Formulation and Evaluation of Ocular Insert of Femiciclovir

VIVEK SHARMA*
Vivek.kcp2022@gmail.com
Research scholar, Roorkee College of Pharmacy, Roorkee, Uttarakhand
Dr. VIPIN KUKKAR
ASSOCIATE PROFESSOR
Roorkee College of Pharmacy, Roorkee, Uttarakhand

ABSTRACT

To prepare ophthalmic inserts of Femiciclovir, a drug of choice for Herpes simplex virus (HSV) infection, with the aim of improving the release pattern of the drug over a period of 12h.

Methods: *Inserts containing Femiciclovir were prepared using a water-soluble polymeric matrix of polyvinyl alcohol and methylcellulose by the film casting method. The effects of agents increasing viscosity, hydrophobic polymers and osmotic agents on the swelling and release characteristics of the inserts were examined. Differential scanning calorimetry (DSC) and stability studies of the prepared inserts stored at 25 C for six months were also carried out.*

Results: *The method used for the formulation of ocular inserts is solvent casting method. Because it was a simple and effective method. The % drug release was found 80-90%.*

INTRODUCTION

Controlled and sustained delivery of ophthalmic drugs continues to remain a major focus area in the field of pharmaceutical drug delivery with the emergence of new, more potent drugs and biological response modifiers. (**Bourlais C *et al* 1998)**

The major objective of clinical therapeutics is to provide and maintain adequate concentration of drugs at the site of action. In ocular drug delivery, the physiological constraints imposed by the protective mechanisms of the eye lead to poor absorption of drugs with very small fractions of the instilled dose penetrating the cornea and reaching the intraocular tissues. (**Gulsen D *et al* 2004**)

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.(**Gaudana R, *et al* 2010)** Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. An ocular drug delivery system is a new novel drug delivery system and this technique is incepted in the beginning of the last decade. Literature survey reveals that not much work has been done in reference to anti-glaucoma, antidiabetic, macular degeneration, retinal damage, dry eye syndrome, diabetic retinopathy and Sjögren's disease. (**Meseguer G *et al* 1998**)

ANATOMY AND PHYSIOLOGY OF EYE: The eye is a unique organ from anatomical and physiological point of view, in that it contains several highly different structures with specific physiological functions. The specific aim of designing a therapeutic system is to achieve the optimal

concentration of a drug entity at the active site for the appropriate duration. The primitive ophthalmic solutions, suspension, and ointment dosage forms are no longer sufficient to combat ocular diseases.

The eye has two segments. A smaller, transparent anterior segment that makes up one-sixth of the eyeball, and an opaque posterior segment that forms the remaining five-sixths of the eyeball. (**van der Bijl P *et al* 2001)**

1.1 Structure of Eye

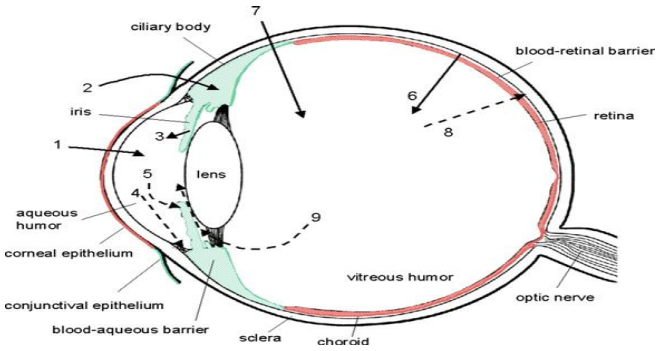

Fig 1.1 Structure of Eye (urtti et al 2006)

Following section describes the eye parts along with the problems arising with conventional ocular preparation**.**

Ophthalmic Drug Delivery System: Drug delivery systems for eyes requires the need to study complete structure and functions of eye in order to overcome the challenge making to attack the protective barrier of eye with no eternal tissue injury. Research till now in drug delivery techniques for eyes focused towards various drug deliverance techniques developing such kind of system which will not only facilitate the contact time of active agent at the ocular area but also delay the elimination process of drug. In this field ocular inserts would be the most innovative step. The main purpose of preparing ocular inserts will be to enhance the ocular bioavailability of drug and maintaining the concentration of drug within the desired site. (**Mannermaa E *et al* 2006)**

