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Design, Development and Process Validation of Antibiotic-Loaded Ocular Inserts

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ABSTRACT

The present study aimed to formulate and evaluate Levofloxacin-loaded ocular inserts for sustained ocular drug delivery using the solvent casting method. Conventional ophthalmic formulations, such as eye drops, exhibit poor bioavailability due to rapid precorneal elimination and drainage from the ocular cavity, resulting in reduced therapeutic efficacy and the need for frequent administration. To overcome these limitations, ocular inserts were developed using gelatin, chitosan, and HPMC K4M as film-forming polymers, with PEG 400 as a plasticizer and benzalkonium chloride as a preservative. Preformulation studies, including melting point determination, Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC), were performed to assess drug purity and compatibility with the selected excipients. The prepared ocular inserts were evaluated for physical appearance, thickness, weight variation, folding endurance, tensile strength, drug content uniformity, and in-vitro drug diffusion. All formulations exhibited satisfactory physicochemical characteristics, acceptable mechanical strength, and uniform drug distribution. In-vitro diffusion studies demonstrated sustained drug release for up to 10 hours. Among all formulations, F3 exhibited an optimal drug release profile along with satisfactory mechanical properties and stability. Drug release kinetic analysis indicated that the release profile predominantly followed zero-order kinetics and the Korsmeyer–Peppas model, suggesting a non-Fickian diffusion mechanism. Stability studies further confirmed that the optimized formulation remained stable without significant changes in physical appearance or drug content. The results suggest that Levofloxacin-loaded ocular inserts may serve as a promising sustained-release ocular drug delivery system by improving precorneal residence time, potentially enhancing ocular bioavailability, and improving patient compliance compared with conventional ophthalmic dosage forms.

***Keywords*:** *Levofloxacin, Ocular inserts, Sustained drug delivery, Solvent casting method, HPMC K4M, Chitosan, Gelatin, In-vitro diffusion, Drug release kinetics, Ophthalmic drug delivery.*

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INTRODUCTION

Ocular drug delivery remains one of the major challenges in pharmaceutical research. One of the primary difficulties in administering drugs to the eye is maintaining an adequate drug concentration at the target site for a prolonged period. The complex anatomical structure, physiological functions, and biochemical composition of the eye act as protective barriers against the entry of foreign substances. These natural defense mechanisms make it challenging to deliver therapeutic agents effectively to ocular tissues without causing tissue irritation or damage. With the advancement of sensitive diagnostic techniques and therapeutic approaches, there is an increasing demand for efficient and innovative ocular drug delivery systems [1]. The therapeutic efficacy of drugs used in the treatment of ocular disorders can be improved by prolonging their residence time on the corneal surface. Various conventional formulations incorporate viscosity-enhancing agents or water-insoluble ointment bases to increase drug contact time with the ocular surface. However, these approaches provide only limited improvement over conventional ophthalmic solutions and are often unable to maintain a consistent drug concentration at the target site. Consequently, frequent administration is required to achieve the desired therapeutic effect, which may adversely affect patient compliance [2].

Ocular Inserts as Sustained-Release Ocular Drug Delivery Systems

Ocular inserts are specialized ophthalmic dosage forms designed to prolong drug residence time in the eye and provide controlled and sustained drug release. They are generally placed in the conjunctival sac, where they release the incorporated drug over an extended period. These systems offer several advantages over conventional ophthalmic preparations [3].

The major advantages of ocular inserts include:

Increased ocular residence time: Prolongs drug contact with ocular tissues, thereby extending therapeutic activity and potentially improving ocular bioavailability.

Sustained drug release: Provides controlled and prolonged drug release at a predetermined rate.

Accurate dosing: Ensures precise drug administration and minimizes variations associated with conventional eye drops.

Reduced systemic absorption: Minimizes drug loss through nasolacrimal drainage and may reduce systemic exposure.

Improved patient compliance: Reduces the frequency of administration and minimizes fluctuations in drug concentration.

Targeted drug delivery: Offers the potential to deliver drugs to internal ocular tissues through alternative routes, including conjunctival and scleral pathways.

Improved stability: Certain ocular insert formulations may provide better shelf stability than conventional aqueous ophthalmic solutions.

Reduced preservative-related reactions: Preservative-free ocular inserts can minimize the risk of irritation and hypersensitivity reactions.

CLASSIFICATION OF OCULAR INSERTS

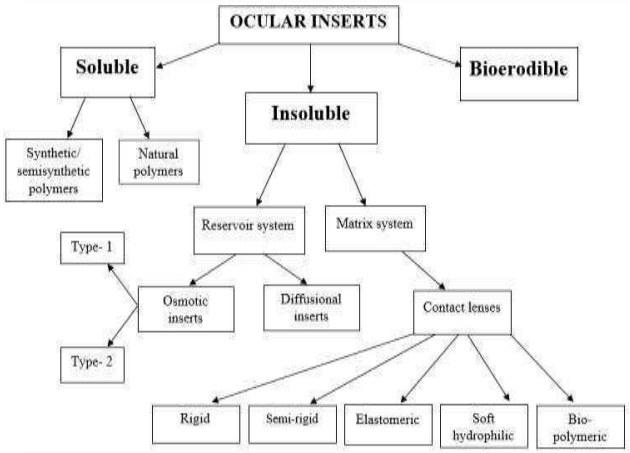


Figure 01: Classification of Ocular Inserts

ANATOMY AND PHYSIOLOGY OF THE EYE [4]

