INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

# FORMULATION AND EVALUATION OF ECONAZOLE NITRATE OCULAR *IN-SITU* GEL

**Veedhi Rathawa, Ummehani Kalla, Sharav Desai, Hitesh Jain*, D. B. Meshram**
*Pioneer Pharmacy Degree College, Vadodara, Gujarat, India.*

**ARTICLE INFO**

**Article history**
Received 01/12/2021
Available online
31/12/2021

**Keywords**
Econazole Nitrate,
In Situ Gel,
Ocular,
Ph Triggered.

**ABSTRACT**

Objective: To develop in-situ ocular gel containing econazole nitrate for the treatment of ocular fungal keratitis with increasing residence time into the cornea for improvement of ocular bioavailability of drug. Experimental work: In-situ ocular gel containing econazole nitrate was formulated by pH responsive method using carbopol 940 as a pH sensitive polymer and different grades of HPMC as viscosifying agent. The formulated batches were evaluated for drug content, pH, gelling time, spreadability, viscosity, gelling strength and in vitro drug release. Stability study was also performed for final formulation. Result and Discussion: The drug content and pH of the formulation were found to be satisfactory. The gelling strength was found to be in the range of 34 seconds to 91 seconds. The viscosity and spreadability of the formulations were found to be satisfactory. All the prepared formulations passed the sterility testing. Formulation F5 containing 0.2 % Carbopol 940 and 0.6 % HPMCK4M showed highest 80.30 % drug release and was stable. The developed formulations showed sustained release of drug up to 8 hrs. From in-vitro drug release studies, it could be concluded that the developed in-situ gelling systems were thus a better alternative to conventional eye drops. Conclusion: The in-situ ocular gel could enhance precorneal residence time with increased viscosity and provided better release profile of drug.

***Corresponding author***
**Dr. Hitesh Jain**
M. Pharm., Ph. D
Associate Professor
Pioneer Pharmacy Degree College,
Vadodara, Gujarat 390019.
hitesh_hitachi@rediffmail.com

*Please cite this article in press as **Dr. Hitesh Jain** et al. Formulation and Evaluation of Econazole Nitrate Ocular in-Situ Gel . Indo American Journal of Pharmaceutical Research.2021:11(12).*

## INTRODUCTION

Eye drops that are conventional ophthalmic delivery systems frequently result in poor bioavailability and therapeutic response because high tear fluid turnover and dynamics cause rapid pre-corneal elimination of the drug. A high frequency of eye drop instillation is associated with patient non-compliance. Inclusion of excess drug in the formulation in an attempt to overcome bioavailability problem is potentially dangerous if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct. Various formulations like inserts, ointments, suspensions, and aqueous gels, have been developed in order to get longer the residence time of instilled dose and improve the ophthalmic bioavailability. [1,2] Econazole nitrate is a broad-spectrum antifungal agent that inhibits the ergosterol synthesis and thereby alters the normal function of the cell membrane and cause death of the fungus. It has short half of 2-4 hours. It is slightly soluble in water and well absorbed through the cornea. [3, 4]

## MATERIAL AND METHOD:

### Material:

Econazole Nitrate was purchased from Yarrow chem products, Mumbai. HPMC grades were purchased from Chemdyes Corporation, Carbopol 940 was purchased from SDFCL, β-cyclodextrin (β-CD) and Hydroxypropyl-β-cyclodextrin (HP-β-CD) was purchased from Balaji drugs. All other chemicals were used of analytical grade.

### Method:

The in-situ gelling polymer was added slowly in distilled water with continuous stirring until completely dissolved. Another polymeric solution was made and allows to hydrate overnight. After mixing and complete hydration of polymers, a separate solution of drug was added to the polymeric solution. The resultant solution was thoroughly mixed until uniform and clear solution is formed. Final volume was made by adding required volume of distilled water and prepared in situ gel was sterilized by membrane filtration method. The detail composition of in situ gel is given in table no. 1.

