Drug delivery from commercial contact lenses: hydrodynamic conditions effect

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Abstract: Nowadays, eyedrops are the most used vehicle of ocular drug administration to treat ocular diseases. The eyedrops' method has some disadvantages, namely a significant drug loss due to quick absorption into bloodstream, which may cause undesirable side effects and drug elimination as a result of lachrymal turnover. [1,2]
In order to overlap these disadvantages, some efforts have been made to develop new drug delivery systems that promote drug residence time in the eye and to guarantee controlled drug delivery profiles. Therefore, contact lenses, as drug delivery systems, seem to be a promising method to reach these issues. [3]
This study aimed to evaluate drug release profiles in different release environments, and temperature influence in contact lenses swelling and characterization after and before drug loading, in order to verify possible changes in wettability and transmittance values. In this study, were used two different commercial contact lenses: SofLens, conventional hydrogel contact lenses (Balafilcon A) and PureVision, silicone based contact lenses (Hilafilcon B), both from Baush&Lomb. Were also used two different ophthalmologic drugs: levofloxacin and chlorohexidine.
The results obtained suggest temperature influence in contact lenses swelling, changes in drug release profile depending on release conditions and no significant differences in contact lenses wettability and transmittance values after drug loading.
Key words: contact lenses, levofloxacin, chlorohexidine, drug release, release conditions, hydrodynamic conditions.

1 Introduction

Eyedrops are the most common treatment in ocular diseases. However, after instillation, less than 5% is absorbed by the cornea. The remaining 95% of the total drug administrated is lost due to lacrimal turnover and bloodstream absorption. In fact, drug residence in the eye is less than 5 minutes. Thereby, therapeutic effectiveness is compromised and some undesirable side effects can take place because a significant amount of drug enters into the bloodstream.

In order to overlap eyedrops disadvantages, several studies have been made with drug delivery systems (DDS) using ophthalmologic drugs. From all procedures studied, therapeutic contact lenses seem to be one of the most promising techniques with several potential advantages as compared with eyedrops. Therapeutic contact lenses, acting as DDS, increase drug residence time in the eye and improve bioavailability.

Improvements in biomaterials industry have, also, played an important role in the contact lenses development. Hydrogel (conventional contact lenses) and silicone based contact lenses are widely used and very common in this kind of research. Conventional contact lenses have higher water content (hydrophilic hydrogel) which means higher comfort to the patient while wearing it. However, conventional lenses have low oxygen permeability which carry some corneal problems, such as hypoxia. On the other hand, silicone based contact lenses have good oxygen transmissibility, allowing more oxygen to reach the cornea than the hydrogel ones, which allows extended wear. However, silicone is a hydrophobic material, which has some disadvantages to patients' comfort during contact lenses wearing. Yet, some developments have been made to mitigate these disadvantages. Currently, hybrid contact lenses are often used. This approach results from superficial silicone contact lenses treatment in order to improve their wettability, and therefore they become more comfortable. There are several of these treatments, to improve contact lenses' wettability. For instance, plasma treatment, which is achieved by plasma oxidation of the silicone hydrogel. In this way, wettable contact lenses with good oxygen permeability can be achieved.

There are also other characteristics needed to guarantee an efficient therapeutic contact lenses, namely optical, chemical and mechanical properties. As examples, among others: transmittance is essential to guarantee good visual acuity; biocompatibility to avoid some harmful effect in eye tissues.; Swelling behavior to be the capability of contact lenses to swell water and change their shape according to the swelling degree; heat conductivity to dissipate heat from the ocular tissue.

2 State of art

Significant advances have been made in DDS area. Nowadays, DDS is a multidisciplinary science with scientists in universities and industries working together in order to create/improve promising DDS. As a result, there have been developed different approaches to address ophthalmic issues. [3]

For instance, there are device-based approaches frequently used in targeting the posterior segment of the eye. In fact, it is considered a challenging task due to drug loss, drug toxicity and anatomical barriers. Therefore, systemic drug delivery is not a desirable method to treat posterior segments of the eye. In this way, some ophthalmologic devices were developed, like I-Vation™ (Figure 1), that is a helix coil device with a thin cap on the top. This device is made from ethylene vinyl acetate (EVA) and polyvinyl alcohol (PVA). Its helical shape improves drug delivery area and avoids scleral sutures to be anchoring. The cap remains under sclera in order to facilitate drug loading and device removal.[6,7]

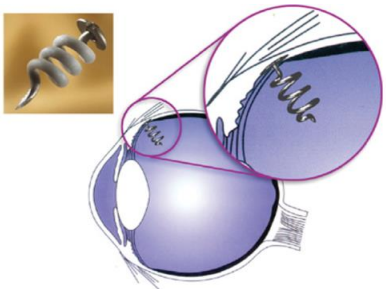

Figure 1: I-Vation™ in the sclera. Image edited from [6]

I-Vation™ is a non-biodegradable device. However, there are some kinds of biodegradable devices like Ozurdex®, used to treat diabetic macular edema. This device is a cylindrical matrix of poly(lactic-co-glycolic acid) (PLGA) and the drug storage, in the matrix, is released during matrix and polymer degradation. This device is able to release drug for up to 6 months.[6,7]

