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Formulation and Evaluation of Ocular Inserts of Gentamicin Sulfate for Enhanced Ocular Drug Delivery

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Abstract

Ocular drug delivery remains one of the most challenging pharmaceutical endeavors due to the eye's unique anatomical and physiological characteristics, including corneal permeability limitations and tear washout. Conventional ophthalmic formulations, such as solutions and suspensions, result in poor bioavailability, with only 1-10% of topically applied drugs achieving systemic absorption. This study presents the formulation and comprehensive evaluation of ocular inserts containing Gentamicin sulfate, an aminoglycoside antibiotic, to overcome the inherent limitations of traditional delivery systems. The study involved the preparation of polymeric films using polyvinyl pyrrolidone and methyl cellulose as matrix polymers, followed by rigorous physicochemical and *in vitro* drug release characterization. Ocular inserts were evaluated for thickness, weight variation, drug content uniformity, surface pH, and moisture absorption. In vitro dissolution studies were conducted using a USP Type I apparatus and K.C. cells to assess drug permeation profiles. The developed ocular inserts exhibit controlled drug release, improved residence time, and uniform drug distribution. This investigation underscores the potential of ocular inserts as an effective alternative to conventional ophthalmic formulations, offering prolonged contact time, reduced systemic side effects, and enhanced therapeutic efficacy for bacterial eye infections.
Keywords: Ocular inserts, Gentamicin sulphate, polymeric films, ocular drug delivery, *in vitro* release study, bioavailability, polyvinyl pyrrolidone, methyl cellulose, physicochemical evaluation

1. Introduction

1.1Background and Significance of Ocular Drug Delivery

The eye is a highly specialized organ with complex anatomy and physiological mechanisms that protect ocular tissues from foreign substances. These protective mechanisms, while essential for maintaining ocular health, pose formidable challenges for pharmaceutical scientists seeking to deliver therapeutic agents to ocular tissues. The cornea, a major barrier to drug penetration, possesses lipophilic outer layers and hydrophilic inner layers, making it selective in permitting drug passage. Additionally, the conjunctiva, the mucous membrane covering the sclera and internal eyelid, presents another significant barrier to drug absorption.

The physiological defense mechanisms of the eye—tear production and blinking reflexes—although protective, significantly limit the residence time of topical medications. These factors contribute to the poor bioavailability of conventionally administered ophthalmic drugs, with typical absorption rates ranging from 1% to 10% of the instilled dose. This limitation necessitates frequent instillation of drugs, increasing the risk of systemic adverse effects and reducing patient compliance.

1.2 Conventional Ocular Drug Delivery Systems and Their Limitations

Traditional ophthalmic formulations include solutions, suspensions, and ointments. While solutions offer convenience and ease of administration, they provide minimal contact time with ocular tissues. Although capable of delivering higher drug concentrations, suspensions may cause ocular irritation. Ointments provide longer contact time but compromise vision due to ocular surface coating. These limitations underscore the necessity for innovative drug delivery systems that can overcome biological barriers while maintaining patient comfort and therapeutic efficacy.

1.3 Ocular Inserts: A Promising Alternative

Ocular inserts represent a significant advancement in ophthalmic drug delivery. These are solid or semi-solid preparations designed to be placed on or into the eye, providing sustained, controlled drug release over extended periods. By maintaining a prolonged drug reservoir in contact with ocular tissues, inserts can enhance bioavailability and reduce the frequency of drug administration. The concept of ocular inserts encompasses various designs, including soluble and insoluble inserts, with applications ranging from

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antibiotic delivery to artificial tear replacement.

1.4 Gentamicin Sulfate: The Model Drug

Gentamicin is an aminoglycoside antibiotic widely used in ophthalmology for treating bacterial eye infections. Its broad-spectrum activity against gram-negative and certain gram-positive bacteria makes it an ideal candidate for ocular delivery. However, conventional gentamicin solutions require frequent instillation (every 4-6 hours) for therapeutic efficacy, limiting patient compliance and increasing systemic exposure. The development of sustained-release ocular inserts containing gentamicin addresses these limitations while maintaining therapeutic drug concentrations at the ocular surface.