The human eye is a highly specialized sensory organ responsible for vision. It is a nearly spherical structure situated within the bony orbital cavity and is composed of several tissues that focus, transmit, and detect light. Anatomically, the wall of the eyeball consists of three distinct layers or coats:

Outer fibrous layer (Sclera and Cornea)

Middle vascular layer (Choroid, Ciliary Body and Iris)

Inner nervous layer (Retina)

1. Sclera

The sclera, commonly known as the white of the eye, is the tough, opaque outer covering of the eyeball. It provides structural support, maintains the shape of the eye, and protects the internal ocular structures. Six extraocular muscles are attached to the sclera and are responsible for controlling eye movements. The optic nerve exits through the posterior region of the sclera. In children, the sclera is relatively thin and may appear bluish due to the visibility of underlying tissues. With advancing age, it may develop a yellowish appearance.

2. Choroid Layer

The choroid is the highly vascular, pigmented middle layer of the eye, located between the sclera and retina. It contains numerous blood vessels that supply oxygen and nutrients to the outer layers of the retina. Anteriorly, the choroid continues into the ciliary body, which plays an important role in the accommodation of the lens and production of aqueous humour. The iris, which forms the coloured portion of the eye, regulates the amount of light entering through the pupil.

The crystalline lens is a transparent, biconvex structure situated behind the iris and pupil. The space between the cornea and iris is known as the anterior chamber, while the space between the iris and lens is known as the posterior chamber. Both chambers contain aqueous humour, which helps maintain intraocular pressure and provides nutrients to avascular ocular tissues. The large posterior cavity behind the lens is filled with a transparent, gel-like substance called vitreous humour.

3. Retina

The retina is the innermost nervous layer of the eye and contains specialized light-sensitive cells known as photoreceptors. These photoreceptors are of two types: rods and cones. Rods are responsible for vision under dim-light conditions, whereas cones are responsible for colour vision and visual acuity under bright-light conditions. The retina converts incoming light into electrical nerve impulses, which are transmitted to the brain through the optic nerve, ultimately enabling visual perception.

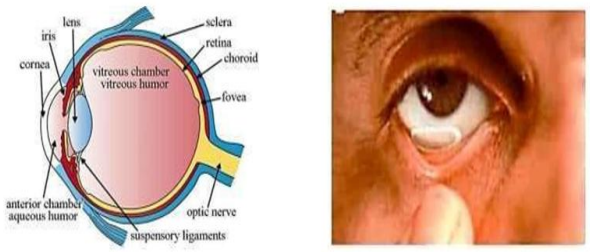


Figure 02: Anatomy and Physiology of the Eye

FORMULATION METHOD FOR OCULAR INSERTS

1. Solvent Casting Method [5]

The solvent casting method is widely used for the preparation of polymeric ocular inserts. Initially, the required quantity of polymer is accurately weighed and dissolved or dispersed in a suitable solvent with continuous stirring until a homogeneous polymeric solution is obtained. A suitable plasticizer is then added with continuous stirring to improve the flexibility and mechanical strength of the prepared films. The accurately weighed drug is incorporated into the polymeric solution and mixed thoroughly to obtain a uniform drug dispersion.

The resulting solution is poured into a suitable Petri dish or casting mould and allowed to dry under controlled conditions at room temperature. After complete solvent evaporation, the dried films are carefully removed from the mould and cut into the required dimensions using a suitable cutting device. The prepared ocular inserts are stored in airtight containers under appropriate conditions until further evaluation.

PROCESS VALIDATION [6]

Pharmaceutical process validation is an essential component of current Good Manufacturing Practices (cGMP). It provides documented evidence that a manufacturing process consistently produces products meeting predetermined quality standards and specifications. Process validation plays an important role in ensuring product quality, safety, efficacy, and manufacturing consistency.

The primary objective of process validation is to establish documented evidence demonstrating that a specific manufacturing process is capable of consistently producing products that meet predetermined specifications and quality attributes.

Process Validation[7]

Process validation is defined as the systematic collection and evaluation of documented evidence to establish a high degree of assurance that a manufacturing process consistently produces products meeting predefined quality requirements.

Objectives of Process Validation

1. To minimize batch-to-batch variability.
2. To ensure product quality, safety, and reliability.
3. To minimize manufacturing defects and associated costs.
4. To ensure consistency and reproducibility of the manufacturing process.
5. To establish the stability and robustness of the production process.

Advantages of Process Validation [8]

1. Ensures consistent product quality and reproducibility.
2. Facilitates monitoring and control of critical manufacturing parameters.
3. Reduces the risk of manufacturing errors and product defects.
4. Supports statistical evaluation of process and product data.
5. Improves confidence in manufacturing consistency and overall product quality.

MATERIALS AND METHODS

Materials

Levofloxacin was procured from Yarrow Chem, Mumbai. HPMC K4M, gelatin, chitosan, benzalkonium chloride, PEG 400, and other analytical-grade chemicals were obtained from S.D. Fine-Chem Limited, Mumbai. All chemicals and reagents used in the study were of analytical grade.