Artificial intra ocular lenses (IOL) have been investigated and new methodologies have been developed. IOL's after eye surgery are commonly used to replace crystalline functions. Firstly, IOL's were uniquely used to correct refractive diseases. Some experiments were made by Eperon et al.[8] combining artificial IOL's with biodegradable polymeric DDS load with two anti-inflammatory drugs: triamcinolone acetonide (TA) and cyclosporine (CsA), in order to avoid postoperative ocular inflammation (Figure 2).[8]

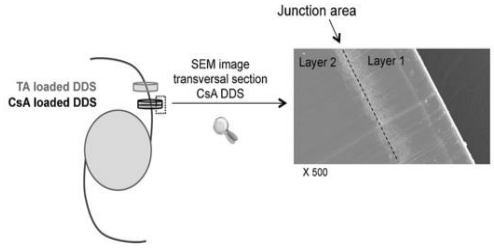

Figure 2: Artificial IOL combined with a biodegradable DDS. Image edited from [8].

This new methodology addresses in a simultaneously way both inflammatory and refractive issues. Thus, IOL-DDS were demonstrated to inhibit intraocular inflammation for at least 3 months after cataract surgery, representing a potential novel approach to this surgery in eyes with pre-existing uveitis.[8]

Therapeutic contact lenses are another approach widely investigated with several variants. Liposomes, nanoparticules and vitamin E have been investigated to improve drug release profile to increase drug residence time, bioavailability and burst effect reduction. These studies have shown promising results due to their biocompatibility, biodegradability and capability to encapsulate ophthalmic drugs.[9-11] Chauhan et al.[10] increased Timolol release from 1 - 2h to about 2 - 4 weeks by Timolol encapsulation in highly crosslinked nanoparticles in contact lenses. According to the work of Paradiso et al [11], vitamin E loading in commercial silicone contact lenses increases the duration of Levofloxacin (LEVO) and chlorohexidine (CHX). Extended release is provided due to vitamin E aggregation, which constitutes a barrier effect to drug release. Chauhan et al [12] demonstrates an increase in the drug release time from a few hours to several days, using vitamin E combined with Timolol, wearing continuously ACUVUE® TruEye™.

Other interesting studies revealed promising results.

3 Materials and Methods

3.1 Materials

Two different contact lenses types were used, both from Bausch & Lomb: PureVision®, a silicone based contact lens – Balafilcon A, diopter-3.5, 36% H_2O, 101 Dk, diameter of 14 mm and can be used for 30 days. SofLens® ,that were also used, are a conventional hydrogel contact lens, diopter-3,5, 59% H_2O, 22 Dk, diameter of 14,2 mm and can be used on a daily basis. Levofloxacin 98%, Sigma-Aldrich (Madrid, Spain). Chlorohexidine 98%, Sigma-Aldrich (Madrid, Spain). Sodium chloride 99.9%, from Merck. Acetonitrile (HPLC grade), Fisher Scientific. Phosphoric Acid 85%, Sigma Aldrich. Triethylamine 99%, Sigma Aldrich. Saline solution 130 mM (SS). Distilled and Milli-Q deionized water (DI) were used for all preparations.

3.2 Solution and Contact Lenses Preparation

In order to remove all substances from contact lenses, each contact lens was washed by immersion in DI, which was renewed 5 times every 1h30. Contact lenses were dried in a hoover at 50 ºC during 14h and weighted in a dry state. After each drug delivery trial, contact lenses were washed, dried and stored in a dry receipt.

3.3 Contact Lens Characterization

3.3.1 Swelling

Both contact lenses, in a dry state, were placed in test tubes filled with 15 mL of SS at different temperatures: 4ºC, 20 ºC (room temperature) and 40 ºC. The samples were periodically weighted after careful wiping with absorbent paper, to remove excess liquid on lenses' surface. Swelling capacity, *SC*, was determined using equation 1:

$$SC = \frac{W_T - W_0}{W_0} \times 100$$

where W_0 is the weight of the dry sample and W_t is the weight at time t. When equilibrium is achieved, W_t is practically constant, it corresponds to the constant weight value, W_∞, which allows a calculation of the capacity of water absorption, W_{AC}, defined by:

$$W_{AC} = \frac{W_\infty - W_0}{W_\infty} \times 100$$

Temperature influence in contact lenses was also investigated. After equilibrium, the sample temperature was changed to room temperature, remaining at it for 90 minutes. After that, sample temperature was changed again for more 90 minutes to their respective initial temperature. Each step samples were collected wiping with absorbent paper and weighted. The tests were always made in triplicate.

3.3.2 Transmittance

Optical studies were performed in hydrated contact lenses, mounted in quartz cuvette, which was placed in a spectrophotometer (Thermo Scientific Multiskan GO) at 25 ºC. Wavelength measures range was 400 nm to 700 nm. The trials were performed to both contact lenses, without drug and load with both drugs. These tests were, also, always made in triplicate.

