

# Formulation, Development and Evaluation of Ophthalmic Solution of Timolol Maleate 0.5%

Yadav Komal Nanasaheb<sup>1</sup>, Mali Monika Ramesh<sup>2</sup>,  
Lande Sukumar maruti<sup>3</sup>, Bendgude Rupali Ravindra<sup>4</sup>

<sup>1,2</sup>Lecturer, Shri Ganpati Institutes of Pharmaceutical Sciences

<sup>3</sup>Associate Professor, Shri Ganpati Institutes of Pharmaceutical Sciences

<sup>4</sup>Professor, Shri Ganpati Institutes of Pharmaceutical Sciences

## Abstract:

Delivery of medication to the human eye is an integral part of medical treatment. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. The preparation may have any several purposes like therapeutic, prophylactic or palliative. The versatility of dosage form enables therapeutic agent to be suitable for function of preparation. Therapeutically active formulation may be designed to provide extended action for either convenience or reduction in dose frequency, improved bioavailability of an agent or improved delivery to target tissue. The residence time of an ocular preparation may range from few seconds (ophthalmic solutions) to hours (gel, ointments), to months or years (intra ocular or periocular dosage forms). Ophthalmic preparations are similar to parenteral dosage form in their requirements for sterility as well as consideration for osmotic pressure (tonicity), preservation, and tissue compatibility, avoidance of pyrogens and particulate matter and suitable packaging.

**Keywords:** Ophthalmic, Timolol maleate.

## Formulation Parameters for Ophthalmic Solution:

Ophthalmic solutions should be prepared and preserved according to whether they are to be used in surgical procedures, in clinic or office or by the patient at home. There is an optimum pH level at which the solution of individual drugs should be buffered in order to obtain the maximum efficiency and stability. Deterioration of the drugs used is greatly diminished when they are dispensed at proper pH. Preservative solutions in proper strength have been shown to be adequate for preservation of ophthalmic solutions. Important factors to be considered in formulating an ophthalmic solution include the following

- Clarity
- Sterility.
- Osmolarity.
- pH, buffering.

- Preservation.
- Solubility.
- Stability in appropriate vehicle.
- Viscosity.
- Suitable packaging and storage of finished product.

### **Materials & Methodology:**

Timolol Maleate USP, Benzalkonium chloride USP, Dibasic Sodium phosphate USP, Monobasic Sodium Phosphate USP, Sodium hydroxide USP, Water for Injection, Growth Media, Neutralizer media, Three-piece containers, BFS containers and Glass containers.

### **Physical characterization of drug sample:**

Description: The received sample Timolol Maleate was subjected to the following tests for its characterization:

Nature of drug sample: The drug sample was observed visually and viewed under the Compound microscope for the determination of its nature and then the results were compared with the official books and British Pharmacopoeia and Ph Eur 2006.

Color of drug sample: The drug sample was viewed visually for the determination of its color and then the results were compared with the British Pharmacopoeia and Ph Eur 2006.

Loss on drying: Loss on drying was performed for the sample of Timolol maleate according to method specified in British Pharmacopoeia and Ph Eur. It was determined on 1.000 g of Timolol sample by drying at 1000C-1050C for 4 hours. The results were then compared with those given in the official books and British Pharmacopoeia and Ph Eur 2006.

Solubility: The solubility of the Timolol maleate sample was carried out in different aqueous and organic solvents like water, glacial acetic acid, methylene chloride, Chloroform and methanol according to British Pharmacopoeia. The results were 60 then compared with those given in the official books and British Pharmacopoeia and Ph Eur 2006.

### **Analytical characterization of drug sample:**

Absorbance: Dissolve 0.5 g of Timolol maleate in 0.12 N Hydrochloric acid and dilute to 25 L with the same solvent. The absorbance of the solution measured at 294 nm, is not greater than 0.3 on dried basis.

Optical Rotation: Dissolve 50 mg per ml in 0.1 N Hydrochloric acid. The angle of optical rotation must be between -11.70 and -12.50 ( $\lambda = 405$  nm).