1.5. Rationale of the study

Ocular infections represent a significant clinical challenge, affecting millions of individuals globally. Bacterial keratitis, conjunctivitis, and other anterior segment infections require prolonged antimicrobial therapy. Current gentamicin formulations necessitate frequent administration—often four to six times daily—creating substantial burdens on patient compliance and increasing the risk of overdosage or underdosage scenarios. The development of sustained-release ocular inserts would address this clinical gap by extending drug residence time and reducing administration frequency. By increasing the contact time between the drug and ocular tissues, inserts overcome the limitations imposed by tear washout and blinking reflexes. Polymeric matrices enable zero-order or near-zero-order release kinetics, maintaining therapeutic drug concentrations at ocular tissues while minimizing systemic exposure. This approach represents a paradigm shift from symptom-based frequent instillation to sustained therapeutic delivery, potentially improving clinical outcomes while enhancing patient convenience.

1.6. Objectives of the study

This study aimed to develop and evaluate polymeric ocular inserts containing gentamicin sulfate to improve drug delivery to the eye. The specific objectives included designing inserts with biocompatible and mucoadhesive polymers for sustained drug release, evaluating their physicochemical properties (such as thickness, weight variation, drug content, pH compatibility, and moisture absorption), analyzing drug release behavior using standardized methods, identifying optimal polymer combinations for effective performance, and optimizing plasticizer use to enhance mechanical properties without affecting drug release.

2. Material and Methods

2.1. Materials

The active pharmaceutical ingredient used in this study was Gentamicin sulfate, a white or almost white hygroscopic powder that is freely soluble in water and practically insoluble in alcohol. The polymers used to formulate the ocular inserts included Polyvinyl Pyrrolidone (PVP), Carboxymethyl cellulose (CMC), and Methyl Cellulose (MC). Polyethylene Glycol 400 (PEG 400) was used as a plasticizer for selected batches.

2.2. Methods

2.2.1 Analytical Method

The method for quantitation of Gentamicin sulphate was established using U.V. spectrophotometry. A solution of the drug in distilled water was scanned, revealing a maximum UV absorption (λmax) at 233 nm. Standard calibration curves were prepared in both distilled water and phosphate buffer (pH 7.4).

2.2.2 Loading dose Calculation

The circular ocular film die had a diameter of 1 cm, yielding a surface area of 0.785 cm^2. The gentamicin dose incorporated was calculated based on therapeutic requirements and formulation percentages.

2.2.3 Preparation of the Ocular Film

Ocular films were prepared using the solvent casting technique. Polyvinyl pyrrolidone and methyl cellulose were dissolved in distilled water with gentle heating (40-50°C). Gentamicin sulphate was dissolved separately in minimal distilled water and incorporated into the polymer solution with continuous stirring. PEG 400 was added as a plasticizer to enhance mechanical flexibility. The resulting homogeneous solution was poured into glass Petri dishes, allowed to dry at room temperature (25±2°C) for 48 hours, and subsequently cut into appropriate dimensions using a circular die.

2.2.4. Ocular Insert Formulation

Formulation Design: Two main batches of Gentamicin sulphate films were prepared:
Batch A (formulated without a plasticizer) and Batch B (formulated with PEG 400 as a plasticizer)

Table 1: Composition of Gentamicin sulphate cast film - Batch A (Without Plasticizer)

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Ingredients	A-1	A-2	A-3	A-4	A-5	A-6
Polyvinyl Pyrrolidone	400 mg	600 mg	400 mg	600 mg	------	------
Carboxymethyl cellulose	600 mg	400 mg	------	------	400 mg	600 mg
Methyl Cellulose	------	------	600 mg	400 mg	600 mg	400 mg
Gentamicin Sulphate	1.99 mg	1.99 mg	1.99 mg	1.99 mg	1.99 mg	1.99 mg

