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Formulation and Evaluation of Latanoprost Ophthalmic Gel for Enhanced Ocular Bioavailability

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ABSTRACT

One of the main causes of permanent blindness is glaucoma, a chronic eye condition that is mostly linked to high intraocular pressure (IOP). As a prostaglandin F2α analogue, the well-known IOP-lowering drug latanoprost has a limited ocular bioavailability due to its rapid removal from the eye's surface when applied as conventional eye drops. In order to improve precorneal retention time and prolonged medication release, this study aims to create and assess an ocular gel formulation based on latanoprost. The formulation was prepared using Carbopol 940 and HPMC (K15M and E3) as mucoadhesive polymers, propylene glycol for solubility enhancement, and benzalkonium chloride and EDTA as antimicrobial preservatives. Important characteristics such as pH, viscosity, gel strength, osmolality, drug content, and in vitro drug release were assessed for the gel. The medication release profile was evaluated using simulated tear fluid in Franz diffusion cells. Formulations F9 and F10 outperformed the other trial batches in terms of physicochemical properties and achieved 100% release with sustained release over 8 hours. There was no microbiological contamination, according to the sterility test. The outcomes showed that, in comparison to eye drops, the gel formulation offers a more regulated drug delivery profile and successfully extends ocular residence duration. In the treatment of glaucoma, this may result in increased therapeutic effectiveness, decreased dosage frequency, and greater patient compliance.

Keywords: *Latanoprost, ophthalmic gel, glaucoma, intraocular pressure (IOP), prolonged drug release.*

1. INTRODUCTION

Glaucoma has emerged as one of the leading causes of permanent blindness worldwide in the past few decades. Elevated intraocular pressure (IOP) is the main symptom of this multifactorial optic neuropathy. If treatment is not received, this condition eventually destroys the retinal ganglion cells and results in progressive loss of vision. [1] The pathophysiology of glaucoma is influenced by a number of variables, even though the most significant and manageable risk factor is still high intraocular pressure. [2]

Latanoprost, a synthetic prostaglandin $F_2\alpha$ analogue, increases uveoscleral outflow and lowers IOP by specifically stimulating FP receptors in the ciliary body. [3] When applied topically, latanoprost is an isopropyl ester prodrug that easily penetrates the corneal epithelium. The active free acid is then hydrolysed by corneal esterases and reaches its maximum concentration in the aqueous humour after two hours. [4] Latanoprost has a low incidence of significant side effects, negligible systemic absorption, and higher effectiveness in decreasing intraocular pressure when compared to other types of ocular hypotensive. [5] However, because of tear turnover and blinking, traditional eye drops formulations sometimes have fast precorneal clearance, which leads to poor bioavailability (typically less than 5%), requiring regular dosage. [6]

Ophthalmic gels last longer on the eye's surface than ordinary drops and are easier to apply than ointment. Their ability to adhere to the eye as a result to their sticky gel base slows down the rate at which tears wash them away or drain them down

the tear ducts. [7] These gels can therefore offer a prolonged drug release profile, keeping therapeutic levels of latanoprost in the anterior chamber for a long time, which may lower the frequency of doses and enhance patient adherence. [8]

Among polymers commonly employed in ophthalmic gels, carbomers (e.g., Carbopol 940) and cellulose derivatives (e.g., hydroxypropyl methylcellulose) are favoured for their mucoadhesive properties and capacity to form clear, stable gels at physiologic pH. [9] When neutralized, the cross-linked polyacrylic acid Carbopol 940 quickly expands, forming a high-viscosity matrix that improves precorneal retention. As a viscosity modifier and contributor to the gel's shear-thinning properties, hydroxypropyl methylcellulose helps patients feel more comfortable while blinking.[10] Frequently used as a co-solvent, propylene glycol facilitates drug solubilization and preserves gel clarity. [11] Benzalkonium chloride and other preservatives are commonly used to prevent microbiological contamination. [12]

This formulation provides benefits for individuals who have poor compliance or unpleasant responses to frequent instillations may benefit most from prolonged IOP reduction that results from increased precorneal residence time. The gel's semi-solid state improves patient tolerability by increasing viscosity without significantly impairing eyesight, as is the case with ointments. Gels may reduce the peak-trough variations that are typical of eye drops by preserving a more constant drug concentration at the site of action, resulting in more stable IOP control. Last but not least, the controlled-release profile could reduce the overall dosage over time, which might diminish the risk of chronic ocular surface toxicity and cumulative exposure to excipients and preservatives. [13,14]

2. MATERIALS AND METHODS:

Materials:

Latanoprost was procured from Lee Pharma Limited, Telangana. Carbopol-940, HPMC K100, HPMC E3, Propylene glycol, Benzalkonium chloride, Ethylenediaminetetraacetic acid (EDTA), Tris Hydrochloric acid, all these chemicals were of analytical grade and purchased from local suppliers.