OCULAR BIOAVAILABILITY: Bioavailability of drugs administered to the eye is an important consideration. There are physiologic factors, which can affect a drug's ocular bioavailability including protein binding, drug metabolism and nasolacrimal drainage. Other factors as the physicochemical characteristics of the drug substance, and product formulation are important. Systemic administration of a drug to treat ocular disease would require high concentrations of circulating drug in the plasma to achieve therapeutic concentrations in the aqueous humor, which involves the increased risk of side effects. Topical administration is more direct, but a conventional preparation of ophthalmic drug, such as aqueous solution is relatively inefficient as therapeutic systems. A large proportion of the topically applied drug is immediately drained from the conjuctival sac into the nasolacrimal duct or is cleared from precorneal area. There are several approaches in ocular delivery to make better ocular bioavailability. (**Shen J *et al* 2011)**

Formulation Method of Ocuserts

Solvent Casting Method In this method no. of batches are formulated in different proportion. The polymer is dissolved in suitable solvent. Into this solution plasticizer is added following

continuous stirring .The accurately weighed amount of drug is added to above solution and a uniform dispersion is obtained. When the proper blend is formed the solution is casted into the petridish using inverted funnel to allow slow and uniform evaporation at room temperature until the film is dried. The dried films thus obtained the film is cut into proper size and shape using cork borer. The ocuserts are prepared and storage is done in air tight container. (**Liang H *et al* 2009**)

Glass Substrate Technique In this method the p polymer is soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution. The solution is filtered. Required amount of drug is added and vortexed for 15minutes to dissolve the complex in polymer solution. Plasticizer is added to the above solution. The viscous solution is obtained and kept aside for 30 minutes until air bubbles are removed. Formulation of controlled release films occurs. The films are casted by discharging solution into the center of leveled glass mould and allowing it to dry at room temperature for 24 hrs. The dried films are cut to form ocusert in definite shape and size Then, the matrix is placed between the rate controlling membranes using gum which is non-toxic, non-irritating, and water insoluble. They are wrapped in aluminium foil separately and stored in a descicator. (**Liang H *et al* 2009)**

Melt Extrusion Technique Drug and the polymer are passed through sieve having mesh size of60#, weighed and blended. In this mixture plasticizer is added. The blend is then discharged to the container of melt flow rate apparatus and extruded. The extrudate was cut into appropriate size and packed in polyethylene lined aluminium foil, heat sealed and sterilized by using gamma rays. **(Liang H *et al* 2009)**

DRUG PROFILE
Famiciclovir

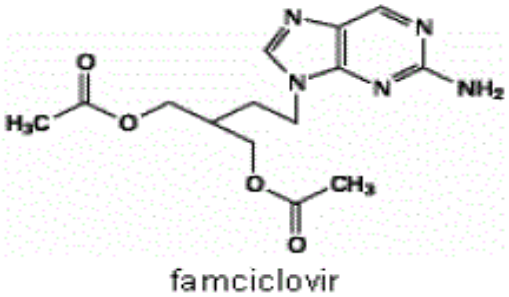

Fig 2.1 Structure of Famiciclovir

Sodium alginate : It is a sodium salt of alginic acid.

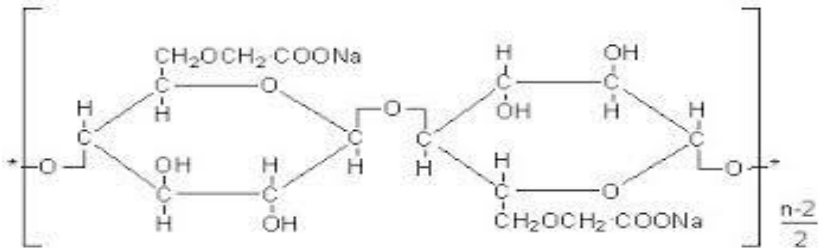

Fig 2.2 Structure of Sodium alginate

PH DETERMINATION OF DRUG AND POLYMER

1% solution of both drug and polymer was prepared by using distilled water and pH of both drug and polymer was measured using pH meter.

