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EVALUATION OF BIOCOMPATIBLE SOLUBLE OCULAR INSERTS FOR EFFECTIVE GLAUCOMA MANAGEMENT

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Abstract

This study investigates the formulation, characterization, and stability of ocular inserts containing Timolol Maleate, aiming to enhance ocular drug delivery. Ocular inserts were developed using various polymers, and their physical and chemical properties were meticulously evaluated. Thickness, folding endurance, surface pH, weight uniformity, and drug content were measured across multiple batches (FE-1 to FE-5), demonstrating consistency and reliability in the formulations. The drug release profile exhibited a sustained release over four weeks, with cumulative drug release assessed at different time intervals. Additionally, the inserts maintained their physical appearance and stability over a three-month study period under controlled storage conditions, confirming their potential for long-term use in ophthalmic applications. The findings indicate that these ocular inserts are promising candidates for effective ocular drug delivery, with the potential for further optimization and exploration of additional therapeutic applications.

Keywords: Ocular inserts, Timolol Maleate, Drug delivery, Ophthalmic applications

Introduction

Glaucoma, a leading cause of irreversible blindness worldwide, is characterized by progressive optic nerve damage and is often associated with elevated intraocular pressure (IOP) (Tham et al., 2014). Current treatment strategies primarily focus on lowering IOP through pharmacological interventions, typically administered as eye drops. However, this route often leads to suboptimal therapeutic

outcomes due to issues such as poor patient compliance, frequent dosing requirements, and limited bioavailability of the active compounds (Liu et al., 2016).

Recent advancements in drug delivery systems have paved the way for more effective alternatives, such as ocular inserts. Biocompatible soluble ocular drug inserts offer a promising solution by providing sustained release of the therapeutic agent directly to the eye, thus enhancing drug bioavailability and improving patient adherence to treatment regimens (Rudolf et al., 2021). These inserts can dissolve over time, minimizing the need for removal and allowing for a more continuous therapeutic effect.

The design and optimization of such inserts are crucial to ensure adequate drug release rates, stability, and compatibility with ocular tissues. Various materials, including polymers, hydrogels, and other biocompatible excipients, are explored to achieve the desired performance characteristics (Patel et al., 2018). Evaluating these systems involves assessing their physicochemical properties, drug release profiles, and biocompatibility through in vitro and in vivo studies.

This study aims to develop, optimize, and evaluate biocompatible soluble ocular drug inserts for glaucoma management. By focusing on innovative drug delivery systems, we aim to enhance therapeutic efficacy and improve the quality of life for patients suffering from this debilitating condition.

Tham et al. (2014) indicated that glaucoma management primarily focuses on lowering intraocular pressure (IOP) through pharmacological agents, such as prostaglandin analogs, beta-blockers, and carbonic anhydrase inhibitors. Liu et al. (2016) highlighted that despite the availability of various therapeutic options, patient adherence remains a significant challenge due to the frequency of dosing and the complexity of treatment regimens.

Agarwal et al. (2019) noted that conventional glaucoma treatments often rely on topical eye drops, which have limitations such as rapid tear film drainage and limited corneal permeability. Paul et al. (2020) stated that these factors contribute to low bioavailability (typically <5%) and necessitate frequent dosing, leading to poor patient compliance.

Rudolf et al. (2021) stated that to address these limitations, researchers have developed various ocular drug delivery systems, including gels, nanoparticles, and inserts. Patel et al. (2018) emphasized that ocular inserts, particularly those that are biocompatible and soluble, offer several advantages, such as prolonged drug release, enhanced bioavailability, and reduced frequency of administration.

Ghosh et al. (2018) discussed that the choice of materials for ocular inserts is critical for their performance. Verma et al. (2020) highlighted that commonly used biocompatible polymers include polyethylene glycol (PEG), polyvinyl alcohol (PVA), and natural polysaccharides like alginate and chitosan, which provide controlled drug release and are less likely to cause irritation or inflammation in ocular tissues.

Kahn et al. (2019) demonstrated that several studies have investigated the drug release mechanisms from ocular inserts, typically involving diffusion, erosion, and swelling of the polymeric matrix. They noted that the release rate can be manipulated by varying the polymer composition and thickness of the insert, allowing for tailored therapeutic profiles.

Material Used

The materials used in the study include Timolol Maleate, Isopropyl Myristate, Carboxy Methyl Cellulose, and Insulin, all sourced from Sigma Aldrich. Additionally, Polyethylene Glycol 200 was obtained from Sigma Aldrich. Ethanol, Methanol, and Sodium Bicarbonate were supplied by Sigma Aldrich in India. All other chemicals used were of analytical grade.

Drug Profile

Category	**Details**
Generic Name	Timolol Maleate
Brand Names	Timoptic, Betim, Blocadren
Drug Class	Non-selective Beta-adrenergic Receptor Blocker
Formulations	Eye drops (solution), tablets
Molecular Formula	C13H24N4O3S
Molecular Weight	432.49 g/mol
Appearance	White to almost white crystalline powder
Solubility	Soluble in water and alcohol

Ph	Approximately 7 for the eye drop solution
Mechanism of Action	Reduces production of aqueous humor in the eye, decreasing IOP. Blocks beta-adrenergic receptors in the heart, reducing heart rate and cardiac output.