Assay: Assay was performed using digital potentiometer. About 800 mg of Timolol maleate was accurately weighed, and was transferred to 400-mL beaker, 90 ml of Glacial acetic anhydride was added, and stirred to dissolve. Titration was performed with 0.1 N Perchloric acid. The end point was determined potentiometrically, using a glass silver electrode system. The first two inflection points were used. A blank determination was performed. Each ml of perchloric acid is equivalent to 43.25 mg of C<sub>13</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>S. C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>.

### **Formulation studies:**

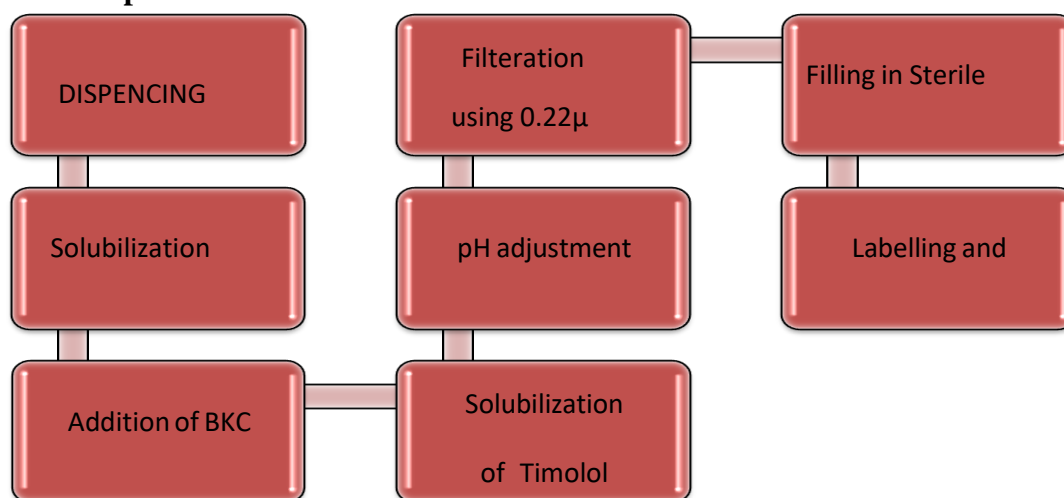
Development Strategy: Development of Timolol Maleate ophthalmic solution is divided in to two phases as follows.

## 1. Prototype Formulation Development:

The following excipients were scientifically identified based on their functional. The rationale for selecting the excipients is given below

Sr No	Name of the Excipients	Category	Uses
1	Benzalkonium chloride	Preservative	Benzalkonium chloride prevents bacterial and fungal contamination of the product during its shelf life.
2	Dibasic Sodium Phosphate	Buffering agent, Sequestering agent	Buffering agent and electrolyte replenisher, when combined with other phosphates
3	Monobasic Sodium Phosphate	Buffering agent, Sequestering agent, Emulsifying agent	Buffering agent and electrolyte replenisher, when combined with other phosphates
4	Sodium hydroxide	Alkali	For pH adjustment

## 2. Process Development



## 3. Manufacturing Process:

Dibasic Sodium Phosphate and Monobasic Sodium Phosphate were dissolved in water for injection by the slow addition. pH was adjusted to the 6.8-7.0 using 5% sodium hydroxide.

To this container with buffer solution of phosphates, Benzalkonium chloride was added with continuous stirring.

After solubilizing the excipients, to this solution the Timolol maleate USP was added and mixed vigorously until it dissolved in the solution.

The solution pH was adjusted to the 6.8-7.0 using 5% Sodium hydroxide solution.

The volume was made with water for injection.

Bulk Timolol maleate solution was filtered through 0.22 μ PVDF sterilizing grade filter. Solution was filled into two types of LDPE containers and glass containers in sterile area (Class 100) under Laminar Air Flow. LDPE containers were pre-sterilized with gamma radiation. Glass containers were washed with filtered water for injection and were sterilized by Dry Heat Sterilization (160°C for 2 hours).

Both filled LDPE and Glass vials were inspected individually against black and white surface for particulate matter. Above procedure was followed for all the six batches each of 500 ml.

**Formulation Design:**

The proposed formula was optimized by varying the concentration of Benzalkonium chloride. The quantities of Timolol maleate and other excipients were kept constant. As the aim of the present study was to optimize the concentration of BKC in formulation for Timolol maleate (0.5%) ophthalmic solution.

