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FORMULATION AND EVALUATION OF UNOPROSTONE ISOPROPYL OPHTHALMIC SOLUTION, 0.15% W/V

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ABSTRACT

Glaucoma is a progressive, neurodegenerative optic nerve disease that can cause significant visual morbidity and affects over 60 million people worldwide. The latest marketed product in the form of ophthalmic solution to treat the glaucoma is RESCULA® with a novel prostaglandin analogue, Unoprostone Isopropyl as active ingredient at 0.15% w/v. Characterization by laser diffraction of the marketed product revealed the drug product in the nano emulsion form. The API, Unoprostone Isopropyl is a clear colorless viscous oily liquid, practically insoluble in water and poorly permeable. The formulation utilized 1% Polysorbate 80 as solubilizer; 0.05% Disodium Edetate as preservative, chelating agent and antioxidant; 0.015% Benzalkonium Chloride as preservative; 4.3% Mannitol as osmotic agent; Sodium Hydroxide / Hydrochloric Acid at quantity sufficient for pH adjustment. The final product was sterilized through filtration using polyvinylidine filters. The filtrate was packed in Low Density polyethylene bottle with dropper insert capped with High Density Polyethylene closure. The stability of the product was evaluated and found to be stable in both upright and horizontal position at ICH recommended accelerated stability condition of 40°C / 25% RH.

KEYWORDS: Sonication, Sterile filtration, Stability.

INTRODUCTION

Unoprostone Isopropyl is a prostaglandin analogue indicated for lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1] Unoprostone Isopropyl is a clear colourless viscous oily liquid, practically insoluble in water

and poorly permeable.[2] The challenging aspect is to formulate the insoluble oily API into solubilized ophthalmic solution. The brand / reference / marketed product, RESCULA® available in the market comprises 1.5 mg Unoprostone Isopropyl, 0.015% Benzalkonium Chloride, Mannitol, Polysorbate 80, Edetate Disodium, Sodium Hydroxide, Hydrochloric Acid and Water For Injection packed in bottle, dropper tip made of Low Density Polyethylene and caps made of polypropylene polymer.[3] In this research, drug product was designed utilizing brand listed ingredients and ensured comparable Physico-chemical attributes and stability to that of the marketed product. Moreover to achieve cost effectiveness, the finalized composition was stabilized and packed in bottle, dropper tip made of Low density polyethylene and caps made of cheaper and widely available HDPE polymer. Glaucoma is a progressive, neurodegenerative optic nerve disease that can cause significant visual morbidity and affects over 60 million people worldwide.[4] By making a cost-effective generic ophthalmic solution of Unoprostone Isopropyl, it will impart greater benefit by reducing the intraocular hypertension thereby restoring the eye sight of diseased population at large.

LITERATURE

Youmin Wang and team investigated the stability of an ophthalmic solution formulation of Unoprostone isopropyl (UI), a prostaglandin like compound, in two types of packaging materials, polypropylene (PP) and low-density polyethylene (LDPE).[5] Remo Susanna Jr and team reviewed the recent literature available on the clinical efficacy of prostanoids namely Latanoprost and Unoprostone Isopropyl as well as the studies directly comparing these drugs.[6] Patents relevant to synthesis, method of uses of the drug product and composition of the drug product includes US 5001153, US 5151444, US 5166178, US 5212200, US 5208256, US 5221763, US 6458836 and US 6770675.[7]

OBJECTIVE

The objective is to develop an ophthalmic solution of Unoprostone Isopropyl, 0.15% w/v which would be comparable to the marketed product, RESCULA® with respect to physico-chemical properties and stability characteristics.