**Table I: Formulation Table of Batches (F1-F12).**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Econazole Nitrate (mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Carbopol 940 (%) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| HPMC K15M (%) | 0.4 | 0.6 | 0.8 | - | - | - | - | - | - | - | - | - |
| HPMC K4M (%) | - | - | - | 0.4 | 0.6 | 0.8 | - | - | - | - | - | - |
| HPMC E15LV (%) | - | - | - | - | - | - | 0.4 | 0.6 | 0.8 | - | - | - |
| HPMC E50LV (%) | - | - | - | - | - | - | - | - | - | 0.4 | 0.6 | 0.8 |
| Methyl Paraben (%) | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |
| Distilled Water (ml) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

## EVALUATION OF *IN SITU* GEL

### pH of in-situ gel:

pH of each formulation was determined by using pH meter which was previously calibrated using standard buffer of pH 4 and pH 7. pH was Measured by taking 1 ml formulation which was diluted with simulated tear fluid pH 7.4. [5]

### Drug content:

1 ml of formulation was taken in 10 ml of volumetric flask and at that point diluted with simulated tear fluid pH 7.4 up to 10 ml. Yet again 1 ml quantity from this solution was taken and diluted with 10 ml of simulated tear fluid pH 7.4. Lastly, the absorbance of prepared solution was measured at 212 nm against blank reagent using UV visible spectrophotometer. [6]

### Viscosity measurement:

Viscosity of prepared formulation was determined using Brookfield viscometer with spindle no. 62 at 50-100 rpm at temperature 37±0.5 C. Spindle was lowered perpendicularly into gel placed in a beaker taking care that the spindle does not touch the bottom of beaker. Reading were recorded after 30 sec. [7]

### Gelling time:

The gelling time was determined by dropping the formulation in a test tube containing 2.0 ml of freshly prepared simulated tear fluid pH 7.4 and the gelation was observed by visual examination. [8]

### Gelling strength:

The prepared gel was placed in 100 ml measuring cylinder the probe was placed on the gel and a weight was placed on the probe. The probe was allowed to penetrate at a distance of 5 cm and time required for penetration was noted as a gelling strength. [9]

**Spreadability:**

For the determination of spreadability excess of sample was applied in between 2 glass slide and was compressed to uniform thickness by placing 100- gram weight over the upper glass slide for 5 minutes. Weight 50 gram was added to pan. Time required separating the two slides i.e. the time in which the upper glass slide move over the lower plate was taken as measure of spreadability. [10]

**S= (m*1)/t Where,**

S= Spreadability
m= weight tied to upper slide
t= time taken
1= length moved on upper glass slide

**In vitro drug release:**

The drug release of the Econazole Nitrate in-situ ophthalmic gel was measured using Franz diffusion cell with dialysis membrane (mol. Wt. 12000D) as a barrier. Assembly was set and the temperature was maintained at 37±0.5°C, then 2 ml of in-situ ophthalmic gel of Econazole Nitrate was Filled in the donor compartment, which was separated by the receptor compartment with the dialysis membrane. The receptor compartment was filled with the simulated tear fluid pH 7.4. 1 ml aliquots of sample were withdrawn at regular time intervals and replaced with an equal volume of simulated tear fluid pH 7.4 as fresh receptor medium. The samples were appropriately diluted with simulated tear fluid pH 7.4 and analyzed spectrophotometrically at 212 nm. [11]

**Sterility testing:**

The sterility testing was performed by using fluid thioglycolate and soyabean casein medium respectively. The method used for sterility testing was the direct inoculation method, in which 2 ml of test liquid was aseptically transferred to fluid thioglycolate medium (FTM 20 ml) and soyabean casein digest medium (SCDM20 ml) separately. The liquid was mixed with the media. The inoculated media is incubated for not less than 14 days at 30 C to 35 thioglycolate medium and 20℃ to 25 in the case of soyabean casein digest medium. [12]

**Stability study:**

Formulation F5 was placed in ambient color vials and seal with aluminum foil for a short-term stability study at 40±2 C and 75±5% RH as per international conference on harmonization states guidelines. Sample was analyzed for clarity, pH, viscosity, gelling time, gelling capacity, drug content and in vitro drug release. [13]

**RESULTS AND DISCUSSION**

The prepared in situ gel was evaluated for various evaluation parameters. The results of various evaluation parameters were found in the acceptable range as shown in table no. 2 and 3.

