Original Article

Comparison of Two Marketed Hydroxypropyl Methylcellulose Based Artificial Tear Drops in Young Patients with Dry Eye Syndrome

Haleh Kangari, Ali Abedini-Talemi*, Alireza Akbarzadeh-Bagheban, Saeed Rahmani

Faculty of Rehabilitation, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Artificial tears have been among the first line of therapy in management of Dry Eye Syndrome (DES). This study was conducted to compare a local artificial tear with an imported one in reduction of DES. This comparison would help to evaluate the cost and benefits of each drop in the proper management of DES.

Materials and Methods: In this double-blind randomized clinical trial study, a total 65 students meeting our inclusion criteria for DES entered the study. The OSDI questionnaire, TBUT, corneal and conjunctival staining and Schirmer test, were performed. The patients were divided into two groups by block randomization. Group 1 received first drop and group 2 received second drop. Both groups were instructed to use the drops 4 times a day for 14 days. The same tests were performed by the same examiner who was blind to the treatment type after two weeks. Repeated measured ANOVA was used to analyze the data.

Results: A total of 58 patients completed the study. In both groups, after the intervention, the OSDI scores ($P<0.001$), TBUT score ($P=0.041$), corneal ($P<0.001$) and conjunctival staining scores ($P<0.001$) showed improvement in compare to those before the intervention. However, the Schirmer test score did not show significantly difference before and after intervention. In comparing two groups the OSDI scores, the TBUT score, the corneal and conjunctival staining scores and the Schirmer scores did not show statistically significant difference.

Conclusion: The two artificial tears equally reduced the symptoms and signs of DES in two weeks.

Keywords: Artificial Tear, Dry Eye Syndrome, Hydroxypropyl Methylcellulose

***Corresponding Author:** Ali Abedini-Talemi. Faculty of Rehabilitation Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +98 (21) 77542057, Email:.aliabedinit@gmail.com

Please cite this article as: Kangari H, Abedini-Talemi A, Akbarzadeh-Bagheban A, Rahmani S. Comparison of Two Marketed Hydroxypropyl Methylcellulose (HPMC) Based Artificial Tear Drops in Young Patients with DES. Novel Biomed. 2015;3(4):193-9.

Introduction

Dry eye syndrome (DES) is a multifactorial disease caused by a disturbance in the lacrimal function unit. The components of this unit are the lacrimal glands, ocular surface and the lids which are all connected by the sensory and motor nerves. This unit controls the tear film and responds to environmental, endocrinological and cortical stimuli[1]. This condition can be caused by lack of tears, excessive evaporation of tears, or inflammatory diseases of the eye and eyelid. The patients with DES usually feel discomfort, irritation, and foreign body sensation in their eyes[2]. Among daily activities, prolonged reading, watching televisions and computer visual tasks have shown to exacerbate the symptoms of DES[3,4]. In additions, some

climate and environmental conditions have been reported to influence DES[5-9]. For example, low humidity (Relative Humidity below 30%) in indoor environments such as offices, cars, airplane cabins, and extreme temperatures, sun exposure, dust, air pollution, and wind in outdoor environments exacerbate the symptoms of DES[5-9]. These symptoms, whether mild or severe, transient or persistence have been reported to reduce the patients' quality of life[10,11].

The epidemiological studies have reported the prevalence rate of DES as 14.6% to 57.5%[12-22]. Due to the widespread use of computers professionally or for entertainment, DES is highly prevalent in youth[23]. Artificial tears are among the first line of therapy in management of DES[24]. They are used commonly combined with other treatments such oral omega-3 essential fatty acid supplements, mucin secretagogues, short term steroids and daily cyclosporine A, to combat the inflammatory nature of the disease[25]. Frequent eye care visits and different treatment options impose high costs to patients and health care systems[26].

Due to their non-invasive nature and low side effect profile, artificial tears have remained the main stay of therapy for DES[27]. Almost all tear substitutes rapidly replace the moisture layer of tears[28] and quickly reduce the symptoms. In USA, approximately7 to 10 million Americans spend 320 million dollars per year on artificial tear products[29]. In USA, many clinical trials have been conducted to evaluate their efficacy and to compare them with each other[27].

In Iran, different brands of artificial tears are available in the market. Selecting the proper product that suits the patient, with reduced costs remains a challenge for the clinician and the patients.