PREFORMULATION STUDIES [9]

Preformulation studies represent an essential initial stage in pharmaceutical formulation development. These studies involve the systematic evaluation of the physicochemical and biopharmaceutical properties of the drug substance, both individually and in combination with selected excipients.

The major parameters investigated include physical appearance, colour, melting point, solubility, micromeritic properties, drug–excipient compatibility, and other relevant analytical characteristics. The results obtained from these investigations provide essential information for selecting suitable excipients and developing an effective and stable formulation.

Determination of Melting Point [10]

The melting point of Levofloxacin was determined using the capillary tube method. A small quantity of the drug was introduced into a capillary tube sealed at one end. The capillary tube was placed in a digital melting point apparatus, and the temperature at which the drug melted was recorded. The experiment was performed in triplicate, and the mean melting point was calculated.

Drug–Excipient Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR) [11]

Drug–excipient compatibility was investigated using Fourier Transform Infrared (FTIR) spectroscopy (Bruker). FTIR spectra were recorded for the pure drug, individual polymers, physical mixtures of the drug and polymers in a 1:1 ratio, and the selected formulations using the potassium bromide (KBr) pellet method.

Each sample was thoroughly mixed with KBr and compressed into a transparent pellet. The prepared pellets were scanned over the spectral range of 4000–400 cm^{-1}. The characteristic absorption bands were evaluated to identify possible interactions between the drug and selected excipients.

Differential Scanning Calorimetry (DSC) [12].

Differential Scanning Calorimetry (DSC) analysis was performed on pure Levofloxacin, physical mixtures, and selected medicated films. Approximately 3–5 mg of each sample was accurately weighed and sealed in aluminium pans.

The samples were heated at a constant rate of 10°C/min over a temperature range of 25–200°C using a DSC-60 instrument (Shimadzu, Japan). Thermograms were recorded using the associated Shimadzu software and thermal analysis system. The instrument was

calibrated for temperature and enthalpy using indium as the reference standard. Nitrogen gas was used as the purge gas at a flow rate of 40 mL/min.

ANALYTICAL METHODS

1. Preparation of 0.2 M Sodium Hydroxide (NaOH)

Accurately weigh 8 g of sodium hydroxide and dissolve it in distilled water. Transfer the solution into a 1000 mL volumetric flask and make up the volume to 1000 mL with distilled water.

2. Preparation of 0.2 M Potassium Dihydrogen Phosphate (KH_2PO_4)

Accurately weigh 27.218 g of potassium dihydrogen phosphate and dissolve it in distilled water. Transfer the solution into a 1000 mL volumetric flask and make up the volume to 1000 mL with distilled water.

3. Preparation of Phosphate Buffer (pH 7.4)

Transfer 50 mL of 0.2 M potassium dihydrogen phosphate solution into a 200 mL volumetric flask. Add 22.4 mL of 0.2 M sodium hydroxide solution and make up the volume to 200 mL with distilled water. Verify the final pH using a calibrated pH meter.

Preparation of Standard Drug Solution

Accurately weigh 100 mg of Levofloxacin and transfer it into a 100 mL volumetric flask. Dissolve the drug in phosphate buffer (pH 7.4) with sonication, and make up the volume to 100 mL using the same buffer to obtain the stock solution.

Further dilutions were prepared using phosphate buffer (pH 7.4) to obtain the required working concentrations for analytical studies.

Determination of Absorption Maximum (λmax)[13]

The standard drug solution was appropriately diluted with phosphate buffer (pH 7.4) to obtain concentrations within the required analytical range. The diluted solutions were scanned using a UV–Visible spectrophotometer over a wavelength range of 200–400 nm.

The wavelength of maximum absorbance (λmax) of Levofloxacin was determined from the absorption spectrum and found to be approximately 287 nm in phosphate buffer (pH 7.4).

FORMULATION OF LEVOFLOXACIN-LOADED OCULAR INSERTS

Levofloxacin-loaded ocular inserts were prepared using gelatin, chitosan, and HPMC K4M as film-forming polymers by the solvent casting method.

The required quantities of the selected polymers were accurately weighed and dispersed in a suitable volume of distilled water. The polymer solutions were allowed to hydrate and swell for approximately 15–20 minutes with continuous stirring until a uniform solution was obtained. In the case of chitosan, the polymer was dissolved separately in a small quantity of 1% v/v acetic acid solution to facilitate solubilization.

Separately, the required quantity of Levofloxacin was dissolved in a suitable volume of distilled water. PEG 400 was added as a plasticizer and mixed thoroughly. The drug solution was then gradually incorporated into the polymer solution with continuous stirring using a magnetic stirrer to obtain a homogeneous casting solution.

The resulting solution was degassed under vacuum to remove entrapped air bubbles and poured into a glass mould measuring 4 × 4 cm, placed on a level surface. The solution was allowed to dry at room temperature for approximately 24 hours to facilitate film formation and solvent evaporation.

After complete drying, the films were carefully removed from the mould and cut into suitable dimensions for ocular application. The prepared ocular inserts were wrapped in butter paper and stored in a desiccator until further evaluation.