3.3.3 Wettability

Wettability measures were performed in contact lenses with and without drugs. It was performed by contact angle measuring through captive bubble method. Both contact lenses were load with both drugs with a concentration of 5 µg/ml. With captive bubble method, contact angle values were measured placing an air bubble onto lens surface, using an inverted syringe. The images were acquired using a video camera (JAI CV-A50) connected to a microscope (Wild M3Z) and to a frame grabber (data translation DT3155). The image analysis was performed using the ADSA-P software (axisymmetric drop shape analysis profile). The measurements were performed over 10 samples, at room temperature, and in DI water.

3.2 Drug loading and drug releasing

Dried contact lenses were loaded with LEVO and CHX by soaking in 15 ml of drug solution, with a concentration of 5 mg/ml during 14h at 20 ºC and isolated from light. In the case of PV – LEVO, concentrations of 10 mg/ml and loading time of 7 days were also used. In this case, the first 14h of loading time were at room temperature and after that, they were placed in a fridge at 4 ºC to avoid drug degradation. LEVO was dissolved in SS while CHX was dissolved in simple DD water due to its limited solubility in SS. Both solutions were magnetically stirred for about 5 min to obtain a homogeneous solution. In order to remove drug excess in lenses surface, they were dipped in DI, and liquid excess was removed using absorbent paper.

Drug release experiments were performed in static and dynamic conditions. In static conditions, load samples were immersed in 4 mL of SS in closed test tubes at 35 ºC, under stirring (150 rpm). These conditions simulate the eye conditions and ensure that the concentration of LEVO and CHX remain below their solubility limit. Periodically, 150 µl of the supernatant were collected and replaced with 150 µl of fresh SS. In static conditions, other approach took place. Every time equilibrium was reached, supernatant was completed and replaced with 4 ml of fresh SS. This procedure was repeated until no more drug was released. In the other hand, with dynamic conditions, a microfluidic cell was used to perform drug release (Figure 3). This approach allows continuous SS flux with a rate of 65 µl/min due to a bomb action. In this way, contact lenses, soaked in a cell with 650 µl, have fresh SS permanently. Drug samples were collect by a closed receipt to avoid drug evaporation.

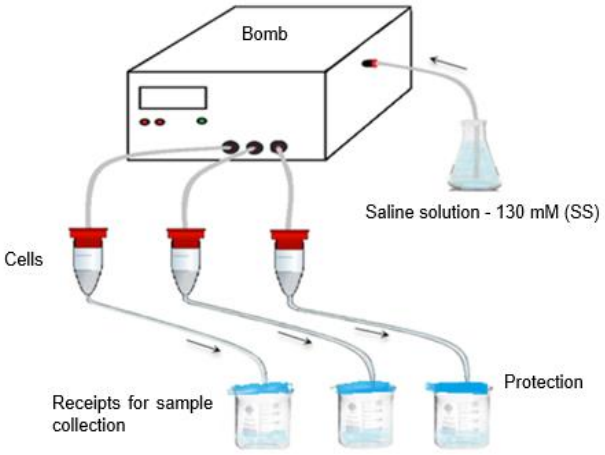

Figure 3: Microfluidic cell.

This approach was an interesting improvement compared with static conditions trials. In-vitro conditions are closer to eye conditions, since supernatant volume was reduced more than 6 times and a continuous SS flux was a good approximation to lacrimal turn over. The relation between lachrymal eye volume and lachrymal turnover is similar when compared with cell volume and SS flux.

Drug quantification was made using two different methods, according with what has been done in the laboratory. In this way, LEVO samples concentration was determined using a High Performed Liquid Chromatograpfy (HPLC) at wavelength of 290 nm, with a Jasco UV–vis detector and a C-18 column Nova-Pak Watters. The mobile phase, involving water, acetonitrile, phosphoric acid and trimethylamine (86/14/0.6/0.3 in volume), was introduced into the column at a flow rate of 1 mL min and a pressure of 14 MPa, according to the method described by Wong et al. [13]. CHX samples concentration was determined using the spectrophotometer (Thermo Scientific Multiskan GO) described on 3.3.2, with a wavelength of 255 nm. These tests were always made in triplicate.

4 Results and Discussion

4.1 Temperature effect on Swelling

Swelling degree from PV and SL's contact lenses at 4 ºC, 20 ºC (room temperature) and 40 ºC are shown in Figure 4 and Figure 5.

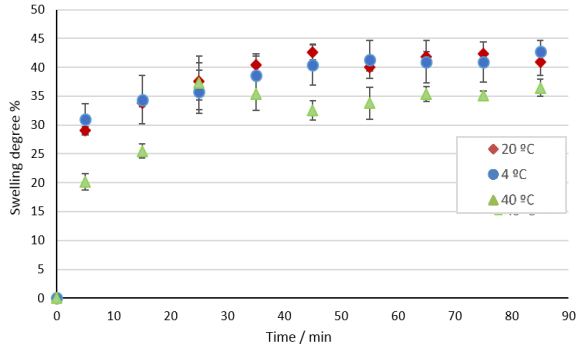

Figure 4: PureVision swelling degree at different temperatures.