The purpose of this study was to compare two marketed hydroxypropyl methylcellulose (HPMC) based artificial tear drops on the improvement of DES in young patients after two weeks. An Iranian drop [hydroxypropyl methylcellulose 0.3g and 0.1 g of Dextran 70, with benzalkonium chloride (BAK) as preservative] is manufactured in multi-dose bottles. Due to local production, the price and availability of this product is adequate. In comparison, a French non-persevered hydroxypropyl methylcellulose, manufactured in single dose units are imported with high costs and the availability might become limited.

Methods

This study is double-blind randomized clinical trial. The subjects for this study were recruited from the students in Shahid Beheshti University of medical sciences, Faculty of Rehabilitation Sciences. At first, the subjects completed the ocular surface disease index (OSDI) questionnaire. The examination of the ocular surface and the eyelids was performed with a slit lamp biomicroscope to rule out any other ocular diseases. The inclusion criteria were: having a score > 20 in OSDI questionnaire and no use any types of artificial tears during the previous three months. The exclusion criteria were as follows: 1- patients with an allergy, infection, or eye surface problems (e.g., pterygium); 2- patients using contact lenses; 3- patients using ophthalmic drugs, such as steroidal or non-steroidal anti-inflammatory, antihistamines, and glaucoma medications during the previous month, or systemically using drugs influencing tear production, such as antihistamines, cortisones, hormones, beta-blockers, antidepressants, and chemotherapy drugs; 4- patients with a history of ophthalmic surgical operations; 5- patients undergoing radiotherapy; 6- patients allergic to hydroxypropyl methylcellulose; and 7- pregnant or breastfeeding patients.

For the patients who met the above criteria, the purpose of the study was explained. If willing, they were asked to sign the informed consent form which was prepared based on the Declaration of Helsinki. The protocol was accepted by the Deputy of Research, and ethical committee at Shahid Beheshti University of medical Sciences. The protocol number is 1392-1-93-11907.

Examinations

The patients were examined in two visits; one before the intervention and one after 14±2 days of using the specified artificial tear. The following tests were performed by the same examiner in two visits and the examiner was blind to type of artificial tears used by the subjects.

To assess patients' DES-related symptoms, a validated OSDI questionnaire[30] was used. One examiner asked the questions from Persian translated version, from each participant orally, and filled the corresponding responses in the forms. The OSDI, is a 12-question

survey, with a five point scale answers (0=none of time and 4=all of the time), with higher scores representing greater disability. The total OSDI score is calculated based on the following formula=100 (sum of severity for all questions answered)/4 (Total number of questions answered), where the severity was graded on a scale of: 0=none of the time, 1=some of the time, 2=half of the time, 3=most of the time, 4=all of the time. A score of 100 corresponds to complete disability while a score 0 corresponds to no disability.

Following the completion of the questionnaire, the tear break up time (TBUT) assessment was performed using Lowther's technique in right eye[31]. A sterile fluorescein strip (Indicator, Elham Teb co) was moistened using non preserved saline. Excessive solution was shaken off. The strip was touched gently to the superior bulbar conjunctiva with care, not to instill too much solution or cause excessive reflex tearing. After a few blinks, the patient was asked to close the eyes and then keep them open. The time between the eye opening and the appearance of the first dry spot was measured in seconds. The measurements were taken three times. For each subject, the TBUT were averaged and the average values were compared before and after the intervention.

The conjunctiva and the cornea were examined after instillation of fluorescein, with cobalt blue filter of Topcon SL-30 biomicroscope (Tokyo Kogaku Kikai K.K, Made in Japan). Punctuate staining was recorded using a standardized grading system of 0-3 for each of the five area on the corneal diagram[32].

The Schirmer test was performed in right eye, with anesthetic, measuring the basic tear secretion; a drop of Tetracaine 0.5% (Anestocaine, Sina Darou) was applied to the eye. The eye was gently dried with tissue paper over closed lids to mop up any excess secretion. After one minute, the filter paper was folded at 5 mm from one end and inserted at the junction of the middle and outer third of the lower lid. After 5 minutes, the filter paper was removed and the amount of wetting was measured by a ruler[33].