**Table 2: Evaluation parameters of in situ gel (F1 - F12).**

| Batch no. | Drug Content % (±S.D.) | pH (±S.D.) | Gelling Time (sec) (±S.D.) | Spreadability gcm/sec (±S.D.) |
|---|---|---|---|---|
| F1 | 97.29 ± 0.18 | 6.55 ± 0.20 | 11 ± 0.062 | 38.85 ± 0.942 |
| F2 | 97.45 ± 0.23 | 6.48 ± 0.18 | 8.1 ± 1.413 | 34.44 ± 0.081 |
| F3 | 96.13 ± 0.05 | 6.45 ± 0.11 | 7.4 ± 0.250 | 29.25 ± 0.237 |
| F4 | 97.01 ± 0.25 | 6.84 ± 0.14 | 10.2 ± 1.124 | 26.54 ± 0.061 |
| F5 | 98.67 ± 0.075 | 6.8 ± 0.05 | 4.5 ± 0.932 | 51.19 ± 0.472 |
| F6 | 98.52 ± 0.09 | 6.52 ± 0.12 | 6.0 ± 0.566 | 21.95 ± 0.035 |
| F7 | 95.11 ± 0.08 | 6.08 ± 0.1 | 9.1 ± 0.045 | 39.75 ± 1.126 |
| F8 | 96.51 ± 0.1 | 6.11 ± 0.07 | 10 ± 0.206 | 36.37 ± 0.08 |
| F9 | 95.25 ± 0.16 | 6.28 ± 0.22 | 8.4 ± 0.033 | 31.42 ± 0.062 |
| F10 | 96.67 ± 0.28 | 6.71 ± 0.09 | 9.2 ± 1.145 | 45.29 ± 0.92 |
| F11 | 96.74 ± 0.56 | 6.6 ± 0.24 | 7.9 ± 0.120 | 41.68 ± 1.15 |
| F12 | 97.31 ± 1.21 | 6.75 ± 0.15 | 6.2 ± 0.059 | 37.01 ± 0.59 |

*Each observation values are expressed as mean ±S.D. of n=3

**Table 3: Evaluation parameters of in situ gel (F1-F12).**

| Batch no. | Viscosity (cps (±S.D.) | | Gelling Strength (sec) (±S.D.) |
|---|---|---|---|
| | Solution | Gel | |
| F1 | 92 ± 0.22 | 162 ± 0.64 | 46 ± 0.94 |
| F2 | 131 ± 0.61 | 310 ± 0.67 | 68 ± 1.24 |
| F3 | 152 ± 1.021 | 390 ± 0.82 | 73 ± 0.47 |
| F4 | 68 ± 0.08 | 171 ± 1.01 | 34 ± 0.81 |
| F5 | 94 ± 1.12 | 237 ± 0.92 | 51 ± 1.69 |
| F6 | 103 ± 0.72 | 321 ± 0.59 | 67 ± 0.40 |
| F7 | 78 ± 1.31 | 210 ± 0.56 | 40 ± 1.02 |
| F8 | 148 ± 0.26 | 369 ± 0.41 | 56 ± 0.43 |
| F9 | 222 ± 1.09 | 428 ± 0.22 | 62 ± 0.77 |
| F10 | 98 ± 0.05 | 299 ± 0.29 | 53 ± 0.47 |
| F11 | 126 ± 1.21 | 278 ± 0.52 | 70 ± 1.26 |
| F12 | 145 ± 0.9 | 348 ± 0.09 | 85 ± 1.11 |

*Each observation values are expressed as mean ±S.D. of n=3.

**In vitro drug released study**

Amongst all these formulations, the maximum drug release was found to be 80.3 % for F5 and it was also observed that drug release decreases by increasing the concentration of polymers as shown in figure 1 to 4.