Batches were planned by taking different concentrations viz.0.0 % v/v, 0.01%,0.012%, 0.016%, and 0.02% ,0.024 % v/v of BKC, Timolol maleate 0.5%, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate and Sodium hydroxide to adjust pH between 6.8 and 7.0 and volume was made up by water for injection.

**Table: Composition of Timolol Maleate Ophthalmic Solution.**

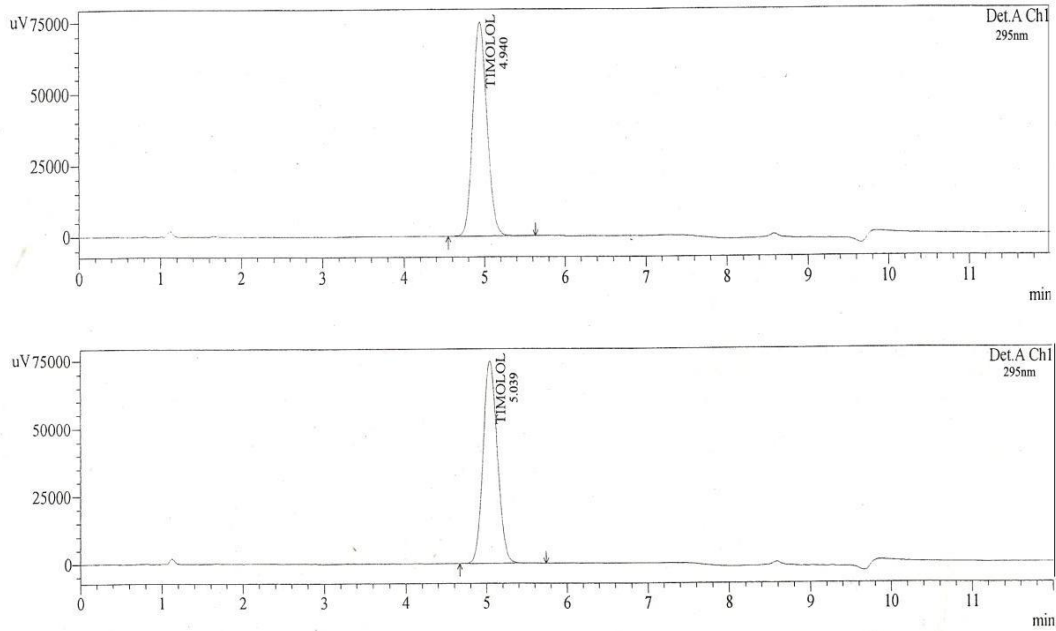
Name of ingredients	Formulation Batches					
	OPT/TIM/T-001	OPT/TIM/T-002	OPT/TIM/T-003	OPT/TIM/T-004	OPT/TIM/T-005	OPT/TIM/T-006
Timolol maleate	6.8 mg/ml	6.8 mg/ml	6.8 mg/ml	6.8 mg/ml	6.8 mg/ml	6.8 mg/ml
Benzalkonium chloride*	0.0% v/v	0.01% v/v	0.012% v/v	0.016% v/v	0.02% v/v	0.024% v/v
Dibasic Sodium Phosphate	30.42 mg/ml	30.42 mg/ml	30.42 mg/ml	30.42 mg/ml	30.42 mg/ml	30.42 mg/ml
Monobasic Sodium Phosphate	6.10 mg/ml	6.10 mg/ml	6.10 mg/ml	6.10 mg/ml	6.10 mg/ml	6.10 mg/ml
Sodium hydroxide	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH
Water for injection	QS	QS	QS	QS	QS	QS

**Results of stability/containter compatibility study:**

In stability/container compatibility study drug product was evaluated for assay of Timolol maleate and Benzalkonium chloride at initially, stress condition and at accelerated condition. Analysis was done by using HPLC. Other evaluated parameters are pH, Osmolality, Drop size and Water loss.

The chromatograms for assay of Timolol maleate at each time point of the stability are as shown below.