MATERIALS AND METHODS

Materials

Unoprostone Isopropyl from Yonsung; Mannitol from Roquette; Polysorbate 80, Edetate Disodium, Sodium Hydroxide and Hydrochloric Acid from Avantor Performance Materials;

Benzalkonium Chloride from FeF Chemicals; LDPE dropper bottles, LDPE dropper inserts and HDPE closures from Clinicare;

Equipments / Instruments

Osmometer of Fisher Scientific; Dissolved Oxygen Meter of Hanna Instruments; Stopwatch of Casio; Micro & Ultramicro balance of Mettler Toledo; Viscometer of Brookfield; Particulate Counter of Particulate Measuring Systems; Malvern Zetasizer of Malvern Instruments; Aseptic Filtration System of Merck Millipore; 0.22 micron PVDF Filter and Filter Cartridge of Merck Millipore; Laminar Flow Hood of Krishna Scientific Suppliers; Sonicator of Fisher Scientific; Nitrogen Cylinder with gauge & Oxygen Cylinder with gauge of DC Ranganathan Agency; Photostability chamber, 40°C / 75% RH stability chamber, -20°C Stability chamber, 55°C Stability chamber, 30°C / 65% RH Stability Chamber, 2-8°C Stability chamber, 40°C / 75% RH stability chamber, Hot Air Oven and Autoclave of Thermolab Scientific Equipments; Microscopic Particle Count using SMZ-168-TP Motic Trinocular Stereomicroscope equipped with MT3i camera, PM-LED illuminator and IMT i-solution software; HPLC of Waters; UV Spectrophotometer of Shimadzu; FTIR of Thermofisher; pH Meter of Hanna Instruments and Lab Stirrer of Remi Motors.

METHODS

Sterility test, Osmolality & Osmolarity, pH, Viscosity, Particle Size Distribution, Preservative Efficacy Testing, Water Conductivity, Deliverable Volume, Minimum Fill, Particulate Matter, Specific Gravity, Light diffraction measurement of particle size, Anti-microbial agents content, Pyrogen test, Bacterial Endotoxin test, Antimicrobial effectiveness testing, Visible particulates, Method of Analysis of Mannitol, Edetate Disodium, Benzalkonium Chloride and Polysorbate 80 were done as per USP.

EXPERIMENTATION

API Characterization

Unoprostone Isopropyl was characterized with respect to Appearance, Water, Related Substances, Assay and Solubility.

Marketed Product Characterization

The marketed product was characterized for quantitative amounts of in-actives viz Mannitol, Polysorbate 80, Edetate Disodium, Benzalkonium Chloride by HPLC; Appearance, Fill Volume, Drop weight, pH, Specific gravity, Osmolality, Viscosity, Buffering Capacity,

Preservative Content, Microscopic Particle Count, Assay, Related Substances, Particle Size, Zeta Potential Conductivity and Packaging configuration.

Preliminary Formulation

In about 3/4th of the stated quantity of Sterile Water For Injection Mannitol, EDTA Disodium, Benzalkonium Chloride and Polysorbate 80 were dissolved and the pH of the solution was adjusted to 5.75 ± 0.75 with 1N NaOH or 1N HCl and then API was dissolved in the pH adjusted solution and finally the volume was made up with Sterile Water For Injection. Then the whole solution was filtered through 0.22 micron PVDF filter. The whole activity was carried out under aseptic environment in Laminar Flow Hood. The prototypes were evaluated for Description, Assay (Before & after filtration), Related Substances and pH. The samples were also stability evaluated for the same tests mentioned.

Manufacturing Process Optimization

The batch size of the drug product was scaled up from 250 mL batch size (Prototype) to 6000 mL batch size. The final filtered drug product was characterized for the following studies.

Manufacturing Processing Condition

To study the effect of oxygen on the product and to evaluate the need of inert atmosphere during the processing conditions, experiments were carried out to compare the effects of oxygen and nitrogen; one batch was purged with nitrogen and another with compressed air. The samples were analyzed for assay and impurity profile.

pH Optimization Study

The pH range proposed for the finished product is 5.75 ± 0.75. Trials were manufactured with the bulk pH adjusted at the lower side (5.0) and higher side (6.5) of pH range. Both the batches were monitored for assay and impurities.

Photo Stability Study

Photo stability study was conducted for the test product and the time required for the given exposure standards are as given below:

A. 15 Hours exposure equivalent to visible light.

B. 6 Hours equivalent exposure to UV Light.

The marketed product, RESCULA® is supplied in sterile low-density polyethylene bottle with a low-density polyethylene dropper tip, a turquoise polypropylene closure in a pack size

of 7.5 ml. The test formulation was filled in sterile low density polyethylene bottle with a low density polyethylene dropper tip and high density polyethylene closure in a pack size of 7.5 ml for photo stability. The bottles were placed in horizontal position to achieve maximum exposure of the light. The comparison of the exposed sample and Initial sample with respect to the impurities was done.

