

# Formulation Development and Compatibility Study for BTD (Brimonidine Tartrate, Timolol Maleate, and Dorzolamide HCl) used in the Management of Glaucoma Disease

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## Abstract

**Objective:** The main objective of the present study was to develop a stable formulation and manufacturing process of fixed dose combination of antiglaucoma drug (BTD) which contains brimonidine tartrate, timolol maleate, and dorzolamide hydrochloride. **Materials and Methods:** Compatibility study with regard to product contact materials such as platinum-cured silicone tube, SS 316L (metal), and nylon membrane filter was evaluated by analysis of their description, pH, and assay using instruments such as pH meter and high-performance liquid chromatography (HPLC). **Results:** Formulations were analyzed and results were found well within specified limits. BTB formulation was prepared by dissolving all the ingredients in water for injection under continuous stirring, and the solution was filtered through sterilized 1.2  $\mu$  nylon pre-filter and followed by 0.2  $\mu$  nylon filter. **Conclusion:** Compatibility study was performed to evaluate the physical and chemical stability of BTB formulation, and all data indicate that BTB formulation was physically compatible and chemically stable.

**Key words:** Brimonidine tartrate, dorzolamide hydrochloride, filter compatibility, glaucoma, timolol maleate, intraocular pressure, silicone tube compatibility, stainless steel compatibility

## INTRODUCTION

Glaucoma is a condition of the eye in which there are progressive cupping and atrophy of the optic nerve head and deterioration of the visual fields. Primary open-angle glaucoma is the most common type of glaucoma. Angle closure glaucoma and congenital glaucoma are treated primarily by surgical methods, although short-term drug therapy is used to decrease intraocular pressure (IOP) before surgery.<sup>[1]</sup>

The therapeutic goal in treating glaucoma is reducing the IOP, a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. IOP is determined as the balance between the production of aqueous fluid in the eye and egress of aqueous fluid out of the eye. Reduction of IOP may be accomplished by decreasing the

rate of production of aqueous humor or increasing the rate of outflow of aqueous humor from the eye.

Drugs used in the therapy of primary open-angle glaucoma include a variety of agents with different mechanisms of action. Beta-adrenergic blocking agents such as timolol may be used alone or in conjunction with other agents, and they lower IOP by decreasing the rate of aqueous production. Carbonic anhydrase inhibitors such as dorzolamide used to reduce the IOP by a direct action on the ciliary epithelium to suppress the secretion of aqueous humor. Alpha-2 adrenergic

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agonists such as brimonidine tartrate are used lower the IOP by the secretion of aqueous humor.

## MATERIALS AND METHODS

### Materials

Brimonidine tartrate was procured from Indoco remedies, Maharashtra, timolol maleate was procured from Gangwal chemicals, Mumbai, and dorzolamide hydrochloride from Biocon Ltd, Bangalore.<sup>[2]</sup>

Polyoxyl 40 stearate was from Borax and sodium chloride was from RANKEM, Mumbai, mannitol was from AVANTOR, Gujarat, and benzalkonium chloride from UBI-CHEM, U.K., was received from J.T. Baker. Low-density polyethylene (LDPE) containers are procured from Thermodors, Mumbai.<sup>[3-6]</sup>

### Method

Hot water for injection was stored in a sterilized S.S. 316 L jacketed manufacturing tank equipped with stirrer.<sup>[7-11]</sup>

Cooling of water for injection was done up to 50-60°C by circulating chilled water through jacket of the manufacturing tank. Dissolve borax, sodium chloride, mannitol, and polyoxyl 40 stearate to get clear solution. Add dorzolamide HCl, brimonidine tartrate, and timolol maleate and dissolved in water for injection in the tank under stirring stir well to get a clear solution. Volume was adjusted with water for injection, and bulk solution was blanketed with nitrogen gas. pH of bulk solution (at 25°C) was recorded, and the pH should be 5.0-6.0. Finally, the solution is filtered through sterile 1.2  $\mu$  nylon pre-filter followed by 0.2  $\mu$  nylon filter.