FORMULATION TABLE

The formulation composition is presented below, retaining your original experimental quantities.

Table 01: Formulation Composition of Levofloxacin-Loaded Ocular Inserts

Ingredients (mg, unless specified)	F1	F2	F3	F4	F5	F6
Levofloxacin	120	120	120	120	120	120
Gelatin	30	40	50	–	–	–
HPMC K4M	50	50	50	50	50	50
Chitosan	–	–	–	30	40	50
Benzalkonium chloride	0.03	0.03	0.03	0.03	0.03	0.03
PEG 400	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Phosphate buffer (pH 7.4) (mL)	25	25	25	25	25	25

FORMULATION OF OCULAR INSERTS

Levofloxacin-loaded ocular inserts were prepared using gelatin and chitosan at different concentrations (30, 40, and 50 mg) in combination with a constant concentration of HPMC K4M (50 mg) by the solvent casting method.

The prepared ocular inserts were evaluated for their physical appearance, flexibility, mechanical strength, and drug release characteristics. Formulations containing lower polymer concentrations exhibited fragile films that were difficult to handle and remove from the mould. Increasing the polymer concentration improved the mechanical strength of the inserts but also influenced film thickness and drug release.

Based on these observations, polymer concentrations ranging from 30 to 50 mg were selected for further investigation. PEG 400 was incorporated as a plasticizer to improve flexibility and mechanical strength, while benzalkonium chloride was included as a preservative. Phosphate buffer (pH 7.4) was used as the casting medium.

EVALUATION OF FORMULATED LEVOFLOXACIN-LOADED OCULAR INSERTS

The prepared Levofloxacin-loaded ocular inserts were evaluated for various physicochemical and mechanical parameters, including physical appearance, thickness, weight variation, surface pH, folding endurance, tensile strength, moisture absorption, moisture loss, drug content uniformity, and in-vitro drug release studies.

1. Physical Appearance [14]

The prepared ocular inserts were visually examined for physical appearance, including colour, shape, surface smoothness, transparency, and the presence of cracks or air bubbles.

2. Thickness [15]

The thickness of the ocular inserts was measured at three different locations using a digital vernier caliper. Ten inserts from each formulation were evaluated, and the mean thickness and standard deviation were calculated to assess thickness uniformity.

3. Weight Variation [16]

Weight variation was determined by randomly selecting five ocular inserts from each formulation. Each insert was individually weighed using an electronic analytical balance. The mean weight and standard deviation were calculated to assess weight uniformity.

4. Surface pH

The prepared ocular inserts were placed in 1 mL of distilled water and allowed to equilibrate for 15 minutes. The surface pH was measured using a calibrated pH meter. The experiment was performed using three randomly selected inserts from each formulation, and the mean pH and standard deviation were calculated.

5. Folding Endurance [17]

Folding endurance was evaluated to determine the flexibility and mechanical strength of the ocular inserts. Each insert was repeatedly folded at the same position until visible cracks or breakage occurred. The total number of folds required to produce breakage was recorded as the folding endurance value.

6. Tensile Strength [18]

The tensile strength of the prepared ocular inserts was evaluated using a universal testing machine. Film samples measuring 4 × 1 cm^2 were individually clamped between the fixed and movable grips of the instrument. A gradually increasing force was applied until the film ruptured. The force required to break the film was recorded, and tensile strength was calculated using the appropriate formula.

7. Percentage Moisture Absorption

The percentage moisture absorption test was performed to evaluate the moisture uptake capacity and physical stability of the ocular inserts.

The prepared inserts were initially weighed and placed in a desiccator maintained at the specified relative humidity using a saturated salt solution. After three days, the inserts were removed and reweighed. The percentage moisture absorption was calculated using the following formula:

% Moisture Absorption=Wf−WiWi×100%Moisture Absorption=WiWf−Wi×100

Where:

WiWi = Initial weight of the insert.

WfWf = Final weight of the insert.

8. Percentage Moisture Loss [19]

The percentage moisture loss test was performed to determine the moisture loss of the prepared ocular inserts under dry conditions.

Initially, the inserts were weighed and placed in a desiccator containing anhydrous calcium chloride. After three days, the inserts were removed and reweighed. The percentage moisture loss was calculated using the following formula:

% Moisture Loss=Wi−WfWi×100%Moisture Loss=WiWi−Wf×100

Where:

WiWi = Initial weight of the insert.

WfWf = Final weight of the insert.

9. Drug Content Uniformity

The drug content of the prepared ocular inserts was determined using the UV–Visible spectrophotometric method. A film sample measuring 2 × 2 cm^2 was accurately weighed and dissolved in 100 mL of phosphate buffer (pH 7.4). The resulting solution was filtered, and its absorbance was measured at the predetermined wavelength using a UV–Visible spectrophotometer. The drug concentration was calculated using the previously established calibration curve of Levofloxacin. All measurements were performed in triplicate, and the results were expressed as mean percentage drug content ± standard deviation.