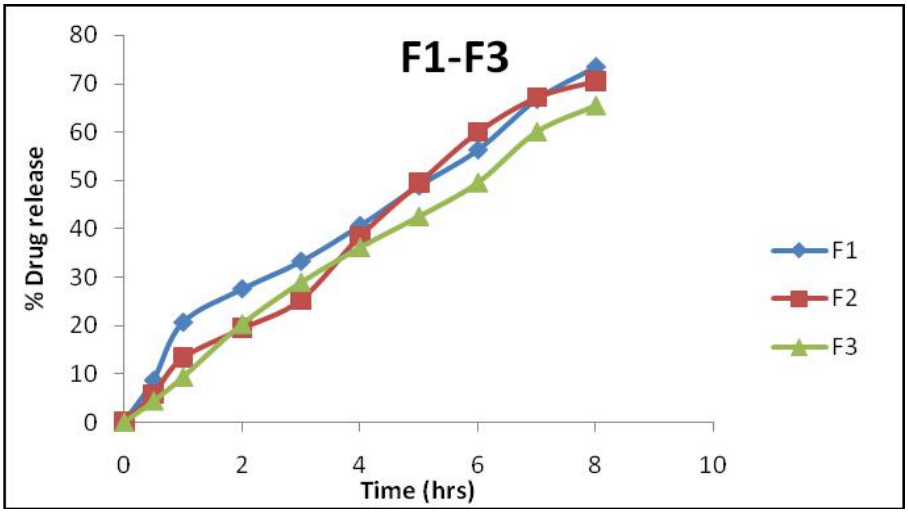


**Figure 1: In vitro drug released from F1-F3.**

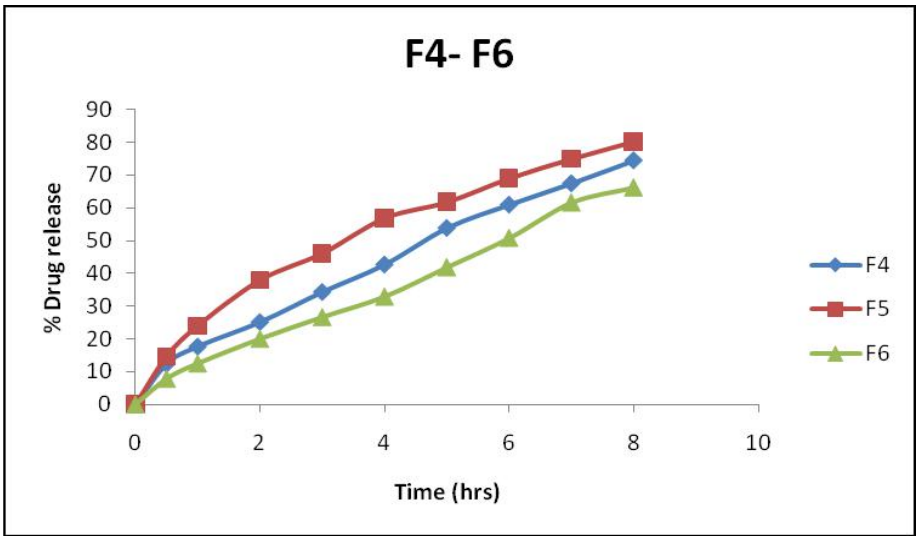


**Figure 2: In vitro drug released from F4-F6.**

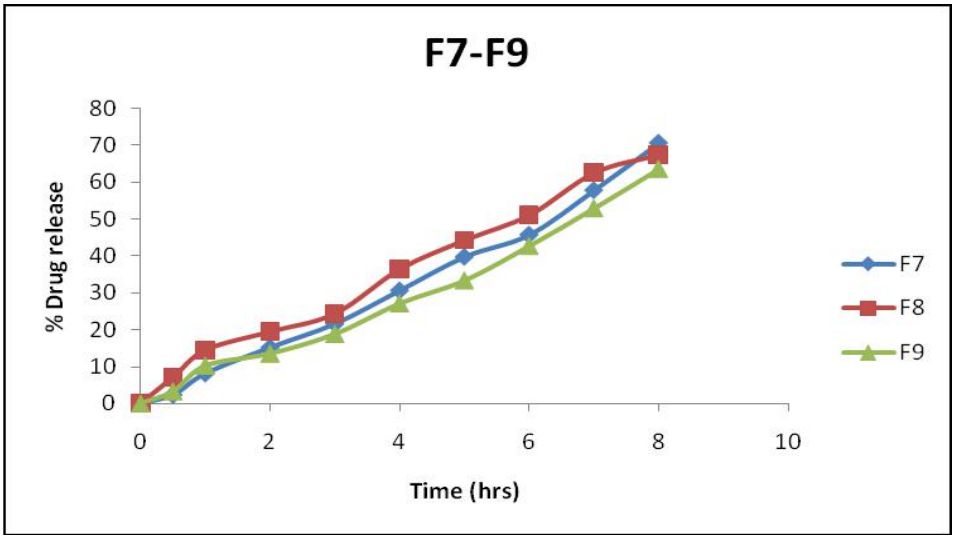


**Figure 3: In vitro drug released from F7-F9.**

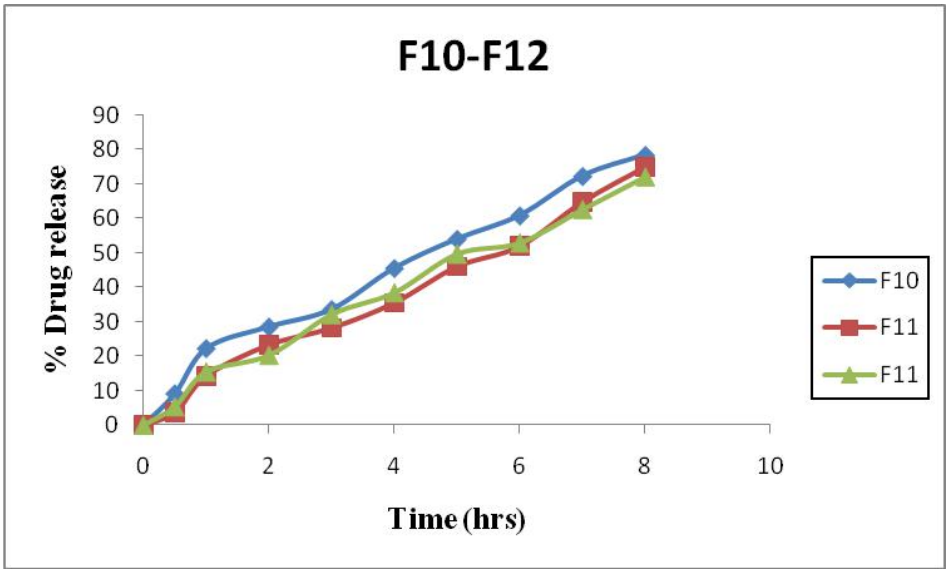


**Figure 4: In vitro drug released from F10-F12.**

**Sterility testing**

The prepared formulations were passed the test for sterility, as there was no appearance of turbidity and hence no evidence of aerobic/anaerobic bacteria growth when incubated for not less than 14 days in fluid thioglycolate medium and soyabean casein digest medium.

**Stability study of formulation F5**

Formulation F5 was subjected for stability study and evaluated for various evaluation parameters. From the results as shown in table 4 and figure 5 it was found that there was no major changes in the physical properties as well as in the drug release. Hence formulation F5 was stable.

**Table 4: Evaluation of F5 after stability study.**

| Physical properties | Initial | At 40±2 C/75±5% RH |
|---|---|---|
| Drug content (%) | 98.67 ± 0.075 | 99.13±0.524 |
| pH | 6.8 ± 0.05 | 7.41±0.263 |
| Viscosity (cps) | 94 ± 1.12 237 ± 0.92 | 104±1.32 243±0.74 |
| Gelling time (sec) | 4.5 ± 0.932 | 4.2±0.156 |
| Spreadability (gcm/sec) | 51.19± 0.472 | 49±0.207 |
| Gelling strength (sec) | 51 ± 1.69 | 57±1.423 |