### Manufacturing steps with equipments used

Manufacturing steps	Equipments used
Bulk preparation	SS 316 vessel
Filtration	Sterile 1.2 $\mu$ nylon pre-filter and 0.2 $\mu$ nylon filter
Filling	Low-density polyethylene container
Container sealing	Polypropylene nozzles and high-density polyethylene cap

### Evaluation parameters

Pre-formulation is defined as that phase of research and development process, where physical, chemical, and mechanical properties of drug substance are characterized

alone and when combined with excipients to develop safe, effective, stable formulation, and robust, reproducible manufacturing process. All excipients are well documented in different pharmacopoeia.<sup>[12]</sup>

As a part of pre-formulation studies, following compatibility and stability studies were performed:

- Metal (SS 316L) compatibility study
- Platinum cured silicone tubing compatibility study
- Filter compatibility study
- Stopper compatibility
- Filter validation study.

### Stainless steel vessel (SS 316L) compatibility study with unfiltered bulk solution

SS 316L vessel is used as a storage tank for prepared solution and as such must not interact with the brimonidine tartrate, timolol maleate, and dorzolamide HCl (BTD) product. The effect of SS 316L vessel on formulation was tested. About 60 mL of the unfiltered bulk solution was stored in SS316L vessel and was kept at room temperature for 48 h. Samples were periodically collected from the container at 24 h and 48 h and given for analysis of the bulk solution for description, pH, and assay. The analytical results are given in Table 1.

### Platinum-cured silicone tube compatibility study with unfiltered bulk solution

In pharmaceutical manufacturing, silicone tubing is used in transfer of solution and as such must not interact with the drug (BTD) product. About 60 mL of the unfiltered bulk solution was stored in glass container. Clean dried and autoclaved platinum-cured silicone tubing of approximate 10 cm length was immersed into the glass container and kept at room temperature for 48 h. Samples were periodically collected from the container at 24 and 48 h and given for analysis of the bulk solution for description, pH, and assay. The analytical results are given in Table 2.

### Nylon membrane filters compatibility study with unfiltered bulk solution

The compatibility study of filter is the most important test for sterility of any aseptic formulation. About 40 mL of the unfiltered bulk solution was stored in glass container. Clean and dried 1.2  $\mu$ m and 0.22  $\mu$ m nylon membrane filter was immersed into the glass container, and the container was kept at room temperature for 48 h. Samples were periodically collected from the container at 24 and 48 h and given for analysis of the bulk solution for description, pH, and assay. The analytical results are given in Table 3.

**Table 1: Stainless steel vessel (SS 316L) compatibility data for BTD drug product**

Tests	Specification	Initial	24 h	48 h
Description	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH	Between 5.0 and 6.0	5.64	5.62	5.62
Assay by HPLC				
Brimonidine tartrate	Not<90% and not>110% of labeled amount	100.8	100.6	100.1
Timolol maleate	Not<90% and not>110% of labeled amount	101.4	100.8	100.2
Dorzolamide hydrochloride	Not<90% and not>110% of labeled amount	106.1	105.9	105.2

BTD: Brimonidine tartrate, timolol maleate, and dorzolamide hydrochloride, HPLC: High-performance liquid chromatography

**Table 2: Platinum-cured silicone tube compatibility data for BTD drug product**

Tests	Specification	Initial	24 h	48 h
Description	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH	Between 5.0 and 6.0	5.64	5.60	5.60
Assay by HPLC				
Brimonidine tartrate	Not<90% and not>110% of labeled amount	100.8	100.5	100.3
Timolol maleate	Not<90% and not>110% of labeled amount	101.4	100.8	100.0
Dorzolamide hydrochloride	Not<90% and not>110% of labeled amount	106.1	105.9	105.6

BTD: Brimonidine tartrate, timolol maleate, and dorzolamide hydrochloride, HPLC: High-performance liquid chromatography

