J Nanostruct 12(1): 170-177, Winter 2022

RESEARCH PAPER

Investigation of Releasing Therapeutic Solutions from Soft Contact Lens Surfaces Constructed by Nanoparticles

Elena T. Zhilyakova, Denis K. Naplekov, Anastasiya Yu. Malyutina *, Dariya A. Fadeeva, Natalya V. Avtina, Natalya N. Shestopalova, Alexander V. Bondarev

Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia

ARTICLE INFO

Article History:
Received 15 September 2021
Accepted 10 December 2021
Published 01 January 2022

Keywords:
Drug delivery
Glaucoma
Myopia
Nanoparticles
Ophthalmology
Soft contact lenses

ABSTRACT

The eye has many barriers with specific anatomies that make it difficult to deliver drugs to targeted ocular tissues, and topical administration using eye drops or ointments usually needs multiple instillations to maintain the drugs' therapeutic concentration because of their low bioavailability. A drug-eluting contact lens is one of the more promising platforms for controllable ocular drug delivery, and, among various manufacturing methods for drug-eluting contact lenses, incorporation of novel polymeric vehicles with versatile features makes it possible to deliver the drugs in a sustained and extended manner. Contact lenses for ophthalmic drug delivery have become very popular, due to their unique advantages like extended wear and more than 50% bioavailability. To achieve controlled and sustained drug delivery from contact lenses, researchers are working on various systems like polymeric nanoparticles, etc. This article reveals the recent achievements in the field of alternative drug delivery in ophthalmology to treat glaucoma combined with myopia. During in vitro experiments it was demonstrated that lossless and prolonged drug delivery is feasible if soft contact lenses of various materials are utilized as drug carriers. However, among two studied model solutions, only one of them passed all drug release tests with all five types soft contact lenses materials.

How to cite this article
Zhilyakova E T, Naplekov D K, Malyutina A Y, Fadeeva D A, Avtina N V, Shestopalova N N, Bondarev A V. Investigation of Releasing Therapeutic Solutions from Soft Contact Lens Surfaces Constructed by Nanoparticles. J Nanostruct, 2022; 12(1):170-177. DOI: 10.22052/JNS.2022.01.016

INTRODUCTION

It is known that during the instillation of eye drops, a number of therapeutic problems arise: because of the frequency of the instillation themselves, irritation of the mucous membrane of the eye is possible, the action of drug agents is limited to the anterior chamber of the eye, etc. In addition, leakage of a part of the administered drug from the conjunctival sac and its elimination through the tear duct should be taken into account, which reduces the effectiveness of pharmacotherapy [1]. In turn, soft contact lenses (SCL), used as a means of delivery of pharmacological agents, regulate the continuous release of an active pharmaceutical ingredient (API) during the entire time of contact of the ophthalmic therapeutic system "SCL: medicinal composition" with cornea eyes. Early studies of the prolongation of the action of eye drops using various types of contact lenses showed the advantages of this technical solution. This is the non-invasiveness of the method, the willingness