Preformulation study

Physical Property (Organoleptic property): The physical examination involved assessing the organoleptic properties of Latanoprost, including its colour, odour, and overall appearance.

Solubility Study: This study was assessed in various solvents, including water, alcohol, and ethyl acetate. Excess API was added to separate beakers containing each solvent, and the mixtures were periodically shaken. Whatman filter paper grade no. 41 was then used to filter the solutions. Spectrophotometric methods were then used to analyse the filtered solutions.

Determination of pH: The pH values of solutions containing specific strengths of excipients were measured using a calibrated pH meter.

Analytical Method:

Identification by IR Spectroscopy: Latanoprost IR spectrum was taken using the Diffused Attachment reflectance mode.

UV Spectroscopy:

Preparation of Diluent: Take methanol and water in an 80:20 v/v ratio.

Drug Standard Solution Preparation for UV Identification: After weighing and transferring 1 mg of latanoprost API into a 10-milliliter volumetric flask, thoroughly mix with 7 millilitres of diluent. dissolved by sonication. Use a mixture of diluent to make up the mark. Additionally, pour 1 ml into a 50 ml volumetric flask, add diluent, and thoroughly mix.

The standard solutions of Latanoprost were individually scanned between the wavelength range of 400 nm to 200nm. The obtained spectrum exhibited significant absorbance peaks.

The Latanoprost UV spectrum is acquired by scanning the wavelength range of 200 to 400 nm at a moderate scan speed. The obtained spectrum is then compared qualitatively to the spectrum obtained from a standard reference.

Preparation of Calibration curve:

Standard stock solution preparation involved carefully transferring a precise quantity of Latanoprost standard 1 mg into a 10 ml volumetric flask. The mixture was then sonicated to aid in dissolving after 7 ml of the diluent was added. The flask was then filled up to the mark with the diluent and thoroughly mixed. This stock solution was further diluted using appropriate volumes of diluent to prepare a series of linear solutions.

Compatibility study: To determine the compatibility of the selected excipients at the proposed concentration with the API, it is necessary to conduct a related substance analysis on drug-excipient combinations in the form of physical mixtures. The analysis of compatibility samples involved both visual observation and chemical analysis.

Visual Examination: The physical compatibility between the drug substance and different excipients was investigated to identify suitable excipients that would ensure stability and reliability. The samples were visually inspected, and their physical

characteristics were documented. Any changes in appearance were carefully noted and recorded.

Chemical Analysis: Initial samples were subjected to drug content analysis, where both the drug substance and mixtures of excipients were examined. The objective was to detect the presence of any additional component produced and then content of main drug will reduce. This determination gives clarity to any incompatibility of drug in presence of excipient. In chemical analysis of compatibility is a widely employed method for studying drug/excipient combinations and identifying potential incompatibilities.

Method for preparation of Latanoprost gel: Latanoprost ophthalmic gel was prepared using a stepwise compounding process. Accurately weighed quantities of Carbopol-940, HPMC K15M, HPMC E3, Latanoprost, benzalkonium chloride, EDTA, and Tris hydrochloride were used. Initially, Carbopol was dispersed in purified water to form a slurry. HPMC K15M and E3 were dissolved separately in water to form a homogeneous polymeric solution.

To create a clear drug solution, latanoprost was dissolved in ethanol and then diluted with water. EDTA and benzalkonium chloride were dissolved in water to form the preservative phase. The drug solution was added to the Carbopol slurry at 45 ± 5°C, followed by gradual addition of the HPMC solution and then the preservative phase under continuous stirring.

The pH was adjusted to 6.5 ± 0.5 using Tris hydrochloride buffer at 50 ± 5°C. Finally, purified water was added to adjust the final volume and viscosity. The formulation was aseptically filled into sterilized containers and sealed.

Specific Gravity (g/cm³): The density of a material in relation to water is measured by its specific gravity, sometimes referred to as its relative density. Specific gravity is usually calculated in respect to the densest state of water for solids and semi-solids, and to room temperature air for gases. The specific gravity of gel formulation was measured by densitometer - DMA 4200 M, manufactured by Anton Par.