**Table 3: Nylon membrane filters compatibility data for BTD drug product**

Tests	Specification	Initial	24 h	48 h
Description	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH	Between 5.0 and 6.0	5.64	5.58	5.56
Assay by HPLC				
Brimonidine tartrate	Not<90% and not>110% of labeled amount	100.8	100.1	100.0
Timolol maleate	Not<90% and not>110% of labeled amount	101.4	100.9	100.4
Dorzolamide hydrochloride	Not<90% and not>110% of labeled amount	106.1	105.7	105.5

BTD: Brimonidine tartrate, timolol maleate, and dorzolamide hydrochloride, HPLC: High-performance liquid chromatography

### LDPE container compatibility study with filtered BTD formulation

The container-closure system is an essential part of the final presentation of a pharmaceutical product. It defines the closure, protection, and functionality of a container while it ensures the safety and quality of the drug product over the product shelf life. To establish the compatibility of BTD formulation with LDPE container, prepared bulk solution of BTD formulation was filtered through 1.2  $\mu$  and 0.22  $\mu$  nylon membrane filters. Filtered solution was filled in 5 mL LDPE container, stoppered and sealed with Nozzles and outer cap. Containers were subjected for clarity, pH, and Assay. The analytical results of container compatibility study are given in Table 4.

## RESULTS AND DISCUSSION

The main objective of the present study was to formulate a stable formulation of BTD formulation in compliance with the approved manufacturing formula [Table 5]. Pre-formulation study was performed to evaluate the compatibility of drug product with different materials. Compatibility study of BTD formulation with platinum-cured silicon tubes, metal (SS 316L), nylon membrane filters, and LDPE containers was performed. Compatibility study results indicate that there was no significant degradation in BTD formulation in contact with platinum-cured silicon tubes, metal (SS316 L), and nylon membrane filters at room temperature over a period of 24 h and 48 h, respectively [Tables 1-3]. Compatibility study of product with LDPE container was also studied at time

**Table 4:** LDPE container compatibility data for BTD drug product

Tests	Specification	Initial	24 h	48 h
Description	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH	Between 5.0 and 6.0	5.64	5.55	5.56
Assay by HPLC				
Brimonidine tartrate	Not<90% and not>110% of labeled amount	100.8	100.2	100.4
Timolol maleate	Not<90% and not>110% of labeled amount	101.4	100.5	100.4
Dorzolamide hydrochloride	Not<90% and not>110% of labeled amount	106.1	105.8	105.5

LDPE: Low-density polyethylene, BTD: Brimonidine tartrate, timolol maleate, and dorzolamide hydrochloride, HPLC: High-performance liquid chromatography

**Table 5:** Manufacturing formula and manufacturing steps

Ingredients name	% of ingredients	Quantity per mL
Dorzolamide hydrochloride	2	20 mg/ml
Brimonidine tartrate	0.2	2 mg/ml
Timolol maleate	0.5	5 mg/ml
Polyoxyl 40 stearate	7	70 mg/ml
Borax	0.56	5.6 mg/ml
Sodium chloride	0.1	1 mg/ml
Mannitol	0.5	5 mg/ml
Benzalkonium chloride	0.02	0.2 mg/ml
Purified water	Quantity sufficient	Quantity sufficient to 100 mL

intervals, and the results were found well within the specified limits [Table 4]. From the above data, it is clear that there is no incompatibility with three combinational drugs with excipients. Hence, the drugs are combined and formulated as fixed dose combination and safely to use in ophthalmic field.

## CONCLUSION

A stable formulation and fixed dose combination of BTD formulation were developed and evaluated. Compatibility study of drug product with product contact material was performed. Based on the results obtained, it can be concluded that BTD drug product was found compatible with platinum-cured silicone tubes, metal SS 316L, nylon membrane filters, and plastic containers. The materials and methods used in this study prove that the drug does not have any physical and chemical incompatibilities and found to be stable.

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