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DEVELOPMENT OF STABLE LATANOPROST OPHTHALMIC COMPOSITION USING NANOEMULSION APPROACH

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Abstract: Latanoprost is water insoluble and is unstable against heat stress due to hydrolysis of the isopropyl ester in the latanoprost molecule. Therefore, the storage condition of latanoprost ophthalmic solution, Xalatan® brand, was in a cold temperature (2–8^{o}C). We formulated a favorable ophthalmic nanoemulsion of latanoprost using poloxamer as emulsifier which showed good heat stability. The assays of the latanoprost ophthalmic nanoemulsions adjusted to pH 5.5, 6.5 and 7.5 were 100.8%, 100.6% and 99.4% after storage for 8 weeks at 60^{o}C, respectively. The possibility of room temperature storage for the latanoprost ophthalmic nanoemulsion was demonstrated.

Keywords: Latanoprost; Ophthalmic nanoemulsion; Poloxamer; Stability

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INTRODUCTION

Formulation studies of ophthalmic preparations have often been confronted with a problem of drug instability in water. Drugs that were unstable in water were formulated by the addition of stabilizing agents such as antioxidant agents and chelating agents.[1] Epinephrine solution was prevented from oxidative degradation by the addition of ascorbic acid.[2] Another approach is to keep the drugs in a cold storage temperature to suppress decomposition reactions. There are many ophthalmic products that should be stored in a refrigerator at cold temperature, [3] but it may impair compliance and the convenience of patients.

Latanoprost ((+)-isopropyl (Z)-7-[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxyl -5-phenylpentyl]cyclopentyl]-5-heptenoate) is an ester prodrug analogue of prostaglandin F2a that has been investigated for potential treatment of primary open-angle glaucoma and ocular hypertension (Fig. 1). [4-6]

Xalatan® (Pfizer, NY, USA), latanoprost ophthalmic solution, has been exploited commercially in many countries in the world. The storage condition of Xalatan® is at cold temperature (2–8^{o}C). Latanoprost is not stable in water against heat stress, [7] which is probably due to hydrolysis of isopropyl ester in latanoprost molecule.

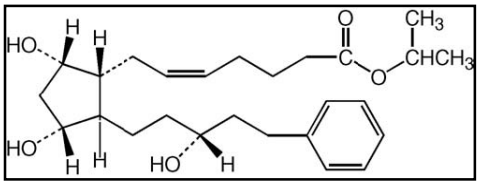

Figure 1: Latanoprost

Preparation of an oil-in-water (o/w) type nanoemulsion is one of the approaches to stabilize a drug that is unstable in water if oil/water partition co-efficient of the drug is high, because there is little water in the oil phase of the emulsions. Although emulsifier is needed to manufacture nanoemulsions, high concentration of surfactants may cause ocular toxicity hence here we used the approved daily intake quantity of poloxamer.[8] Water-soluble polymers [9] were used as emulsifiers instead of surfactants, since they can form a thick adsorbed layer, which would play a role of stabilizer of oil droplets.[10] Poloxamer is widely accepted to pharmaceutical preparations due to its history of usefulness, stabilization and safety.[11]

Latanoprost ophthalmic preparation stable at room temperature is a requisite. Therefore, we formulated latanoprost ophthalmic nanoemulsion having good stability against heat stress using Poloxamer as an emulsifier.

Experimental

Material and Methods

Latanoprost was purchased from Sai Advantum Ltd., Hyderabad. Xalatan® purchased from local pharmacy shop and was used as control formulation in stability experiments. Super refined castor oil was procured from Croda Chemicals, Mumbai as gift sample. Poloxamer was procured from Signet Chemicals, Mumbai. Milli-Q 0.2 µ filtered purified water were used. Acetonitrile (HPLC grade) was purchased from Merck Specialties. Other reagents for formulations were Pharmacopoeial grade and for analysis HPLC grade or the high purity grade commercially available.

An HPLC system (LC2010 C_{HT}, Shimadzu, Japan) was composed of an autosampler, a pump, a UV detector and data processing software (LC Solution). An octadecyl silica column (Inertsil 3V, 250mm, 4.6 mm i.d., 5 µ) was used. Analysis of latanoprost was carried out using 63% (v/v) acetonitrile containing 1.7% diluted phosphoric acid aqueous solution and 37% v/v water as mobile phase at a flow rate of 1.0 ml/min at 25°C. Detection was performed at 200 nm. The injection volume was 50 µl.

To find the most suitable oil for our formulation super refined castor oil (0.5% w/v), latanoprost (0.005% w/v) was dissolved in the same by high speed stirrer at 16000 rpm for 10 min at room temperature. Prepared aqueous solution of Poloxamer, sodium chloride as tonicity agent, sodium phosphate as buffer and adjust the pH using suitable acidic or alkaline solution.