Viscosity Measurement: After performing auto zeroing, the spindle is attached to the instrument, and the sample is gradually poured into the sample holder. The temperature is set to 25°C, and the instrument is operated according to the specified parameters. Once the desired spindle rotation speed, constant torque, and temperature are reached, the instrument is started in program mode. The average reading of the five replicate measurements is recorded and reported. The parameters for Brookfield Viscometer are as follows

Table 1. Parameters for Brookfield Viscometer

Spindle	LV1(61)
Sample Volume	8-10 ml (sufficient volume to depth the spindle)
Speed	75 RPM
Temperature	25°C
Time interval	20 Seconds
Readings	5
Torque	10-100%

Gel Strength: A 25 ml volume of the gel was added to a 50 ml graduated cylinder, and a 14 g weight was put on top of the gel. The gel strength, was evaluated by measuring the time in seconds required for the weight to penetrate 5 cm into the gel. All measurements were taken three times to ensure accuracy.

Osmolality: The osmolality of ophthalmic gel measure mOsmol/kg of gel formulation by osmometer. The measurement is important for eye formulation due to formulation comes direct contact into eyes. It measures the total concentration of dissolved particles in a solution.

In-vitro Drug Release Study:

Preparing Simulated Tear Fluid Medium: 0.67 grams of sodium chloride, 0.20 grams of sodium bicarbonate, and 0.008 grams of calcium chloride dihydrate were weighed and transferred into 100 milliliters of water with pH 7.4.

Preparation of standard solution: Weighed and transfer 1 mg of latanoprost standard into 20 ml volumetric flask add 2 ml methanol sonicated to dissolve add medium upto mark and mixed well. Further diluted 5 ml of stock solution to 50 ml with simulated tear fluid mixed well.

Procedure: Set the Franz diffusion cell, The cell consisted of glass donor and receptor compartment. add simulated tear fluid (STF) into the cell, this was placed on magnetic stirrer in the thermostatically controlled shaker bath. The temperature of the medium was maintained at 37°C ± 0.5°C. measured amount of gel formulation spread uniformly on a dialysis membrane which was in contact with receptor medium. The media of cell was stirred at 20 RPM for agitation. 1 ml of Samples were

withdrawn at periodic interval and same volume of fresh medium was replaced.

The release study sample were analysed using UV spectroscopy at 220 nm wavelength. simulated tear fluid (STF) as a blank solution and calculated the % release of drug.

Drug Content:

Preparation of solutions

Preparation of Buffer solution: To prepare the solution, measure and transfer 0.5 ml of orthophosphoric acid in 1000ml of water mixed well. The solution was thoroughly mixed.

Mobile phase preparation: A mixture was prepared by combining 0.5% orthophosphoric acid and Acetonitrile in a ratio of 30:70 v/v. The mixture was thoroughly mixed and subjected to sonication to remove any dissolved gases.

Preparation of diluent: The diluent was made up of a 15:85 v/v combination of water and methanol.

Preparation of Standard Solution for Latanoprost: Measure and transfer 2 mg of Latanoprost standard to a 50 mL volumetric flask. To promote dissolving, about 30 mL of diluent was added and the mixture was sonicated for 10 minutes. After cooling the solution to room temperature, it was filled to the mark with diluent. Then, 6 ml of standard solution was diluted into a 20 ml volumetric flask and mixed thoroughly with diluent. A 0.45µ PVDF membrane syringe filter was used to filter the fluid, which contained 12 ppm of latanoprost.

Preparation of Test Solution: Weight accurately 30gm of Latanoprost ophthalmic gel was carefully measured and transfer into a 50 volumetric flask with a wide mouth, 30 ml of a diluent was added to flask, followed by a 10-minute sonication process. After cooling, 2 ml of the mixture was diluted in a 50ml volumetric flask with diluent. After complete mixing, the solution was filtered using a 0.45µ PVDF membrane syringe filter (concentration of Latanoprost sample: - 12 PPM).

Procedure: The analysis was carried out in a precise order, beginning with the injection of a blank solution (diluent), followed by the injection of a standard solution (repeated six times). Finally, a sample solution was injected once. Chromatograms were recorded for each injection, and the peak areas (response) were measured. The percentage assay of the drug in the gel sample was determined using a specific formula.