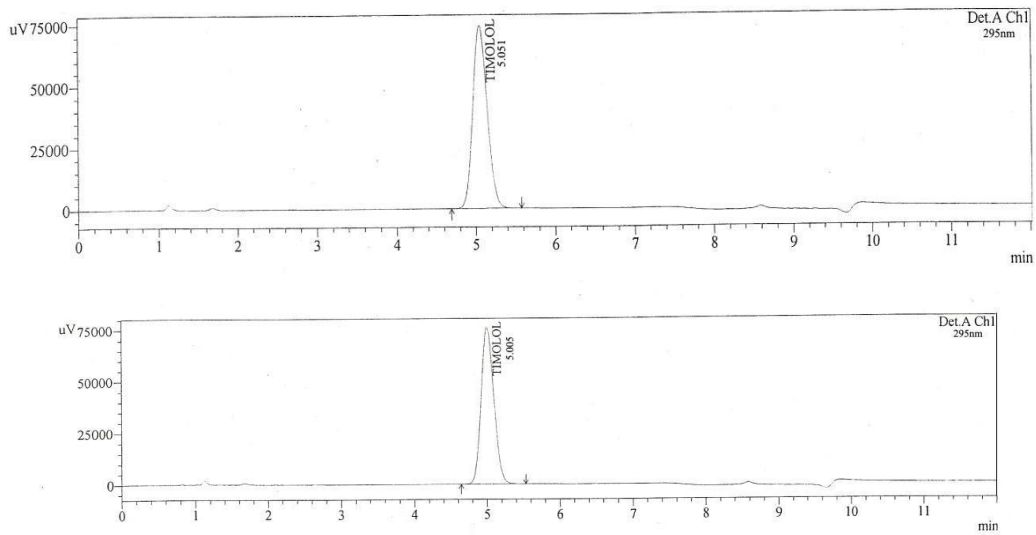
**Initial**



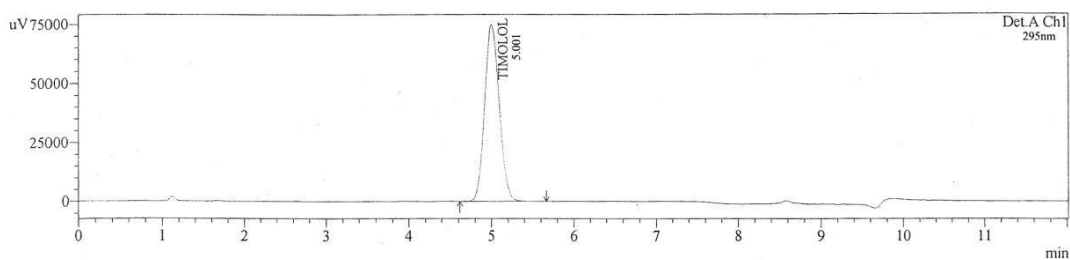
**Fig : Chromatograms for Timolol maleate assay at Initial**

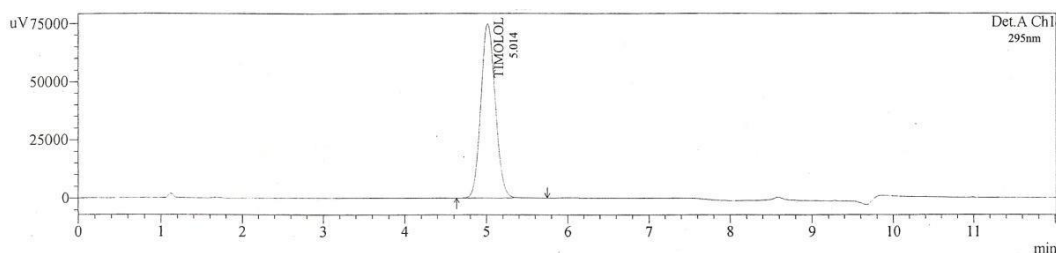
**Three piece container**

**1 week**



**2 weeks**





**Fig : Chromatograms for Timolol maleate assay at Stress condition in Threepiece container**

### Conclusion:

From the results of Preservative efficacy test, it was found that Benzalkonium chloride (0.02% v/v) and (0.024% v/v) showed 2 log reductions at 6 hours and 5 log reductions at 24 hours and no recovery at 28<sup>th</sup> day for bacteria. For fungi it showed log reduction as stated in criteria, 2 log reductions at 7<sup>th</sup> day and no recovery at 28<sup>th</sup> day. Both these concentrations passed the criteria according to British Pharmacopoeia. As the aim of study was to minimize the concentration, it will be preferable to use 0.02% v/v concentration of BKC in Timolol maleate 0.5% ophthalmic solution.