Intervention

The two types of artificial tears contained compounds derived from cellulose. The first one was a single-dose eye drop, has been made by a French company and containing 1.6 mg of hypromellose (hydroxypropyl methylcellulose) per 0.5 ml, Excipients: (Sorbitol, sodium dihydrogen phosphate dehydrate, disodium dodecarbohydrate, water for injection) q.s 0.5 ml. The second one was a multi-dose eye drop, has been made by an Iranian company, containing 0.3 gram hydroxypropyl methylcellulose and 0.1 mg of Dextran 70 with the preservative benzalkonium chloride (BAK).

The subjects meeting the inclusion criteria were divided into two groups based on their score in OSDI. Using random blocks, the first and the second group received French and Iranian eye drops, respectively. The patients were blind to the names of the medication and were instructed to use the eye drops 4 times a day for 14 days. In addition, lid hygiene was recommended in the mornings; the base of lashes had to be cleaned at the lid margins with the foam created by baby shampoo (Firouz baby shampoo, Firouz Health Group). The patients were asked return to the clinic for a follow-up visit in two weeks.

The independent *t* test and Chi-square test were used to ensure the equality of the two groups at the baseline. The results of the two groups, before and after intervention, were compared using repeated measured ANOVA, with one between subject factor and one within subject factor (time: before, after). In all analyses, α error was considered to be 0.05.

Results

In this study, from 65 patients who participated, only 58 completed the trial (5 patients in the first group and 2 patients in the second group did not complete their examination). In the first group, one patient showed an allergic reaction to the drug, and the drug was discontinued immediately. Six patients did not return to the clinic for follow-up visit. Therefore, 58 patients (27 patients in the first group and 31 patients in the second group) were completed the study. The difference between the two groups in terms of sex distribution was not significant (P=0.149). The mean age of the participants in the first and the second group was 24.22±6.43years and 25.97±8.56 years, respectively and , there was no significant difference between the groups (P=0.393).

The means and standard deviations of OSDI score, TBUT, conjunctival and corneal staining scores,

Table 1: Clinical characteristics of the two groups before and after the intervention.

	Before the intervention		P value	After the intervention	
	Group 1	Group 2	Comparing groups before intervention	Group 1 (French drop)	Group 2 (Iranian drop)
OSDI score	43.72±17.10	39.65±15.91	0.353	32.06±15.35	30.11±16.32
TBUT (sec)	7±2.5	7.29±2.39	0.654	7.78±2.74	8.23±2.88
Conjunctival score	6.81±3.02	7.48±2.34	0.348	5.67±2.41	5.23±1.82
Corneal score	1.37±1.47	1.29±1.21	0.821	0.63±0.92	0.58±0.71
Schirmer test (mm)	11.18±5.39	11.8±6.26	0.690	11.7±5.60	13.24±6.54

OSDI: Ocular Surface Disease Index questionnaire
TBUT: Tear Breakup Time
P value: Level of significance (<0.05)

Schirmer test score in the first and the second groups, before and after the intervention are presented in table 1.

The OSDI scores after the interventions showed a significant decrease to those before the intervention (P<0.001). However, the two drugs did not significantly differ (P=0.454), and the interaction between the drug type and time was not significant (P=0.482).The TBUT results after the intervention showed a significant increase to those before the intervention (P=0.041). However, the two drugs did not differ significantly (P=0.514). The interaction between drug type and time was not significant (P=0.848).

The conjunctival staining scores after the intervention showed a significant decrease to those before the intervention (P<0.001). The two drugs showed similar effects (P=0.836). Furthermore, the interaction between the drug type and time was not significant (P=0.094). The corneal staining scores after the intervention also showed a significant decrease to those before the intervention (P<0.001). However, the drugs did not show different effects (P=0.807), and the interaction between the type of drug and time was not significant (P=0.904).

The Schirmer test scores, after the intervention showed an increase to those before the intervention, but the increase was not significant (P=0.143). The two drugs showed similar effects (P=0.455), and the interaction between the drug type and time was not significant (P=0.489).