RESULTS AND DISCUSSION

The present study was undertaken to formulate and evaluate Levofloxacin-loaded ocular inserts using different polymer combinations by the solvent casting method. The primary objective was to develop a sustained-release ocular drug delivery system capable of prolonging drug residence time and providing controlled drug release compared with conventional ophthalmic preparations.

The prepared formulations were evaluated for their physicochemical characteristics, mechanical properties, drug content uniformity, and in-vitro drug release behaviour.

Preformulation Studies

Determination of Melting Point

The melting point of Levofloxacin was determined using the capillary tube method with a digital melting point apparatus. The experiment was performed in triplicate, and the mean melting point was found to be 214°C. This value was within the reported melting point range of 213–219°C, indicating consistency with the reported literature value.

ANALYTICAL METHOD

Determination of Absorption Maximum (λmax)

The absorption spectrum of Levofloxacin was recorded using a UV–Visible spectrophotometer

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(Shimadzu UV-Vis 1700) over a wavelength range of 200–400 nm in phosphate buffer (pH 7.4).

The maximum absorption wavelength (λmax) was found to be 287 nm.

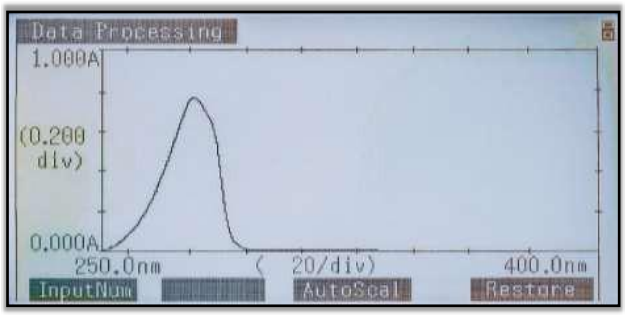


Figure 03: UV Absorption Spectrum of Levofloxacin

Calibration Curve of Levofloxacin

The calibration curve of Levofloxacin was prepared using phosphate buffer (pH 7.4) as the solvent. Different concentrations of the drug were prepared, and their absorbance values were measured at 287 nm using a UV–Visible spectrophotometer.

The calibration curve demonstrated a linear relationship between drug concentration and absorbance over the investigated concentration range. The regression coefficient (R^2) was found to be 0.9988, indicating good linearity.

Table 02: Calibration Data of Levofloxacin in Phosphate Buffer (pH 7.4)

S. No.	Concentration (µg/mL)	Absorbance (Mean ± SD)
1	0	0
2	5	0.1566 ± 0.0083
3	10	0.3062 ± 0.0178
4	15	0.4280 ± 0.0107
5	20	0.5820 ± 0.0297
6	25	0.7108 ± 0.0162

Calibration equation:

y=0.0283x+0.0102y=0.0283x+0.0102

R2=0.9988R2=0.9988

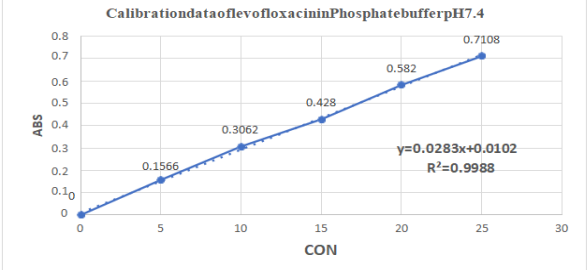


Figure 04: Calibration Curve of Levofloxacin in Phosphate Buffer (pH 7.4)

DRUG–EXCIPIENT COMPATIBILITY STUDIES

FTIR Analysis

The FTIR spectra of pure Levofloxacin and its physical mixtures with HPMC K4M, gelatin, and chitosan were recorded to investigate possible drug–excipient interactions.

The characteristic absorption bands of Levofloxacin were retained in the physical mixtures, indicating the absence of significant changes in the characteristic functional groups. These observations suggest that the selected polymers were compatible with Levofloxacin under the investigated conditions.

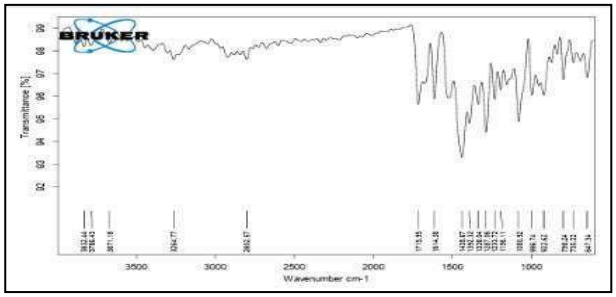


Figure 5: FTIR Spectrum of Pure Levofloxacin

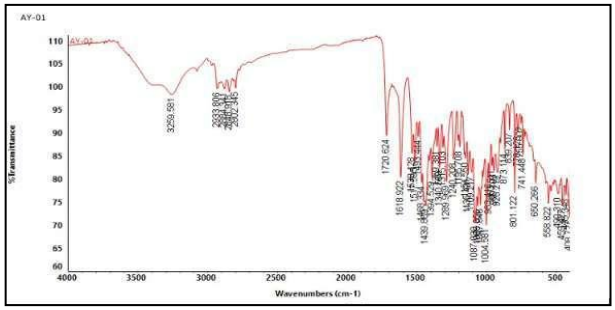


Figure 06: FTIR Spectrum of Physical Mixture of Levofloxacin, HPMC K4M, and Gelatin