FORMULATION DEVELOPMENT

Formulation of Blank Films

Table 1.1 Composition of blank films

Formulation Code	HPMC K4 M (mg)	Sodium Alginate (mg)	PVA (mg)	Gelatin (mg)	Di Butyl Pthalate (ml)	Water (ml)
F1	100	-	100	-	1	15
F2	-	100	100	-	1	15
F3	-	-	100	100	1	15
F4	100	-	-	-	1	15
F5	-	100	-	-	1	15
F6	-	-	100	-	1	15
F7	-	-	-	100	1	15

Formulation of Famiciclovir Films

Table 1.2 Composition of Famiciclovir Films

Formulation Code	Drug famiciclovir (mg)	HPMC K4 M (mg)	Sodium Alginate (mg)	PEG(400) (ml)	Water (ml)
F1	100	100	100	1	15
F2	100	150	150	1	15
F3	100	200	200	1	15
F4	100	250	250	1	15
F5	100	300	300	1	15
F6	100	350	350	1	15
F7	100	400	400	1	15
F8	100	450	450	1	15

2RESULTS AND DISCUSSIONS

2.1 IDENTIFICATION OF DRUG

2.1.1 Determination of melting point: The melting point of drug was found to be 256.4ºc. The reported melting point of drug famiciclovir is 256- 257^{0}C. Thus, drug was identified as famiciclovir and found to be pure.

2.2 Standard plot of famiciclovir in distilled water: The maximum absorption of famiciclovir drug in distilled water was found to be 251.5 nm. The stock solution of famiciclovirwas prepared by dissolving 100 mg of famiciclovirin 100ml of distilled water and suitable dilution were made and absorbance was taken in UV spectroscopy at 251.5nm.

Table2.2 Standard plot analysis of Famiciclovir in distilled water

S.NO	Concentration (µg/ml)	A_1	A_2	A_3	Mean absorbance	S.D
1	2	0.103	0.101	0.099	0.101	±0.002
2	4	0.204	0.205	0.208	0.205	±0.002
3	6	0.304	0.308	0.310	0.307	±0.003
4	8	0.400	0.400	0.398	0.399	±0.001
5	10	0.493	0.501	0.502	0.498	±0.005

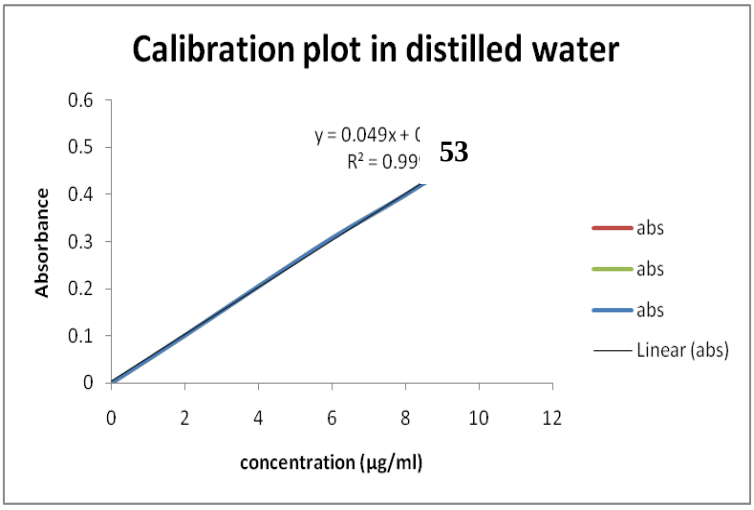

Fig 2.2 Standard plot of famiciclovir in distilled water

Standard plot of famiciclovir in phosphate buffer

S.NO	Concentration (µg/ml)	A_1	A_2	A_3	Mean absorbance	S.D
1	2	0.099	0.098	0.099	0.098	±0.001
2	4	0.202	0.203	0.201	0.202	±0.001
3	6	0.310	0.309	0.310	0.308	±0.001
4	8	0.406	0.406	0.405	0.405	±0.001
5	10	0.509	0.510	0.508	0.506	±0.001