3. RESULT

Organoleptic properties:

Table 2. Organoleptic properties

Properties	Observation
Colour	White colour powder
Taste	Bitter
Odour	Odourless
Appearance	Powder

Solubility study:

Table 3. Solubility Study

Solvent	Solubility (mg/ml)	Solubility
Water	32.5	Sparingly soluble
Alcohol	46.2	Very soluble
Ethyl acetate	42.8	Very soluble

Identification by IR Spectroscopy:

Take the 10 mg of Latanoprost API, this was individually mixed and thoroughly triturated in a mortar and pestle. The resulting mixture was then transferred onto a plate, and an infrared (IR) spectrum was obtained using the Diffused Attachment

reflectance mode.

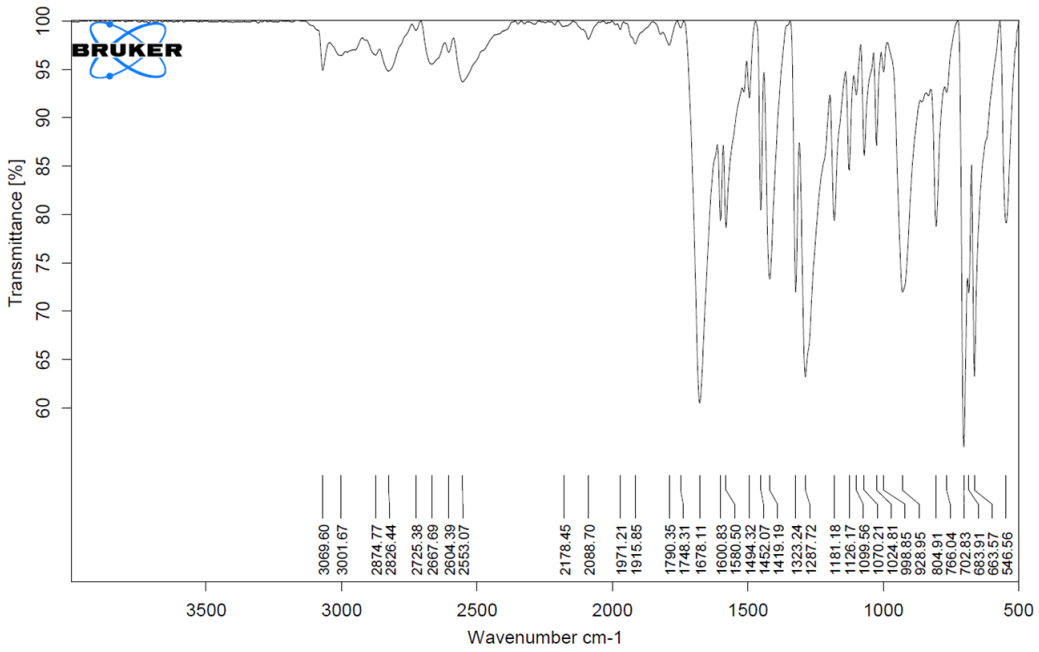

Figure 1. IR Spectrum of Latanoprost API

Table 4. IR peak Assignment value of Latanoprost

Standard IR Ranges (cm^{-1})	IR Ranges (cm^{-1})	Functional Group
3200-2700	3069.60	O-H Stretching
1688-1668	1678.11	C=C Stretching
1450-1375	1419.19	C-H Bending
1150-1085	1126.17	C-O Stretching

UV Spectroscopy:

The API's UV spectrum is acquired by scanning the wavelength range of 200 to 400 nm at a moderate scan speed. The obtained spectrum is then compared qualitatively to the spectrum obtained from a standard reference. An analytical wavelength of 220 nm has been chosen for analysis. 220 nm was selected as analytical wavelength.