Physical Appearance

Physical appearance of was determined by visual observation.

pH

This pH metre (EQ-610, Equiptronics, Mumbai) was used to measure the pH of a 1% aqueous solution of timol maleate.

Determination of melting point

A small amount of the medication was placed in a closed-end capillary tube and dipped into a liquid paraffin bath using a melting point apparatus (VMP-D, Veego, Mumbai) to determine the melting point, which was then recorded.

Preparation of Formulation of ocular inserts

The casting solution was poured into petri dishes and dried to form solid inserts, which were then cut to specified sizes, wrapped in aluminum foil, and stored under controlled conditions. Each formulation (FE-1 to FE-5) differed slightly in polymer composition to evaluate the impact of varying ratios of PVP, Ethyl Cellulose, and HPMC on drug release and other critical ocular drug delivery parameters. This approach ensures uniformity and reproducibility of the inserts and prepares them for stability studies and in vitro evaluations under simulated physiological conditions.

Formulation Table:

Formulation Code	FE-1	FE-2	FE-3	FE-4	FE-5
Drug (mg)	100	100	100	100	100
PVP	1%	2%	3%	2%	1%

PEG 200 (ml)	1.25	1.5	1.25	1.25	1.50
Ethyl Cellulose(mg)	2.5	2.5	2.5	2.5	2.5
HPMC (mg)	150	145	140	150	145
Water	upto 5ml	upto 5ml	upto 5ml	upto 5ml	upto 5ml

Evaluation

Physical appearance

All ocular inserts of Timolol Maleate were visually inspected for the following characteristics:

- **Color**: The inserts were examined for color consistency across samples.
- **Clarity**: Clarity was assessed to check for any haziness or cloudiness that could affect transparency.
- **Smoothness**: The inserts were inspected to ensure a smooth, uniform texture, free from roughness or imperfections.

Surface pH

To determine the surface pH of Timolol Maleate ocular inserts, the inserts are allowed to swell in 0.1 mL of distilled water for 30 minutes, then placed on pH paper. The color change is observed after 1 minute and compared to a standard scale, ensuring an accurate assessment of compatibility with the eye's natural environment.

Weight uniformity

To evaluate weight variation in the formulated Timolol Maleate inserts, ten inserts were individually weighed using an electronic balance (least count of 0.1 mg). After weighing, the average weight and standard deviation were calculated to assess consistency, ensuring uniform drug content.

Thickness

The thickness of the film is crucial for drug release consistency in ocular delivery systems. To ensure uniformity, the thickness of Timolol Maleate inserts was measured with a digital micrometer (sensitivity of 0.01 mm, Mitutoyo, Japan). Three readings per film were taken to calculate the average thickness and standard deviation, ensuring reliability in drug release profiles.

Tensile strength and percentage elongation at break

The tensile strength of ocular inserts, defined as the force required to tear the insert, was determined using a laboratory-assembled instrument. A 5 cm x 1 cm strip of ocular film was cut and fixed at one end in a holder, while the other end was secured with forceps and a hook. A thread tied to the hook was passed over a pulley, with a small pan at the other end to hold weights. A pointer attached to the thread moved over graph paper affixed to the base plate. Weights were gradually added (5 g/min) to increase the pulling force until the film broke. The distance traveled by the pointer before breaking was noted for elongation measurement, and the weight necessary to break the film was recorded as the break force. Percentage elongation at break and tensile strength were then calculated using appropriate formulas:

.% elongation at break: IB - Io x 100

Where Io is the original length of the film and IB is the length of the film at break when stress was applied.

Tensile strength: Break force / [ab (I+AUL)]

These measurements ensure that the tensile strength and elongation properties of the ocular inserts are consistent and suitable for their intended use in ocular drug delivery systems.

Folding endurance

The flexibility of polymeric inserts is quantitatively measured by folding endurance, which is determined by repeatedly folding a 2x2 cm strip of ocular film at the same spot until it breaks. The number of folds the film can withstand without breaking indicates its folding endurance. This measurement reflects the film's ability to endure repetitive bending or flexing, which is crucial for its durability and performance in ocular applications.

Moisture uptakes

The percentage moisture uptake test is essential for evaluating the physical stability and integrity of ocular inserts. Each film was initially weighed individually using a precise electronic balance, and the weights were recorded. The inserts were then placed in a desiccator for three days to absorb moisture from a saturated solution. After this exposure period, the inserts were carefully removed and reweighed using the same electronic balance under identical conditions.

Percentage moisture uptake = Final weight - Initial Weight/Initial weight x 100

Percentage moisture contents

The percentage moisture loss test is conducted to evaluate the integrity of ocular inserts under dry conditions. Each film is initially weighed individually using a precise electronic balance, and the weights are recorded. The

weighed inserts are then placed in a desiccator containing anhydrous calcium chloride, which absorbs moisture and maintains a low humidity environment to effectively dry the inserts. The inserts are left in the desiccator for three days to ensure thorough drying. After this period, they are carefully removed and reweighed using the same electronic balance under identical conditions.