Table 2: Composition of Gentamicin sulphate cast film - Batch B (With 0.3ml PEG 400 Plasticizer)

Ingredients	B-1	B-2	B-3	B-4	B-5	B-6
Polyvinyl Pyrrolidone	400 mg	600 mg	400 mg	600 mg	------	------
Carboxymethyl cellulose	600 mg	400 mg	------	------	400 mg	600 mg
Methyl Cellulose	------	------	600 mg	400 mg	600 mg	400 mg
Polyethylene Glycol 400	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml
Gentamicin Sulphate	1.99 mg	1.99 mg	1.99 mg	1.99 mg	1.99 mg	1.99 mg

2.2.5. Evaluation of Ocular Polymeric Films: The formulated ocular inserts were evaluated for both physicochemical properties and *in vitro* release profiles:
Thickness: Measured at different points on the film using a dead weight thickness gauze to calculate the mean value.

- **Weight Variation:** Three films from each formulation were randomly selected, weighed individually, and the mean weight was calculated.
- **Drug Content Uniformity**: Inserts were crushed, suspended in 5 ml of distilled water, filtered through a 0.5 µm syringe filter, and analyzed spectrophotometrically at 233 nm using an internal standard.
- **Surface pH:** Determined by placing two drops of distilled water over the film to allow swelling, followed by taking a reading with pH paper on the film's surface.
- **Percentage Moisture Absorption:** To check physical stability, weighed films were placed in a desiccator containing a saturated solution of aluminum chloride (providing 79% humidity) for 3 days. The films were then reweighed to calculate the percentage of moisture absorbed using the following formula

$$\text{Moisture Absorption}(\%) = \frac{\text{Final weigt} - \text{Initial Weight}}{\text{Initial Weight}} \text{X}100$$

In Vitro Dissolution Study: Conducted using a USP Type I Dissolution Apparatus to simulate physiological eye conditions. Inserts were placed in a dissolution chamber containing 250 mL of distilled water (pH 7.4) at 37 ± 1°C. Over 260 minutes, 3 mL aliquots were withdrawn at specific intervals and analyzed spectrophotometrically at 233 nm.
In Vitro Permeation Study: Conducted using a K C Cell biochemical donor-receiver compartment model equipped with a commercial semipermeable transparent cellophane membrane, acting as a simulated corneal epithelial barrier. The donor compartment was maintained with 0.7 ml of water for injection (representing the simulated tear volume), while the reservoir contained 12 ml of water, continuously stirred. Drug content in the reservoir was analyzed using a UV-visible spectrophotometer over an 8-hour period.

3. Results and Discussion

3.1. Physicochemical Evaluation of Ocular Films: Physical examination of the formulated ocular inserts revealed that the films were smooth and largely translucent. The films were subjected to a series of physicochemical evaluations to determine their suitability for ocular administration, including thickness, weight variation, drug content uniformity, surface pH, and percentage moisture absorption.
The mean film thickness ranged from 2.8 µm to 97.4 µm for Batch A (formulated without a plasticizer), while Batch B (formulated with PEG 400 as a plasticizer) ranged from 15.5 µm to 79.3 µm. The average weight of the ocular films ranged between 10.24 mg and 13.39 mg for Batch A, and between 11.85 mg and 15.51 mg for Batch B.
The surface pH of the ocular films must be compatible with ocular tissues to avoid irritation. The surface pH ranged from 4.7 to 5.8 in Batch A and from 5.7 to 6.6 in Batch B, making them generally suitable for the sensitive ocular environment. Drug content uniformity analysis showed that the drug was well-dispersed, with content ranging from 1127.25 µg to 1406.18 µg in Batch A, and 1257.43 µg to 1578.45 µg in Batch B. Moisture absorption was generally higher in Batch A (9.31% to 12.03%) compared to Batch B (3.53% to 7.35%).