* *Corresponding Author Email: malyutina_a@bsu.edu.ru*

of patients to follow the usual contact correction, the possibility of combined treatment and correction of ametropia, etc. These approaches have been improved with the advent of new materials for SCL, especially with the appearance of hydrophilic polymers with increased moisture content [2]. For example, J.B. Ciolino et al. used SCL with latanoprost on monkeys. It was found that in the case of the use of SCL, intraocular pressure during the day was more stable than with the instillation regimen [3]. C.C. Peng et al. used silicone SCL soaked in timolol and vitamin E on dogs with simulated glaucoma. The levels of lowering intraocular pressure when using MCL and eye drops were comparable [4]. F. A. Maulvi et al. in the manufacture of SCL, gold nanoparticles were included in its structure in order to increase the incorporated amount of timolol maleate and its faster release. The kinetics of the release of timolol from SCL in an in vivo experiment (rabbits) showed a longer hypotensive effect under the same conditions of saturation with a solution of timolol SCL with and without gold nanoparticles [5]. Thus, the prospect of such studies is beyond doubt, especially in the age of excessive load on the human organ of vision. The purpose of this preliminary fragment of large-scale studies was to study the process of release of a number of drug compounds in model solutions from the surface of SCL from various materials. There are many innovations on therapeutic contact lenses to treat anterior ocular diseases which uses soaking method, molecular imprinting, entrapment of drug-laden colloidal nanoparticles, drug plate, ion ligand polymeric systems, supercritical fluid technology, etc [6-9]. Colloidal nanoparticles laden therapeutic contact lens technique is based on the ability of colloidal nanoparticles (polymeric nanoparticles, liposomes, niosomes, micro-emulsion, micelles, etc.) to entrap or encapsulate drug and control its release rate from contact lenses. Such formulated nanoparticular system (10 to 100 nm) is dispersed in HEMA monomers and polymerized using ethylene glycol-dimethacrylate (EGDMA) and photo initiator (DarocurÕ) to fabricate therapeutic contact lenses. Drug laden nanoparticles prevent the interaction of drug with polymerization mixture and also offer additional resistance to drug release. Thus the nanoparticles loaded contact lenses can deliver drugs at controlled rate for extended period of time. Drug loaded nanoparticles or globules (microemulsion) also bypass, to some extent, drug metabolism from the enzymes like lysosomes, present in the tear/corneal epithelial surface. The researchers have being successful in developing therapeutic contact lenses for extended drug delivery, while at the same time the transparency (optical), oxygen permeability, ion permeability, mechanical properties, and swelling behavior of contact lenses was altered for comfort wear [10-13]. First method developed to load drugs into contact lenses was by soaking contact lenses in drug solutions, but nearly all the drug in contact lenses was released within 1–3 h [14-17]. To overcome this drawback, many techniques to design therapeutic contact lenses have been developed, including a molecular imprinting technique, the entrapment of drug-loaded colloidal micro- and nanoparticles, drug-loaded implants in the contact lenses, sustained drug release using ionic interactions, drug delivery with vitamin E diffusion barriers, and supercritical fluid technology [18–21].

MATERIALS AND METHODS

The following types of soft contact lenses were purchased for this study: Dailies AquaComfort Plus» (nelfilcon A); Bausch&Lomb «SofLens Daily Disposable» (hilafilcon B); Bausch&Lomb «BioTrue One-day» (nesofilcon A); Johnson & Johnson «Acuvue 1-Day Moist» (etafilcon A); Alcon «Air Optix Colors» (lotrafilcon B). For this study, the following active pharmaceutical substances were used: brimonidine tartrate (NDA 20613/S-031), Betaxolol hydrochloride (EP 8.0 07/2011:1072), pyridoxine hydrochloride (EP 8.0 01/2010:0245). The following model solutions were used in the work, selected from the line of those studied by technological priorities (working numbering of samples was kept): Model solution 1: brimonidine tartrate 0.006 g; pyridoxine hydrochloride 0.009 g; sodium hyaluronate 0.015 g; water purified for injetions up to 3 mL. Model solution 2: betaxolol hydrochloride 0.017 g; pyridoxine hydrochloride 0.009 g; sodium hyaluronate 0.015 g; water purified for injetions up to 3 mL. Quantitative determination of brimonidine tartrate in model solutions for the saturation of SCL [22]. To conduct the identification and assay tests on brimonidine tartrate in model solutions, a spectrophotometer SF-104. 1 ml of the model solution was transferred using an automatic pipette into a 200 ml volumetric flask, 5 ml of purified water was added thereto with the same pipette to completely

transfer the active pharmaceutical substance. The solution was slightly shaken, after which its volume was led up to 200 ml with the same solvent, followed by shaking. The optical density was measured using the following instrument settings: wavelength range 220-310 nm, optical density axis ranges 0.000-1.000, fast measurement mode. The conclusion about the identification test of brimonidine tartrate was made based on the absorption maximum at 247 ± 1 nm. The optical density at this wavelength was taken to calculate the quantitative content of the substance in the solution according to the specific absorption coefficient, using the below formula.

$$X = \frac{200 \times A}{E_{1см}^{1\%} \times l}, \quad (1)$$

Where X is concentration of brimonidine tartrate in a sample (%), 200 is dissolution rate, A – optical density of a sample at 247 nm, $E_{1см}$ is specific absorption coefficient, 588, l is optical path length, cm. Quantitative determination of betaxolol hydrochloride in model solutions for the saturation of SCL. To conduct the identification and assay tests on betaxolol hydrochloride in the model solution, the same sample preparation algorithm and analysis conditions were used as for brimonidine tartrate, but an aliquot volume was dissolved in 50 ml of purified water. The quantitative content of betaxolol hydrochloride was calculated according to formula 1 using the specific absorption coefficient equal to 38 and the actual determined optical density, which was observed at 274 ± 1 nm. Quantitative determination of pyridoxine hydrochloride in model solutions for the saturation of SCL. To conduct the identification and assay tests on pyridoxine hydrochloride in the model solution, the same sample preparation algorithm and analysis conditions were used as for brimonidine tartrate. The quantitative content of pyridoxine hydrochloride was calculated according to formula 1 using the specific absorption coefficient equal to 313 and the actual determined optical density, which was observed at 292 ± 1 nm.

