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Daily disposable contact lenses as a platform for ocular drug delivery of cyclosporine A

Ola Michałkiewicz [1], Iwona Nowak [1], Rafał Nowak [2], Iwona Rykowska [1]

[1] Adam Mickiewicz University, Faculty of Chemistry, ul. Uniwersytetu Poznanskiego 8, 61-614 Poznan, Poland

[2] Department of Ophthalmology, Military Institute of Medicine, ul. Szaserów 128, 04-141, Warsaw, Poland

Corresponding author: olamic@amu.edu.pl (Ola Michałkiewicz)

Abstract: Ophthalmic drug delivery is an important area of research that aims to improve the efficacy and convenience of treatment for various eye conditions. There are multiple ways in which drugs can be delivered to the eye, including eye drops, ointments, gels, and inserts. The most prevalent way of administering medication to the eye is through eye drops. They are easy to use and can be self-administered by patients. Nonetheless, eye drops have the disadvantage of being prone to removal by tears, which may result in insufficient drug absorption and reduced effectiveness. Irregular use of active substances can exacerbate the disease, resulting in prolonged treatment with questionable efficacy. Soft contact lenses that serve as ophthalmic drug delivery systems (DDS) can become a viable substitute for traditional treatments. These polymeric lenses can be embedded with various active compounds, some of which are not readily soluble in water or physiological fluids. One such drug is Cyclosporine A (CyA), an immunosuppressant with a high molecular weight and hydrophobic properties, chronically used to treat dry eye syndrome (DES). The article discusses the development of a method for modifying Hilafilcon B contact lenses obtained from drugstores with Cyclosporine A (CyA). The drug was administered to the lenses using an immersion technique, and the process parameters were monitored to control drug release efficiency and profile. The drug release was measured in an Artificial Lacrimal Fluid (ALF) buffer, mimicking tear fluid with a pH of 7.9. The stability of CyA in this buffer was assessed. For the parameters used, the best drug application and release profile was achieved by immersing the contact lenses for 24 hours at 25 °C in a CyA solution containing 20 µg/ml of the active substance and adding 5 mg/ml of Vitamin E.

Keywords: contact lenses, cyclosporine A, vitamin E, drug delivery systems, dry eye syndrome

1. Introduction

In ophthalmic medicines, ensuring a balanced delivery of the active ingredient to the eye remains challenging. Still, eye drops are the most popular way of providing medication to the eye structure (Lanier, 2021). Admittedly, they are simple in use and allow for patient self-administration but are burdened with numerous disadvantages leading to reduced effectiveness and unsatisfactory therapeutic effects.

In turn, ointments and gels provide more extended contact with eye structures, but they worsen vision and cause excessive discomfort in use (Ding, 1998).

Other known ophthalmic drug delivery systems are inserts such as punctal plugs and contact lenses. Punctal plugs are tiny devices inserted into the tear duct to slow down the drainage of tears and increase the contact time of the medication with the eye so it can be used to release drugs gradually over time (Jehangir et al., 2016).

Recent breakthroughs in ocular medication supply include the development of sustained-release and nanoparticle-based drug delivery systems (Xu et al., 2018). Such innovative approaches may improve pharmaceutical efficacy while reducing undesired side effects. Sustained-release drug delivery systems based on soft contact lenses can provide continuous and regulated drug delivery by slowing

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the release of medication over time (Maulvi et al., 2016a). This method may assist in treating eye problems such as glaucoma, inflammation and dry eye syndrome (Hui, 2017).

Dry eye syndrome (DES) is a condition that occurs when an imbalance in the tear film is present, leading to inadequate lubrication and protection of the ocular surface. DES can result in eye irritation, dryness, and blurred vision (Barabino et al., 2012; Lemp et al., 2007). The environment (dry air, high-speed air), preservatives in ophthalmic formulae, and mechanical damage are the main factors that contribute to DES (Gayton, 2009; Lemp et al., 2007).

