health concern. The disease is often associated with elevated intraocular pressure (IOP), which is considered the most significant modifiable risk factor in the onset and progression of glaucomatous damage. Persistent elevation of intraocular pressure exerts mechanical and vascular stress on the optic nerve head, resulting in gradual loss of visual field and deterioration of visual function. Since vision loss caused by glaucoma is irreversible, early diagnosis and effective long-term management are essential for preserving visual health and improving patient quality of life. The management of glaucoma primarily focuses on reducing intraocular pressure to prevent or slow the progression of optic nerve damage. Various therapeutic approaches, including pharmacological treatment, laser therapy, and surgical intervention, are available for controlling intraocular pressure. Among these, topical ocular medications remain the first-line treatment due to their convenience, effectiveness, and non-invasive nature. Timolol Maleate is one of the most extensively prescribed antiglaucoma agents and belongs to the class of non-selective beta-adrenergic receptor antagonists. It acts by reducing aqueous humor production from the

ciliary body, thereby lowering intraocular pressure and minimizing the risk of optic nerve damage. Owing to its proven efficacy and favorable therapeutic profile, Timolol continues to be widely utilized in glaucoma therapy. Despite the clinical success of conventional Timolol eye drops, their therapeutic effectiveness is often limited by several physiological barriers associated with ocular drug delivery. The eye possesses numerous protective mechanisms, including blinking, tear secretion, tear turnover, nasolacrimal drainage, and corneal barriers, which rapidly eliminate administered drugs from the ocular surface. As a result, only a small fraction of the applied dose is absorbed into ocular tissues, while the majority is lost through drainage and systemic absorption. Consequently, conventional ophthalmic formulations typically exhibit poor bioavailability, short precorneal residence time, and reduced therapeutic efficiency. Frequent administration is often required to maintain adequate drug concentrations, which may decrease patient compliance, especially in chronic conditions requiring lifelong treatment. To overcome these limitations, extensive research has been directed toward the development of novel ophthalmic drug delivery systems capable of prolonging ocular residence time and enhancing drug absorption. Among the various approaches investigated, ophthalmic ointment gels have gained considerable attention due to their ability to combine the beneficial characteristics of both ointments and gels.

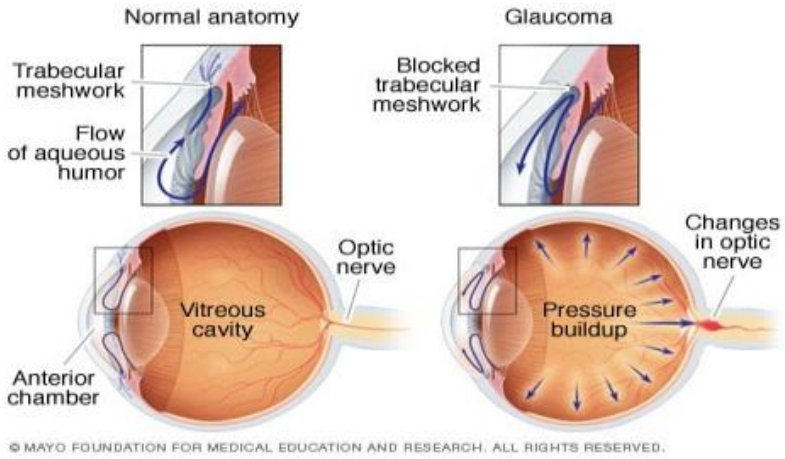


Figure No.1 Glaucoma

PRE-FORMULATION STUDIES

Pre-formulation studies were performed to evaluate the physicochemical and biopharmaceutical properties of Timolol before formulation development. These studies provided essential information for the selection of suitable excipients, optimization of formulation parameters, and prediction of stability-related issues. Since ophthalmic preparations require high standards of safety, efficacy, and stability, pre-formulation assessment played a crucial role in the successful development of the Timolol-loaded ophthalmic ointment gel.

Organoleptic Characteristics

Organoleptic evaluation was performed to assess the physical characteristics of Timolol, including color, odor, appearance, and physical state. These parameters provide preliminary information regarding the identity and purity of the drug substance. The observed characteristics also serve as reference standards during formulation development and stability studies. Any significant change in appearance or odor may indicate degradation, contamination, or incompatibility with formulation components.

Solubility Studies

Solubility studies were carried out in various solvents and buffer systems to determine the dissolution behavior of Timolol. The drug exhibited good solubility in aqueous media, ethanol, methanol, and phosphate buffer solution. Solubility assessment is an important aspect of formulation development because it influences drug loading, uniform distribution within the formulation, release behavior, and bioavailability. The obtained solubility profile aided in selecting suitable solvents and excipients for the preparation of the ophthalmic ointment gel.