Discussion

In this study, hydroxypropyl methylcellulose as the effective substance in Iranian and french eye drops reduced the symptoms DES equally. The mean score of the OSDI questionnaire, in both groups significantly decreased after the intervention. When Toda et al.[34] studied the effect of 0.5% HPMC without any preservative on Sjögren and non-Sjögren dry eye patients they observed that the symptoms were reduced in both groups. Nguyen et al[35]. examined the effect of inserts containing HPMC (Lacrisert) on patients with DES and found that inserts were significantly effective in DES treatment. Lanz[36] also compared preserved HPMC (GenTeal, 0.3% HPMC, with sodium perborate as preservative) vs nonpreserved HPMC (Tears Naturale, 0.3% HPMC, 0.1% dextran 70) and found no significant difference between the symptoms of two groups. These findings agree with the result of this study.

In this study, TBUT increased in both groups, but the groups did not differ significantly. The reason for this improvement could be due to reflex blinking upon drop insertion. More blinking could have helped in opening of the meibomian glands, leading to secretion of more lipids in tear, and less rate of tear evaporation. McCann et al.[37] compared the effect of HPMC, sodium hyaluronate, and an emulsion (Emustil unidose: SIFI) on management of patients with DES caused by impaired lipid bilayer. They found that the symptoms and tear evaporation were reduced in the three groups. Lanz[36] found better improvement in TBUT with the preserved Genteal. In this study, a slightly better improvement was observed with the

preserved drop but the difference was not significant. This difference could be due different preservatives used (sodium perborate vs BAK) in two studies.

The results of Schirmer test (with anesthetic) before the intervention did not differ significantly from those after the intervention. Although an increase in the volume of baseline tear was expected after the use of artificial tears, no change was observed. The increase in volume might have happened shortly after the application of the eye drops and at the time of testing, a long time might have passed since the instillation of the drop. Lanz[36] also found better improvement in the Schirmer test with the preserved Genteal. In this study, a slightly better improvement in observed with the preserved drop but the difference was not significant. In this study, a slightly better improvement was observed with the preserved drop but the difference was not significant. This difference could be due different preservatives used (sodium perborate vs BAK) in two studies.

In both groups, the conjunctival and corneal staining scores, after the intervention, were reduced significantly ($P<0.001$). The improvement of epithelial cells in the cornea and conjunctiva were in line with reduction of patients' complaints. The absence of preservative does not appear to be advantageous in terms of reducing the corneal and conjuntival stains. However, these results might be due to the short-term use of these eye drops. Some studies have emphasized the side effects of preservatives on eye surface and tears, including corneal and conjunctival tissue damage, loss of goblet cells, preventing the growth of new cells, and accelerating cell death[38-44]. Benzalkonium chloride (BAK) is one the most commonly used preservatives with good antimicrobial activity[27]. An exaggerated instillation regimen, two drops of 0.02% BAK solution, every 3 minutes for 1 hour (i.e. a total of 40 drops), has shown 4 fold increase in corneal damage; while the mild regimen, two drops every 30 minutes for 2h, eight drops in total, induces only a minimal morphological change[45]. However other preservatives have shown better safety profile than BAK[27]. The incidence of most of the side effects depends on concentration of preservatives and long duration of their use. Therefore, artificial tears without preservatives are still recommended for patients with persistent symptoms or those who require higher doses of the drops. Although other preservatives have shown better safety profile than BAK[27], but we did not observe any side effects for short time about the drop containing BAK.

Conclusion

The two artificial tears compared in this study, equally reduced the signs and symptoms of DES in two weeks. Considering the lower cost and better availability of the local product, the Iranian eye drop could be prescribed to young patients with transient symptoms of DES to impose less cost to these patients. For further improvement of signs and symptoms of DES, longer clinical trials are required to observe the efficacy of these two drops in longer periods and in combination with other treatment modalities.

Acknowledgments

This article is a part of Ali Abedini-talemi's thesis for Master of Science degree in Shahid Beheshti University of Medical Sciences, Faculty of Rehabilitation.

Conflict of Interest

The authors have no financial interest in the products discussed in this article.

References

1. Lemp MA, Foulks GN. The definition & Classification of Dry Eye Disease: Guidelines from the 2007 International Dry Eye Workshop. The Ocular Surface. http://tearfilm.org/pdfs/OM-Definition&Classification.pdf.

2. Chalmers RL, Begley CG. Repeatability of habitual symptoms as measured by the dry eye questionnaire (DEQ). Invest ophthalmol Vis Sci 2004 [E-Abstract 3455].