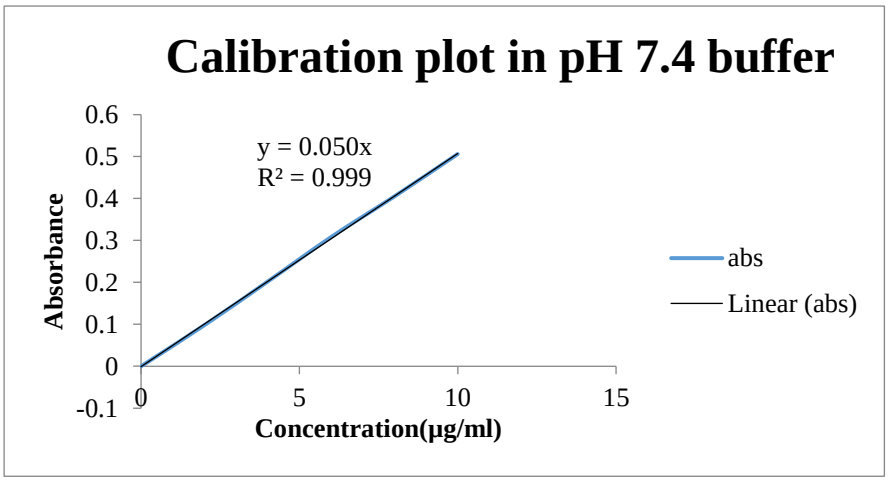

Fig 2.3Standard plot of famiciclovir in pH 7.4 Phosphate buffer

SUMMARY AND CONCLUSION

Melting point evaluation, FTIR scan and UV scan of famiciclovir was performed. From the result of above studies it may be concluded that the drug was pure with no impurities and can be used in preparing ocular inserts.

In analytical studies calibration curve of Famiciclovir was prepared in pH 7.4 simulated tear fluid. On the basis of values of R^2 and slope it was concluded that standard plots were suitable for use in analysis of preformulation of famiciclovir.

The incompatibility study was performed for one month at the room temperature. The samples were analyzed and it was found that there was no interaction, physically or chemically between the drug and polymer.

The method used for the formulation of ocular inserts is solvent casting method. Because it was a simple and effective method. The % drug release was found 80-90%.

References

1. Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems--recent advances. *Prog Retin Eye Res.* 1998;17:33–58. doi: 10.1016/S1350-9462(97)00002-5

2. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. *Invest Ophthalmol Vis Sci.* 2004;45:2342–2347. doi: 10.1167/iovs.03-0959.

3. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. *AAPS J.* 2010;12:348–360. doi: 10.1208/s12248-010-9183-3

4. Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. *Pharm Res.* 2009;26:1197–1216. doi: 10.1007/s11095-008-9694-0.

5. Bochot A, Fattal E. Liposomes for intravitreal drug delivery: a state of the art. *J Control Release.* 2012;161:628–634. doi: 10.1016/j.jconrel.2012.01.019.

6. Kim SH, Lutz RJ, Wang NS, Robinson MR. Transport barriers in transscleral drug delivery for retinal diseases. *Ophthalmic Res.* 2007;39:244–254. doi: 10.1159/000108117.