Evaluation Of Comparative Physico-Chemical Characteristics Of Marketed Product And Test Product

The proposed formulation was also studied for pH, Specific Gravity, Osmolality, Viscosity, Buffering Capacity, Microscopic Particle Count, Particle Size, Zeta potential, Conductivity and Drop weight and compared with the marketed product.

Filter Validation Study

The filter validation study comprises Product Bubble Point Study, Compatibility Study and Bacterial Retention Study.

A. Product Bubble Point Study

The Bubble point determination studies of sterilizing grade (0.22 micron) hydrophilic Durapore® membrane wetted with Unoprostone Isopropyl Ophthalmic Solution 0.15% was performed. Sterilizing Grade (0.22 micron) hydrophilic Durapore® membranes with a filtration surface area of 13.8 cm^2 were used to determine the minimum bubble point for this product. The purpose of this study is to check the filter integrity by means of bubble point determination. Test Specifications: Sterilizing grade (0.22 micron) hydrophilic Durapore® membrane. Minimum standard bubble point with pure water: ≥ 50 psi (23°C). Temperature: The test measurements with purified water were done at 22 ± 4°C and Unoprostone Isopropyl Ophthalmic Solution 0.15% were done at 20-25°C.

B. Filter Compatibility Study

The compatibility study of the sterilizing grade (0.22 micron) hydrophilic Durapore® membrane with Unoprostone Isopropyl Ophthalmic Solution 0.15% was performed. Sterilizing-grade (0.22 micron) hydrophilic Durapore® membranes with a filtration surface area of 13.8 cm^2 were used for the tests. The filter compatibility study comprised of four elementary tests: Bubble point variation determination, Flow rate variation determination, membrane mass variation determination and visual examination. The study used one lot of product and each elementary test is performed on three different filters from the same lot. The

study was performed over 11.11 hours of soaking period of the filters in Unoprostone Isopropyl Ophthalmic Solution 0.15%. Test Specifications: Sterilizing grade (0.22 µm) hydrophilic Durapore® membrane Minimum standard bubble point with pure water ≥ 50 psi (23°C). Temperature: The test measurements with purified water were done at 22 ± 4°C and Unoprostone Isopropyl Ophthalmic Solution 0.15% were done at 20-25°C.

C. Bacterial Retention Study

The purpose of this study is to provide Brevundimonas *diminuta* American Type Culture Collection (ATCC) 19146 retention data for 0.22 µm Durapore® membrane after exposure to Unoprostone Isopropyl Ophthalmic Solution 0.15%. 47 mm discs with a filtration surface area of 13.8 cm^2 were used for the Unoprostone Isopropyl Ophthalmic Solution 0.15% membrane bacterial retention validation study. The Brevundimonas *diminuta* challenge inoculums was inhibited by Unoprostone Isopropyl Ophthalmic Solution 0.15% as demonstrated in the viability study. Therefore, a modified test was performed. The test filters were conditioned with sterile product, rinsed and challenged with Saline Lactose Broth. A final portion of the rinse filtrate was assayed and proven not to be bactericidal to Brevundimonas *diminuta*.

Stability Study

The finalized product was stability evaluated at accelerated condition, 40°C / 25%RH in both horizontal and upright orientation and the details were reported.

RESULTS AND DISCUSSION

API Characterization

From the API characterization, Table.1 it is evident that the API is an oily liquid and is practically insoluble in Water.

Table 1: Api Characterization.

Appearance	**Colourless to pale yellow oil**
Related Substances Any other impurity Total impurities	 Not detected Not detected
Assay	99.9%
Solubility	Practically insoluble in Water Freely soluble in Acetonitrile Ethanol, 2-Propanol, Ethyl Acetate, Diethyl Ether, 1,4-Dioxane and Hexane

Marketed Product Characterization

Based on the tabulated information, in Table.2 it was decided to develop the formulation matching the appearance and Physico-chemical properties of the marketed product, RESCULA® (Unoprostone Isopropyl Ophthalmic Solution) 0.15%.