The primary treatment of dry eye syndrome involves eye drops known as artificial tears (ATs) (Moshirfar et al., 2014). Its function is to moisturise the eyeball surface and promote tear film stability. Various artificial tears are available, including hyaluronic acid, carboxymethyl cellulose, or polyethene glycol (Semp et al., 2023). Another class of drugs used in DES include cyclosporin and lifitegrast, which inhibit inflammation and increase tear production (Tong et al., 2020; White et al., 2019). CyA (Ikervis, Restasis, Cequa) and lifitegrast (Xiidra) are mainly administered as eye drops or ointment (de Oliveira & Wilson, 2019; Hovanesian et al., 2021).

The amount of active component that reaches treated tissue and has a pharmacologic effect is referred to as drug bioavailability. It depends on several factors, such as the active substance nature, drug formulation, drug administration method, eye physiology, and biological eye barriers (Xu et al., 2018).

Low active substance bioavailability (estimated at roughly 5% for eye drops), poor dose repeatability, and poor patient adherence have all contributed to the development innovative drug delivery systems.

Several strategies have been introduced to increase divers ophthalmic drugs bioavailability (Downie et al., 2021; Mahaling & Katti, 2016; Xu et al., 2018). For example, prodrugs or nanoparticles can increase the permeability of drugs and reduce their degradation. The use of eye inserts, ophthalmic gels, or new systems, such as liposomes or microspheres, may, in turn, increase the contact time of the drug with the eye surface and increase tissue penetration. Also, combining drugs with different mechanisms of action can improve therapeutic efficacy and reduce the likelihood of drug resistance.

It is considered that contact lenses as reservoirs of ophthalmic drugs - drug-modified contact lenses (DMCLs) (Le Le Bourlais et al., 1997) - have several advantages over traditional drug supply systems. CLs have the potential to supply drugs sustainably over a prolonged time and can improve patient compliance due to their non-invasive nature (Li & Chauhan, 2006; Mcnamara et al., 1999). Additionally, the drug release rate can be controlled by adjusting the drug loading and the properties of the contact lens material, such as the porosity and hydrophilicity. It has also been shown that contact lenses can be designed to release the drug in response to environmental stimuli, such as changes in pH or temperature, allowing for targeted drug delivery to specific regions of the eye (Filipe et al., 2016; Lanier et al., 2020; Musgrave & Fang, 2019; Rykowska et al., 2021; Zaki et al., 2019). Based on mathematical modelling, it has been estimated that drug-modified contact lenses can increase the bioavailability of active substances to about 50% (Gause et al., 2016).

However, there are still significant obstacles to employing contact lenses as drug reservoirs, such as guaranteeing drug stability over time, drug inertia to the lens material, and no effect on the lens's optical properties. Finally, the drug's dosage must ensure effectiveness and patient safety while causing no adverse effects.

For the reasons stated, increasing ophthalmic medicine availability requires a multidisciplinary approach considering the drug's physicochemical properties, the presence of ocular barriers (cornea, conjunctiva, and sclera) and the desired therapeutic impact.

Cyclosporine A is an immunosuppressant widely used in many areas of medicine, such as transplantology, ophthalmology, nephrology, dermatology, and rheumatology (Glowacka et al., 2020; Mutschler et al., 2016). CyA effectively treats dry eye syndrome, although the exact mechanism is not entirely understood (Periman et al., 2020). It is believed that CyA reduces inflammation and promotes tear production, alleviating DES symptoms (Stevenson et al., 2000).