7. Lee SJ, He W, Robinson SB, Robinson MR, Csaky KG, Kim H. Evaluation of clearance mechanisms with transscleral drug delivery. *Invest Ophthalmol Vis Sci.* 2010;51:5205–5212. doi: 10.1167/iovs.10-5337.
8. Schoenwald RD. Ocular drug delivery. Pharmacokinetic considerations. *Clin Pharmacokinet.* 1990;18:255–269. doi: 10.2165/00003088-199018040-00001.
9. Vaka SR, Sammeta SM, Day LB, Murthy SN. Transcorneal iontophoresis for delivery of ciprofloxacin hydrochloride. *Curr Eye Res.* 2008;33:661–667. doi: 10.1080/02713680802270945.
10. Tirucherai GS, Dias C, Mitra AK. Corneal permeation of ganciclovir: mechanism of ganciclovir permeation enhancement by acyl ester prodrug design. *J Ocul Pharmacol Ther.* 2002;18:535–548. doi: 10.1089/108076802321021081
11. Gunda S, Hariharan S, Mitra AK. Corneal absorption and anterior chamber pharmacokinetics of dipeptide monoester prodrugs of ganciclovir (GCV): in vivo comparative evaluation of these prodrugs with Val-GCV and GCV in rabbits. *J Ocul Pharmacol Ther.* 2006;22:465–476. doi: 10.1089/jop.2006.22.465.
12. Gallarate M, Chirio D, Bussano R, Peira E, Battaglia L, Baratta F, Trotta M. Development of O/W nanoemulsions for ophthalmic administration of timolol. *Int J Pharm.* 2013;440:126–134. doi: 10.1016/j.ijpharm.2012.10.015.
13. Tirucherai GS, Mitra AK. Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir. *AAPS PharmSciTech.* 2003;4:E45. doi: 10.1208/pt040345. [
14. Vulovic N, Primorac M, Stupar M, Brown MW, Ford JL. Some studies on the preservation of indometacin suspensions intended for ophthalmic use. *Pharmazie.* 1990;45:678–679.
15. Meseguer G, Buri P, Plazonnet B, Rozier A, Gurny R. Gamma scintigraphic comparison of eyedrops containing pilocarpine in healthy volunteers. *J Ocul Pharmacol Ther.* 1996;12 :481–488. doi: 10.1089/jop.1996.12.481.
16. Gebhardt BM, Varnell ED, Kaufman HE. Cyclosporine in collagen particles: corneal penetration and suppression of allograft rejection. *J Ocul Pharmacol Ther.* 1995;11:509–517. doi: 10.1089/jop.1995.11.509. [
17. Saettone MF, Chetoni P, Cerbai R, Mazzanti G, Braghiroli L. Evaluation of ocular permeation enhancers: in vitro effects on corneal transport of four beta-blockers, and in vitro/in vivo toxic activity. *Int J Pharm.* 1996;142:103–113. doi: 10.1016/0378-5173(96)04663-7.
18. van der Bijl P, van Eyk AD, Meyer D. Effects of three penetration enhancers on transcorneal permeation of cyclosporine. *Cornea.* 2001;20:505–508. doi: 10.1097/00003226-200107000-00013
19. Burgalassi S, Chetoni P, Monti D, Saettone MF. Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. *Toxicol Lett.* 2001;122:1–8. doi: 10.1016/S0378-4274(01)00261-2.
20. Keister JC, Cooper ER, Missel PJ, Lang JC, Hager DF. Limits on optimizing ocular drug delivery. *J Pharm Sci.* 1991;80:50–53. doi: 10.1002/jps.2600800113.
21. Hornof MD, Bernkop-Schnürch A. In vitro evaluation of the permeation enhancing effect of polycarbophil-cysteine conjugates on the cornea of rabbits. *J Pharm Sci.* 2002;91:2588–2592. doi: 10.1002/jps.10258.

22. Kurz D, Ciulla TA. Novel approaches for retinal drug delivery. *Ophthalmol Clin North Am.* 2002;15:405–410. doi: 10.1016/S0896-1549(02)00034-2.
23. Cholkar K, Patel SP, Vadlapudi AD, Mitra AK. Novel strategies for anterior segment ocular drug delivery. *J Ocul Pharmacol Ther.* 2013;29:106–123. doi: 10.1089/jop.2012.0200.
24. Mannermaa E, Vellonen KS, Urtti A. Drug transport in corneal epithelium and blood-retina barrier: emerging role of transporters in ocular pharmacokinetics. *Adv Drug Deliv Rev.* 2006;58:1136–1163. doi: 10.1016/j.addr.2006.07.024
25. Shen J, Gan L, Zhu C, Zhang X, Dong Y, Jiang M, Zhu J, Gan Y. Novel NSAIDs ophthalmic formulation: flurbiprofen axetil emulsion with low irritancy and improved anti-inflammation effect. *Int J Pharm.* 2011;412:115–122. doi: 10.1016/j.ijpharm.2011.03.041
26. Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. *Prog Retin Eye Res.* 2002;21:15–34. doi: 10.1016/S1350-9462(01)00017-9.
27. Liang H, Brignole-Baudouin F, Rabinovich-Guilatt L, Mao Z, Riancho L, Faure MO, Warnet JM, Lambert G, Baudouin C. Reduction of quaternary ammonium-induced ocular surface toxicity by emulsions: an in vivo study in rabbits. *Mol Vis.* 2008;14:204–216.
28. Tajika T, Isowaki A, Sakaki H. Ocular distribution of difluprednate ophthalmic emulsion 0. 05% in rabbits. *J Ocul Pharmacol Ther.* 2011;27:43–49. doi: 10.1089/jop.2010.0093
29. Liu Y, Lin X, Tang X. Lipid emulsions as a potential delivery system for ocular use of azithromycin. *Drug Dev Ind Pharm.* 2009;35:887–896. doi: 10.1080/03639040802680271.
30. Karasawa F, Ehata T, Okuda T, Satoh T. Propofol injection pain is not alleviated by pretreatment with flurbiprofen axetil, a prodrug of a nonsteroidal antiinflammatory drug. *J Anesth.* 2000;14:135–137. doi: 10.1007/s005400070020.
31. Yamaguchi M, Ueda K, Isowaki A, Ohtori A, Takeuchi H, Ohguro N, Tojo K. Mucoadhesive properties of chitosan-coated ophthalmic lipid emulsion containing indomethacin in tear fluid. *Biol Pharm Bull.* 2009;32:1266–1271. doi: 10.1248/bpb.32.1266
32. Lang J, Roehrs R, Jani R. *Remington: The Science and Practice of Pharmacy.* 21. Philadelphia: Lippincott Williams & Wilkins; 2009. Ophthalmic preparations; p. 856. [Google Scholar]
33. Scoper SV, Kabat AG, Owen GR, Stroman DW, Kabra BP, Faulkner R, Kulshreshtha AK, Rusk C, Bell B, Jamison T, Bernal-Perez LF, Brooks AC, Nguyen VA. Ocular distribution, bactericidal activity and settling characteristics of TobraDex ST ophthalmic suspension compared with TobraDex ophthalmic suspension. *Adv Ther.* 2008;25:77–88. doi: 10.1007/s12325-008-0019-9.
34. Kinoshita S, Awamura S, Oshiden K, Nakamichi N, Suzuki H, Yokoi N. Rebamipide (OPC-12759) in the treatment of dry eye: a randomized, double-masked, multicenter, placebo-controlled phase II study. *Ophthalmology.* 2012;119:2471–2478. doi: 10.1016/j.ophtha.2012.06.052. [
35. Sasaki H, Yamamura K, Mukai T, Nishida K, Nakamura J, Nakashima M, Ichikawa M. Enhancement of ocular drug penetration. *Crit Rev Ther Drug Carrier Syst.* 1999;16:85–146. doi: 10.1615/CritRevTherDrugCarrier-Syst.v16.i1.20.
36. Fukuda M, Hanazome I, Sasaki K. The intraocular dynamics of vancomycin hydrochloride ophthalmic ointment (TN-011) in rabbits. *J Infect Chemother.* 2003;9:93–96. doi: 10.1007/s10156-002-0219-1