Table 2: Marketed Product Characterization.

Particulars	Results
Brand Name	RESCULA® 0.15%
Generic Name	Unoprostone Isopropyl Ophthalmic Solution, 0.15% w/v
Manufacturer	Manufactured for: Sucampo Pharma Americas, LLC. Bethesda, MD 20814, Made in Japan
Label Claim	Each mL contains: 1.5 mg of Unoprostone Isopropyl; Benzalkonium Chloride 0.015% is added as preservative.
Storage	Store between 2°C-25°C (36°-77°F)
Pack	Sterile low-density polyethylene bottle with a low-density polyethylene dropper tip and a turquoise Polypropylene closure.
Excipients	Mannitol, Polysorbate 80, Edetate Disodium, Sodium Hydroxide or Hydrochloric Acid (to adjust pH) and Water for injection.
Quantitative details of Excipients (Reverse Engineering By HPLC)	Mannitol: 4.3% Polysorbate 80: 1.0% Benzalkonium Chloride: 0.015% Edetate Disodium: 0.05%
Appearance	Clear colorless solution
Fill Volume	5 mL
Drop Weight	Average drop weight is 33.695 mg (Range: 31.12 mg to 35.31 mg)
pH	Average is 5.8 (Range: 5.6 to 5.9)
Specific Gravity	Average is 1.02532 (Range: 1.00592 to 1.04725)
Osmolality	Average is 245.3 mOsm/kg (243 mOsm/kg to 248 mOsm/kg)
Viscosity	Average is 1 cps [Spindle no. 21; 100 RPM]
Buffering Capacity	0.5 mL (Range: 0.5 mL to 0.5 mL)
Preservative Content (%)	101.4 (Benzalkonium Chloride)
Microscopic Particle Count	> 10 microns NMT 20 Particles > 25 microns NMT 5 Particles
Related Substances (%) Individual Unknown Impurity Total Impurities	 0.249 0.691
Assay (%)	103.7
Particle Size	19.90 nm
Zeta Potential	4.88 mv
Conductivity	0.302 µs/cm

Preliminary Formulation

According to the prescribed order of addition and mixing of ingredients the formulation was done without any overages to check on the assay of critical ingredients. The characterization details were tabulated in Table.3 and are evident that the manufacturing steps followed in-fact resulted in a uniform drug product without any physic-chemical changes.

Table 3: Preliminary Formulation.

S.No	Ingredients	mg / mL	Without 5% Overage g / batch		
1	Unoprostone Isopropyl	1.50	0.375		
2	Mannitol	43.00	10.750		
3	Polysorbate 80	10.00	2.500		
4	Benzalkonium Chloride	0.15	0.0375		
5	EDTA Disodium	0.50	0.125		
6	Sodium Hydroxide	Adjust the pH to 5.75±0.75	Adjust the pH to 5.75±0.75		
7	Hydrochloric Acid	Adjust the pH to 5.75±0.75	Adjust the pH to 5.75±0.75		
8	Sterile Water For Injection	Adjust to 1 mL	Adjust to 250 mL		
Assay before filtration			100.29		
Assay after filtration			100.18		
Tests			**Initial**	**2-8°C- 1 month**	**30°C/65%RH -1 month**
Description			**Clear colorless solution**		
pH Limit			6.0	6.1	6.1
Assay			100.2	100.7	98.1
Highest Unknown Impurity			0.026	0.257	0.341
Total Impurity			0.048	0.462	1.107

Manufacturing Process Optimization

The batch size of the drug product was scaled up from 250 mL batch size (Prototype) to 6000 mL batch size (Table.4). In this batch nitrogen purging was done before and after API addition to reduce the dissolved oxygen level in the solution. The final filtered drug product was characterized for the further optimization study evaluation.

Table 4: Composition For 6 Litre Batch Size For Optimization Study.