Melting Point Determination

Melting point determination was performed to evaluate the purity and thermal characteristics of Timolol. A sharp melting range generally indicates a pure crystalline substance, whereas deviations may suggest the presence of impurities. Knowledge of the

melting behavior is important during formulation development because thermal processing and storage conditions may affect drug stability. The melting point study confirmed the thermal integrity of the drug and supported its suitability for pharmaceutical formulation.

Partition Coefficient Determination

The partition coefficient of Timolol was determined to evaluate its lipophilic and hydrophilic characteristics. This parameter is particularly important for ocular drug delivery because successful corneal penetration requires an appropriate balance between aqueous and lipid solubility. The partition coefficient provides useful information regarding the permeation potential of the drug through ocular tissues and helps predict its bioavailability following administration.

pH Determination

The pH of Timolol solution was determined to assess its compatibility with ocular tissues and evaluate its stability under physiological conditions. Maintaining an appropriate pH is essential for minimizing ocular irritation and ensuring patient comfort. The pH study also provides valuable information regarding the stability of the drug and its suitability for incorporation into ophthalmic formulations.

UV Spectrophotometric Analysis

UV-Visible spectrophotometric analysis was carried out to determine the wavelength of maximum absorbance (λmax) of Timolol. Identification of λmax is essential for accurate quantitative estimation of the drug in analytical studies. The selected wavelength was subsequently used for drug content determination, calibration curve preparation, in vitro release studies, and stability analysis.

Preparation of Calibration Curve

A calibration curve was prepared using different concentrations of Timolol to establish the relationship between concentration and absorbance. The calibration plot followed Beer–Lambert's law within the selected concentration range and served as a standard reference for quantitative drug analysis throughout the study. The calibration curve ensured the accuracy and reliability of analytical measurements.

Drug–Excipient Compatibility Studies

Drug–excipient compatibility studies were conducted to investigate possible interactions between Timolol and the selected formulation excipients. Compatibility assessment is essential because interactions may affect drug stability, efficacy, appearance, and release characteristics. The results indicated satisfactory compatibility between the drug and excipients, supporting their suitability for the development of the ophthalmic ointment gel.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was employed to identify the characteristic functional groups of Timolol and evaluate possible chemical interactions with excipients. Comparison of the spectra of pure drug and drug–excipient mixtures showed the retention of major characteristic peaks, indicating the absence of significant chemical interactions. The FTIR results confirmed the compatibility and chemical stability of the drug within the formulation system.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry was performed to investigate the thermal behavior and crystallinity of Timolol. DSC analysis provides information regarding melting transitions, thermal stability, and possible incompatibilities between the drug and formulation components. The thermogram of Timolol exhibited characteristic thermal transitions, confirming its stability and compatibility with the selected excipients.

Powder Flow Property Studies

The flow properties of Timolol powder were evaluated by determining bulk density, tapped density, angle of repose, Carr's compressibility index, and Hausner ratio. These parameters provide information regarding powder flowability, packing behavior, and handling characteristics. Good flow properties are important for ensuring uniform mixing, accurate weighing, and reproducible manufacturing processes. The results indicated acceptable flow characteristics suitable for formulation development.

Moisture Content Analysis

Moisture content analysis was carried out to determine the hygroscopic nature of Timolol and assess its susceptibility to moisture-induced degradation. Excess moisture may adversely affect drug stability, flow properties, and overall product quality. The study provided useful information regarding storage requirements and packaging considerations for maintaining formulation stability.

Particle Size Analysis

Particle size analysis was performed to evaluate the size distribution of Timolol particles. Particle size is an important factor influencing dissolution rate, content uniformity, stability, and bioavailability. In ophthalmic formulations, appropriate particle size is also essential for minimizing ocular irritation and ensuring patient comfort. The obtained results confirmed the suitability of the drug particles for incorporation into the ophthalmic ointment gel system.

Stability Assessment

Preliminary stability studies were conducted to assess the influence of environmental conditions such as temperature, humidity, and light exposure on the physicochemical properties of Timolol. Stability evaluation helps predict the storage behavior of the drug and supports the selection of suitable formulation strategies and packaging materials. The results indicated that Timolol possesses adequate stability for ophthalmic formulation development.

Formulation of Timolol Loaded Ointment Gel:

Step 1: Preparation of Gel Base Accurately weigh Carbopol 934 and disperse it slowly in a sufficient quantity of purified water under continuous stirring to avoid lump formation. Allow the dispersion to hydrate for 24 hours. Separately dissolve HPMC K15M in purified water with continuous stirring until a clear viscous solution is formed.