Table 3: Summary of Physicochemical Properties (Ranges for Batch A and Batch B)

Evaluation Parameter	Batch A (Without Plasticizer)	Batch B (With PEG 400 Plasticizer)
Thickness (µm)	2.8 – 97.4	15.5 – 79.3

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Weight Variation (mg)	10.24 – 13.39	11.85 – 15.51
Drug Content Uniformity (µg)	1127.25 – 1406.18	1257.43 – 1578.45
Surface pH	4.7 – 5.8	5.7 – 6.6
Percentage Moisture Absorption	9.31% – 12.03%	3.53% – 7.35%

3.2 *In Vitro* Drug Release (Dissolution) Study: To simulate the physiological conditions of the eye, an *in vitro* dissolution study was conducted over 260 minutes using a USP Type I Dissolution Apparatus. All formulated batches successfully sustained drug release for more than 4 hours.
However, a clear distinction in release profiles was observed between the two batches. Formulations lacking a plasticizer (Batch A) achieved a total cumulative drug release ranging from 65.714% to 74.328% at the end of the 260-minute period. In contrast, the formulations incorporating the plasticizer (Batch B) demonstrated a superior release profile, achieving total cumulative drug releases between 77.4% and 85.408%

3.3. *In Vitro* Permeation Study The permeation study, designed to simulate the corneal epithelial barrier using a semipermeable membrane in a K C Cell, was conducted over a period of 8 hours. The trends observed in the dissolution study were mirrored in the permeation results. Batch A formulations reached maximum permeation levels of 69.01% to 79.295%. Meanwhile, Batch B formulations achieved significantly higher permeation rates, ranging from 78.771% to 91.367%.

Table 4: Final Cumulative Percentage Drug Release for All Formulations.

Formulation Code	Polymer Composition	Cumulative % Release (Dissolution - 260 mins)	Cumulative % Release (Permeation - 8 hours)
A-1	PVP : CMC (400:600)	68.203%	69.01%
A-2	PVP : CMC (600:400)	72.757%	78.72%
A-3	PVP : MC (400:600)	65.714%	71.664%
A-4	PVP : MC (600:400)	74.328%	79.295%
A-5	CMC : MC (400:600)	72.553%	73.027%
A-6	CMC : MC (600:400)	71.971%	71.27%
B-1	PVP : CMC (400:600) + PEG	80.879%	83.083%
B-2	PVP : CMC (600:400) + PEG	77.485%	78.771%
B-3	PVP : MC (400:600) + PEG	83.004%	85.714%
B-4	PVP : MC (600:400) + PEG	**85.408%**	**91.367%**
B-5	CMC : MC (400:600) + PEG	83.004%	84.262%
B-6	CMC : MC (600:400) + PEG	77.400%	79.967%

Cumulative amount of Drug release (%)vs time(Batch A)

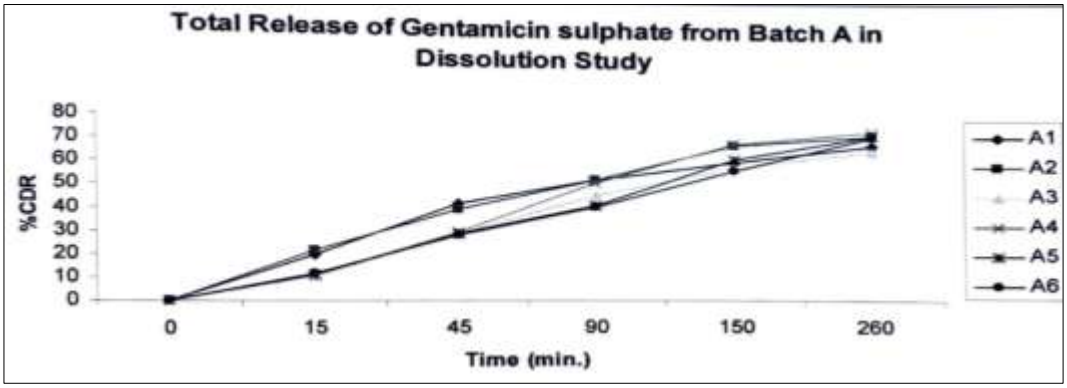

Fig 1: *In vitro* drug release Study.