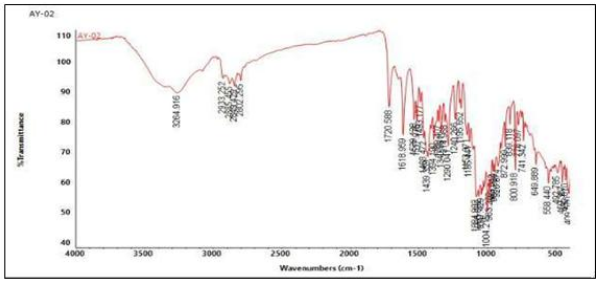


Figure 07: FTIR Spectrum of Physical Mixture of Levofloxacin, HPMC K4M, and Chitosan

DSC Analysis

Differential Scanning Calorimetry was performed to evaluate the thermal behaviour of pure Levofloxacin and its physical mixtures with selected polymers.

The thermograms showed endothermic peaks at 123.40°C for pure Levofloxacin and 237.83°C for the physical mixture. These thermal transitions were evaluated to investigate possible interactions between the drug and excipients.

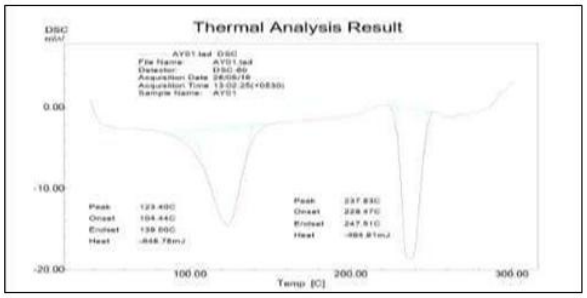


Figure 08: DSC Thermogram of Pure Levofloxacin

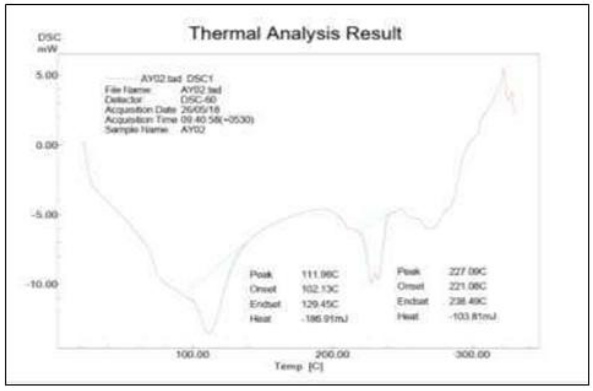


Figure 09: DSC Thermogram of Levofloxacin, HPMC K4M, and Gelatin

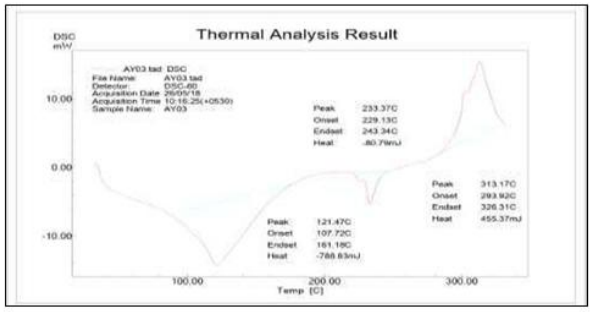


Figure 10: DSC Thermogram of Levofloxacin, HPMC K4M, and Chitosan

EVALUATION PARAMETERS

Table 03: Evaluation Parameters of Levofloxacin-Loaded Ocular Inserts

Formulation	Thickness (mm), Mean ± SD	Weight (mg), Mean ± SD	Folding endurance, Mean ± SD
F1	0.21 ± 0.01	12.5 ± 0.30	100 ± 5
F2	0.24 ± 0.01	13.8 ± 0.30	115 ± 7
F3	0.27 ± 0.02	15.2 ± 0.50	125 ± 7
F4	0.23 ± 0.01	13.2 ± 0.30	110 ± 8
F5	0.26 ± 0.02	14.6 ± 0.40	130 ± 10
F6	0.29 ± 0.02	16.0 ± 0.50	142 ± 7.5

Drug Content Uniformity

The drug content of Levofloxacin-loaded ocular inserts was determined for all formulations in triplicate, and the results were expressed as mean ± standard deviation.

The drug content of formulations F1–F3 ranged from 97.2 ± 0.8% to 99.1 ± 0.6%, whereas formulations F4–F6 showed values ranging from 96.8 ± 0.7% to 98.7 ± 0.5%. These results indicate relatively uniform drug distribution within the prepared polymeric films.

Table 04: Drug Content Uniformity of Levofloxacin-Loaded Ocular Inserts

Formulation	Drug content (%) (Mean ± SD)
F1	97.2 ± 0.8
F2	98.5 ± 0.7
F3	99.1 ± 0.6
F4	96.8 ± 0.7
F5	97.9 ± 0.6
F6	98.7 ± 0.5

Tensile Strength

Tensile strength is an important mechanical parameter used to evaluate the strength and resistance of ocular inserts against mechanical stress during handling and administration.