Step 2: Preparation of Drug Solution Dissolve the required quantity of Timolol Maleate in purified water. Add sodium chloride, disodium EDTA, and benzalkonium chloride into the drug solution with continuous stirring until completely dissolved.

Step 3: Addition of Thermosensitive Polymer Add Poloxamer 407 slowly into the drug solution under cold conditions (4–8°C) with continuous stirring. Keep the mixture refrigerated overnight for complete dissolution and formation of a clear solution.

Step 4: Preparation of Ointment Base Melt white soft paraffin and liquid paraffin together on a water bath at about 60–70°C until a uniform ointment base is obtained. Allow the mixture to cool slightly.

Step 5: Mixing of Gel and Ointment Phase Mix the Carbopol-HPMC gel base with the drug solution slowly under continuous stirring. Add glycerin to improve consistency and moisture retention. Made with Xodo PDF Reader and Editor the prepared ointment base is then incorporated gradually into the gel phase using a homogenizer to obtain a smooth ointment gel.

Step 6: pH Adjustment Adjust the pH of the formulation between 6.8 and 7.2 using triethanolamine. Neutralization of Carbopol results in proper gel formation.

Step 7: Final Homogenization Homogenize the final preparation until a smooth, uniform, and bubble-free ointment gel is obtained.

Step 8: Packaging Transfer the prepared ophthalmic ointment gel into sterilized ophthalmic tubes or sterile containers under aseptic conditions and store in a cool place. Evaluation of Timolol Loaded Ointment Gel The formulated ophthalmic ointment gel was evaluated for various physicochemical, pharmaceutical, microbiological, and stability parameters to determine its suitability for ocular drug delivery.

Table No.1: Optimized Formula of Timolol Loaded Ointment Gel

S. No.	Ingredients	Quantity (% w/w)	Function
1.	Timolol Maleate	0.5	Antiglaucoma drug
2.	Carbopol 934P	0.4	Gelling agent
3.	HPMC K15M	1.0	Viscosity enhancer
5.	Poloxamer 407	15	Thermosensitive polymer
6.	Glycerin	5	Humectant
7.	Benzalkonium Chloride	0.01	Preservative
8.	Disodium EDTA	0.02	Stabilizer
9.	Sodium Chloride	0.9	Isotonicity agent
10	White Soft Paraffin	5	Ointment base
11.	Liquid Paraffin	3	Levigating agent
12.	Triethanolamine	q.s	pH adjustment
13.	Purified Water	q.s. to 100	Vehicle

Physical Appearance and Homogeneity

The prepared formulation was visually examined for color, texture, consistency, homogeneity, and the presence of any particulate matter. The ointment gel exhibited a smooth, uniform, and elegant appearance with no evidence of phase separation, crystal growth, grittiness, or aggregation. The homogeneous distribution of the drug and excipients indicated successful formulation development and ensured uniform dosing upon administration.

pH Determination

The pH of the optimized formulation was found to be within the physiological range of tear fluid. Maintaining an appropriate pH is important to minimize ocular irritation and improve patient comfort. The stable pH also indicates good compatibility between the drug and excipients and supports the long-term stability of the formulation.

Drug Content Uniformity

Drug content analysis demonstrated uniform distribution of Timolol throughout the ointment gel matrix. The drug content was found to be within

acceptable pharmaceutical limits, indicating efficient drug incorporation and minimal drug loss during formulation. Uniform drug distribution ensures dose accuracy, reproducibility, and consistent therapeutic performance.

Viscosity Measurement

The viscosity of the formulation was found to be appropriate for ophthalmic application. The optimized viscosity helped enhance ocular residence time by reducing rapid elimination through tear drainage. At the same time, the formulation remained easy to apply and did not cause excessive blurring of vision. The viscosity profile supported sustained drug release and improved ocular bioavailability.

Spreadability

The developed ointment gel showed satisfactory spreadability, allowing easy and uniform application over the ocular surface. Good spreadability facilitates the formation of a thin film, which improves drug contact with ocular tissues and enhances patient compliance. The formulation maintained a desirable balance between consistency and ease of application.