RESULTS AND DISCUSSIONS

In the process of developing the composition and technology of an ophthalmic system based on SCL, special attention should be paid to the duration and completeness of the process of API release from the surface of the SCL to the surface of the affected eye [23]. The results of a study of API release of model ophthalmic solutions from the surface of SCL are presented in Figs. 1-4.

As can be seen from Fig. 1, the release of brimonidine tartrate model solution 1 from SCL occurs within one hour. The amount of drug released into the solution simulating the environment of the eye tissues was 98.13-99.35% of the previously absorbed amount. Moreover, the most complete (99.35%) release of brimonidine tartrate is characteristic of MCLs made from

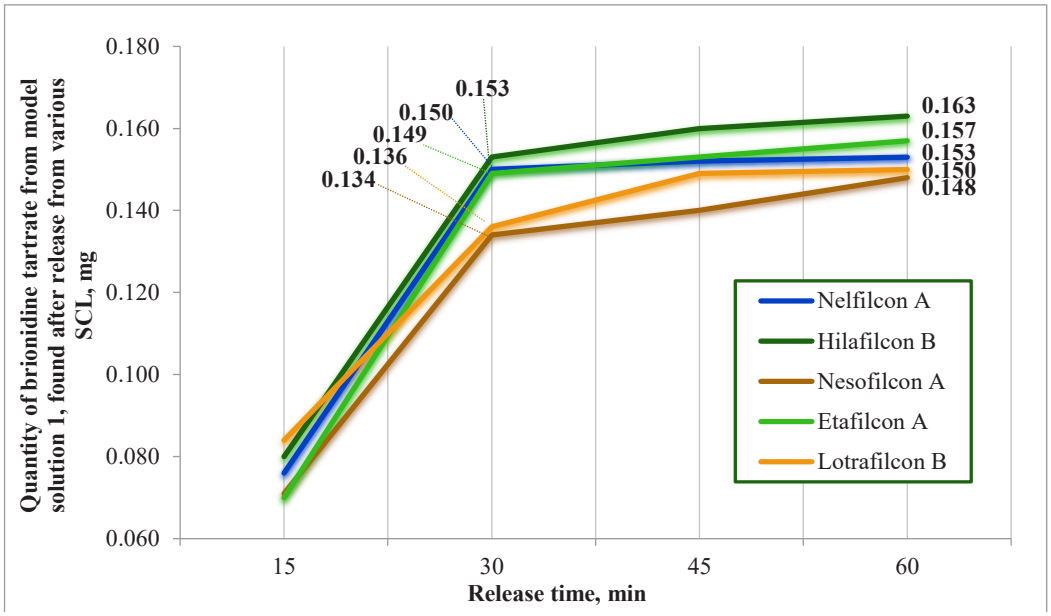

Fig. 1. The dynamics of the release of brimonidine tartrate model solution 1 into 0.9% sodium chloride solution from SCL.