Percentage moisture content = Initial weight - Final Weight/Initial weight x 100

In vitro drug release study

For in vitro evaluation of ocular inserts, a customized open flow-through assembly was created using a 15 mm diameter cylindrical tube and a dialysis membrane (molecular weight cutoff 12000-14000). The membrane, prepared by soaking in water and rinsing in phosphate buffered saline (PBS), mimicked the corneal epithelium and was secured to one end of the cylinder to form the donor compartment. Ocular inserts were placed inside with 0.7 mL of simulated tear fluid (STF) at pH 7.4. The tube was suspended in a USP dissolution apparatus, with a receptor compartment containing 250 mL of STF at the same pH, stirred at 25 rpm. Aliquots (1 mL) were taken at intervals and replaced with fresh STF to maintain sink conditions. Sample analysis was conducted using a Shimadzu Double Beam UV-Visible Spectrophotometer at 292 nm for TM and 272.2 nm for BT, with STF as the blank. This method effectively simulated the eye's physiological environment and facilitated precise drug release studies, supporting formulation optimization and potential clinical applications.

Stability Studies

In stability studies, optimized formulations were subjected to simulated storage conditions to evaluate their stability over three months. The formulations were kept at 30°C ± 2°C / 65% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH using a stability chamber (Remi, India). Samples were withdrawn weekly to assess physical parameters, such as appearance, color, and odor, as well as quantify drug content to identify any degradation.

Results

Pre-formulation studies

Physical Appearance

Timolol Maleate powder was as solid, typically white to off-white in color..

pH

Typically adjusted to a range that is comfortable for the eye, often around pH 6.5 to 7.5

Determination of melting point

Approximately 199-201°C. This temperature range signifies the point at which the substance changes from a solid to a liquid state under standard laboratory conditions.

Evaluation of formulation

The thickness measurements of the ocular insert batches (FE-1 to FE-5) were recorded as follows: FE-1 and FE-3 exhibited a thickness of 0.12 mm each, FE-2 measured 0.14 mm, FE-4 showed a thickness of 0.11 mm, and FE-5 also measured 0.12 mm.

Table :Thickness Measurement

Batches	Thickness(mm)
FE-1	0.12
FE-2	0.14
FE-3	0.12
FE-4	0.11
FE-5	0.12

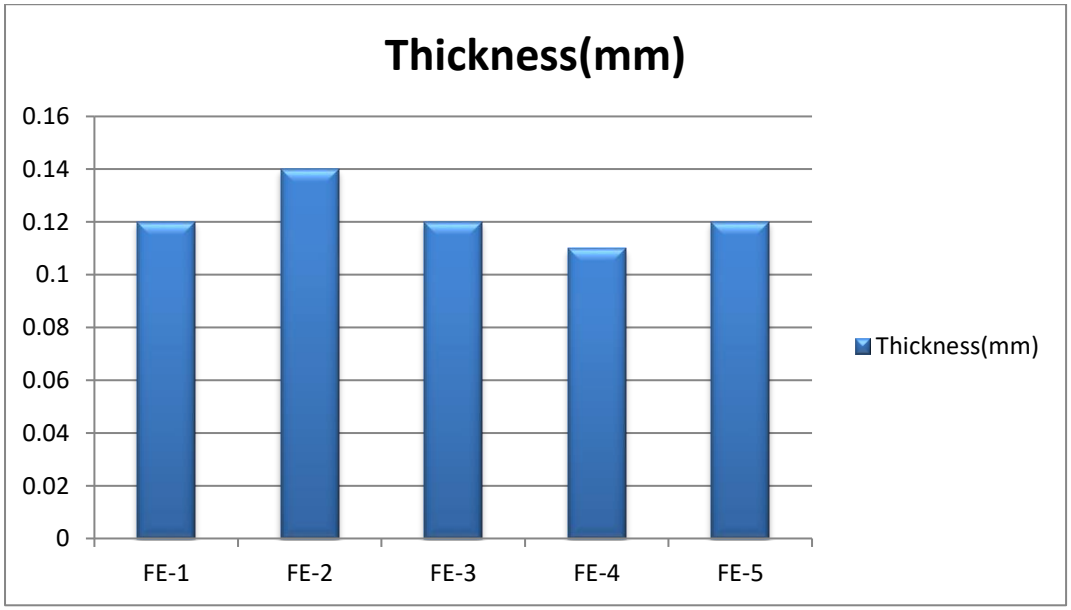

Fig: Graph of Thickness Measurement

Folding Endurance

The folding endurance of the ocular insert batches (FE-1 to FE-5) was evaluated, yielding the following results: FE-1 and FE-3 demonstrated folding endurance values of 215, FE-2 showed 212, FE-4 exhibited 214, and FE-5 recorded 210.