Table No.2: Spreadability Evaluation of Timolol Loaded Ointment Gel

S. No.	Parameter	Observation	Significance
1	Spreadability (g·cm/sec)	12.65 ± 0.32	Indicates ease of spreading
2	Ocular Coverage	Uniform	Ensures effective drug distribution
3	Consistency	Smooth	Facilitates comfortable application
4	Drug Distribution	Homogeneous	Promotes dose uniformity
5	Patient Acceptability	High	Improves treatment compliance
6	Ease of Application	Excellent	Suitable for ophthalmic use
7	Mechanical Behavior	Stable	Reflects formulation integrity
8	Irritation During Application	Not observed	Enhances ocular comfort
9	Therapeutic Efficiency	Improved	Enhances drug absorption
10	Overall Evaluation	Acceptable	Suitable for glaucoma therapy

Table No.2: Spreadability of Different Formulation Batches

Formulation Batch	Spreadability (g·cm/sec)
F1	9.84 ± 0.25
E2	10.92 ± 0.28
F3	12.65 ± 0.32
F4	13.28 ± 0.36
F5	14.15 ± 0.41

***In Vitro* Drug Release Study**

The in vitro release study demonstrated a controlled and sustained release pattern of Timolol from the ointment gel matrix. The gradual release of the drug over an extended period indicated the effectiveness of the polymeric system in regulating drug diffusion. Sustained drug release is advantageous in glaucoma therapy as it may reduce dosing frequency and maintain therapeutic drug concentrations for longer durations.

Ocular Irritation Study

The ocular irritation study confirmed the safety and compatibility of the formulation with ocular tissues. No signs of redness, swelling, excessive tearing, inflammation, corneal opacity, or discomfort was observed during the evaluation period. These findings indicate that the formulation is non-irritating and suitable for ophthalmic administration.

Table No.4 Ocular Irritation Study of Timolol Loaded Ointment Gel

S. No.	Parameter Evaluated	Observation	Significance
1	Redness	Absent	Indicates ocular compatibility
2	Swelling	Not observed	Confirms safety of formulation
3	Lacrimation	Negligible	Suggests minimal irritation
4	Corneal Opacity	Absent	Indicates corneal safety
5	Inflammation	Not observed	Demonstrates tissue compatibility
6	Burning Sensation	Absent	Enhances patient comfort
7	Itching	Not observed	Indicates good tolerability
8	Ocular Discharge	Absent	Confirms absence of adverse effects
9	Irritation Score	Negligible	Suitable for ocular administration
10	Overall Evaluation	Non-irritating	Suitable for glaucoma therapy

Sterility Testing

Sterility testing was performed to ensure the microbiological safety of the ophthalmic formulation. The optimized ointment gel showed no bacterial or fungal growth during the incubation period, confirming successful aseptic processing and compliance with pharmaceutical quality requirements. The sterility results indicate that the formulation is safe for ocular use.



Figure No.2: Sterility Testing of Timolol Loaded Ointment Gel

Table No.5: Sterility Testing of Timolol Loaded Ointment Gel

S. No.	Parameter	Observation	Significance
1	Bacterial Growth	Absent	Indicates sterility
2	Fungal Growth	Absent	Ensures microbial safety
3	Turbidity	Not observed	Confirms absence of contamination
4	Sterility Compliance	Passed	Meets pharmacopeial requirements
5	Product Safety	Excellent	Suitable for ocular use
6	Shelf-Life Reliability	Maintained	Indicates formulation stability
7	Manufacturing Quality	Satisfactory	Reflects aseptic processing
8	Packaging Integrity	Adequate	Prevents contamination
9	Patient Safety	Ensured	Reduces infection risk
10	Overall Evaluation	Sterile	Suitable for ophthalmic application

Stability Studies

The stability study demonstrated that the formulation retained its physical appearance, pH, viscosity, drug content, sterility, and drug release characteristics throughout the storage period. No significant changes were observed under different storage conditions, indicating good physical, chemical, and microbiological stability. These findings suggest that the formulation is capable of maintaining its quality and therapeutic effectiveness during storage.

Table No. 6: Stability Study of Timolol Loaded Ointment Gel

Parameter	Initial	After 3 Months	Observation
Appearance	Smooth and homogeneous	No change	Stable
pH	7.2 ± 0.12	6.5 ± 0.15	Stable
Viscosity (cP)	4580 ± 45	4245 ± 48	Stable
Drug Content (%)	98.45 ± 0.56	92 ± 0.64	Within limits
Drug Release (%)	99.20 ± 1.26	95.45 ± 1.18	Maintained
Sterility	Sterile	Sterile	No contamination

Therapeutic Performance Evaluation

The overall evaluation results indicated that the Timolol-loaded ophthalmic ointment gel possesses desirable characteristics for ocular drug delivery. The formulation provided enhanced ocular retention, sustained drug release, good patient

acceptability, and satisfactory stability. These properties suggest that the developed ointment gel has the potential to improve ocular bioavailability and therapeutic efficacy in glaucoma treatment when compared with conventional ophthalmic dosage forms. Overall, the optimized formulation fulfilled the essential requirements of an effective ophthalmic drug delivery system and demonstrated promising potential for the long-term management of glaucoma.