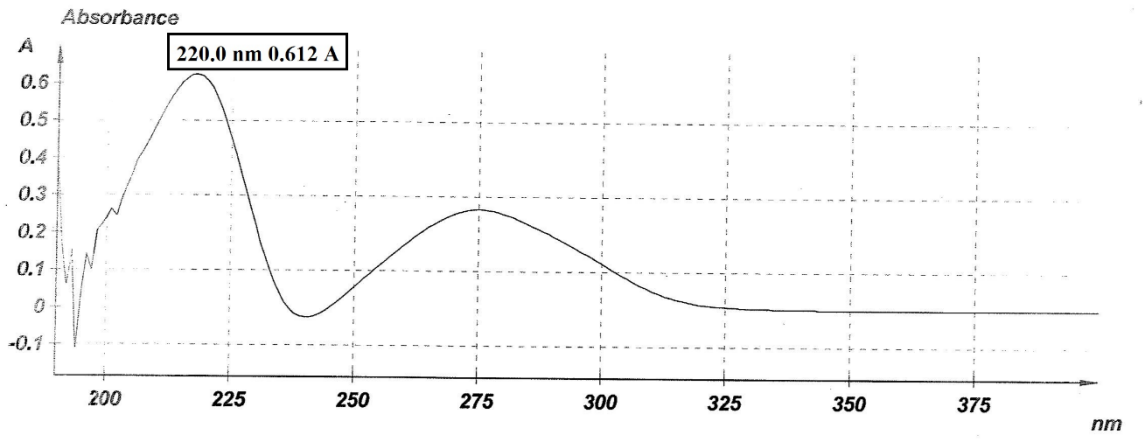

Figure 2. UV Spectrogram of Latanoprost

Preparation of calibration curve

The solutions were measured at a wavelength of 220 nm against a blank solution of water and methanol.

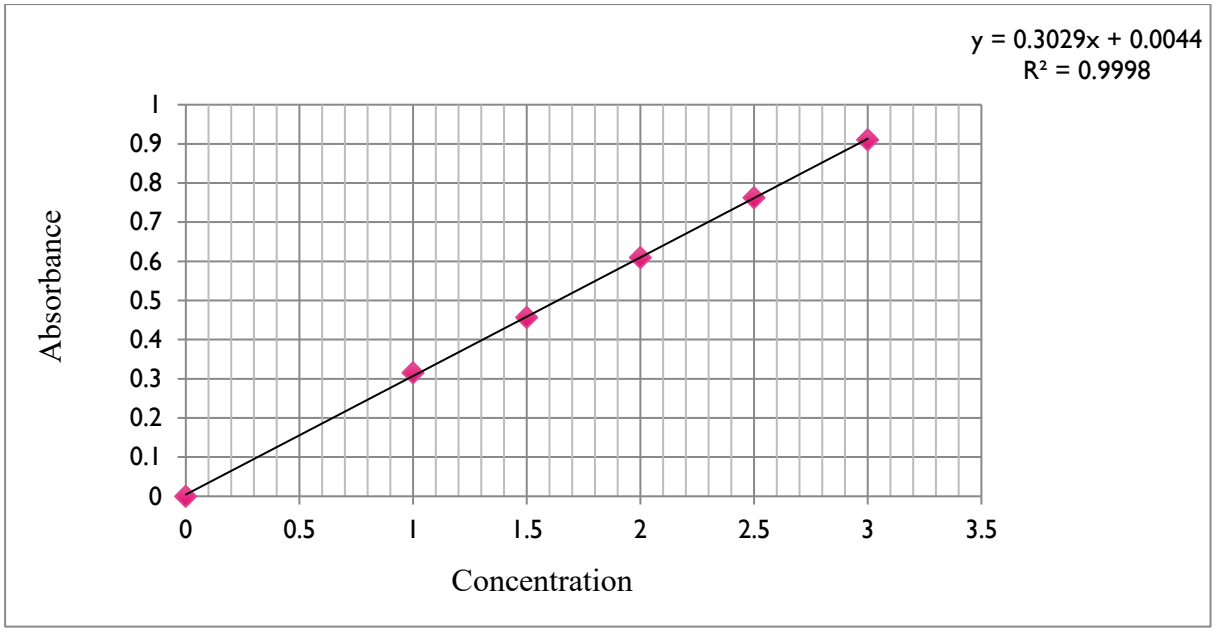

Figure 3. Calibration Curve of Latanoprost

Drug excipient compatibility study:

The compatibility between the drug and excipients was evaluated by analyzing mixtures of the excipient and drug substance using HPLC analysis. The performance of the excipients was assessed in the study of drug-excipient compatibility.

Table 5. Drug excipient compatibility study

Sr. No.	API + Excipients	Description	Drug content
1	API	Off white Powder	99.5%
2	API + Carbopol-940	Off white Powder	98.2%
3	API + HPMC K15M	Off white Powder	98.4%
4	API + HPMC E3	Off white Powder	98.1%
5	API + Propylene glycol	White to off white Powder	99.4%
6	API + Benzalkonium Chloride	White Powder	99.5%
7	API + EDTA	White Powder	99.6%
8	API + Tris Hydrochloric acid	Clear solution	98.4%
9	Placebo	Off white Powder	99.2%

Specific Gravity

The ophthalmic gel should be free from particles because of it directly comes into a eyes contact. The specific gravity measures the weight per ml of gel formulation.