The tensile strength of all formulations was determined and expressed as mean ± standard deviation. Formulations F1–F3 exhibited tensile strength values ranging from 0.32 ± 0.02 to 0.48 ± 0.03 kg/mm², whereas formulations F4–F6 showed values ranging from 0.36 ± 0.02 to 0.55 ± 0.04 kg/mm².

The results demonstrated an increase in tensile strength with increasing polymer concentration. This may be attributed to improved film-forming properties and intermolecular interactions within the polymeric matrix.

Table 05: Tensile Strength of Levofloxacin-Loaded Ocular Inserts

Formulation	Tensile strength (kg/mm²) (Mean ± SD)
F1	0.32 ± 0.02
F2	0.40 ± 0.02
F3	0.48 ± 0.03

F4	0.36 ± 0.02
F5	0.45 ± 0.03
F6	0.55 ± 0.04

IN-VITRO DRUG RELEASE STUDIES

In-vitro drug release studies were performed to investigate the release behaviour of Levofloxacin from the prepared ocular inserts. The percentage cumulative drug release was determined at predetermined time intervals for all six formulations (F1–F6).

Table 06:. In-vitro Drug Release Profile of Levofloxacin-Loaded Ocular Inserts

Values retained from the supplied experimental data; release values are expressed as percentage cumulative drug release (Mean ± SD).

Time (min)	F1	F2	F3	F4	F5	F6
5	6.10 ± 0.08	5.20 ± 0.07	4.30 ± 0.06	5.80 ± 0.08	4.90 ± 0.07	4.00 ± 0.06
10	11.20 ± 0.09	9.80 ± 0.08	8.60 ± 0.07	10.90 ± 0.09	9.40 ± 0.08	8.10 ± 0.07
15	15.80 ± 0.10	14.10 ± 0.09	12.90 ± 0.08	15.60 ± 0.10	13.80 ± 0.09	12.40 ± 0.08
30	22.50 ± 0.12	20.10 ± 0.11	18.60 ± 0.10	21.90 ± 0.12	19.80 ± 0.11	17.90 ± 0.10
45	28.30 ± 0.14	25.90 ± 0.13	23.70 ± 0.12	27.80 ± 0.14	25.10 ± 0.13	22.90 ± 0.12
60	34.80 ± 0.16	31.90 ± 0.15	29.10 ± 0.14	33.90 ± 0.16	30.80 ± 0.15	28.40 ± 0.14
90	42.60 ± 0.18	39.20 ± 0.17	35.80 ± 0.16	41.50 ± 0.18	38.10 ± 0.17	34.90 ± 0.16
120	50.40 ± 0.20	46.70 ± 0.19	42.90 ± 0.18	49.20 ± 0.20	45.80 ± 0.19	41.70 ± 0.18
180	62.80 ± 0.22	58.30 ± 0.21	53.60 ± 0.20	61.90 ± 0.22	57.40 ± 0.21	52.80 ± 0.20
240	72.50 ± 0.24	68.10 ± 0.23	62.90 ± 0.22	71.80 ± 0.24	66.90 ± 0.23	61.70 ± 0.22
300	80.90 ± 0.26	76.40 ± 0.25	70.80 ± 0.24	79.80 ± 0.26	74.90 ± 0.25	69.50 ± 0.24
360	88.20 ± 0.28	83.70 ± 0.27	77.10 ± 0.26	87.10 ± 0.28	82.40 ± 0.27	75.90 ± 0.26
420	93.90 ± 0.30	90.20 ± 0.29	83.60 ± 0.28	92.80 ± 0.30	88.90 ± 0.29	82.10 ± 0.28
480	97.80 ± 0.32	95.10 ± 0.31	89.40 ± 0.30	96.90 ± 0.32	93.40 ± 0.31	87.60 ± 0.30
540	99.20 ± 0.34	98.00 ± 0.33	93.80 ± 0.32	99.00 ± 0.34	96.70 ± 0.33	91.20 ± 0.32
600	–	–	97.50 ± 0.35	–	–	95.80 ± 0.34

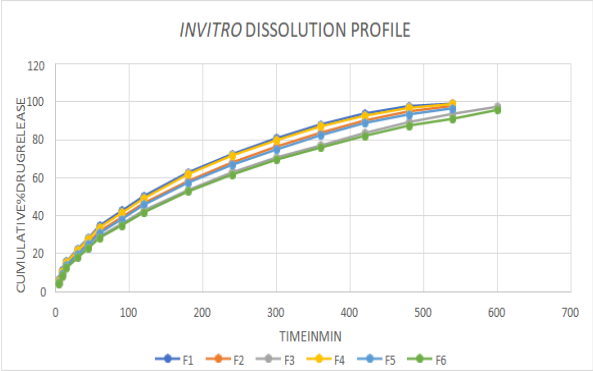


Figure 11: In-vitro Drug Release Profiles of Levofloxacin-Loaded Ocular Inserts

DRUG RELEASE KINETICS (KINETIC MODELLING)

To investigate the drug release mechanism, the in-vitro drug release data of the prepared Levofloxacin-loaded ocular inserts (F1–F6) were fitted to different mathematical kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

The regression coefficients (R^2) obtained from the zero-order kinetic model ranged from 0.9523 to 0.9652, indicating a reasonable correlation with zero-order release behaviour. The Higuchi model also demonstrated a high degree of linearity, suggesting the involvement of diffusion in the drug release process.

