INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUATION OF OPHTHALMIC IN-SITU GEL OF TRAVOPROST

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ABSTRACT

In the present study, an attempt to formulate in-situ gel of Travoprost for controlled ocular delivery was undertaken. The formulation was carried out with a thermosensitive polymer Poloxamer 407 and a mucoadhesive polymer Carbopol 934. The prepared formulations were studied for physical appearance, pH, gelling time, gel duration, gelation temperature, viscosity, drug content, drug diffusion and other characteristics ideally required for in situ gelling systems. FTIR studies established the compatibility of drug and selected excipients. Stability studies as per ICH guidelines established the stability of the formulation. The study revealed that in situ gelling system can provide a controlled ocular drug delivery of Travoprost upto 8 hours.

Key Words: 1 Travoprost, Poloxamer 407, Carbopol 934, in-situ gelling system**.**

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INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists. Ophthalmic in situ gelling systems are the formulations, in which the drug is in solution form on storage and exhibits sol-to-gel transition upon instillation into the cul-de-sac of the eye. This system combines the advantage of solution and gel, i.e., accurate and reproducible administration of drug and prolonged residence time.

Glaucoma is a group of eye diseases which result in damage to the optic nerve and vision loss (the intraocular pressure >21mmHg). Travoprost is a prostaglandin analogue used for controlling the progression of glaucoma or ocular hypertension, by Reducing intraocular pressure (1-3).

Materials

Travoprost, Poloxamer 407 and Carbopol 934 were Purchased from Medwin chemicals, Malappuram, Kerala. All other chemicals, reagents and solvents used were of analytical grade.

Drug- excipient compatibility study

The infrared (IR) spectra were recorded using an FTIR spectrophotometer .The spectra obtained for Travoprost and physical mixtures of Travoprost with other excipients were compared to check compatibility of drug with excipients.

PREPARATION OF FORMULATION

Preparation of Ophthalmic in-situ gelling drug delivery systems

The required volume of distilled water was cooled down to 4°C. To this the weighed quantity of Poloxamer 407 was then slowly added to the cold water with continuous stirring. The dispersions were stored in a refrigerator at 4°C overnight for complete solvation. Travoprost solution was prepared and added in small volumes into polymeric solution with stirring. The stirring was continued for 10 min to obtain a homogenous mixture. Carbopol 934 solution was prepared by dissolving Carbopol 934 in distilled

water and added to the above solution. This was followed by addition of Benzalkonium chloride (0.01%w/v), Sodium chloride (0.9%w/v) and EDTA, and mixed. The pH of the solution was adjusted to 7.4 by adding 0.1N NaOH. The samples were then stored at 4°C prior till further analysis (Table-1).

Table-1 Formulation of Travoprost in-situ gel

INGREDIENTS	F1	F2	F3	F4
	(%w/v)	(%w/v)	(%w/v)	(%w/v)
Travoprost	0.004	0.004	0.004	0.004
Poloxamer 407	18	18	18	18
Carbopol 934	0.25	0.5	1.0	1.5
Benzalkonium Chloride	0.01	0.01	0.01	0.01
Sodium Chloride	0.9	0.9	0.9	0.9
EDTA	0.001	0.001	0.001	0.001
Purified water (q.s)	100	100	100	100
Sodium hydroxide (0.1N for pH adjustment)	q.s.	q.s.	q.s.	q.s.

EVALUATION OF FORMULATIONS (4-6)

Physical Appearance

The physical appearance of all the formulations was visually inspected to check the clarity.

pH

The pH of prepared travoprost ophthalmic solution was determined by using a digital pH meter.

Thermosensitivity Evaluation

The thermosensitivity of Travoprost ophthalmic solution was determined uing the parameters like Gelation temperature, Gelling time, Gel Duration.

Drug content

Drug content was determined by taking 1ml of the Travoprost ophthalmic solution and diluting it to 100ml with distilled water. 5ml of the above solution was withdrawn and further diluted to 25 ml with distilled water. Concentration was determined by using UV visible spectroscopy at 280 nm.

Viscosity

The rheological measurements were calculated using Brookfield viscometer.

Isotonicity

Few drops of formulation were mixed with few drops of freshly drawn blood and then taken into a slide. The slide was observed under 45 x magnifications for any change in shape of blood cells.

