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# Formulation Development and Evaluation of Ophthalmic gel of Netarsudil

**Nilesh Mahajan [1*] , , Khanderao Jadhav [2] , Rishikesh Bachhav [3] , Prashant Patil [4]**
1,2* Department of Pharmaceutics, KCT's R. G. Sapkal College of Pharmacy, Anjneri, Nashik-422212 (M.S.), India
3 Department of Pharmacology, KCT's R. G. Sapkal College of Pharmacy, Anjneri, Nashik-422212 (M.S.), India
4 Department of Pharmaceutics N N Sattha College of Pharmacy, Ahmednagar-414001(M.S.), India
* Corresponding Author: Mr. Nilesh Mahajan
E mail id: nileshmahajan016@gmail.com

**ABSTRACT**
*The study aimed to enhance patient compliance in Glaucoma treatment by developing a novel, long-acting gel formulation of Netarsudil, thereby reducing dosing frequency. Utilizing drug delivery systems (DDS) for precise release control and targeted delivery, carrier technology played a crucial role, involving coupling the drug with gel, nanoparticles, or liposomes to modulate characteristics. The gel, developed through the phase mixing method, incorporated Carbopol-934 as a bioadhesive polymer, Propylene glycol as a viscosity modifier, and Benzalkonium Chloride, EDTA as preservatives. Evaluation encompassed viscosity, pH, gel and bioadhesive strength, assay, in vitro drug release, and stability studies, with drug- excipient compatibility assessed via FTIR studies. The formulated ophthalmic gel exhibited optimal viscosity and drug release profiles. Investigation into polymer concentration variations on drug release indicated promising characteristics such as bioadhesive strength and stability. This study addresses challenges related to dosing frequency and patient compliance, presenting a significant advancement in Glaucoma therapy. Through the integration of carrier technology, meticulous excipient selection, and comprehensive evaluation, the developed long-acting gel of Netarsudil holds potential for effective Glaucoma management.*
***Keywords:*** *Ophthalmic gel, Netarsudil, carbapol 934, propylene glycol ,Benzalkonium Chloride, EDTA.*

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## INTRODUCTION

Ophthalmic preparations refer to sterile forms of medication designed for instillation into the eye. These formulations are meticulously compounded, free from foreign particles, and intended for administration at various sites within the eye like the cornea, conjunctiva, and sclera. This precision aims to enhance bioavailability and achieve the desired therapeutic effects effectively [1]. Given the eye's sensitivity, it can be susceptible to infections caused by bacteria, viruses, or other factors. Traditional treatment options include solutions, suspensions, ointments, and gels. However, these methods have drawbacks, such as rapid clearance from the cornea, frequent drug application, and limited duration of action [2, 3]. To address these issues, innovative formulations have emerged, with ophthalmic gels being a notable example. When applied to the eye, these gels enhance bioavailability within the ocular region by extending the duration the medication remains in the eye. This extension of contact time serves to counteract tear-induced dilution, discourages excessive tear drainage through the nasolacrimal pathway, and facilitates optimal absorption of the medication [4]. As a result, patient adherence is improved, dosing frequency is reduced, and the overall therapeutic outcome is enhanced.

## MATERIAL AND METHODS

Netarsudil was obtained from Nuland Lab Hyderabad as a gift sample, Carbapol 934 was purchased from Research-Lab Fine chem. Industry-Mumbai. Propylene glycol was purchased from avantor lab.Benzalkonium chloride and etheylenediaminetetraacetic acid(EDTA) was purchased from spectrum lab. Hydrochloric acid was purchased from merck lab .

**Development of Netarsudil Ophthalmic gel**

Composition of formulation trails for Netarsudil Ophthalmic Gel shown in Table 1.