The occurrence of dry eye syndrome is attributed to inflammation of the eye surface and lacrimal glands responsible for protecting and moisturising the eye surface. CyA works by suppressing the immune system and reducing the activity of T-cells involved in the inflammatory response. By reducing

inflammation, CyA can improve the function of the lacrimal glands and increase tear production. It can also promote the growth of goblet cells in the conjunctiva, producing mucus that helps lubricate the eyes. In this way, CyA can help to alleviate symptoms such as burning, itching, and dryness (Periman et al., 2020). The soaking technique (Xu et al., 2018), in which CLs are submerged in a drug solution for a predefined loading duration (Maulvi et al., 2016), is the first, cost-effective, and extensively utilised way of creating drug-modified contact lenses. The common disadvantage of this approach is the difficulty in maintaining an even distribution of the medicine in the lens material and guaranteeing a uniform drug dosage in the requisite period. The problem is crucial when delivering low-affinity to the aquatic environment drugs investigated.

One of the described methods to increase the efficiency of lens loading with hydrophobic drugs is combining Vitamin E (VE) as a diffusion barrier into the polymer network. The presence of lipophilic aggregates is supposed to slow down the elution of the drug and thus prolong the delivery of balanced drug doses (C. C. Peng et al., 2012). Authors have shown that VE extends the drug release time from silicone hydrogel (SiH) lenses from 14 to 20 days (20% of VE) (C.-C. Peng & Chauhan, 2011). What's essential, combining Vitamin E hasn't affected the transparency of the lenses and the amount of active substance released - the supply of the drug - from the modified polymer matrix was better balanced (Kim et al., 2010; C. C. Peng et al., 2010).

Research work related to the modification of contact lenses with cyclosporine A discussed in the literature included the application of the immunosuppressant in a variety of ways, such as soaking, as well as methods of integrating cyclosporine A molecules, among others:

- application of CyA supported by a diffusion barrier created by Vitamin E (Peng & Chauhan, 2011),
- drug application using polymeric nanoparticles (Polimeric Nanoparticles, PN) (Maulvi et al., 2017),
- application of the drug in micellar systems (Mun et al., 2019),
- supercritical fluid method (SCF) (Choi et al., 2019) and others.

An innovative and pioneering approach that has recently been used is the creation of microneedle contact lenses, which contain cyclosporine A. Similar to soft contact lenses, they allow for controlled release of the drug, but they stand out against them with a greater potential to penetrate barriers protecting the eyeball resulting from mechanical penetration into the layers of the tear film and cornea (Chaudhari et al., 2021; Datta et al., 2022; Mostafa et al., 2023).In the cited studies, dissolving microneedle CLs made of polyvinyl pyrrolidone (PVP) was prepared (Datta et al., 2022). Complete dissolution of the microneedles occurred one minute after applying the lenses to the porcine eyeball. The results of research on microneedle ocular patches (MOP) have shown that pioneering lenses with a modified structure for soft contact lenses with a smooth texture studied over the past decades can be a source of effective delivery of cyclosporine A.

This paper presents the results of the enrichment of drugstore contact lenses (Hilafilcon B) with CyA. The presented studies concerned the release of cyclosporine A into artificial lacrimal fluid (ALF). The presented research results are an introduction to orthtogonal array design (OAD), the aim of which is to optimize selected parameters affecting the efficiency of cyclosporine A application. These are: soaking time and temperature, addition of Vitamin E and concentrations of CyA solutions. The OAD procedure takes into account the factors listed above with 4-level variability. The results contained in this publication refer to the results related to the temperature of 25 degrees Celsius. The presented research results concern work with commercial lenses made of Hilafilcon B. Cyclosporine A was applied to the lenses without any preservatives or additives increasing its solubility in the solution. The results of a complete multivariate orthogonal analysis can be used in the future to determine the most optimal conditions for effective drug loading affecting the elution of cyclosporine A.

2. Materials and methods

2.1. CyA Solutions

The 0.5 mg/ml cyclosporine A solution was diluted with ALF buffer from the solution for infusion of Sandimmun (Novartis, 50 mg/ml). The procedure was validated using CyA buffered solutions containing 2.5, 5, 7.5, 10, and 15 μg/ml of CyA.

Cyclosporin A (Tokyo Chemical Industry, Japan) was utilised for cargo solutions. A stock CyA solution in water (20 μg/ml) was prepared. The concentrations of the loading solutions were 2.5, 10 and 15 μg/ml, respectively.