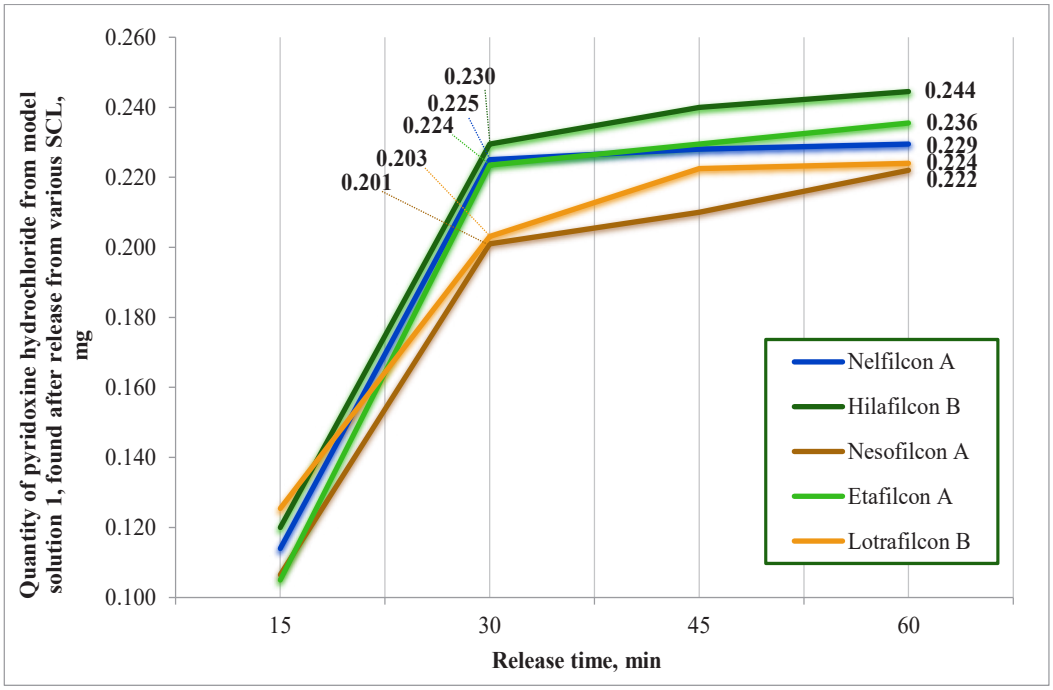

Fig. 2. The dynamics of the release of pyridoxine hydrochloride model solution 1 into 0.9% sodium chloride solution from SCL.

hilafilcon B. The smallest amount (98.13%) of the drug was resolved into the solution from the surface of SCL from nesofilcon A. All SCL materials are characterized by a more intense release of the model solution from the surface during the first 30 minutes of the experiment, after which the process speed was significantly slowed down.

Fig. 2 shows that the release profile of pyridoxine hydrochloride model solution 1 from SCL is absolutely identical to the release profile

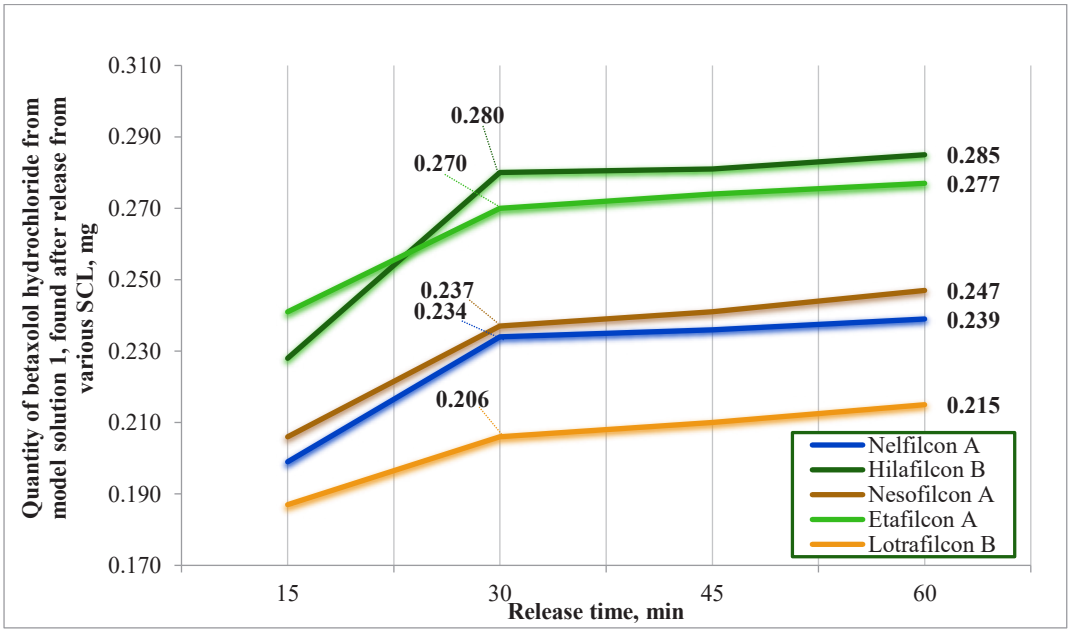

Fig. 3. The dynamics of the release of betaxolol hydrochloride model solution 2 into 0.9% sodium chloride solution from SCL.