S.No	Ingredients	g / batch		
1	Unoprostone Isopropyl	9.00		
2	Mannitol	258.00		
3	Polysorbate 80	60.00		
4	Benzalkonium Chloride	0.90		
5	EDTA Disodium	3.00		
6	Sodium Hydroxide	Adjust the pH to 5.75±0.75		
7	Hydrochloric Acid	Adjust the pH to 5.75±0.75		
8	Sterile Water For Injection	Adjust to 6000 mL		
Tests		**Initial**	**2-8°C 3 months**	**30°C / 65%RH 3 months**
Description		**Clear colorless solution**		
pH		5.9	6.1	5.9
Assay		102.9	99.2	96.2
Highest Unknown Impurity – NMT 1.0%		ND	0.362	0.518
Total Impurities		ND	0.477	0.760

Manufacturing Processing Condition

From the Table.5 results it is evident that no significant difference between oxygen purged batch and nitrogen purged batch.

Table 5: Manufacturing Process Condition Study.

Tests	Initial	With Oxygen Purging		With Nitrogen Purging	
		40°C/75%RH 24 hours	**55°C 24 hours**	**40°C/75%RH 24 hours**	**55°C 24 hours**
Highest Unknown Impurity	ND	ND	ND	ND	ND
Total Impurity	ND	ND	ND	ND	ND
Assay	102.9	100.3	103.1	102.8	102.3

pH Optimization Study

From the Table.6 results it is evident that the product was found to be stable between pH 5.0 to 6.5.

Table 6: pH Optimization Study.

Tests	pH 5.0	pH 6.5
Description	Clear colorless solution	
Preservative Content (Benzalkonium Chloride)	97.9	98.1
Highest Unknown Impurity	ND	ND
Total Impurity	ND	ND
Assay	100.2	100.1

ND – Not Detected

Photo Stability Study

From the Table.7 results it is evident that the product was found to be stable with the selected packaging configuration i.e. low density polyethylene bottle with a low density polyethylene dropper tip and high density polyethylene closure.

Table 7: Photo Stability Study.

Tests	Initial	Photo Exposed
Description	Clear colorless solution	
Highest Unknown Impurity	ND	ND
Total Impurity	ND	ND
Assay	102.9	99.8

ND – Not Detected

Evaluation Of Comparative Physico-Chemical Characteristics Of Rescula® And Test Product

From the Table.8 results it is evident that the physico-chemical property of the developed product was found to be comparable to the marketed product, RESCULA®.

Table 8: Comparative Physico-Chemical Characteristics.

S.No	Parameters	RESCULA®	Test Product
1	pH	5.8 (Range: 5.6-5.9)	5.8 (Range: 5.8-5.8)
2	Specific Gravity	1.03 (Range: 1.00-1.05)	1.02 (Range: 1.01-1.02)
3	Osmolality	245.3 mOsm/kg (243 mOsm/Kg-248 mOsm/Kg)	248 mOsm/kg (247 mOsm/Kg-249 mOsm/Kg)
4	Viscosity	Average is 1 cps [Spindle no. 21; 100 RPM]	Average is 1 cps [Spindle no. 21; 100 RPM]
5	Buffering Capacity	0.5 mL (Range: 0.5 mL to 0.5 mL)	0.9 mL (Range: 0.9 mL to 1.0 mL)
6	Microscopic Particle Count	> 10 microns NMT 20 Particles > 25 microns NMT 5 Particles	> 10 microns NMT 20 Particles > 25 microns NMT 5 Particles
7	Particle Size	19.90 nm	22.97 nm
8	Zeta Potential	4.88 mV	3.51 mV
9	Conductivity	0.302 µs/cm	0.266 µs/cm
10	Drop Weight (mg)	33.695 mg (31.12 mg to 35.31 mg)	40.455 mg (39.19 mg to 41.77 mg)

Filter Validation Study

The following were the studies done as part of filter validation study. Since the product is sterilized by filtration method, the integrity of the filter used for filtration is essential for ensuring the sterility of the drug product.

A. Product Bubble Point Study

The Bubble Point Ratio (BPR) of (0.22 microns) hydrophilic Durapore® membrane wetted with Unoprostone Isopropyl Ophthalmic Solution 0.15% at 20-25° is equal to 0.580. The product bubble point specifications of the (0.22 micron) hydrophilic Durapore® membrane wetted with Unoprostone Isopropyl Ophthalmic Solution 0.15% at 20-25°C is: Minimum product bubble point specification = Minimum Standard Bubble Point X BPR = 50 X 0.58 = 29 psi.