**Table 1: Composition of formulation trails for Netarsudil Ophthalmic Gel**

| Trials / Ingredient | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Netarsudil | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Carbopol-934 | 0.5 | 0.8 | 0.8 | 0.8 | 1.0 | 1.5 | 1.5 | 1.0 | 1.0 | 1.0 |
| Propylene glycol | - | - | 200 | 300 | 300 | 300 | 400 | 400 | 400 | 400 |
| Benzalkonium Chloride | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| EDTA | - | - | - | - | - | - | - | - | 0.15 | 0.15 |
| Hydrochloric acid | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S |
| Distilled water | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S |
| Total Qty | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |

**Formulation of ophthalmic gel**

The amounts of the drug and additional components were measured in accordance with the specifications in Table 1, and the formulations were then created using the subsequent procedure[5].

**Step 1**. Measuring and allocating the specified number of components.

**Step 2 Creating a Carbopol slurry** In a mixing vessel, combine the specified amount of Carbopol with purified water to form a slurry.

**Step 3. Preparation of Preservative Phase** Utilize a 500 ml beaker with the designated measure of propylene glycol. Stir in the prescribed quantity of preservatives for 10 minutes until achieving a clear solution.

**Step 4. Preparation of Drug phase:** Combine the specified amount of Netarsudil API with purified water and thoroughly blend to produce a clear API solution.

**Step 5**. Incorporate the drug phase into the Carbopol phase to create a consistent solution, maintaining a temperature of 50°C ± 5°C. Introduce the preservative phase into this mixture and blend thoroughly.

**Step 6. pH adjustment** Modify the pH of the bulk substance to reach a pH of 6.0 (with a tolerance of ±0.5) using a 0.1 N HCl solution at a temperature of 50°C (with a tolerance of ±5°C).

**Step 7. Final volume adjustment** Make final weight adjustments by combining the bulk phase and adjusting the weight with purified water.

**Step 8. Sterilization of ophthalmic formulation:**The solution that was prepared underwent autoclaving at a temperature of 120°C for a duration of 30 minutes.

**Step 9. Aseptic filling to container**. The ultimate formulation was transferred with aseptic precautions into a sterilized glass bottle and securely sealed.

**Evaluation of Netarsudil ophthalmic gel**

**1) clarity :** Visual assessment was conducted to examine the clarity of the formulations.

**2) Specific gravity(g/cm3) :** Relative density, commonly referred to as specific gravity, pertains to the density comparison of a substance in relation to another, typically a reference substance like water. In the case of solids and semi-solids, the determination of specific gravity often involves measurement relative to water, necessitating the use of a densitometer.

**3) Viscosity :** Viscosity is determined using a Brookfield viscometer with the utilization of spindle 61.

**4) pH :** pH measurement is conducted using a digital pH meter. The pH values are documented immediately following the preparation.

**5) Measurement of the gel strength:** The assessment of gel strength was executed using a 50 ml graduated cylinder. Within the cylinder, 25 ml of the sample was introduced. A weight of 14.33 grams was positioned on the surface of the gel. The measurement of gel strength involved determining the time, in seconds, taken for the weight to penetrate the gel to a depth of 5 cm under physiological temperature conditions[6]. These measurements were carried out in triplicate (n=3).

**6) Drug Release:** The assessment of drug release from the developed gel was conducted through an in vitro study. A diffusion cell apparatus was employed to study the release pattern of the ophthalmic gel. The diffusion process was facilitated by employing an artificial biological membrane. For the diffusion medium, a solution mimicking artificial tear fluid was used. The setup involved positioning the donor compartment in a manner where the membrane made contact with the diffusion medium. The entire assembly was situated on a thermostatically controlled magnetic stirrer, maintaining the medium's temperature at 37°C. Sampling occurred at specified time intervals (0, 0.50, 1, 2, 2.5, 3, 5, and 8 hours), with 5 ml of sample withdrawn from the compartment. Concurrently, an equal volume of fresh media was introduced to replace

the withdrawn sample. The collected samples were then subjected to High Performance Liquid Chromatography (HPLC) analysis to calculate the extent of drug release.

**7) % drug content :** Potassium dihydrogen orthophosphate (1.36 g) was dissolved in 1000 mL of water, and the pH was adjusted to 3.5 ± 0.05 using dilute Orthophosphoric acid. A mixture of Buffer solution (pH 3.5) and Methanol (70:30, v/v) underwent sonication for degassing[7]. A Netarsudil working standard (25 mg) was dissolved in diluent, cooled, and then diluted to a 50 mL volume in a volumetric flask. Additionally, 5 mL of Netarsudil ophthalmic solution was mixed with 10 mL of diluent, cooled, filtered, and subsequently injected for HPLC analysis. The drug content was quantified via HPLC at 255nm, indicating a concentration of approximately 50 ppm.