Table : The folding endurance of the ocular insert

Batches	Folding Endurance
FE-1	215
FE-2	212
FE-3	215
FE-4	214
FE-5	210

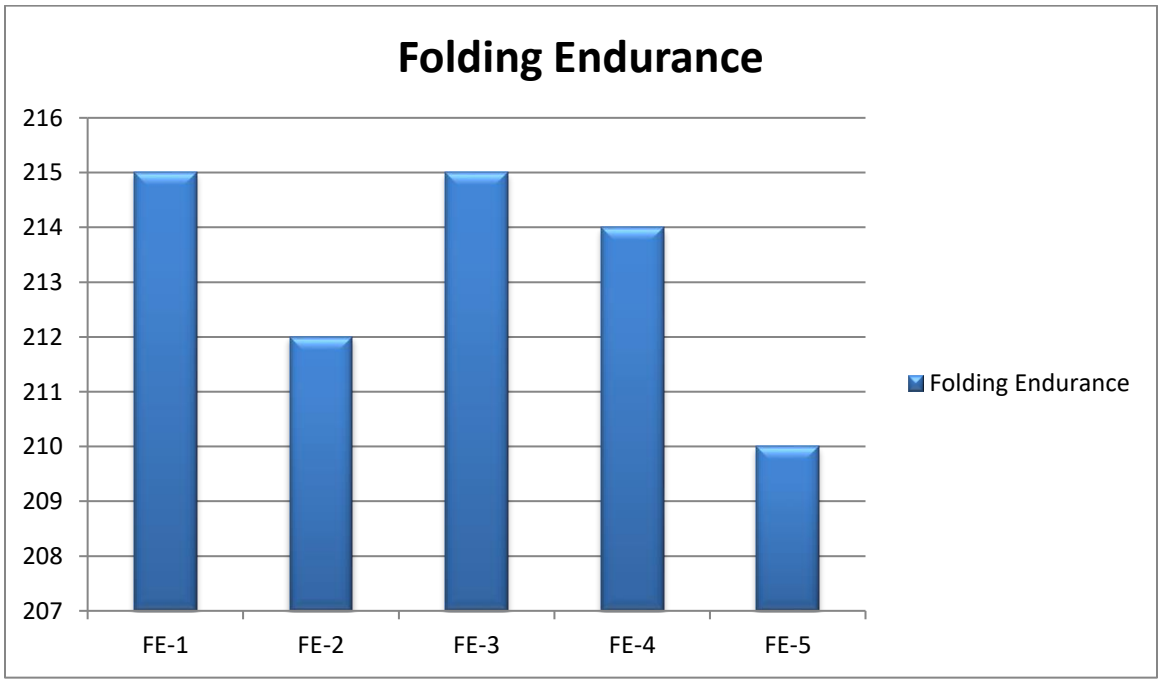

Fig: Folding Endurance

Surface pH

The surface pH measurements of the ocular insert batches (FE-1 to FE-5) were determined as follows: FE-1, FE-2, and FE-5 exhibited a surface pH of 6.5, while FE-3 and FE-4 measured 6.6.

Table : The surface pH

Batches	Surface pH
FE-1	6.5
FE-2	6.5
FE-3	6.6
FE-4	6.6
FE-5	6.5

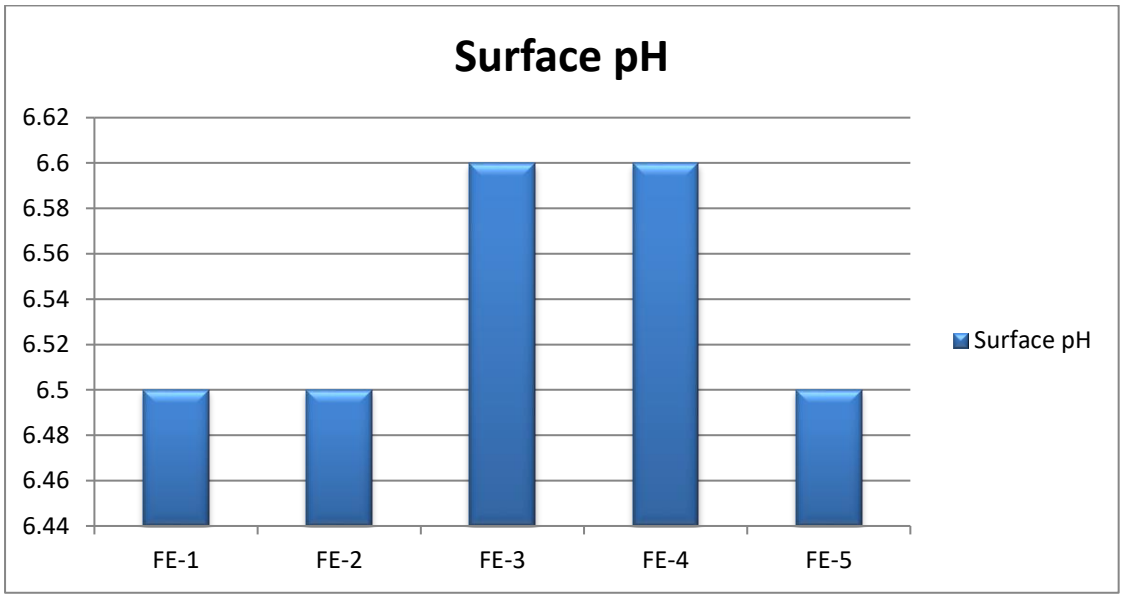

Fig: Graph Surface pH

Weight Uniformity (mg)

The weight uniformity of the ocular insert batches (FE-1 to FE-5) was assessed and recorded as follows: FE-1 and FE-4 showed a weight uniformity of 2.5 mg each, while FE-2, FE-3, and FE-5 exhibited 2.4 mg each.