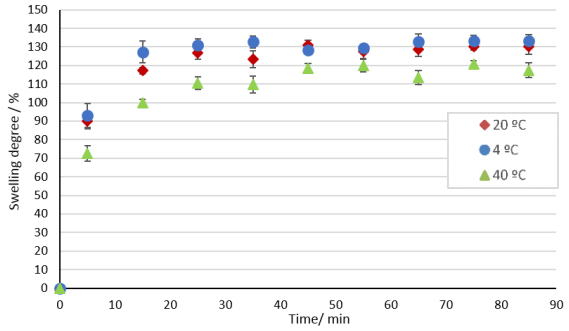

Figure 5: SofLens swelling degree at different temperatures.

As it can be seen above, the swelling degree from both contact lenses at 40 ºC is smaller than swelling degree at 20 ºC, which is very similar to swelling degree at 4 ºC. Although swelling values at 4 ºC are slightly higher than swelling at 20 ºC, the next experiments were done at 20 ºC (room temperature) to reduce laboratorial costs and material simplicity. Several studies have been made related with temperature effect. Ozturk et al[14] demonstrated hydrophobic interactions increment in the hydrogels with higher temperatures, and according to the work of Mah et al[15] in thermophobic hydrogels, the hydrogen links between water molecules and polymer molecules are weaker at higher temperatures. Temperature effect on swelling is shown in Figures 6 and 7.

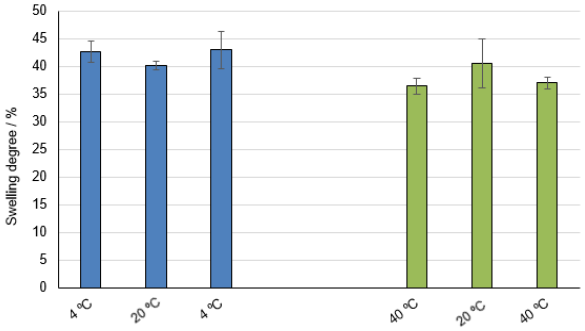

Figure 6: Temperature effect in PV contact lenses.

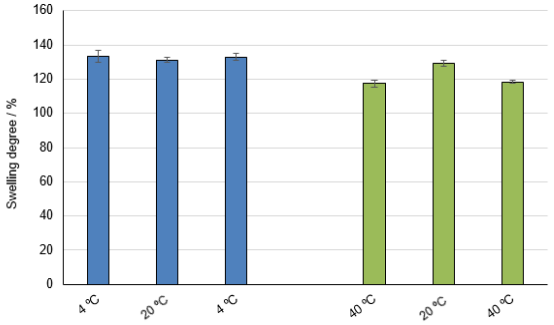

Figure 7: Temperature effect in SL contact lenses.

The swelling degree from both contact lenses is changed by temperature values. There is swelling reversibility in these contact lenses promoted by temperature changes.

4.2 Contact Lens Characterization

In this study, lens characterization was done to both contact lenses, loaded with both drugs and without drugs. Loading lens characterization aimed to assess the possible impact of these drugs in contact lenses properties and wearing comfort. Transmittance (%*T*), Wettability (*W*º) and Water Content (W_c) are listed in table 1. The measured transmittance values are in the range of the ones referred by Baush & Lomb and in previous studies.[16,17]

PV wettability values are significant higher when compared with expected values, since all contact lenses should be hydrophilic in order to guarantee a comfort wearing to all patients. PV are silicone based, which is hydrophobic, however, plasma treatment should increase hydrophilic molecules on contact lenses surface. Although these values in both lenses are identified in other studies[18,19], the contact lenses handling (washed or dried processes) could change some superficial PV properties provided by plasma treatment.

Water content values are similar with bibliography values[17-19], and confirm a greater affinity from SL to water swelling.

Notice that these contact lenses have small dimensions. So, its work handling is very meticulous, being error-prone in weight measures. It could justify some value discrepancies between this study values and bibliography references. Transmittance and wettability values for these contact lenses and for these drugs were not affected by drug loading process.

Table 1: Contact Lens Characterization

Contact Lens	Drug	T (%)	W (º)	W_C (%)
PV	-	87 ± 2	93 ± 2	31 ± 1
PV	LEVO	86 ± 1	91 ± 2	-
PV	CHX	86 ± 1	91 ± 2	-
SL	-	96 ± 1	68 ± 5	57 ± 1
SL	LEVO	94 ± 1	67 ± 4	-
SL	CHX	94 ± 3	67 ± 4	-

4.3 Drug Release in Static Conditions

As mentioned before, static conditions are useful to do comparative studies, due to the simplicity of its laboratorial process.