**8 ) Test of Sterility :** The sterility test is conducted using the direct inoculation method. In this approach, microorganisms are introduced into a culture medium (specifically, soybean casein digest medium) by transferring a 5ml volume of the solution. This mixture is then incubated in an incubator for a period of 14 days at a temperature of 20-25°C. Following the incubation period, the sample is examined. If bacterial growth is detected within the culture medium, the sample is considered to have failed the sterility test. Conversely, if no bacterial growth is observed, the sample is deemed to have passed the sterility test. Turbidity was employed as the detection method through visual observation [8-10].

**9) stability studies:** The stability study encompassed a three-month duration during which the formulation was examined. The stability assessment was conducted under specific conditions, with the temperature maintained at room temperature (40 ± 2 °C) and a relative humidity of 75 ± 5%. Throughout this period, the formulations underwent comprehensive evaluations of their physical attributes at designated intervals of 30 days. These evaluations encompassed characteristics such as appearance, clarity, pH, viscosity, and drug content.

## RESULT AND DISCUSSION

### Physical parameter

### Clarity

Upon meticulous visual examination under both dark and white backgrounds, it was determined that all the formulated ophthalmic gel preparations exhibited no presence of suspended particles. Additionally, all formulations displayed clarity. The prepared formulations are illustrated in Figure 1.

### pH

The pH values of the formulations were presented in Table 2. The pH of all formulations, spanning from F1 to F10, fell within the range of 6.1 to 6.5.

### Rheological study

### Viscosity

The viscosity measurements of all experimental formulation batches are provided in Table 3 , The viscosity of trial batches at various RPM levels is presented in Table 4 and The viscosity of formulation trial batches ranging from F1 to F10 is depicted in Figure 2 for comparison .

### Gel strength

The gel strength values for the trial batches are provided in Table 5. The gel strength was influenced by the concentration of the gelling agent, bioadhesive polymers, and pH. An ideal bioadhesive gel should possess an appropriate gel strength to ensure easy administration and retention within the ocular region without leakage. The gel strength outcomes for all formulations exhibited similar trends as the viscosity results.

### Drug release

The percentage of drug released from the formulated trial batches is presented in Table 6 and The percentage of drug released into tear fluid across various formulation trial batches is depicted in Figure 3. The drug release behavior in an artificial tear fluid environment was examined for various test batches labeled F1 to F10. The drug release profiles were determined at specific time intervals: 0, 0.50, 1, 2, 2.5, 3, 5, and 8 hours.

### Drug content

The drug content percentages for all the formulated trial batches are presented in Table 7. The drug content percentage of all the developed ophthalmic formulations fell within the range of 90% to 99.9%. This indicates that consistent content uniformity was upheld in the formulations.

### Test of Sterility

No turbidity was observed, indicating the absence of bacterial growth, when the optimized formulation was incubated at 20-25°C for 14 days in soybean-casein digest medium. This confirms that the tested preparation successfully passed the sterility test.

**Stability study**

Table 8 presents the outcomes of the stability assessment conducted on the optimized F9 formulation at ambient temperature. The formulations-maintained stability for a duration of up to 3 months at room temperature. Notably, there were no alterations observed in drug content, pH, or clarity during this period.