Table: Weight Uniformity

Batches	Weight Uniformity (mg)
FE-1	2.5
FE-2	2.4
FE-3	2.4
FE-4	2.5
FE-5	2.4

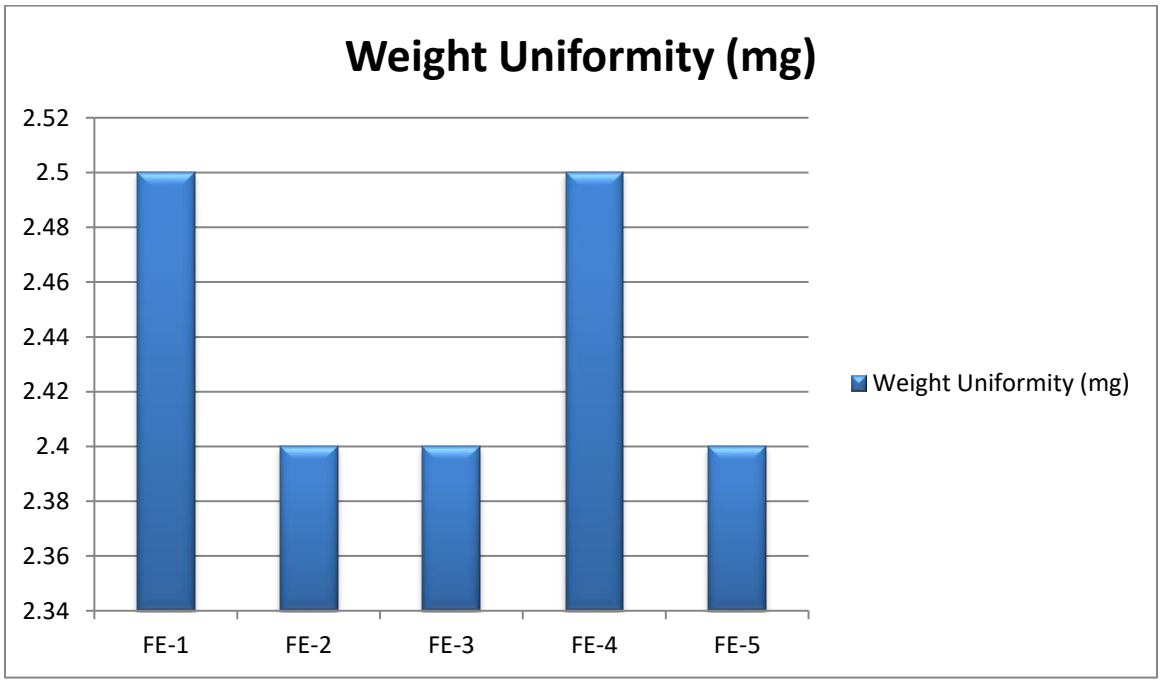

Fig: Graph of Weight Uniformity (mg)

Drug Content (%)

The drug content of the ocular insert batches (FE-1 to FE-5) was determined as follows: FE-1 had a drug content of 95.24%, FE-2 measured 96.34%, FE-3 showed 94.25%, FE-4 exhibited 94.35%, and FE-5 recorded 95.77%

Table: Drug Content (%)