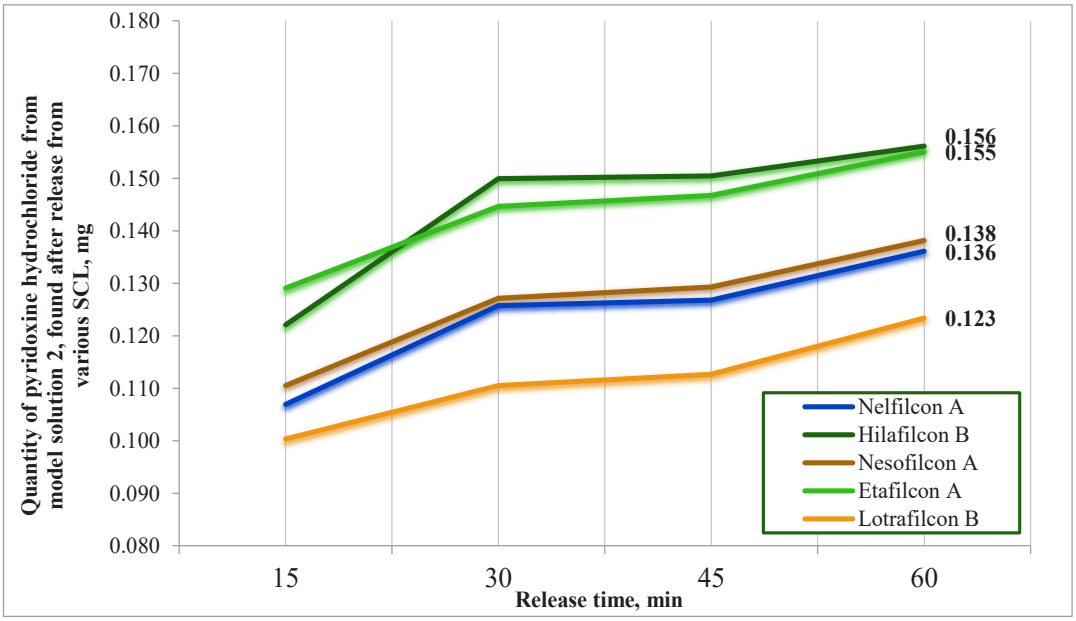

Fig. 4. The dynamics of the release of pyridoxine hydrochloride model solution 2 into 0.9% sodium chloride solution from SCL.

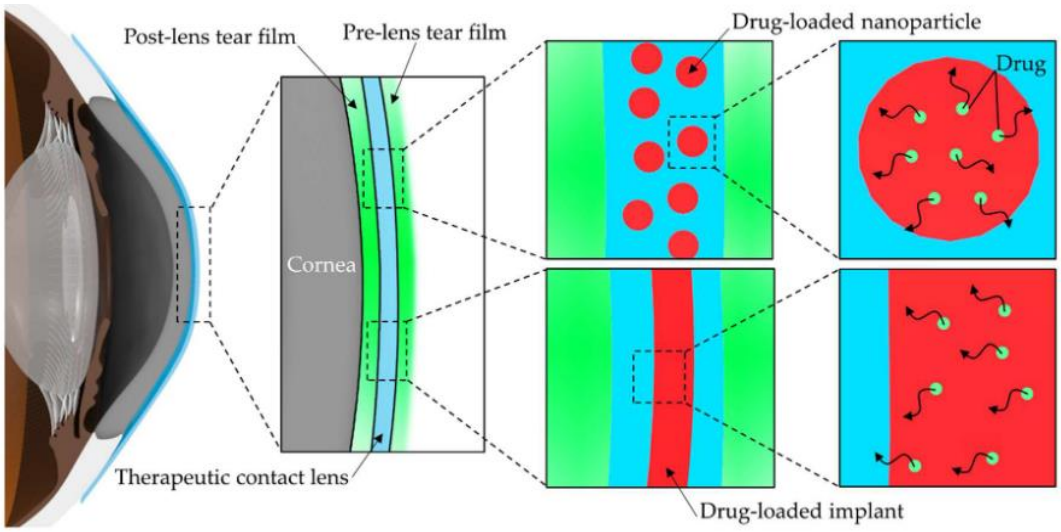

Fig. 5. Schematic of drug release onto the ocular surface from drug-eluting therapeutic contact lens. Typical polymeric vehicles for therapeutic contact lenses include drug-loaded polymeric nanoparticles and drug-loaded polymeric implants inside contact lenses.

of brimonidine tartrate. Namely, the release of pyridoxine hydrochloride most fully passed from the surface of SCLs prepared from hilafilcon B and amounted to 99.35% or 0.229 mg. 0.236 mg (98.13%) of the previously absorbed drug transferred from the surface of the SCL from nesofilcon A to the receiver solution.