**Table 2 : Composition of formulation trails for Netarsudil Ophthalmic Gel**

| Sr. No | Formulation Trial | pH |
|---|---|---|
| 1 | F1 | 6.5 |
| 2 | F2 | 6.4 |
| 3 | F3 | 6.5 |
| 4 | F4 | 6.3 |
| 5 | F5 | 6.5 |
| 6 | F6 | 6.2 |
| 7 | F7 | 6.1 |
| 8 | F8 | 6.2 |
| 9 | F9 | 6.2 |
| 10 | F10 | 6.1 |

**Table 3 : viscosity of all formulated trial batches**

| Sr. No | Formulation Code | Viscosity |
|---|---|---|
| 1 | F1 | 102 |
| 2 | F2 | 106 |
| 3 | F3 | 120 |
| 4 | F4 | 143 |
| 5 | F5 | 165 |
| 6 | F6 | 401 |
| 7 | F7 | 369 |
| 8 | F8 | 249 |
| 9 | F9 | 253 |
| 10 | F10 | 250 |

**Table 4 : Viscosity measurements at various RPM levels**

| | Formulation Trials | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| RPM | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
| 25 | 198 | 208 | 248 | 214 | 249 | 478 | 453 | 370 | 356 | 351 |
| 50 | 157 | 163 | 209 | 186 | 201 | 434 | 402 | 312 | 301 | 298 |
| 75 | 102 | 106 | 120 | 143 | 165 | 401 | 369 | 249 | 253 | 250 |
| 100 | 63 | 73 | 102 | 105 | 133 | 365 | 334 | 218 | 228 | 224 |

**Table 5: The gel strength of all the formulated trial batches**

| Sr. No | Formulation Code | Gel strength |
|---|---|---|
| 1 | F1 | 0.32 |
| 2 | F2 | 0.29 |
| 3 | F3 | 0.41 |
| 4 | F4 | 0.68 |
| 5 | F5 | 0.72 |
| 6 | F6 | 2.10 |
| 7 | F7 | 1.98 |
| 8 | F8 | 1.38 |
| 9 | F9 | 1.38 |
| 10 | F10 | 1.36 |

**Table 6 : % drug release of formulation trial batches**

| Time point | Cumulative % drug release in tear fluid for different trials | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F 3 | F 4 | F 5 | F 6 | F 7 | F 8 | F 9 | F 10 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.50 | 51 | 44 | 69 | 72 | 75 | 32 | 38 | 83 | 85 | 86 |
| 1 | 59 | 49 | 75 | 78 | 81 | 49 | 51 | 86 | 88 | 89 |
| 2 | 63 | 53 | 82 | 84 | 86 | 52 | 63 | 89 | 91 | 91 |
| 2.5 | 75 | 67 | 89 | 90 | 92 | 71 | 76 | 93 | 96 | 95 |
| 3 | 79 | 72 | 90 | 92 | 93 | 86 | 90 | 95 | 98 | 96 |
| 5 | 84 | 77 | 91 | 93 | 95 | 90 | 95 | 98 | 99 | 98 |
| 8 | 86 | 78 | 92 | 95 | 96 | 98 | 98 | 99 | 100 | 100 |

**Table 7: % drug content of all formulated trial batches**

| Sr. No | Formulation Code | Drug content |
|---|---|---|
| 1 | F1 | 90.2 |
| 2 | F2 | 93.3 |
| 3 | F3 | 93.5 |
| 4 | F4 | 95.0 |
| 5 | F5 | 95.6 |
| 6 | F6 | 98.5 |
| 7 | F7 | 98.8 |
| 8 | F8 | 99.9 |
| 9 | F9 | 99.8 |
| 10 | F10 | 99.9 |

**Table 8 : Data from the stability study conducted on batch F9**

| Observations | Initial | Stability period | | |
|---|---|---|---|---|
| | | 1 month | 2 month | 3 month |
| Appearance | Clear colorless viscus gel, practically free from particles. | Clear colorless viscus gel, practically free from particles. | Clear colorless viscus gel, practically free from particles. | Clear colorless viscus gel, practically free from particles. |
| Clarity | 100% | 99.9% | 99.9% | 99.8% |
| pH | 6.2 | 6.2 | 6.2 | 6.2 |
| Drug content | 99.8% | 99.8% | 99.7% | 99.7% |