The release kinetics is greatly affected by release conditions, the type of drug and the type of contact lenses' polymer based[20] as can be seen in the figures below where was experienced CHX and LEVO release from PV and SL. To PV-LEVO was also studied two different release solutions (NaCl solution and water DI solution):

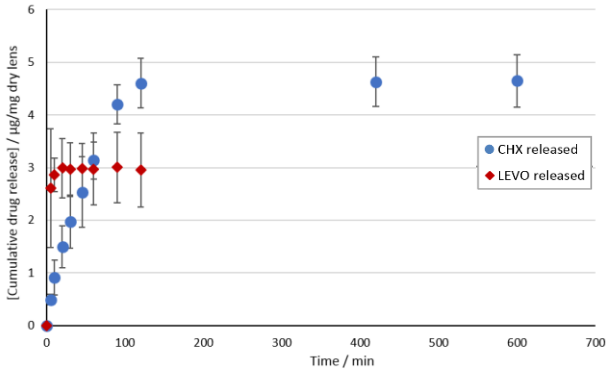

Figure 8: Drug release in PV from a NaCl solution.

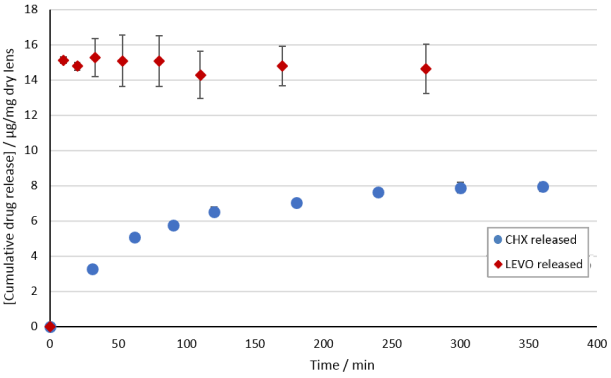

Figure 9: Drug release in SL from a NaCl solution.

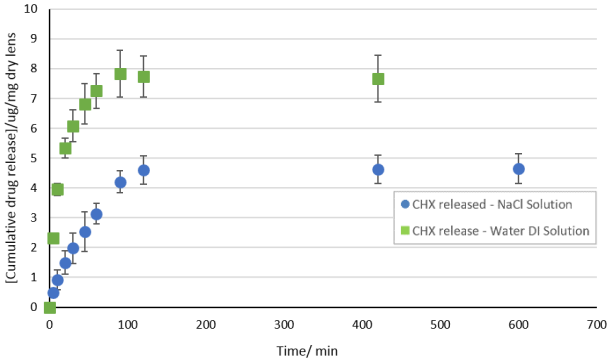

Figure 10: Drug release in PV from a NaCl solution and water DI.

The release kinetics plotted in the Figures above, are very distinctive between themselves depending on the type of drug and type of contact lenses studied. The LEVO release reaches the equilibrium in a few minutes in both contact lenses, however LEVO was released in a higher quantity in SL. In fact, LEVO molecule is lighter compared with CHX's molecule, so it is expected a higher entrance of LEVO in hydrogels which favours the entrance of water, it is the case of SL, so it could justify the higher amount of LEVO released when compared with PV. These results are similar with those obtained by Paradizo et al[19] with a higher quantity of LEVO released in the HEMA/PVP polymer (same polymer which constitutes SL). However in Paradizo work, HEMA/PVP polymer have a lesser water content than TRIS/NVP/HEMA polymer (which has the same polymer basis than PV). These differences can be explained by the presence of extremely hydrophilic monomers in SL network like MAA and NVP.

Regarding with CHX release profile, it was released during few hours. The amount of CHX released was greater in SL and it was released in a more controlled way than PV. In fact, CHX release profile reaches the equilibrium, in PV, in practically 2 hours and in the case of SL reaches the equilibrium in almost 5 hours. This behavior is in line with Paradizo et al.[19] who claimed that CHX (hydrophilic drug) diffuses preferentially into the hydrogels' network with higher water content.

Commercial contact lenses, have a smaller area when compared with hydrogels tested in others bibliographic references. Contact lenses dimensions can be an important factor in the drug release profile since smaller contact lenses could have a faster drug release profile which is a typical behavior from a superficial drug aggregation.

Based on the data plotted in Figure 10, the ionic strength from the solution has influence in the release profile. In fact in water DI solution (lower ionic strength) there was a higher drug release and equilibrium was reached faster when comparing with data from CHX released in a NaCl solution. These values are in agreement with those reported by the studies of Ringet et al[20]. In this study, it was studied the influence of the ionic concentration of the release solution in a caffeine release profile from a hydrogel. Ringet et al conclude that higher ionic concentration in the solution implies lower drug released amount from the hydrogel to the solution. Drug released in water DI has no significant physiologic interest, however it has an important relevance to make comparative studies about the influence of solution concentration in drug released profiles.

In order to conclude about loading time influence and concentration of the drug loaded into contact lenses, in Figures 11 and 12 are plotted, respectively, drug release from PV-LEVO soaked in a solution at different drug concentrations during the same loading time (14h) and drug release from PV-LEVO soaked in a solution with the same concentration but during different loading times (14 hours and 7 days).