3. Schlote T, Kadner G, Frudenthaler N. Marked reduction and distinct pattern of eye blinking in patients with moderately dry eyes during video display terminal use. Graefes Arch Clin Exp Ophthalmol. 2004;242:306–12.

4. Burns DH. Characteristics of visual display units that may cause visual difficulties. Ophthalmic Physiol Opt. 1995;15:99-104.

5. Wolkoff P, Nøjaard JK, Troiano P and Piccoli B. Eye complaints in the office environment: precorneal tear film integrity influenced by eye blinking efficiency. Occup Environ Med. 2005;62:4–12.

6. Wolkoff P, Nøjaard JK, Franck C and Skove P. The modern office environments desiccate the eye? Indoor Air. 2006;16:258–65.

7. Kjæregaard SK, Hempel-Jørgensen A, Mølhave L, Andersson K,

Juto JE and Stridh G. Eye trigeminal sensitivity, tear film stability, and conjunctival epithelium damage in 182-non-allergic, non-smoking Danes. Indoor Air. 2004;14:200–7

8. Wolkoff P, Kjæregaard SK. The dichotomy of relative humidity on indoor air quality. Environ Int. 2007;33:850–7.

9. Khurana AK, Choudhary R, Ahluwalia BK and Gupta S. Hospital epidemiology of dry eye. Indian J Ophthalmol. 1991;39:55–8.

10. Friedman NJ. Impact of dry eye disease and treatment on quality of life. Curr Opin Ophthalmol. 2010;21:310-6.

11. Li M, Gong L, Chapin WZ, Zhu M. Assessment of vision related quality of life in dry eye patients .Invest Ophthalmol Vis Sci. 2012;53:5722-7.

12. chia EM, Mitchell P, Rochtchina E, Lee AJ, Maroun R and Wang JJ. Prevalence and associations of dry eye syndrome in an older population: the blue mountains Eye study. Clin Experiment Ophthalmol. 2003;31:229-32.

13. Galor A, Feuer W, Lee DJ, Florez H, Carter D, Pouyeh B, Prunty WJ and Perez VL. Prevalence and risk factors of dry eye syndrome in a United States veteran's affairs population. Am J Ophthalmol. 2011;152:377-84.

14. Gue B, Lu P, Chen X, Zhang W and Chen R. Prevalence of dry eye disease in Mongolians at high altitude in china: the Henan eye study. Ophthalmic Epidemiol. 2010;17:234-41.

15. Jie Y, Xu L, Wu YYand Jonas JB. Prevalence of dry eye among adults Chinese in the Beijing Eye Study. Eye (Lond). 2009;23:688-93.

16. Liew MS, Zhang M, Kim E and Akpek EK. Prevalence and predictors of sjogrens syndrome in a prospective cohort of patients with aqueous-deficient dry eye. Br J Ophthalmol. 2012; 96:1498-503.

17. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P and Hsu WM. Prevalence of dry eye among an elderly Chinese populations in Taiwan: the shihpai Eye Study. Ophthalmology. 2003;110:1096-101.

18. Schein OD, Munoz B, Tielsch JM, Bandeen-Roche K and West S. Prevalence of dry eye among the elderly. AmJ ophthalmol. 1997;124:723-8.

19. Uchino M, Nishiwaki Y , Mishikawa T , Shirakawa K, Kuwahara E, Yamada M, Dogru M, Schaumberg DA, Kawakita T, Takebayashi T and Tsubota K. Prevalence and risk factors of dry eye disease in japan: Koumi Study. Ophthalmology. 2011;118:2361-7.

20. Uchino M, Schaumberg DA, Dogru M, Uchino Y, Fukagawa K, Shimmura S, Satoh T, et al. Prevalence of dry eye disease among Japanese visual display terminal users. Ophthalmology. 2008;115:1982-8.

21. Viso E, Rodriguez-Ares MT, Gude F. Prevalence of and associated factors for dry eye in a Spanish adult population (the salnes eye study). Ophthalmic epidemiol. 2009;16:15-21.

22. Zhang Y Chen H, Wu X. Prevalence and risk factors associated with dry eye syndrome among senior high school students in a county of Shandong province, china. Ophthalmic Epidemol. 2012;19:226-30.