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Cumulative amount of Drug release (%)vs time(Batch B)

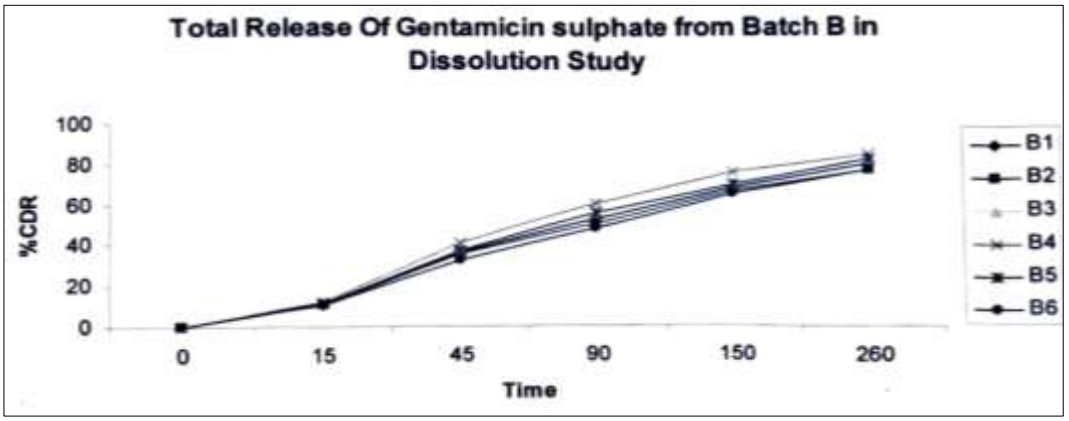
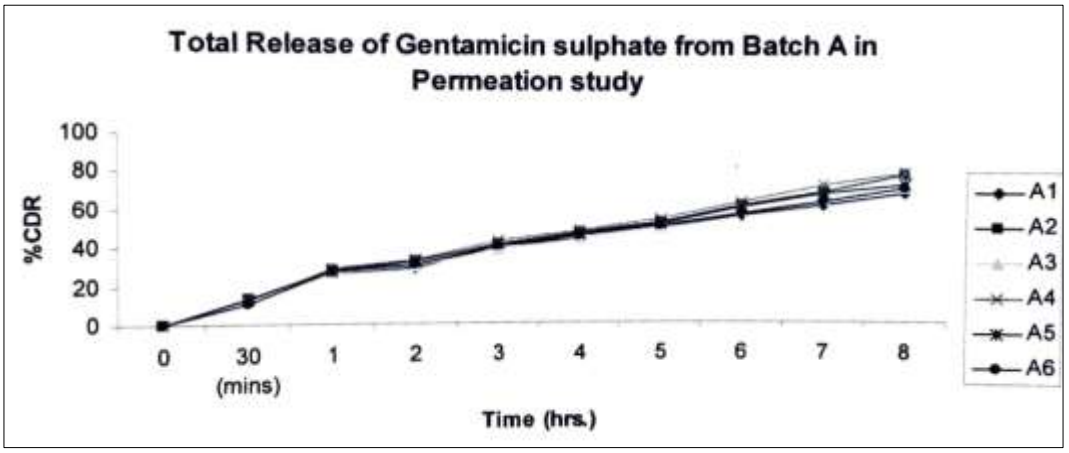
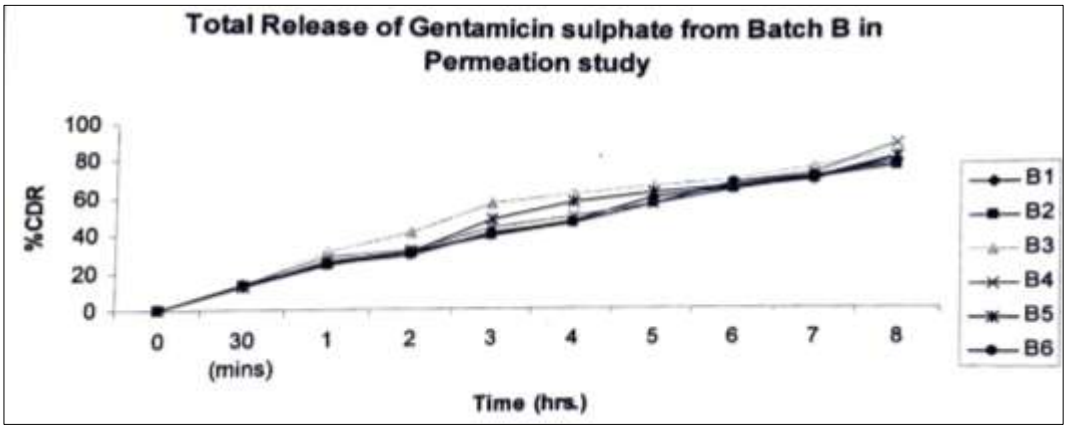