B. Filter Compatibility Study

Bubble Point Variation: 0.311%. Flow Rate Variation: 2.241%. Membrane Mass Variation: 0.37367%. Visual Examination: No Significant visible discoloration, swelling, shredding or dissolution of the test filter has been observed. Given the test results, it concluded that Millipore's sterilizing grade (0.22 µm) Hydrophilic Durapore® membrane are not affected by the Unoprostone Isopropyl Ophthalmic Solution 0.15% for a contact period of about 11.11 hours at 20-25°C.

C. Bacterial Retention Study

The sterilizing grade filter demonstrated acceptable performance, as the membrane retained the *Brevundimonas diminuta* challenge concentration of equal to or greater than 1 X 107 cfu/cm^2 of effective filtration area. The *Brevundimonas diminuta* challenge organism passed through the 0.45 µm filter indicating that it was appropriately sized during test. Sterility of the test system was demonstrated by the absence of microbial growth on the assay filter downstream of the 0.22 µm test filter.

Stability Study

The final product was stability evaluated at accelerated condition, 40°C / 25%RH in both horizontal (Table 10) and upright (Table 9) orientation. Based on the tabulated results, it is clear that the developed drug product is stable at accelerated condition, 40°C / 25%RH in both horizontal and vertical orientation for about 3 months.

Table 9: Accelerated Stability Study – Upright Orientation

40°C / 25%RH – Upright Orientation				
Tests	**Initial**	**1 month**	**2 month**	**3 month**
Description	**Clear colorless solution**			
pH	6.1	6.0	6.0	6.0
Osmolality (mOsm / L)	263	265	267	270

Particulate Matter (Particle per mL)	NMT 50 particles / mL ≥ 10 µm	4.33	4.27	4.28	4.29
	NMT 5 particles / mL ≥ 25µm	0.27	0.25	0.28	0.26
Assay		102.1	101.2	100.1	101.3
Benzalkonium Chloride Content		97.4	98.9	98.2	98.8
Disodium Edetate Content		102.4	101.7	101.2	102.1
Related Substances	Highest Unknown Impurity	ND	ND	ND	0.3
	Total Impurity	0.2	0.2	0.2	0.6
Sterility		**No microbial growth**	**No microbial growth**	**No microbial growth**	**No microbial growth**
Weight Loss		-	0.6% 0.6% 1.1% 0.6% 0.6%	1.2% 1.1% 1.9% 1.1% 1.3%	1.2% 1.1% 2.0% 1.2% 1.1%

ND – Not Detected

Table 10: Accelerated Stability Study – Horizontal Orientation.

40°C / 25%RH – Horizontal Orientation					
Tests		**Initial**	**1 month**	**2 month**	**3 month**
Description		**Clear colorless solution**			
pH		6.0	5.9	6.1	6.0
Osmolality (mOsm / L)		268	266	265	263
Particulate Matter (Particle per mL)	NMT 50 particles / mL ≥ 10 µm	4.31	4.30	4.29	4.32
	NMT 5 particles / mL ≥ 25µm	0.29	0.28	0.31	0.30
Assay		101.1	102.1	101.3	100.9
Benzalkonium Chloride Content		99.2	98.1	99.7	99.9
Disodium Edetate Content		100.7	101.2	100.9	100.8
Related Substances	Highest Unknown Impurity	ND	ND	ND	0.2
	Total Impurity	0.3	0.3	0.3	0.5
Sterility		**No**	**No**	**No**	**No**

	microbial growth	microbial growth	microbial growth	microbial growth
Weight Loss	-	0.8% 0.9% 1.0% 0.7% 0.9%	1.4% 1.3% 1.3% 1.4% 1.4%	1.8% 1.9% 1.8% 1.8% 1.9%

ND – Not Detected

CONCLUSION

An ophthalmic solution of Unoprostone Isopropyl, 0.15% w/v was successfully formulated and was found to be equivalent to the marketed product, RESCULA® with respect to composition, physico-chemical characteristics and stability. The manufacturing process was completely optimized and necessary precautions were taken with respect to order of mixing of ingredients, environment condition, sterilization by filtration etc to make a stabilized drug product of Unoprostone Isopropyl.

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