Table 6. Specific Gravity of all formulated trial batches

Sr. No	Formulation Trial	Specific Gravity
1	F1	1.212
2	F2	1.204

3	F3	1.191
4	F4	1.211
5	F5	1.216
6	F6	1.196
7	F7	1.207
8	F8	1.184
9	F9	1.157
10	F10	1.161

Viscosity

The viscosity of all trial's formulation batches are as follows

Table 7. Viscosity of all formulated trial batches

Sr. No	Formulation Code	Viscosity
1	F1	204
2	F2	199
3	F3	208
4	F4	240
5	F5	290
6	F6	334
7	F7	325
8	F8	298
9	F9	283
10	F10	285

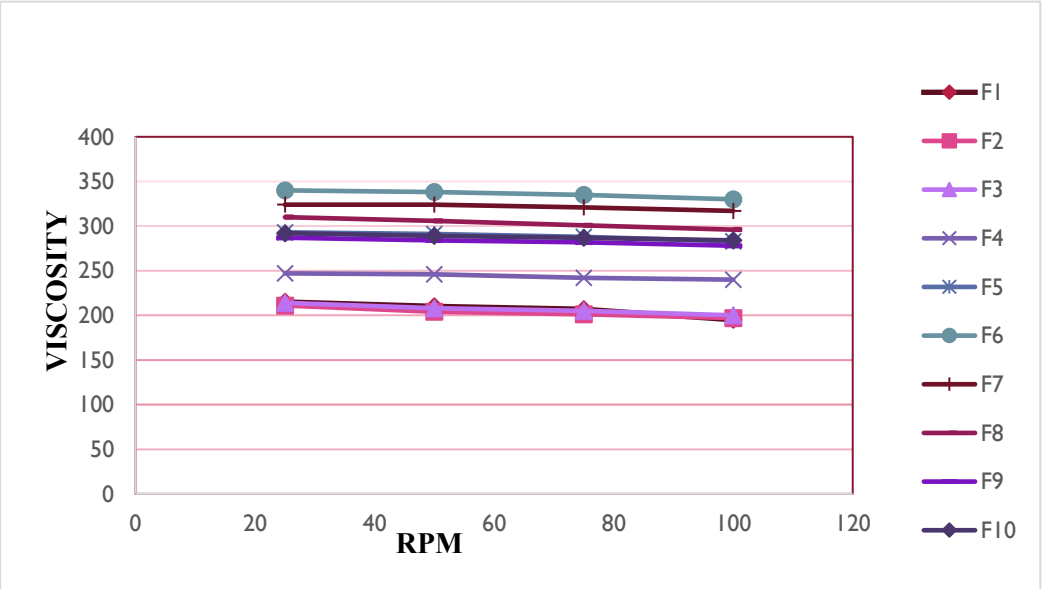

Figure 4. Comparison of viscosity of formulation trials batches from F1 to F10

Gel strength:

The concentration of the gelling agent and bioadhesive polymers, as well as the pH, were identified as factors influencing the gel strength. An effective bioadhesive gel should have an acceptable gel strength, allowing for simple administration and retention in the ocular area without leakage. The gel strength of all formulas showed identical findings as the viscosity tests.

Table 8. Gel strength of all formulated trial batches

Sr. No	Formulation Code	Gel strength
1	F1	1.08
2	F2	1.05
3	F3	1.12
4	F4	1.32
5	F5	1.50
6	F6	1.71
7	F7	1.67
8	F8	1.42
9	F9	1.41
10	F10	1.45

Osmolality

The osmolality of ophthalmic gel was for compatibility with eye fluid.

Table 9. Osmolality of all formulated trial batches

Sr. No	Formulation Code	Osmolality mOsmol/kg
1	F1	312
2	F2	305
3	F3	310
4	F4	301
5	F5	280
6	F6	273
7	F7	261
8	F8	314
9	F9	302
10	F10	295

In vitro drug release Study:

The drug release characteristics of various trial batches (F1 to F10) were investigated using tear fluid media in an in-vitro study by Franz diffusion cell. Drug release profiles were examined at specific time points, including 0, 0.50, 1, 2, 3, 4, 6, and 8 hours.