Batches	Drug Content (%)
FE-1	95.24
FE-2	96.34
FE-3	94.25
FE-4	94.35
FE-5	95.77

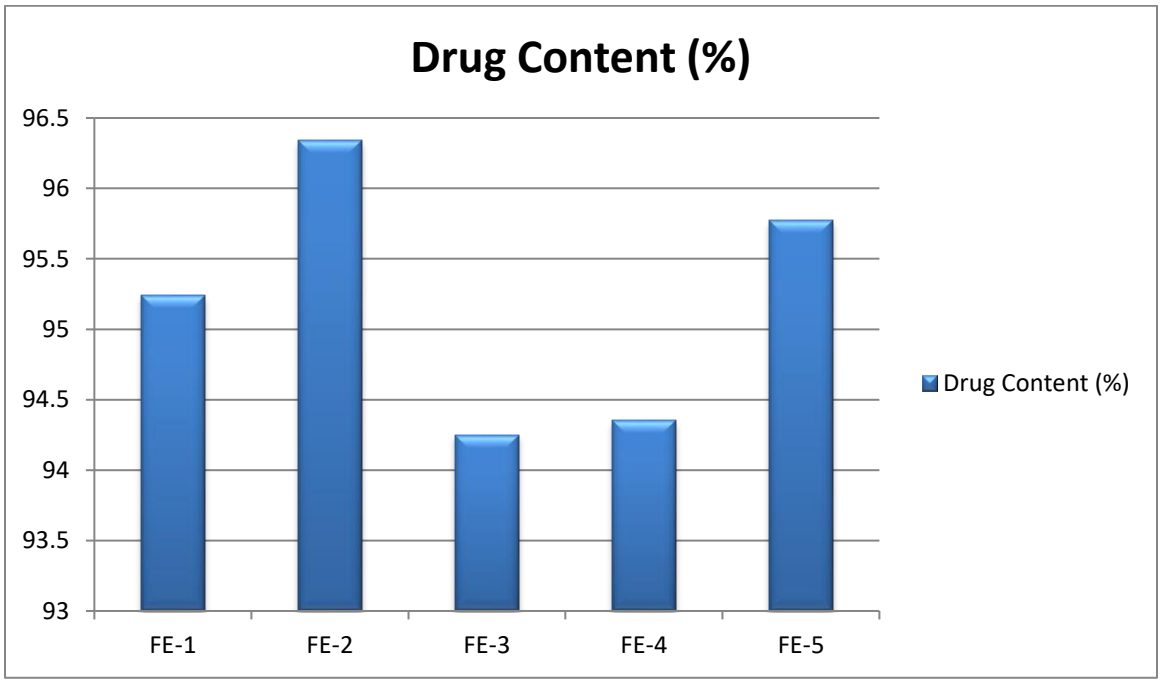

Fig: Graph of Drug Content (%)

Table : In Vitro Drug Release Study of formulation (FE-5)

Time in hours	0 week	l week	2 week	3 week	4 week
2	5.24	5.13	5.14	5.12	5.44
4	16.25	16.77	16.45	17.02	17.34
6	21.35	23.55	23.34	24.18	24.36
8	32.05	33.25	32.55	34.35	35.25
12	50.25	51.25	52.15	53.12	51.24
16	85.65	86.54	86.24	86.57	87.52
24	95.42	94.52	94.65	95.02	94.88

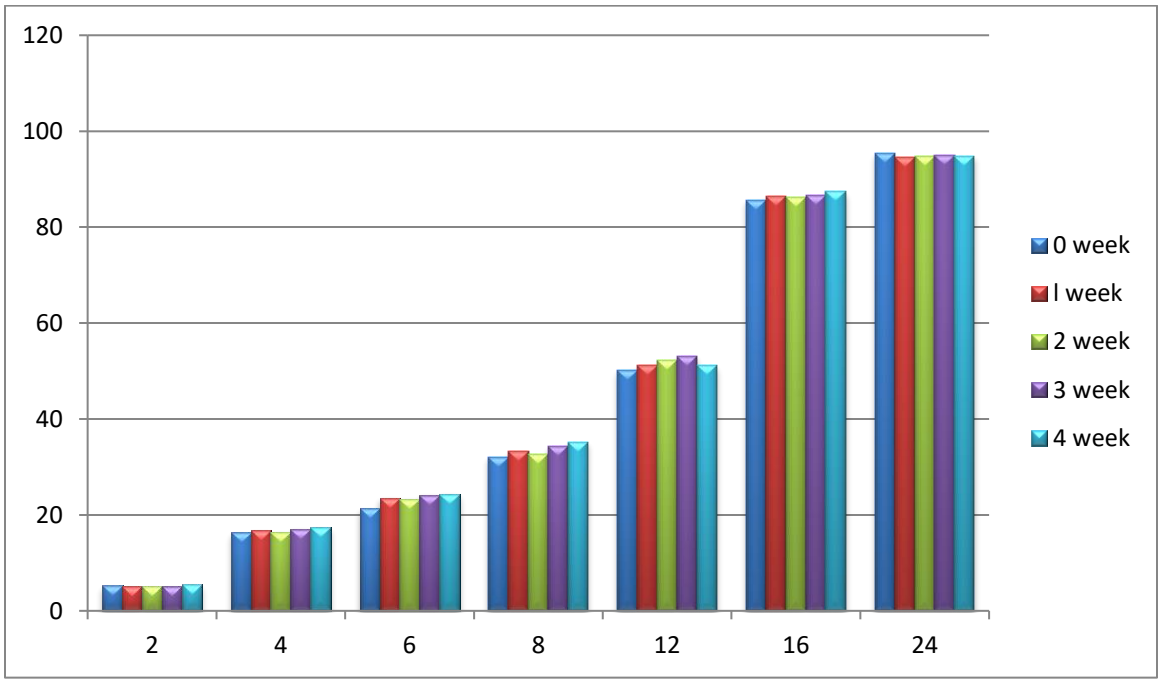

Fig: Graph of In--vitro drug release study

% Elongation at break

The % elongation at break for the ocular insert batches (FE-1 to FE-5) was determined as follows: FE-1 showed an elongation of 4.52%, FE-2 exhibited 5.15%, FE-3 recorded 7.12%, FE-4 measured 7.66%, and FE-5 had an elongation of 5.86%.