All MKL materials are characterized by a more intensive release of the model solution from the surface during the first 30 minutes of the experiment, after which the process speed was significantly slowed down.

As can be seen in Fig. 3, the release of betaxolol hydrochloride in model solution 2 from SCL also takes place within one hour. The release profiles differ significantly for each SCL material:

the release process is less intensive (0.215 mg; 92.27%) for lotrafilcon B, but most fully (0.285 mg; 95.96%) for hilafilcon B.

All SCL materials are characterized by a more intensive release of the model solution from the surface during the first 30 minutes of the experiment, after which the process speed was significantly slowed down.

From the data shown in Fig. 4, it can be seen that the release profile of pyridoxine hydrochloride of model solution 2 is identical to the release profile of betaxolol hydrochloride. The release of pyridoxine hydrochloride most fully passed from the surface of SCLs prepared from chilafilcon B, and amounted to 95.96% or 0.156 mg. 0.236 mg, or 98.13% of the previously absorbed API, passed from the surface of the SCL from nesofilcon A to the receiver solution. In addition, all SCL materials are characterized by a more intense release of the model solution from the surface during the first 30 minutes of the experiment, after which the process speed was significantly slowed down. An important stage in the study of SCL of various materials as a means of prolonged drug delivery is a comparative assessment of the quantities of released active components from the surface of the SCL. You should also take into account such an indicator of the ophthalmic transport system as the time of drug release from the surface of the SCL. In turn, for eye drops, such performance indicators as the time of presence of a drug on the surface of the eye and the minimum amount of drug needed to provide a therapeutic effect are important.

According to published data, the time of the presence of ophthalmic solutions on the surface of the eye, as a rule, does not exceed 3 minutes [1-4]. Data on the minimum required amounts of anti-glaucoma drugs to provide a therapeutic effect were obtained from official instructions for the use of drugs and the results of a study on the release of drugs from SCL are presented in Table 1.

As can be seen from the data given in Table 1, brimonidine tartrate and pyridoxine hydrochloride model ophthalmic solution 1 after the release of all the studied materials from the