The Korsmeyer–Peppas model exhibited the highest regression coefficients, ranging from 0.9935 to 0.9961. The release exponent (n) values ranged from 0.621 to 0.708, suggesting an anomalous or non-Fickian transport mechanism involving both drug diffusion and polymer relaxation.

Table 07: Drug Release Kinetic Parameters of Levofloxacin-Loaded Ocular Inserts

Formulation	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer–Peppas n	Korsmeyer–Peppas R^2
F1	0.9652 ± 0.010	0.9791 ± 0.009	0.9923 ± 0.005	0.621 ± 0.02	0.9961 ± 0.003
F2	0.9604 ±	0.9773 ±	0.9905 ±	0.638 ± 0.02	0.9952 ± 0.004

	0.011	0.010	0.006		
F3	0.9556 ± 0.012	0.9750 ± 0.011	0.9891 ± 0.007	0.682 ± 0.03	0.9940 ± 0.004
F4	0.9641 ± 0.010	0.9785 ± 0.009	0.9912 ± 0.006	0.629 ± 0.02	0.9960 ± 0.003
F5	0.9582 ± 0.011	0.9764 ± 0.010	0.9900 ± 0.006	0.661 ± 0.02	0.9951 ± 0.004
F6	0.9523 ± 0.012	0.9742 ± 0.011	0.9884 ± 0.007	0.708 ± 0.03	0.9935 ± 0.005



Figure 12: Zero-Order Drug Release Kinetic Plot

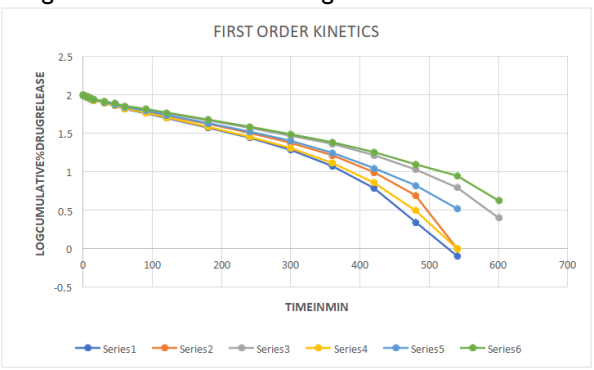


Figure 13: First-Order Drug Release Kinetic Plot

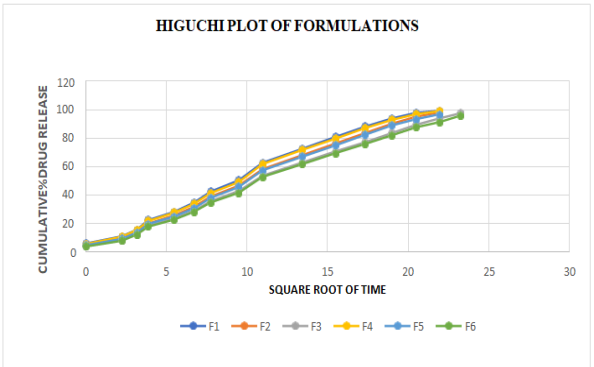


Figure 14: Higuchi Drug Release Kinetic Plot

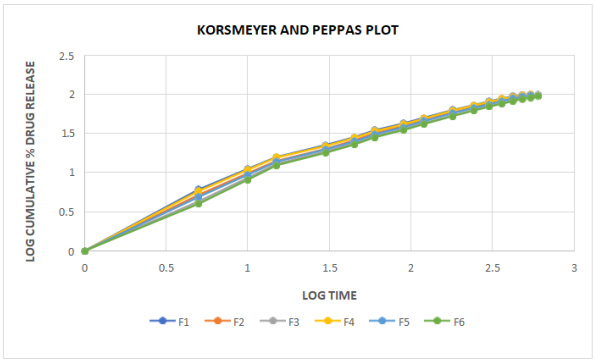


Figure 15: Korsmeyer–Peppas Drug Release Kinetic Plot

CONCLUSION

Levofloxacin-loaded ocular inserts were successfully formulated using gelatin, chitosan, and HPMC K4M as film-forming polymers by the solvent casting method. The prepared ocular inserts exhibited satisfactory physicochemical properties, uniform drug content, adequate mechanical strength, and sustained drug release characteristics. Drug release kinetic analysis indicated that the release mechanism predominantly followed the Korsmeyer–Peppas model, suggesting non-Fickian (anomalous) diffusion. Among all the formulations, F3 demonstrated the most favourable overall performance based on its drug release profile and physicochemical characteristics. The findings suggest that Levofloxacin-loaded ocular inserts may serve as a promising sustained-release ocular drug delivery system with the potential to prolong ocular residence time, improve drug availability at the ocular surface, and enhance patient compliance compared with conventional ophthalmic formulations.

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INFORMED CONSENT AND ETHICAL STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the research work, manuscript preparation, and final approval of the manuscript.

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Not declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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