In the case of PV-LEVO, contact lenses loaded in a solution with 10 mg/ml of LEVO concentration, drug was released practically twice the amount of drug when compared with the amount released in the contact lenses load with 5 mg/ml of LEVO, and it was proved the non-existence of changes in drug release profile. Thereby, it was decided to load all the next experiments in a solution of 5 mg/ml in order to reduce the costs of the experiments.

The drug loading time does not influence significantly the drug release profiles of PV-LEVO which indicates that saturation was achieved after 14 hours of loading. In this

way, it was also decided to load contact lenses during 14 hours.

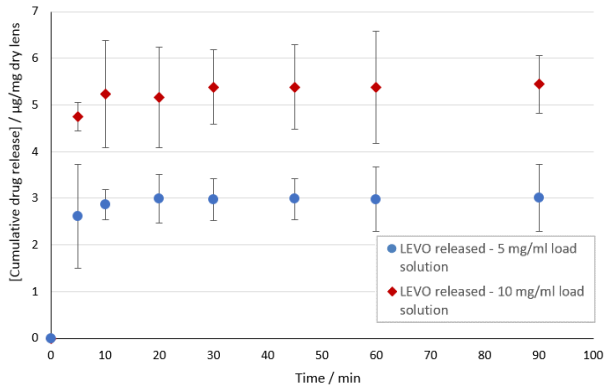

Figure 11: Drug release in PV load at different concentrations.

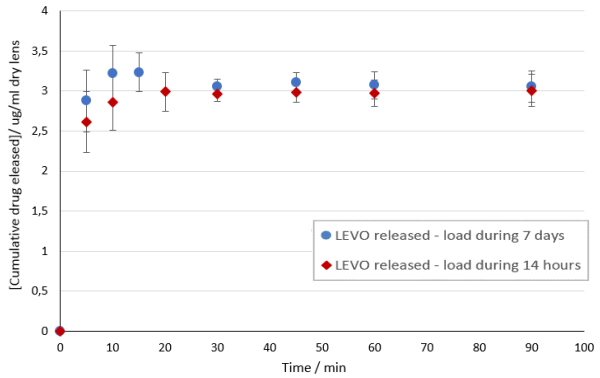

Figure 12: Drug release in PV load with different load times.

4.4 Drug Release in Dynamic Conditions

As mentioned before, static conditions do not adequately describe the drug released kinetics in the eye. In this way, dynamic conditions release fits better in vivo conditions, considering the small tear volume and flow rates found in vivo. Some trials with solution volume decrease were performed in order to achieve that.

In Figure 13 is shown the drug release profile from microfluidic cells compared with the same profile in static conditions, in SL-LEVO. LEVO release profile, from microfluidic cells, is extended in time compared with static conditions. The same results were obtained in PV-LEVO. The amount of drug release is similar in both trials with differences not greater than 3%.

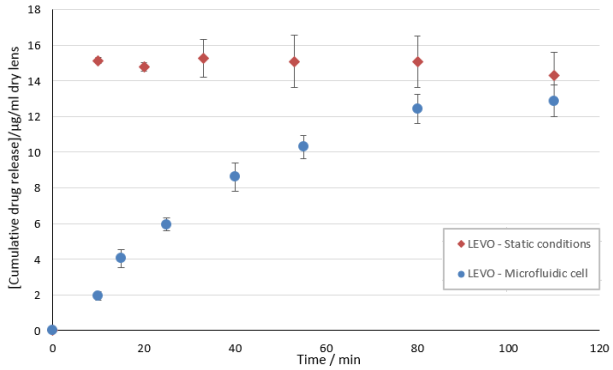

Figure 13: Drug release in PV from static and dynamic conditions.

On the other hand, in the microfluidic trials for CHX, a distinctive behavior was found with more quantity of drug being released, compared with static conditions results. In order to confirm these results, trials in static conditions were performed for SL-CHX and PV-CHX, with solution substitution. In microfluidic cells, the drug release in an extended time was also verified. In Figures 14 and 15 is plotted the drug release profile from static conditions with solution substitution, and the release profile from microfluidic cells in PV-CHX and SL-CHX, respectively. In both figures, red dashed lines are plotted in the exactly moment where NaCl solution was changed to fresh NaCl solution.

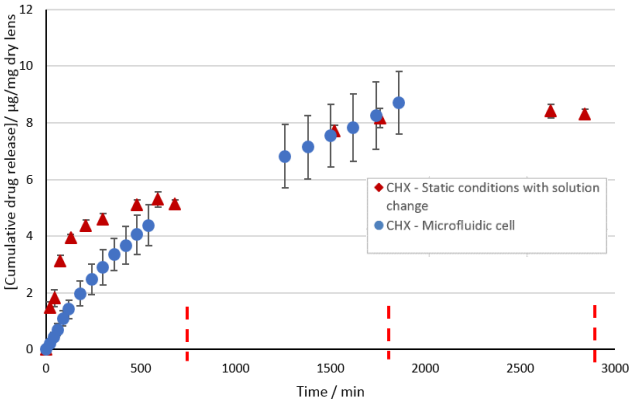

Figure 14: Drug release in PV from a microfluidic cell and static conditions with solution change.