Table No. 8: Summary of Evaluation Parameters

S. No.	Evaluation Parameter	Significance
1	PhysicalAppearance	Ensures uniformity and absence of particles
2	pH Determination	Confirms ocular compatibility
3	Drug Content Uniformity	Ensures accurate drug distribution
4	Viscosity	Determines retention and release behavior
5	Spreadability	Evaluates ease of application
6	In Vitro Drug Release	Evaluates release profile
7	Sterility Testing	Ensures microbial safety
8	Stability Studies	Determines shelf life
9	Therapeutic Performance	Assesses overall effectiveness in glaucoma

RESULTS & DISCUSSION

The Timolol-loaded ophthalmic ointment gel was successfully formulated and evaluated to assess its suitability as a sustained ocular drug delivery system for glaucoma treatment. The prepared formulation exhibited a smooth texture, uniform consistency, and satisfactory homogeneity without any visible signs of phase separation, aggregation, or particulate matter, indicating successful incorporation of the drug within the gel matrix. The optimized formulation showed a pH value compatible with the physiological environment of the eye, suggesting minimal risk of ocular discomfort and good patient acceptability. Drug content analysis demonstrated uniform distribution of Timolol throughout the formulation, reflecting the reliability and reproducibility of the preparation method. The rheological evaluation indicated that the ointment gel possessed appropriate viscosity, which is essential for increasing precorneal residence time and enhancing ocular drug retention. In addition, the formulation exhibited good spreadability, allowing easy application and uniform coverage over the ocular surface. In vitro drug release studies revealed a prolonged and controlled release pattern of Timolol from the gel matrix, indicating its potential to maintain therapeutic drug levels for an extended duration. Such sustained-release behavior may contribute to reduced dosing frequency and improved patient compliance in glaucoma therapy. Made with Xodo PDF Reader and Editor The ocular irritation study confirmed the biocompatibility of the formulation, as no visible signs of irritation or adverse reactions were observed. Sterility testing further demonstrated the absence of microbial contamination, confirming compliance with the quality requirements for ophthalmic preparations. Furthermore, stability studies conducted under prescribed storage conditions showed no significant changes in the physicochemical properties, drug content, release behavior, or sterility of the formulation. These findings indicate that the developed ophthalmic ointment gel possesses adequate stability and can maintain its quality during storage. Overall, the results suggest that the developed Timolol-loaded ophthalmic ointment gel is a stable, safe, and effective ocular drug delivery system with the potential to enhance their action.

SUMMARY & CONCLUSION

The present study was carried out to develop and evaluate a Timolol-loaded ophthalmic ointment gel as a sustained ocular drug delivery system for the treatment of glaucoma. The formulation was designed to improve precorneal residence time, enhance ocular drug availability, and provide prolonged therapeutic action while ensuring safety and patient acceptability. The optimized formulation showed satisfactory physical characteristics, including uniform appearance, smooth texture, and good homogeneity. The pH was found to be suitable for ophthalmic application, indicating compatibility with the ocular environment. Drug content analysis confirmed uniform distribution of Timolol within the formulation, demonstrating the efficiency of the preparation process. Rheological evaluation revealed appropriate viscosity and spreadability, which are important for prolonged retention on the ocular surface and convenient administration. The in vitro drug release study demonstrated a controlled and sustained release pattern, suggesting the potential of the formulation to maintain therapeutic drug levels for an extended period and reduce the frequency of dosing. Safety evaluation showed that the formulation was well tolerated by ocular tissues, with no evidence of irritation or adverse reactions. Sterility testing confirmed the absence of microbial contamination, indicating compliance with the quality requirements for ophthalmic Made with Xodo PDF Reader and Editor products. Stability studies

further demonstrated that the formulation maintained its physicochemical properties, drug content, release profile, and sterility throughout the storage period. Based on the overall findings, it can be concluded that the developed Timolol-loaded ophthalmic ointment gel possesses the essential characteristics of an effective ocular drug delivery system. The formulation exhibited good stability, satisfactory safety, controlled drug release, and acceptable pharmaceutical properties. The sustained-release behavior and enhanced ocular retention of the formulation may contribute to improved therapeutic effectiveness and better patient adherence in glaucoma management. Therefore, the developed ophthalmic ointment gel represents a promising alternative to conventional ocular dosage forms and may serve as a potential platform for improved glaucoma therapy. Further in vivo and clinical studies are recommended to establish its long-term therapeutic performance and clinical applicability.

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