Table 10. % drug release of formulation trial batches.

Time point	% drug release in tear fluid for different trials									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
0.50	38	42	35	52	54	40	39	74	72	68
1	45	50	48	71	70	52	54	84	85	82
2	57	66	60	80	75	64	62	90	89	90
3	66	71	76	86	82	74	75	93	94	94
4	81	82	84	91	90	88	86	96	98	97
6	87	88	91	95	92	91	93	98	100	99
8	92	93	94	97	96	96	95	99	100	100

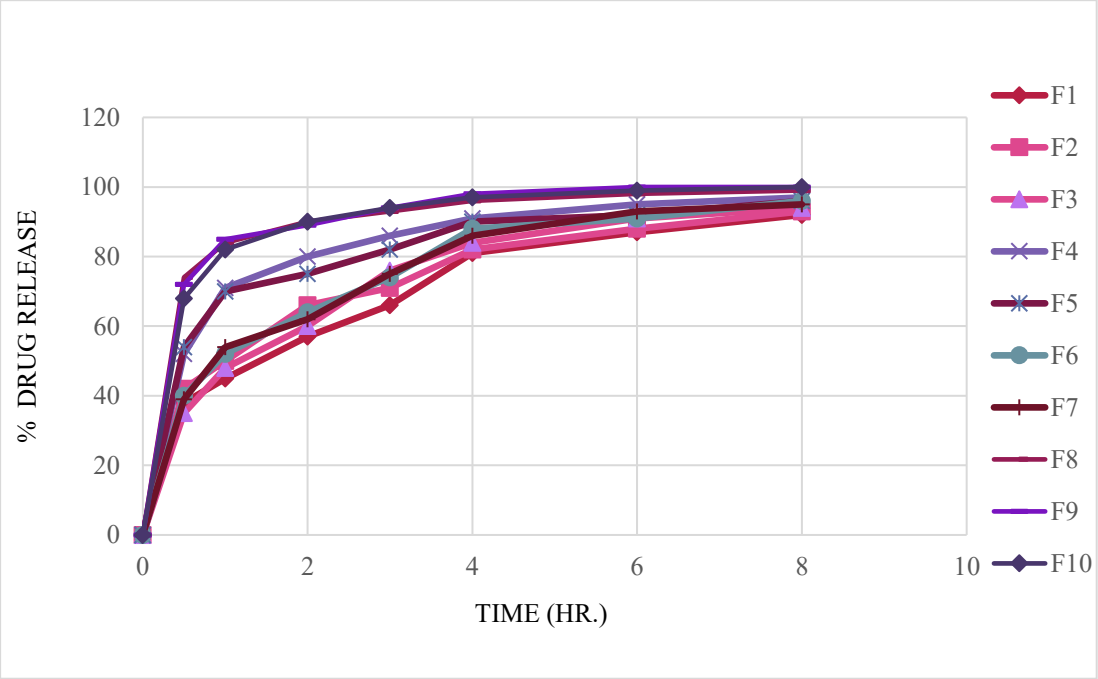

Figure 5. % drug release in tear fluid for different formulation trials batches

Test of Sterility:

The formulation was incubated for 14 days at 20-25°C in fluid thioglycolate medium and soybean-casein digest media. During this time, no turbidity or bacterial growth was seen. As a result, the preparation successfully passed the sterility test.

Table 11. Condition for the test of sterility

Method of sterility test	Direct incubation
medium	Soyabean casein digest
Volume of individual test solution	5 ml
Positive control	Staphylococcus aureus-incubated sterilized media
Negative control	Sterile media

Incubation time	14 days
Incubation temp	20-25°C for bacteria
Method for detection	Visual examination of turbidity

4. CONCLUSION

This study successfully formulated and evaluated a latanoprost ophthalmic gel aimed at addressing the limitations of traditional eye drops. Mucoadhesive polymers such as Carbopol 940 and HPMC were included into the gel to provide it the desired viscosity and structural integrity, which guaranteed continuous drug release and extended precorneal residency. Essential pharmacological requirements, such as optimal pH, suitable osmolality for ocular comfort, and efficient gel strength for irritation-free retention, were satisfied by the improved batches. The gel's ability to sustain steady medication levels throughout time, minimizing the need for frequent application, a major obstacle in the treatment of chronic glaucoma was demonstrated by the in vitro drug release tests.

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