Oil-in-water emulsions adjusted to pH 5.5, 6.5 and 7.5 were prepared containing latanoprost (0.005% (w/v)), super refined castor oil (0.5% w/v) as oil phase, Poloxamer (0.2% w/v) as emulsifier, and sodium chloride (0.6% w/v) or sodium phosphate (0.8% w/v) as a buffering agent. Preparation of emulsion was performed in three steps. As the initial step, 600 ml of water was placed in 1000 ml glass beaker, and Poloxamer (2.0 g), sodium chloride (6.0 g), sodium phosphate and filtered through fluorodyne membrane (FTKDFL, Pall Corp.) were then added to the water and dissolved at 40°C. Separately, latanoprost (0.05 g) was dissolved in super refined castor oil (5.0 g) at 30°C. The super refined castor oil containing latanoprost added to the solution previously heated to 40°C and emulsified by a homogenizer (Ultra Turrax T25, IKA) at 16000 rpm for 10 min. The coarse-emulsion was obtained after adjusting to a fixed volume by water (700 ml). As the second step, the coarse-emulsion was treated by a high-pressure emulsifier (Panda 2K, GEA). The inlet pressure was 110 bar. The individual batches were processed through HPH for 5 discrete volume cycles, and collected into glass beakers. To cool the emulsion, running water, of which the temperature was controlled at 15°C around the metal coil, dissipated the heat produced during the homogenization process. After the treat-

ment, the nanoemulsion was cooled to room temperature (25°C). As the third step, suitable acidic or alkaline aqueous solution adjusted at pH 5.5 and 6.5, and 7.5. The nanoemulsion was diluted by adding the purified water, and then recheck the final pH.

Latanoprost ophthalmic nanoemulsion was filled in 5 ml polyethylene three piece controlled drop containers for ophthalmic. Latanoprost ophthalmic solution, Xalatan®, was also packed in polyethylene container. The nanoemulsion and the solution were stored for an appropriate period at 25°C, and the latanoprost content was monitored in a single assay by HPLC during the stability program.

Results and Discussion

We selected Poloxamer, which is a water-soluble polymer, as emulsifier of the nanoemulsion due to its history of usefulness and safety in the ophthalmic area and itself containing BHT that helps to prevent the product from oxidative degradation.

The nanoemulsion containing 05% (w/v) super refined castor oil and 0.2% (w/v) Poloxamer was prepared using a high-pressure homogenizer. Stability of latanoprost ophthalmic nanoemulsion was examined in polyethylene controlled drop containers. Results of stability were summarized in Table 1.

Table 1

Stability of latanoprost ophthalmic nanoemulsions and Xalatan®

Formulation	Storage condition (°C)	Assay of Latanoprost (%)			
		Initial	1 week	4 weeks	8 weeks
Ophthalmic nanoemulsion (pH 5.5)	25°C	100.0	102.1	99.7	101.2
	60°C	100.0	103.5	99.7	100.8
Ophthalmic nanoemulsion (pH 6.5)	25°C	100.0	100.4	99.3	100.5
	60°C	100.0	99.3	99.1	100.6
Ophthalmic nanoemulsion (pH 7.5)	25°C	100.0	100.0	98.2	99.8
	60°C	100.0	99.0	100.3	99.4
Xalatan® (pH 6.5–6.9)	25°C	100.0	100.7	101.4	98.5
	60°C	100.0	94.4	86.5	76.4

Latanoprost content in Xalatan® decreased to 76.4% after storage for 8 weeks at 60°C. In contrast, latanoprost in ophthalmic nanoemulsions with water phase adjusted to pH 5.5, 6.5 and 7.5 was very stable, and the assays were 100.8, 100.6% and 99.4% after storage for 8 weeks at 25°C, respectively. Latanoprost concentrations in water phase of the emulsions adjusted at each pH were under detection limit by HPLC

(detection limit 51.7 ng/ml, SN = 3). The results suggested that the oil/water partition co-efficient of latanoprost was sufficient to confine it in oil phase and pH of the emulsions did not affect the oil/water partition coefficient of latanoprost. Decrease of latanoprost content both in Xalatan® and in ophthalmic nanoemulsions was not observed under experimental condition for 8 weeks at 25°C, and the contents were 98.5%, 101.2%, 100.5% and 99.8% in Xalatan® and ophthalmic nanoemulsion adjusted at pH 5.5, 6.5 and 7.5, respectively. The results were supported by the report of Morgan et al. (2001), which mentioned that the stability of latanoprost was strongly temperature-dependent.

Conclusion

In the present study, stability of latanoprost in an ophthalmic nanoemulsion was examined. The stability of latanoprost was improved in the ophthalmic nanoemulsion, although there is limited stability data due to an ongoing investigation. The possibility of the storage at room temperature for the latanoprost ophthalmic nanoemulsion was demonstrated. The physicochemical stability of the ophthalmic nanoemulsion containing latanoprost should be further investigated.

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