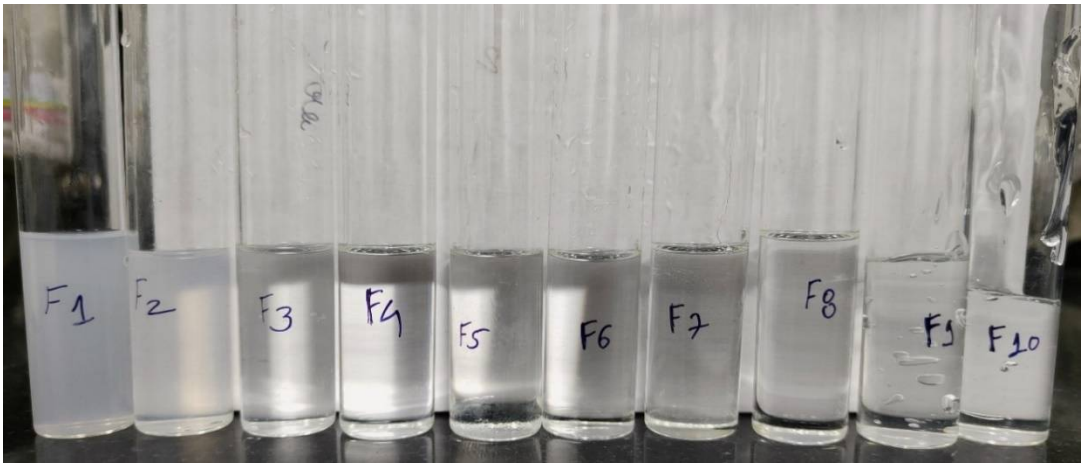


**Figure 1: Prepared Formulation Batches**

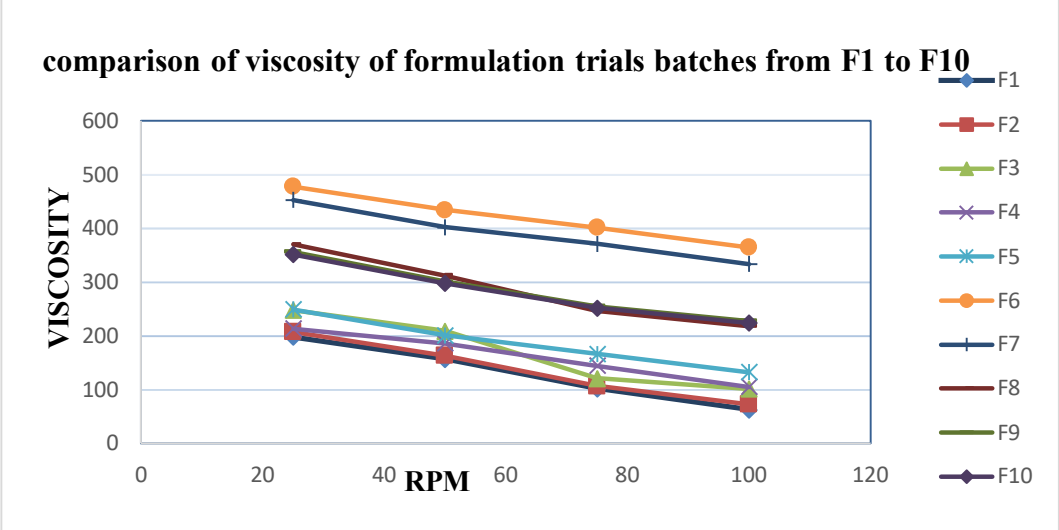


**Figure 2: Comparing the viscosity among formulation trial batches ranging from F1 to F10**

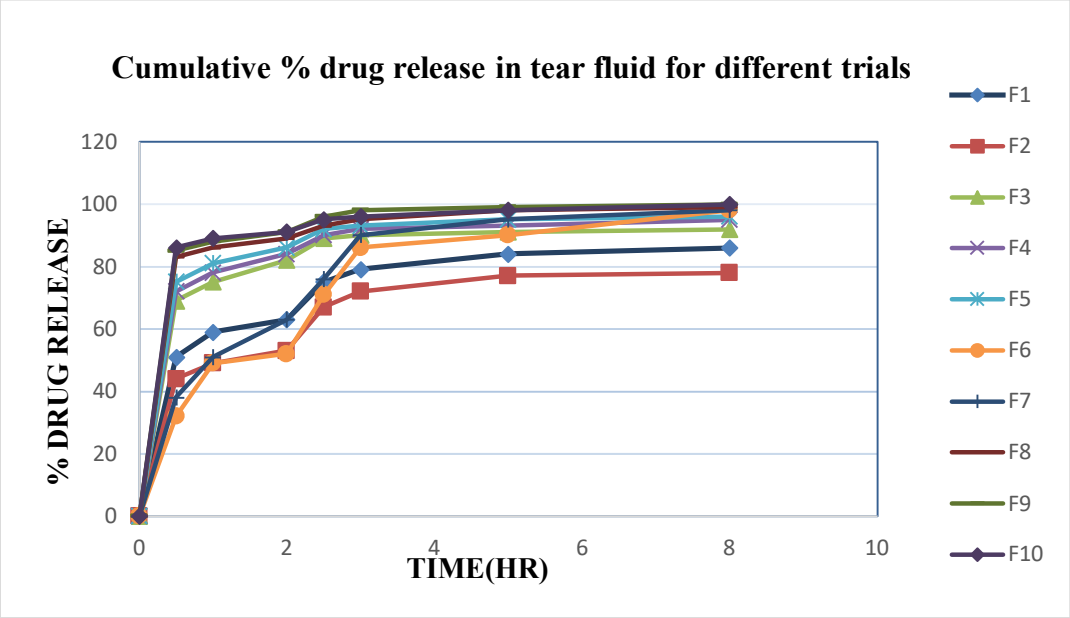


**Figure 3 : % drug release in tear fluid for different formulation trials batch**

## Conclusion

In this work, we successfully developed Netarsudil ophthalmic Drug delivery system which matches with the standard specification. Netarsudil was water soluble & Carbpol was found to be a very effective agent in improving the residence time and hence the permeation improve. We increased the bioavailability of Netarsudil compared with other products of same drug by converting it into gel form. From the literature survey it has been concluded that it is widely used in the treatment of ophthalmic problems. The formulation were stable and robust.

## DECLARTION OF COMPITING INTEREST

The authors state that they do not have any identifiable financial conflicts of interest or personal relationships that might have seemed to affect the research presented in this paper.


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## REFERENCES


1. Sharma Jitendra PK, Banik A, and Dixit S. (2011). Emerging Pattern: Ocular Medication Delivery System, Pharma Science Monitoring: International Journal of Pharmacy, 2(3):1-25.
2. Deshmukh PK, Fursule RA. (2010). Exploration of an innovative environmentally sensitive ocular drug delivery system, International Journal of Pharmaceutical and Biological Sciences, 1(2):1-13.