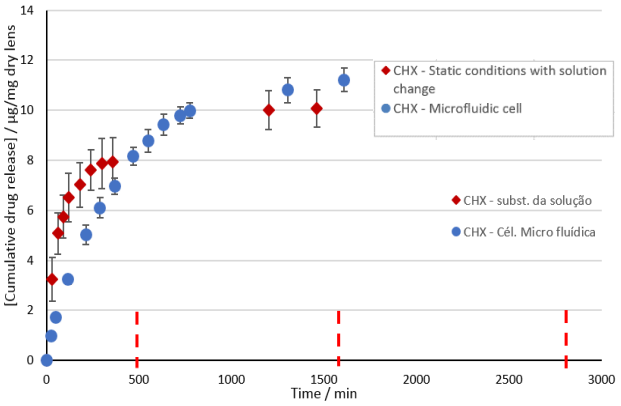

Figure 15: Drug release in SL from a microfluidic cell and static conditions with solution change.

These behaviors take place because. in static conditions, a higher driving force value is produced by the gradient of concentrations between the supernatant and the hydrogels. In contrast, the driving force produced in microfluidic cells is lower, which could justify a more sustained drug release due to its flow conditions and small release volume. These results are in line with other researches: Pimenta A. et al.[21] and Vazquez R, et al.[22] where drug release from static conditions and under flow conditions were tested. In these studies, the drug release

profile was significantly affected by the flow rate and the volume of release.

4.5 Drug Posology

In a QUIXIN© eye drop bottle, LVF is delivered with a 5 mg/ml solution, containing a dosage of 1-2 drops every 2 hours in the first 2 days and 1-2 drops every 4 hours on days 3- 7. Considering that 25 µl is the volume of an eye drop, that less than 5% of the administrated drug is absorbed by the cornea[23], and that contact lenses are used for 16h per day, this posology delivers 0.05-0.1mg per day in the first 2 days and 0,025-0.051 mg in the next 5 days. The estimations for therapeutic needs of the cornea are 2,1-4,2 µg/h and 1,0-2,1 µg/h in the first 2 days and in the next 5 days, respectively. LVF's toxicity studies revealed a high tolerance of the ocular cells at short duration exposure and to drug concentration below 30 mg/ml[24].

In table 2 the values of drug load in both contact lenses are presented.

Table 2: Drug load in PV and SL.

Contact Lens	Drug	[Solution Load]	Drug load per mg/dried lens	Drug load per lens
PV	CHX	5 mg/ml	9 ug	180 µg
PV	LEVO	5 mg/ml	3 ug	60 µg
PV	LEVO	10 mg/ml	5,5 ug	121 µg
SL	CHX	5 mg/ml	11 ug	220 µg
SL	LEVO	5 mg/ml	13 ug	260 µg

Based on table 2 and in the description above, about corneal therapeutic estimations, the total amount of LEVO required to satisfy therapeutic corneal needs is 179 µg per lens. Therefore, the amount of LEVO loaded per lens is not enough to satisfy therapeutic needs. So, assuming that the partition coefficient is independent of the concentration, the contact lenses should be soaked in a solution of 15 mg/ml.

Based on Minassian et al[25], the therapeutic values for CHX are much lower - between 1,8 and 0,7 µg/h. In this way, the CHX amount loaded, for these contact lenses, is enough to satisfy corneal needs.

5 Conclusions

The results reported in this study prove the non-existence of any changes in the contact lenses properties, after loading process with transmittance and wettability keeping practically the same values. Solution's temperature affects the swelling degree, and these contact lenses revealed reversibility in their shape, according to solution's temperature. Release values from static conditions were a very useful way to make comparative studies and drug releasing system performance but, these environment conditions are far from the eye conditions. Microfluidic cell was useful to bring closer these experiments to eye conditions, providing a more reliable information about drug release profiles. CHX release from dynamic conditions revealed to be higher when compared with static conditions. Actually, dynamic conditions revealed more controlled release profiles from both drugs and contact lenses, when compared with static condition values. This behavior suggests that in vivo release profiles will be more controlled due to lower solution volume, which contacts with contact lenses. Time and drug concentration loading, reported no significant changes in release profiles.

Contact lenses posology in this study are strongly influenced by the contact lenses constitution and the kind of ophthalmic drug used. Finally, the amount of CHX loaded in contact lenses is enough to guarantee corneal treatment, but, both contact lenses should be loaded with a higher LEVO concentration in order to satisfy corneal needs.