Fig 2: *In Vitro* Drug Permeation Study,

Cumulative amount of Drug permeated (%)vs time(Batch A)



Cumulative amount of Drug permeated (%)vs time(Batch B)



4. Conclusion

Based on the *in vitro* dissolution and permeation studies conducted, it is concluded that the release profile of Gentamicin sulfate from ocular films is significantly influenced by the presence of a plasticizer. The ocular films formulated without a plasticizer (Batch A) exhibited a notably lower drug release rate compared to those formulated with a plasticizer (Batch B). This enhanced release in Batch B formulations can be directly attributed to the addition of the plasticizer, which increases the penetration of the dissolution medium (distilled water and phosphate buffer) into the polymeric matrix, thereby accelerating the drug release rate and increasing the total percentage of the drug released.

Specifically, the maximum cumulative percentage release was consistently observed in Batch B (with plasticizer) across both the dissolution and permeation studies. For instance, the percent cumulative release in the dissolution study for Batch A ranged from 65.714% to 74.328%, whereas Batch B achieved higher

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releases ranging from 77.4% to 85.408%. Similarly, in the permeation study, Batch A reached a maximum release range of 69.01% to 79.295%, while Batch B demonstrated superior permeation, ranging from 78.771% to 91.367%.

Among all the prepared batches, formulation code B4—which comprises the polymers Polyvinyl Pyrrolidone (PVP) and Methyl Cellulose in a 600:400 ratio, along with the plasticizer—showed the greatest drug diffusion. Furthermore, Formulation B4 exhibited an optimal balance in percentage moisture absorption and drug content uniformity. Therefore, it is concluded that Formulation B4 represents the most promising and suitable candidate for an effective Gentamicin sulfate ocular drug delivery system (Ocusert). The developed ocular inserts represent a significant advancement in ophthalmic pharmaceutical technology, addressing critical challenges in the management of bacterial eye infections. Clinical implementation of these formulations would reduce treatment burden through reduced administration frequency, likely improve patient compliance, and potentially minimize systemic gentamicin exposure—all critical factors in optimizing therapeutic outcomes while ensuring safety.

Future scope of Study: Since the current study establishes a successful *in vitro* baseline, the future scope for this research should include in vivo bioavailability studies in animal models, stability assessment under various storage conditions, and human clinical trials to validate the therapeutic benefits predicted by these *in vitro* studies. Additionally, exploration of biodegradable polymer combinations could enhance patient comfort by eliminating the need for insert removal.

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