2.2. Contact lenses

Silicone hydrogel lenses (Soflens Daily Disposable, Hilafilcon B, water containing: 59%, Bausch&Lomb®) used for the research were purchased at a cosmetic drugstore (Rossmann, Poland). Purchased contact lenses were removed from the original packaging, pre-washed with deionised water, dried to constant weight using a Solid Phase Extraction (SPE) Vacuum Chamber (VISIPREP 57030-U) in air at 25 degrees Celsius and weighed.

2.3. Artificial lacrimal fluid (ALF)

Cyclosporine A loading and releasing buffered solution with pH = 7.9 ± 0.3 that mimicked the environment of human tears referred to as Artificial Lacrimal Fluid (ALF) were used. For ALF preparation, 2.18 g of $NaHCO_3$ (Merck, Poland), 6.78 g of NaCl (Merck, Poland), 1.38 g of KCl (Merck, Poland), and 0.06 g of anhydrous $CaCl_2$ were dissolved (Merck, Poland) in 1000 ml of deionised water (Rozier, 1989).

2.4. Measurement method

Quantitative and qualitative measurements were conducted using a diode array UV-VIS Spectrophotometer (HP 8453) with a mixing module and a thermostatic chamber.

2.5. Calibration curve

The buffered (ALF) solution of CyA is characterised by two absorption bands at 206 and 230 nm. Based on the electronic spectra of CyA in ALF solutions, two calibration curves were plotted for both bands. Experimental values of molar absorption coefficients equal $\varepsilon_{206} = 74\,000 \pm 3\,000 \frac{dm^3}{M \cdot cm}$ and $\varepsilon_{230} = 45\,200 \pm 500 \frac{dm^3}{M \cdot cm}$, as well as the detection and quantification limits, were determined.

The following formulas were used:

$$LOD = \frac{3.3 \times s}{b} \tag{1}$$

$$LOQ = 3 \times LOD \tag{2}$$

where b – is the slope of the straight line, and s – is the standard deviation of the intercept of the calibration curve. Calibration curve parameters are presented in Table 1.

Table 1. Calibration Curve Parameters for CyA solutions in ALF

Parameter	λ_{max} = 206 nm	λ_{max} = 230 nm
Slope	0.055 ± 0,002	0.038 ± 0.001
Intercept	0.06 ± 0,02	0.0021 ± 0.0001
Coefficient of determination (R^2)	0.9946	0.9974
Coefficient (R)	0.9982	0.9987
LOD [μg/ml]	0.9	5.7
LOQ [μg/ml]	2.7	7.1
Linear range [μg/ml]	2.5 ÷ 15	2.5 ÷ 15

2.6. Testing the stability of CyA solutions

Measurements of the stability of therapeutic cyclosporine solutions (10 μg/ml) at two temperatures (5 °C, room temperature 25 °C) with an inert gas atmosphere (Argon 5.0, Linde Gas, Poland) and in its absence were carried out for 170 hours.

2.7. The efficiency of the drug application process/ weight control

Contact lenses were dried and weighed before and after Vitamin E and CyA modification.

2.8. Modification of contact lenses with vitamin E

The VE loading procedure was carried out using disposable 5 ml syringes (BD, Poland) mounted in a solid phase microextraction chamber. The dried contact lens was placed in an open syringe barrel, and then 2 ml of VE ethanol solution (0, 2.5, 5, and 7.5 mg/ml) was added. The barrel was closed, and CL left for soaking. After 24 hours of loading at room temperature, alcohol residues were collected, placed into optical cuvettes, and UV-Vis spectra were recorded. Every test was run with a minimum of 3 CL samples. Following immersion, the lenses were dried under lower pressure to a constant weight and underwent a drug modification technique.