3. Shell, John W. (1984) "Systems for delivering drugs to the eye." Overview of eye health 29, issue 2: 117-128.
4. Nayak, Kritika, and Manju Misra. (2018). "An overview of contemporary drug delivery approaches for the back part of the eye." Biomedicine & Pharmacotherapy 107: 1564-1582.
5. Rozier, Annouk, Claude Mazuel, Jeffrey Grove, and Bernard Plazonnet. (1997). "Evaluation of the functional properties of gellan gum, a polymer-based excipient for ophthalmic formulations." The International Journal of Pharmaceutics 153, no. 2: 191-198.
6. Gondkar SB, Kute PR, Saudagar RB. Crafting, (2015). Elaboration, and Assessment of Ofloxacin In-Situ Ophthalmic Gel, Global Journal of Pharmacy & Pharmaceutical Sciences, 4(11): 800-822.
7. Deshmukh PK, Fursule RA. (2010). Study of a novel environmental responsive ophthalmic drug delivery system, Int J Pharm Biol Sci, 1(2):1-13.
8. Gondkar SB, Kute PR, Saudagar RB. (2015). Formulation, Development and Evaluation Of Ofloxacin In-Situ Ophthalmic Gel, World J Pharm Pharma Sci, 4(11): 800-822.
9. Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Published by the Indian

Pharmacopoeia Commission, Ghaziabad, 2014:59.
10. United States Pharmacopoeial Convention. The United States Pharmacopoeia, 38th Rev. and The National Formulary, 33rd ed. Twinbrook Parkway, Rockville, MD; 2015:125.

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