6 References

1. RATNER, B. D., HOFFMAN, A. S., SCHOE, F. J, LEMONS, J.E, Biomaterials Science - An Introduction to Biomaterials in Medicine, 1996 Academic Press, California – USA.
2. GASSON, A., MORRIS, J.; THE CONTACT LENS MANUAL – A PRATICAL GUIDE TO FITTING; 4 ed. 2010, Elsevier Limited 2010.
3. Drug Delivery Systems, 3ª Edition, 2011. Available at: https://books.google.pt/books?hl=pt-PT&lr=&id=PBfLKBTQk0cC&oi=fnd&pg=PP1&dq=drug+delivery+systems&ots=C16DhhwcWk&sig=PMN3FViO3St-1hnjlzOGfjKYWYo&redir_esc=y#v=onepage&q=drug%20delivery%20systems&f=false,accessed October 8, 2017.
4. Gulsen D, Li C-C, Chauhan A. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery.Curr Eye Res.2005;30(12):1071-80.
5. McDermott M. L., Chandler, J. W., Therapeutic uses of contact lenses," Survey of Ophthalmology, vol. 33, no. 5, pp. 381–394, 1989.
6. Kuno, N, Fujii, S., Ocular Drug Delivery Systems for the Posterior Segment: A Review, Retina Today, (2012) 54-59.
7. Kaji, H., Nagai, N., Nishizawa, M., Abe, T., Drug delivery devices for retinal diseases, Advanced Drug Delivery Reviews, Japan, 2017.
8. Eperon, S. Rodriguez, A., Balaskas, K., Guex-Crosier, Y., A new drug delivery system inhibits uveitis in an animal model after cataract surgery, International Journal of Pharmaceutics 443 (2013) 254– 261.
9. Batista, C. M. et al., Lipossomas e suas aplicações terapêuticas: Estado da arte, *Brazilian Journal of Pharmaceutical Sciences,* vol. 43, 2007.
10. Jung, H. J., Chauhan, A., Temperature sensitive contact lenses for triggered ophthalmic drug delivery, Biomaterials 22 (2012) 2289-2300.
11. P aradiso, P., Serro, A. P., Saramago, B., Colaço, R., Controlled Release of Antibiotics From Vitamin E-Loaded Silicone-Hydrogel Contact Lenses, Journal of Pharmaceutical Sciences 105 (2016) 1164-1172.
12. Peng, C. C., Burke, M. T., Cabria, B. E., Plummer, C., Chauhan A., Extended drug delivery by contact lenses for glaucoma therapy. J Control Release. 162 (2012) 152-168.
13. Wong, A,. et al., Rapid stereospecific high-performance liquid chromatographic determination of levofloxacin in human plasma and urine, Journal of Pharmaceutical and Biomedical Analysis, vol. 15, pp. 765-771, 1997.
14. Ozturk, v., Okay, O., Temperature sensitive poly(N-t-butylacrylamide-co-acrylamide)hydro gels: synthesis and swelling behavior, Polymer 43 (2002) 5017–5026, 2002.
15. Mah, E., Ghosh, R., Thermo-Responsive Hydrogels for Stimuli-Responsive Membranes, Processes 2013, 1, 238-262, 2013.
16. ALVES, Carlos Miguel Teixeira - *Influência da degradação termo-oxidativa nas propriedades das lentes de contacto.* Universidade do Minho – Escola de Ciências, Outubro 2012.
17. Package insert / Fitting Guide - Bausch&Lomb SofLens daily disposable (hilaficon B) visible tinted contact lenses.
18. F. Yañez, L. Martikainen, M. Braga, C. Alvarez-Lorenzo, A. Concheiro, C. Duarte, M. Gil, H. Sousa, "Supercritical fluid-assisted preparation of imprinted contact lenses for drug delivery", Acta Biomaterialia 7 (2011) 1019–1030.
19. P. Paradiso, R. Galante, L. Santos. A. P. Alves de Matos, R. Colaço, A. P. Serro, B. Saramago, *"Comparison of two hydrogel formulations for drug release in ophthalmic lenses"*, Journal of Biomedical Materials Research B: Applied Biomaterials | Aug 2014 vol 102B.

20. R. Ringet, M. M. Talukdar, “Swelling and drug release behavior of xanthan gum matrix”,International Journal of Pharmaceutics 120 (1995) 63-72.

20. A. Pimenta, A. Valente. J. Pereira, H. Filipe, J. Mata, R. Colaço, B. Saramago, A. Serro, Simulation of the hydrodynamic conditions of the eye to 63- better reproduce the drug release from hydrogel contact lenses: experiments and modeling, Drug Deliv. and Transl. Res. (2016) 6: 755–762.

22. R. Vazquez, R. Nogueira M. Orfão, J. Mata, B. Saramago, Stability of triglyceride liquid films on hydrophilic and hydrophobic glasses. J 63-72. Colloid Interface Sci. 2006; 299(1):274–82.

23. C. Bourlais L. Acar, H, Zia, P. Sado, T. Needhm.Ophthalmic drug delivery systemse recent advances, Prog Retin Eye Res. 1998;17(1):33-58.

24. L. Clark, P. Bezwada, K. Hosoi, Comprehensive evaluation of ocular toxicity of topical levofloxacin in rabbit and primate models, J Toxicol Cutan Ocul Toxicol. 2004;23(1):1-18.

25. M. Rahman, G. Johnson, R. Husain, S. Howlader, D. Minassian, Randomised trial of 0.2% chlorhexidine gluconate and 2.5% natamycinfor fungal keratitis in Bangladesh, Br J Ophthalmol. 1998;82(8):919-925.