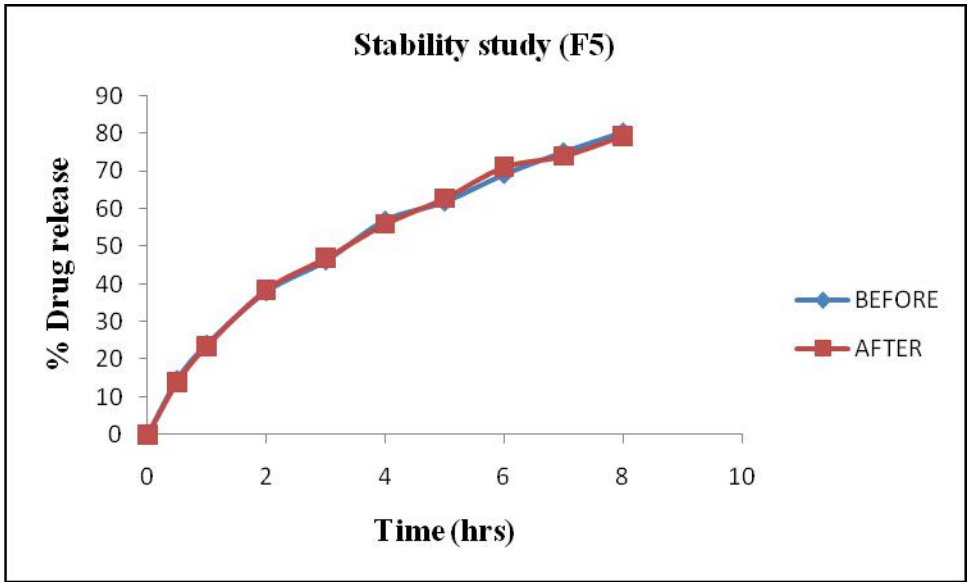


**Figure 5: In vitro drug released of F5 after stability study.**

## CONCLUSION

The research work aimed that formulation and evaluation of Econazole Nitrate ocular in situ gel. The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by use of in situ gel forming solution that are instilled as drop into eye and undergo sol-to-gel transition in cul-de-sac. In present investigation, attempt was made to prepare in-situ ophthalmic gel of Econazole Nitrate with different polymer concentration and polymer grades using pH triggered method. All the formulations were passed the sterility test. The highest drug release was found to be 80.30 % in formulation F5. Stability study confirmed that there were no major changes in the physical properties and drug release, hence the formulation F5 was stable, the study conclusively demonstrated that Econazole Nitrate can be successfully formulated into in-situ ophthalmic gel to obtain sustained release over the extended period of 8 hours.

## ACKNOWLEDGEMENT

We express our gratitude to Yarrow chem products, Mumbai for providing the Econazole API.

**Conflict of interest:**

None

**REFERENCES**


1. Nalla A, Chinnala KM. In-situ ophthalmic drug delivery systems- an overview. IAJPR. 2016; 3(3): 202-208.
2. Nalla A and Chinnala KM. In-situ ophthalmic drug delivery systems- an overview. IAJPR 2016; 3(3): 202-208.
3. Muller GG, Newton K and Rosane S. Antifungals in eye infections: drugs and routes of administration. Rev Bras Oftalmol. 2013; 72(2): 132-141.
4. Laith HS. Formulation of econazole nitrate as a topical solution. Iraqi J. Pharma. Sci. 2005; 14: 20-30.
5. Vijaya C, Goud KS. Ion-activated in situ gelling ophthalmic delivery systems of azithromycin. Indian. J. Pharm. Sci. 2011; 73(6): 615-620.
6. Sirisuru P, Sirisuru P, Parvathi M. Formulation and evaluation of insitu gelling system for ocular delivery of timolol maleate. Int. J. Pharm. Chem. Sci. 2014; 3(1):81-89.
7. Randa Z, Khaled MH, Ahmed K, Ahmed A. Ketorolac tromethamine in-situ ocular hydrogel; preparation, characterization and in-vivo evaluation. Int. J. Drug Deliv. 2011; 3:535-545.
8. Patil S, Kadam A, Bandgar S, Patil S. Formulation and evaluation of an in situ gel for ocular drug delivery of anti-conjunctival drug. Cellul. Chem. Technol. 2015; 49(1):35-40.
9. Ahmed VA, Goli D, Xyloglucan based in-situ gel: formulation development and evaluation of in-situ ophthalmic gel of brimonidine tartarate. Indo Global. J. Pharm. 2018; 8(3): 92-103.
10. Mittal N, Kaur G. In situ gelling ophthalmic drug delivery system: formulation and evaluation. J. Appl. Polym. Sci. 2013:1-9.
11. Ranch K, Patel H, Chavda L, Koli A, Maulvi F, Parikh RK. Development of in situ ophthalmic gel of dexamethasone sodium phosphate and chloramphenicol: a viable alternative to conventional eye drops. J. Appl. Pharm. Sci. 2017; 7(3): 101-108.
12. Arora K, Singh S. Preparation and evaluation of pH and temperature sensitive polymer based in-situ gel for ocular delivery. World J Pharm Pharm Sci.2017; 6(1): 1366-1381.
13. Gupta C, Juyal V, Nagaich U. Formulation, optimization, and evaluation of in-situ gel of moxifloxacin hydrochloride for ophthalmic drug delivery. Int J App Pharma. 2019; 11(4):147-158.