In case of container compatibility study, results for Assay of Timolol maleate and Benzalkonium chloride, pH, Osmolality, drop size and water loss are within range of specifications for Three-piece containers, BFS containers and Glass containers. But Three-piece containers showed better results for compatibility with Timolol ophthalmic solution as compared to the BFS and Glass containers. Therefore, three-piece containers (Low density polyethylene, *PE 1840 H*) are the best containers for Timolol maleate (0.5%) ophthalmic solution.

### References:

1. Chowhan M, Weiner AL, Bhagat H. Encyclopedia of pharmaceutical technology, Drug Delivery: Ophthalmic Route, 3<sup>rd</sup> ed; USA: Informa Healthcare; 2007. vol 2 p.1220-21
2. Macha S, Mitra AK, Hughes PM. Ophthalmic drug delivery system: Overview of Ocular Drug Delivery, 2<sup>nd</sup> ed; Newyork, USA: Marcel Dekker; 2003. p. 1-10.
3. Lang JC, Roches RE, Jani R. Ophthalmic preparations. In: Remington the pharmaceutical science and practice of pharmacy. 21<sup>st</sup> ed. Philadelphia: Lipincott Williams and Wilkins 2005 p.850
4. Gibson M. Pharmaceutical Preformulation and Formulation: Parenteral Dosage Forms, First Indian Reprint, Inerpharm/CRC, 2008 p. 331-54.
5. ASHP [Online] 15 June 2008, [Cited 2008 July 04]; Available from URL : <http://pharmalabs.unc.edu/ophthalmics/text.htm>
6. Ding S, Tien WL. United States Patent. No. 5474979; Date of patent Dec 12, 1995. Available from URL: [www.freepatentsonline.com](http://www.freepatentsonline.com)
7. March WE, Stewart RM, Mandell AI. et al. Arch Ophthalmol, 1982, 100 p.1270.
8. Shell JW, Baker RW. Arch Ophthalmol, 1975; 7 p.1037
9. Gaudana R, Jwala J, Boddu H.S, Mitra AK; Recent Perspectives in Ocular Drug Delivery; Pharmaceutical research (2008) DOI:10.1007/s11095-008- 9694-0
10. Freemantle N, Cleland J, Young P, Mason J, Harrison J (June 1999). "beta Blockade after myocardial infarction: systematic review and meta regression analysis". *BMJ* 318 (7200): 1730–7. PMC 31101. PMID 10381708.

11. Shen, Howard (2008). Illustrated Pharmacology Memory Cards: PharMnemonics. Minireview. pp. 15. ISBN 1-59541-101-1.
12. OFKA. [Online]. 2007 May 22 [cited 2008 August 13] Available from URL: [www.aishikapharma.com/products.htm](http://www.aishikapharma.com/products.htm)
13. Michel JH. Ophthalmic solution: The preparation and sterilization of ophthalmic solutions. California medicine; 71 (06); 414-6
14. Drug distribution and control: Preparation and handling - Guidelines; ASHP Guidelines on Pharmacy prepared ophthalmic products. Page 32-33
15. USP 31 NF 26, 2008, General Chapters:<789> Particulate matter in ophthalmic solutions.Inc. official 8/1/08 - 11/30/08
16. Lachman L., Libermann HA., Kanig JL., The Theory and Practice of Industrial Pharmacy, Sterile Products, 3<sup>rd</sup> ed, Varghese Publishing House, Mumbai, 1991, p. 639-77.
17. Osmolarity-Wikipedia the free encyclopedia. Available from URL: <http://en.wikipedia.org/wiki/osmolarity>
18. Chowhan M.,Weiner AL,Bhagat H. Encyclopedia of pharmaceutical technology, Drug Delivery: Ophthalmic Route, 3<sup>rd</sup> ed; USA: Informa Healthcare; 2007. vol 2 p.1272.