***In Vitro* Drug Release**

In-vitro release study of the solution was carried out in Franz diffusion cell. The formulation was placed in the donor compartment and freshly prepared simulated tear fluid was filled into the receptor compartment. In between donor and receptor compartments, cellophane membrane was placed. The whole assembly was placed on a thermostatically controlled magnetic stirrer and the temperature was maintained at 37 ± 0.5°C. 1 ml of sample was withdrawn at the intervals of 1 hour till 8^{th} hour. Every time the sample was withdrawn, the same volume of fresh medium was replaced. The withdrawn samples were analyzed using spectrophotometer at 280 nm.

Stability Studies

Development of any pharmaceutical product is not complete without proper stability analysis. The stability studies were carried out to assess physical and chemical stability of the product. Stability refers to chemical and physical integrity of dosage unit to maintain protection against physical, chemical and microbial contamination. Stability testing was performed as per ICH guidelines for optimized formulation at 40± 2°C and 75 ± 5 % RH, for a period one month. On completion of stability period the samples were withdrawn and estimated for physical appearance, pH, gelling time, gel duration, gelation temperature, viscosity, isotonicity, drug content and drug diffusion.

RESULTS AND DISCUSSIONS

Determination of solubility

Solubility of Travoprost was performed in various solvents like water and ethanol, and it was found that the drug is soluble in phosphate buffer and water.

Drug-polymer interaction study

The IR Spectra of Travoprost, the mixture of drug with polymer are given in the figure. All the samples were scanned over the wave number region 4000-400 cm-1 using KBr disk method. The selected formulation shows the characteristics peak similar to that obtained in the pure Travoprost indicating that there were no incompatibility between the drug and the excipients used.

Table-2 Evaluation of formulations for appearance, pH, Gelling time, Gelling duration and Gelation temperature

Formulation Code	Polymer concentration (%w/v)	Physical Appearance	pH	Gelation temperature (ºC)	Gelling Time (sec)	Gel Duration (minutes)
F1	0.25	Clear	7.3	34.8 ± 0.82	54±2	590
F2	0.5	Clear	7.3	34.6 ± 0.75	54±1	600
F3	1.0	Clear	7.4	34.8 ± 0.31	55±2	610
F4	1.5	Clear	7.5	34.2 ± 0.75	60±2	620

Drug Content

The drug content was found to be in acceptable range for all the formulations indicating uniform distribution of drug. The percentage drug content of formulations varies from 95-97%.

Viscosity

Viscosity is an important parameter of in-situ gelling systems which impart ideal rheological property to them. Viscosity of formulations F1-F4 was measured at 25 ± 0.5°C and 37 ± 0.5°C representing the storage and the body temperature. Viscosity studies of formulation exhibited a temperature dependent increase in viscosity. The viscosity of solution was recorded low at 25 ± 0.5°C but there was a significant increase in viscosity of the gels at 37 ± 0.5ºC due to sol-gel conversion. The viscosity of formulations at 25 ± 0.5°C was found in the range of 1326 to 1651 cps. When the same formulations were studied for viscosity at 37 ± 0.5°C, a substantial increase of viscosity was observed; the viscosity values of 38450 to 42360 cps were recorded. The rpm was set at 100 for all trials. Viscosity increased with increase in concentration of Carbopol 934 (Table-2).

Isotonicity

The isotonicity test for F1-F4 formulation was performed by mixing few ml of blood and prepared formulation and observed by optical microscopy at a magnification of 45 xs. A sample of blood alone was used as control. Upon viewing on microscope, it was observed that, there was no change in shape of blood cells, i.e., no swelling or shrinkage was observed when compared with that of normal blood cells. This confirms that prepared formulations are isotonic in nature (Table-2).

In Vitro Drug Release

The results of *in vitro* diffusion studies indicated that drug release was in a sustained manner. The concentration of Poloxamer 407 was kept constant in all the formulations and mucoadhesive polymer concentration was varied to evaluate its effect on drug release from in-situ gels. The drug release from in-situ gels was affected by the concentration of thermosensitive polymer and mucoadhesive polymer incorporated. *In vitro* diffusion study of F1 with 0.25%w/v of Carbopol 934 resulted in drug release which extended upto 2 hours (85.25±0.26%). Since the objective was to sustain the drug release over a period of 8 hours, the Carbopol 934 concentration was increased to 0.5%w/v. It was observed that, as Carbopol 934 concentration increased, release could be sustained upto 4 hours (93.39±0.07%). In F3 formulation, Carbopol 934 concentration was further increased to 1.0%w/v, which resulted in a sustained

drug diffusion upto 6 hours. The drug release was also found to be almost complete with 98.05±0.18% in 8 hours. Based on the above study, it was concluded that 1.5%w/v of Carbopol 934 is the optimum concentration as a mucoadhesive polymer (Fig-1).