37. Eguchi H, Shiota H, Oguro S, Kasama T. The inhibitory effect of vancomycin ointment on the manifestation of MRSA keratitis in rabbits. *J Infect Chemother.* 2009;15:279–283. doi: 10.1007/s10156-009-0708-6. [
38. Gray C. Systemic toxicity with topical ophthalmic medications in children. *Paediatric and Perinatal Drug Therapy.* 2006;7:23–29. doi: 10.1185/146300905X75334. [CrossRef] [Google Scholar]
39. Ishibashi T, Yokoi N, Kinoshita S. Comparison of the short-term effects on the human corneal surface of topical timolol maleate with and without benzalkonium chloride. *J Glaucoma.* 2003;12:486–490. doi: 10.1097/00061198-200312000-00008.
40. Whitson JT, Ochsner KI, Moster MR, Sullivan EK, Andrew RM, Silver LH, Wells DT, James JE, Bosworth CF, Dickerson JE, Landry TA, Bergamini MV. The safety and intraocular pressure-lowering efficacy of brimonidine tartrate 0. 15% preserved with polyquaternium-1. *Ophthalmology.* 2006;113:1333–1339. doi: 10.1016/j.ophtha.2006.03.02.
41. Ayaki M, Yaguchi S, Iwasawa A, Koide R. Cytotoxicity of ophthalmic solutions with and without preservatives to human corneal endothelial cells, epithelial cells and conjunctival epithelial cells. *Clin Experiment Ophthalmol.* 2008;36:553–559. doi: 10.1111/j.1442-9071.2008.01803.x. [PubMed] [CrossRef] [Google Scholar]
42. Ayaki M, Iwasawa A, Yaguchi S, Koide R. Preserved and unpreserved 12 anti-allergic ophthalmic solutions and ocular surface toxicity: in vitro assessment in four cultured corneal and conjunctival epithelial cell lines. *Biocontrol Sci.* 2010;15:143–148. doi: 10.4265/bio.15.143
43. Cholkar K, Patel A, Vadlapudi DA, Mitra AK. Novel Nanomicellar Formulation Approaches for Anterior and Posterior Segment Ocular Drug Delivery. *Recent Patents on Nanomedicine.* 2012;2:82–95. doi: 10.2174/1877912311202020082.