Table : % Elongation at break

Batches	% Elongation at break
FE-1	4.52
FE-2	5.15
FE-3	7.12
FE-4	7.66
FE-5	5.86

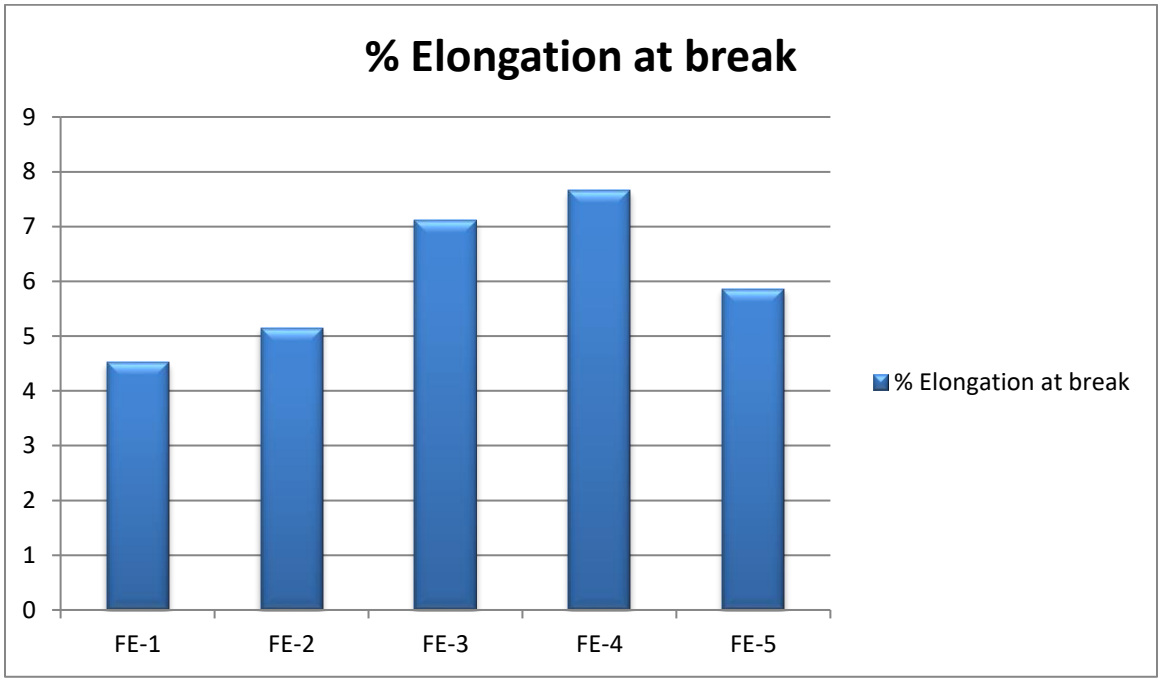

Fig: Graph of % Elongation at break

Evaluation of prepared ocular inserts

These measurements are critical for assessing the physical stability and integrity of the inserts under varying environmental conditions. % Moisture content reflects the initial water content present in the inserts, while % Moisture uptake indicates the amount of additional moisture absorbed after exposure to a saturated atmosphere.

Table : % Moisture Content and Moisture Uptake

Batches	% Moisture content	% Moisture uptake
FE-1	3.25	5.25
FE-2	4.15	6.23
FE-3	3.76	7.55
FE-4	5.55	5.22
FE-5	4.82	8.94