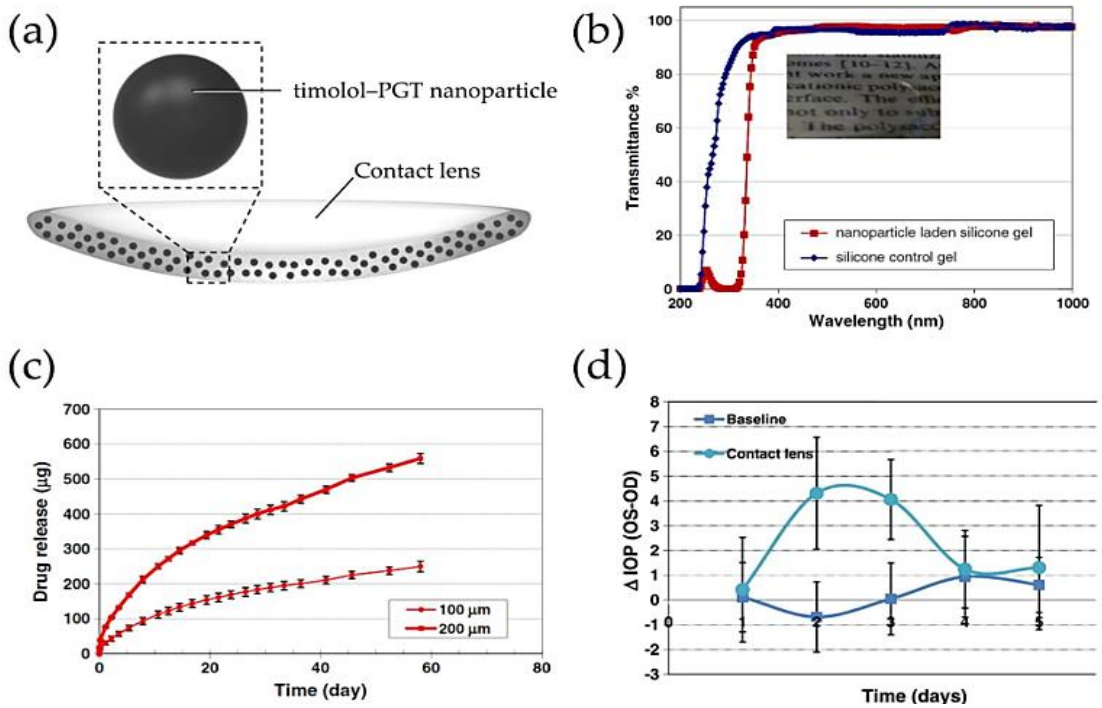

Fig. 6. (a) Schematic of a therapeutic contact lens embedded with timolol–PGT nanoparticles; (b) Transmittance spectra of silicone control and PGT nanoparticle-embedded silicone hydrogel. The inset shows a photograph of the PGT nanoparticle-embedded silicone hydrogel; (c) Cumulative drug release profile from timolol–PGT nanoparticle-loaded hydrogels with 100 and 200 µm thickness, respectively; (d) Pharmacodynamic profile of timolol–PGT nanoparticle-loaded contact lenses in beagle dogs, which was expressed as the difference between the intraocular pressure (IOP) of the untreated (OS) and the treated eye (OD). The IOP-lowering effect due to timolol–PGT nanoparticle-loaded contact lenses was seen on day 2 and day 3. Reprinted with permission from [24].

Table 1. Assessment results of the studied ophthalmic therapeutic systems.

No of model solution	Pharmaceutical substance	Minimum amount, mg	Released API (mg)				
			Nelfilcon A	Hilafilcon B	Nesofilcon A	Etafilcon A	Lotrafilcon B
1	Brimonidine tartrate	0.100	0.153	0.163	0.148	0.157	0.150
	Pyridoxine hydrochloride	0.150	0.229	0.244	0.222	0.236	0.224
2	Betaxolol hydrochloride	0.280	0.285	0.277	0.247	0.239	0.215
	Pyridoxine hydrochloride	0.150	0.156	0.155	0.138	0.136	0.123

surface of the SCL were found in 0.9% NaCl in amounts exceeding the minimum therapeutic. This tentatively suggests that model solution 1 and the studied SCL can be used together as a single ophthalmic therapeutic system. However, for betaxolol hydrochloride and pyridoxine hydrochloride model ophthalmic solution 2, it was found that the process of drug release from the surface of the studied SCL was slightly higher than therapeutic amounts for nelfilcon A alone, amounting to 0.285 and 0.156 mg, respectively. The release of the remaining materials from the SCL surfaces was insufficient. Thus, the use of ophthalmic model solution 2 as part of an ophthalmic therapeutic system is irrational, since it is limited by the possibility of using only with SCL made from nelfilcon A. In addition, the assessment of the processes of saturation and release of SCL is not a predetermining experiment, on the basis of the results of which it can be concluded that the use of one or another composition of the ophthalmic transport system is rational. The final conclusion about the possibility of using a certain composition of a model ophthalmic solution in an ophthalmic transport system can be made only based on the results of biopharmaceutical studies, which involve studying the time and completeness of the passage of active drugs through biological tissue barriers.

CONCLUSION

In the frame of the current study it was feasible to prove that such method of drug loading of SCL as soaking is still relevant. The advantage of studied material of soft contact lenses was demonstrated versus other, highly technological methods such as loading with colloidal particles, binding of molecules of active pharmaceutical substance to the structure of SCL, etc. The main advantage of covering the SCL with mucoadgesive therapeutic solution is its independence on type of surface of soft contact lenses. However, the achieved results are not the finishing point in development of composition of solution for SCL saturation. It's believed, that composition somehow can be adjusted in certain way, when release of therapeutic molecules will last longer than 60 minutes and, thus, will be more accurately controlled. In addition, the assessment of the processes of saturation and release of SCL is not a predetermining experiment, on the basis of the results of which it can be concluded that the use of one or another composition of the ophthalmic transport system is rational. The final conclusion about the possibility of using a certain composition of a model ophthalmic solution in an ophthalmic transport system can be made only based on the results of biopharmaceutical studies, which involve studying the time and completeness of the passage of active drugs through biological tissue barriers. However, the deeper knowledge can be obtained if more advanced approach is applied to biopharmaceutical study of API release.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Zhilyakova E.T, Novikov O.O, Novikova M.Y, Pridachina D.V, Popov N.N. Harmonization of the requirements for