23. Miki Uchino, Debra A. Schaumberg, Murat D Uchino Y, Fukagawa K, Shimmura S, Satoh T, Takebayashi T and Tsubota K. Prevalence of dry eye disease among Japanese visual display Terminal users. Department of ophthalmology, keio university school of medicine, Tokyo japan. 2008;115:11.

24. Aragona P, Papa V, Micali A, Santocono M, Milazzo G. Long term treatment with sodium hyaluronate containing artificial tears reduces ocular surface damage in patients with dry eye. Br J Ophthalmol. 2002;86:181-4.

25. Lin H, Yiu SC. Dry Eye Disease: A review of diagnostic approaches and treatments.Saudi Journal of Ophthalmology. 2014;28:173-81.

26. Waduthantri S, Yong SS, Tan CH, Liang SH, Lee MX, Natarajan S, Hla MH and Tong L. Cost of dry eye treatment in an Asian clinic setting. PLOS One. 2012;7:e37711.

27. Moshirfar M, Pierson K, Hanamaikai K, Santiago-Caban L, Muthappan B, Passi SF. Artificial tears potpourri: a literature review. Clinical Ophthalmology. 2014;8:1419-33.

28. Lemp MA, Goldberg M, Roddy MR. The effect of tear substitutes on tear film break up time. Invest Ophthalmol. 1975;14:255-8.

29. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. Clin ophthalmol. 2009;3:405-16.

30. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Arch ophthalmol. 2000;118(5):615-21.

31. Donald R. Korb JC, Doughty M, Guillon JP, Smith G, Tomlinson A. The Tear Film: structure, function and clinical examination. Butterworth-Heinemann. 2002;138.

32. Lemp MA. Report of the National EYE Institution/Industry Workshop on Clinical Trials In dry Eyes. CLAO. 1995;21:221-32.

33. Donald R. Korb JC, Doughty M, Guillon JP, Smith G, Tomlinson A. The Tear Film: structure, function and clinical examination. Butterworth-Heinemann. 2002;114.

34. Toda I, Shinozaki N, Tsubutak. Hydroxypropylmethyl cellulose for the treatment of severe dry eye associated with sjogren syndrome. Cornea. 1996;15:120-8.

35. Nguyen T, Lutkeny R. Review of hydroxypropylmethyl cellulose inserts for treatment of dry eye. Clin ophthalmol. 2011;5:587-91.

36. Lanz R. Comparison of Genaqua-Preserved Genteal in multidose bottles vs Preservative-Free Tears Naturale in single dose units in patients with moderate to severe Dry Eye. Invest Ophthalmol Vis Sci. 2006;47:E-Abstract 259.

37. McCann LC, Tomilsone A, Pearce EI, Papa V. Effectiveness of artificial tears in the management of evaporative dry eye. Cornea 2012;31:1-5.

38. Baudouin C, Labbe A, Liang H, Paul A, Brignole-Baudouin E. Preservatives in eye drops: the good, the bad and the ugly. Prog Retin Eye Res. 2010;29:312-34.

39. Herrero Vanrell R. Preservatives in ophthalmic formulations. Arch Soc Esp. Ophthalmol. 2007;82:531-2.

40. Noecker R. Ophthalmic preservatives: Considerations for long term use in patients with dry eye or glaucoma. Rev Ophthalmol. 2001;8:73-9.

41. Noecker R. Effect of common ophthalmic preservatives in ocular health. Adv Ther. 2001;18:205-15.

42. Clouzeau C, Golderfrog D, Riancho L, Rostene W, Baudouin C, Bregnole-Baudouin F. Hyperosmolarity potentiates toxic effect of benzalkonium chloride on conjunctival epithelial cells in vitro. Mol Vis. 2012;18:851-63.

43. Epstein S, Ahdoot M, Marcus E, Asbell PA. Comparative toxicity

of preservatives in ophthalmic solutions. J Ocul pharmacol Ther. 2009;25:113-9.
44. De Saint Jean M, Brignole F, Baudouin F, Bauchet A, Feldmann G, Baudouin C. Effect of benzalkonium chloride on growth and survival of change conjunctival cells.Invest ophthalmol Vis Sci. 1999;40:619-30.
45. Furrer P, Mayer JM, Gurny R. Ocular tolerance of preservatives and alternatives. European Journal of Pharmaceutics and Biopharmaceutics. 2002;53:263-80.