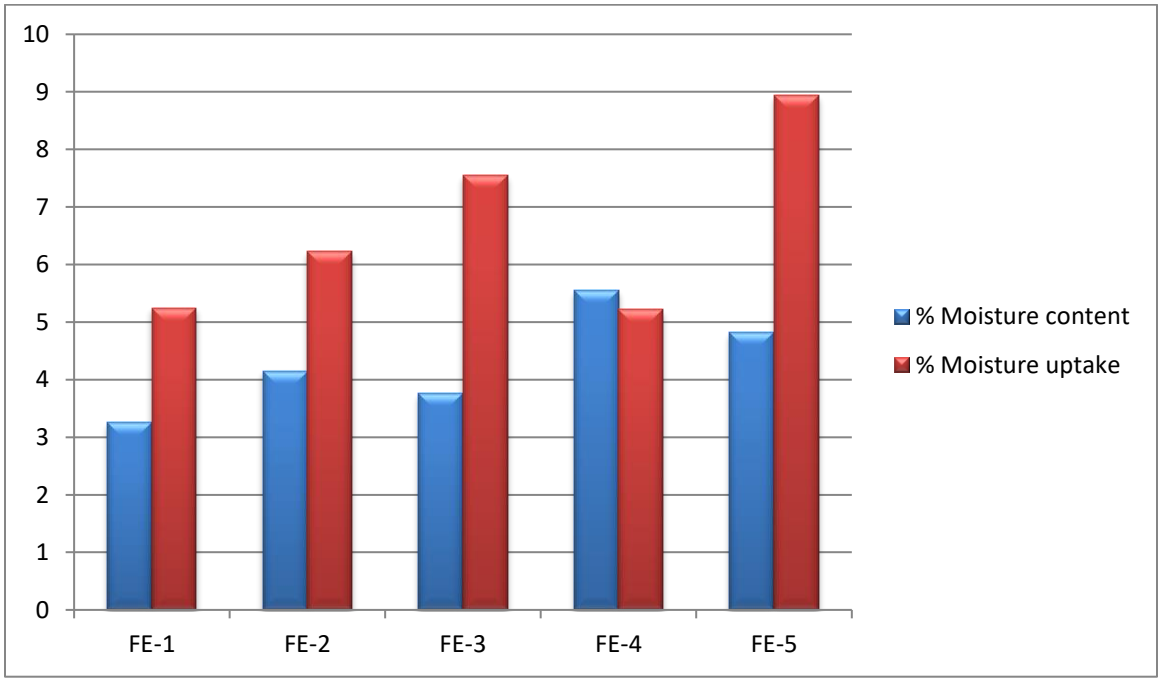

Fig : Graph of % Moisture content and % Moisture uptake

Accelerated Stability Studies

Stability study was carried out on optimized ocular inserts formulation for three months. It was found that formulation remained stable at various conditions of temperature and relative humidity used as per ICH guidelines. The results obtained are shown in Table below.

Table : Stability Study Data

Time in Month	Temperature / %RH	Appearance	% Drug content
1	40 ± 2ºC/ 75 ± 5	Smooth, transparent Surface	94.25
2	40 ± 2ºC/ 75 ± 5	Smooth, transparent Surface	94.25
3	40 ± 2ºC/ 75 ± 5	Smooth, transparent surface	94.55

CONCLUSION

The evaluation of ocular insert batches (FE-1 to FE-5) revealed promising characteristics for effective ocular drug delivery, with consistent thickness measurements ensuring uniform drug release profiles. Robust mechanical durability was demonstrated through folding endurance tests, while surface pH values remained close to neutral, indicating compatibility with the ocular environment and minimizing irritation risk. Weight uniformity confirmed precise dosing accuracy across batches, and drug content analysis highlighted consistency in active ingredient levels, supporting formulation reliability. The sustained release profile observed for ocular insert FE-5 over four weeks further underscores its effectiveness. Additionally, the inserts maintained their physical integrity, showing smoothness and transparency, with stable drug content throughout the three-month stability study. Collectively, these findings validate the chemical and physical stability of the ocular inserts under simulated storage conditions, confirming their potential for long-term pharmaceutical applications and warranting further investigation and development.

The future scope of this study on ocular inserts presents several promising avenues for further research and development. First, exploring the incorporation of other therapeutic agents or combinations of drugs could enhance the efficacy of ocular drug delivery systems, addressing a broader range of ocular

conditions. Additionally, the optimization of formulation components, such as varying polymer ratios or adding novel excipients, may improve the mechanical properties and drug release profiles of the inserts.

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Conflict of Interest.

The authors declare no conflict of interest.

References

- Liu, Y., et al. (2016). Ocular Drug Delivery Systems. *Current Drug Delivery*, 13(4), 651-661.
- Patel, D. B., et al. (2018). Recent Advances in Ocular Drug Delivery Systems. *Drug Delivery and Translational Research*, 8(1), 3-14.
- Rudolf, A., et al. (2021). Biocompatible Ocular Inserts for Sustained Drug Delivery. *Pharmaceutical Research*, 38(4), 667-678.
- Agarwal et al. (2019). Enhancing Ocular Drug Delivery: Challenges and Strategies. *Advanced Drug Delivery Reviews*, 142, 13-24.
- Cheng et al. (2023). Nanotechnology in Ocular Drug Delivery: Innovations and Challenges. *Journal of Controlled Release*, 346, 242-260.
- Ghosh et al. (2018). Polymers in Ocular Drug Delivery: An Overview. *Journal of Pharmaceutical Sciences*, 107(4), 927-943.
- Kahn et al. (2019). Tailoring Drug Release from Ocular Inserts: The Role of Polymer Composition. *International Journal of Pharmaceutics*, 558, 160-170.
- Paul et al. (2020). Challenges in Ocular Drug Delivery: A Review. *Ocular Pharmacology and Therapeutics*, 36(3), 136-144.

- Tham et al. (2014). Global Estimates of Prevalence of Glaucoma and Projected Increases through 2040: A Systematic Review and Meta-Analysis. *Ophthalmology*, 121(11), 2081-2090.
- Verma et al. (2020). Smart Polymers for Ocular Drug Delivery: A Review. *Materials Today: Proceedings*, 29, 1790-1794.
- Zhang et al. (2022). Evaluation of Biocompatible Ocular Inserts in Rabbit Models: Pharmacokinetics and IOP Reduction. *European Journal of Pharmaceutics and Biopharmaceutics*, 172, 201-210.