eye drops in the light of the modern development of pharmaceutical production. Development and registration of Drug Products J. 2014: 1 :20-25.
2. Kiseleva OA, Bessmertniy AM, Filippova OM, Yakubova LV. Advanced technologies in treatment of glaucoma. Effective pharmacology J. 2019: 15 :16-23.
3. Ciolino JB. Ross AE. Tulsan R. et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology. 2016: 123: 2085-2092.
4. Peng CC, Ben-Shlomo A, Mackay EO. Drug delivery by contact lens in spontaneously glaucomatous dogs. Curr. Eye Res. 2012: 37: 204-211.
5. Maulvi FA, Patil RJ, Desai AR. Effect of gold nanoparticles on timolol uptake and its release kinetics from contact lenses: in vitro and in vivo evaluation. Acta Biomater.2019;86:350-362.
6. Ruben, M.; Watkins, R. Pilocarpine dispensation for the soft hydrophilic contact lens. Br. J. Ophthalmol. 1975, 59, 455–458.
7. Lesher, G.A.; Gunderson, G.G. Continuous drug delivery through the use of disposable contact lenses. Optom. Vis. Sci. 1993, 70, 1012–1018.
8. Hull, D.S.; Edelhauser, H.F.; Hyndiuk, R.A. Ocular penetration of prednisolone and the hydrophilic contact lens. Arch. Ophthalmol. 1974, 92, 413–416.
9. Xinming, L.; Yingde, C.; Lloyd, A.W.; Mikhalovsky, S.V.; Sandeman, S.R.; Howel, C.A.; Liewen, L. Polymeric hydrogels for novel contact lens-based ophthalmic drug delivery systems: A review. Contact Lens Anterior Eye 2008, 31, 57–64.
10. White, C.J.; Tieppo, A.; Byrne, M.E. Controlled drug release from contact lenses: A comprehensive review from 1965-present. J. Drug Deliv. Sci. Technol. 2011, 21, 369–384.
11. Guzman-Aranguez, A.; Colligris, B.; Pintor, J. Contact lenses: Promising devices for ocular drug delivery. J. Ocul. Pharmacol. Ther. 2013, 29, 189–199.
12. Bengani, L.C.; Hsu, K.H.; Gause, S.; Chauhan, A. Contact lenses as a platform for ocular drug delivery. Expert Opin. Drug Deliv. 2013, 10, 1483–1496.
13. Maulvi, F.A.; Soni, T.G.; Shah, D.O. A review on therapeutic contact lenses for ocular drug delivery. Drug Deliv. 2016, 23, 3017–3026.
14. Hu, X.; Hao, L.; Wang, H.; Yang, X.; Zhang, G.; Wang, G.; Zhang, X. Hydrogel contact lens for extended delivery of ophthalmic drugs. Int. J. Polym. Sci. 2011, 2011, 814163.
15. Hui, A. Contact lenses for ophthalmic drug delivery. Clin. Exp. Optom. 2017, 100, 494–512.
16. Petrov SYu. Preservatives in ophthalmological drugs: from benzalconium chloride to polyquaternium. Glaucoma. 2013: 4: 82-96.
17. Ciolino JB, Hoare TR, Iwata NG. A drug-eluting contact lens. Invest Ophthalmol Vis Sci. 2009: 50: 3346-3352.
18. Maulvi FA, Choksi HH, Desai AR. Ph triggered controlled drug delivery from contact lenses: Addressing the challenges of drug leaching during sterilization and storage. Colloids Surf. B Biointerfaces. 2017; 157: 72-82.
19. Phan CM, Subbaraman L, Jones L. Contact lenses for antifungal ocular drug delivery: A review. Expert Opin. Drug Deliv. 2014; 11: 537-546.
20. Jung, H.J.; Abou-Jaoude, M.; Carbia, B.E.; Plummer, C.; Chauhan, A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. J. Control. Release. 2013, 165, 82–89.
21. Zhilyakova ET, Novikov OO, Novikova MYu, Popov NN. Development of the composition and technology of an innovative combined drug for the treatment of infectious conjunctivitis of bacterial etiology. Scientific sheets of BelSU. Medicine and Pharmacy.2012;10(129):123-126.
22. Zhilyakova ET, Naplekov DK. The study of the possibility of creating a combined drug for the treatment of glaucoma complicated by myopia. Young scientist J.2014;19(78):107-109.
23. Zhilyakova ET, Timoshenko EYu. Development of the composition and technology of eye drops based on miramistin. Vestn. new medical technologies. Tula. 2007;4(14):143-148.
24. Zhilyakova ET, Novikova My. Modern eye drops with combined content. Scientific sheets of BelSU. Medicine and Pharmacy.2006;6(26):190-193.