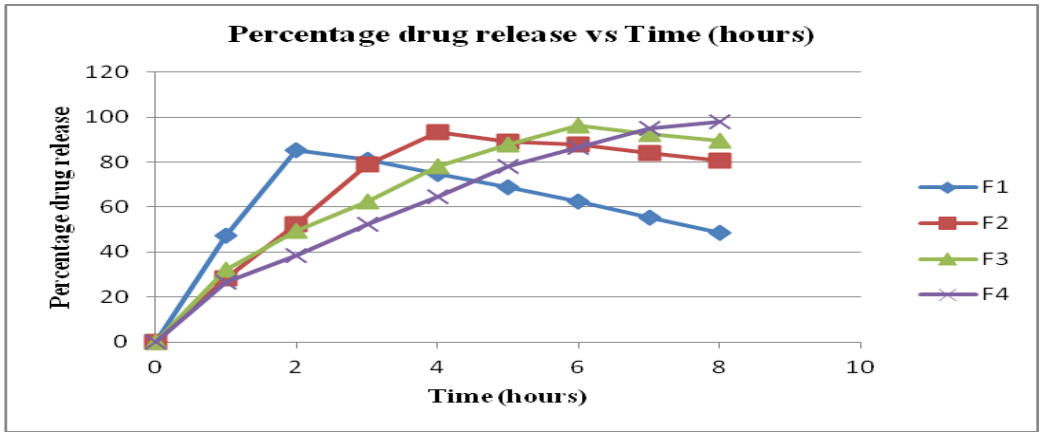

Fig- 1 *In vitro* release profile of F1-F4

Stability Studies

Stability studies were used to determine the shelf life and storage condition of a product. Accelerated stability studies were performed in accordance with ICH guidelines with certain modifications. The studies were carried out for formulation F4, to verify the changes in physical appearance, pH, gelling time, gel duration, gelation temperature, viscosity, drug content and drug diffusion at (40 ± 2^0C) for 1 month. The evaluation of formulations after stability charging showed that there were no significant changes in the test parameters with respect to results obtained before stability charging. Thus it was concluded that the formulations were found to possess stability compliance requirements as per ICH guidelines.

CONCLUSION

The study undertaken concluded that the formulated in-situ gels of Travoprost provided a controlled drug release over 8 hours. But further clinical studies and bioavailability studies are required to prove the safety of use of this formulation for use in humans.

REFERENCES

1. D Jothieswari, B Chandra Obula Reddy, Shaik Soniya, S Karishma, Yarava Dharshini and Kandra Roja. Method development and validation of simultaneous estimation of timolol maleate and travoprost in bulk and in pharmaceutical dosage form by uv-spectroscopy. *Journal of Pharmaceutical Biology*, 7(1), 2017, 22-32.
2. Indian Pharmacopoeia.*The Indian Pharmacopoeia Commission Ghaziabad*; 2007; Volume 1: 45-55, 244, 544-545.
3. Suresh V Kulkarni *, Sandeep HN, Shankar MS, Ranjit Kumar P, Someshwara Rao B, Ramesh B, Ashok Kumar P, effect of a single drop of latanoprost ophthalmic gel on intra ocular pressure in the treatment of glaucoma. *Int.J.Ph.Sci.*,Jan-April 2010;2(1):429-435
4. Maheswara Reddy C, Firoz S, Rajalakshmi R, Ashok Kumar CK. Design and Evaluation of Chloramphenicol Thermoreversible Insitu Gels for Ocular Drug Delivery. *IJIPR;* 2011; 2(2): 131-38.
5. KameswararaoSankula, Saieswar Kota, SrinathNissankarrao. A Review on Design and Development of Thermosensitive Ocular in Situ Gel Ophthalmic Formulation. *AJBPR*; 2014 Nov 18; 1(1):22-27.
6. SirishVodithala, SadhnaKhatry, NaliniShastri, M. Sadanandam. Development and Evaluation of Thermoreversible Ocular Gels of Ketorolac Tromethamine. *International Journal of Biopharmaceutics*; 2010; 1(1): 39-45.