2.9. Loading of cyclosporine A

In the next step, VE-loaded contact lenses (VE-CLs) were exposed to Cyclosporine A solutions. The soaking procedure was conducted at an ambient temperature (25 °C). As before, the process was carried out in disposable syringes. VE-CLs were placed in 2 ml solutions with CyA concentrations varied from 2.5 to 20 μg/ml for a specified loading time. Subsequently, every post-loading solution was collected and stored in fridge conditions for spectrophotometric evaluation. Table 3 show sample designations, loading time and CyA and Vitamin E solutions concentrations.

Table 2. Designations of samples and the corresponding concentrations of VE and CyA loading solutions

# Sample	CyA [μg/ml]	Added VE [μl]	VE [mg/ml] / [%]
40 41 42	10	0	0.0/0.0
43 44 45	15	5	2.5/0.2
46 47 48	20	10	5.0/0.5
37 38 39	2,5	15	7.5/0.7

Table 3. Sample numbering and corresponding CyA concentrations and loading times

# Sample	Cyclosporine A [μg/ml]	Loading time [h]
37 38 39	2.5	144
40 41 42	10	72
43 44 45	15	48
46 47 48	20	24

2.10. CyA release

The release of cyclosporine A was carried out under the specified time regime presented in Table 4. Loaded with active substance VE-CLs, placed in a disposable syringe, were treated with 3 ml of artificial tear fluid (ALF), and left soaked for a specified time (Table 4.). The solution was drained, and the next portion of ALF was introduced into the syringe. The volume of added ALF buffer corresponds to the daily volume of tears produced by a healthy human eye (Xu et al., 2018). Measurements were completed after five hours, which is related to the end of elution of cyclosporine A from the polymer matrix of contact lenses.

Table 4. Cyclosporine A release

Loading CyA [μg/ml]	**Drug release time [min]**										
2.5 10 15 20	5	10	15	15	15	30	30	30	30	60	60

2.11. The control probes

Three control contact lenses were immersed in the ALF solution for each specified soaking time. All collected post-extraction solutions were then tested using UV-VIS spectrophotometry.

2.12. Statistical analysis

Each test was performed in triplicate experiments. Data were expressed as mean ± SD. The results were analysed using MS Excell (MS Office 2010).

3. Results and discussion

In aqueous solutions, cyclosporine can be unstable and prone to degradation. Factors that can affect the stability of cyclosporine solutions include pH, temperature, and exposure to light and air. Before the soaking technique began, the CyA solution's stability at the therapeutic concentration (10 μg/ml) was examined. For this purpose, two solutions of equal concentration were made, whereby one of them was stabilised by an inert gas to minimise the exposure of the solution to atmospheric oxygen (Ar 5.0).

The stability of CyA in buffer solutions was evaluated at 5 °C and 25 °C. No qualitative differences were observed in the absorption spectra profiles recorded during the 170-hour measurement period. The absorbance values for the initial solutions differ slightly (by less than 0.05). This is due to the preparation of independent solutions for measurements. However, in the context of experimental studies, this is a minor difference that does not affect the determination of the studied cyclosporine A decrease profiles.

At a temperature of 5 °C, both solutions with and without argon protective atmosphere were characterised by high and comparable stability (Fig. 1). The percentage loss of CyA after 7- day monitoring did not exceed 13.3% and 8.9%, respectively. The stability of CyA at 5 °C is shown in Fig. 1. The decrease in absorbance in λ_{max} = 230 nm for seven days of storage did not exceed 0.1 AU.

The stability results of CyA in ALF obtained at 25 °C differed from those at 5 °C. It is difficult to determine the reason for the faster decrease in absorbance in the case of an argon-protected solution at 25 degrees Celsius. However, the loss of intensity of the absorption band in the analytical wavelength was in both cases greater than for the cooled solutions, indicating slow degradation processes occurring. The decrease in absorbance in time at room temperature is presented in Fig. 2.

Based on the above, stabilisation of the solutions with inert gas was optional since the maximum planned loading time was three days. It was predicted that the loss of CyA during this period would be at most 1%.

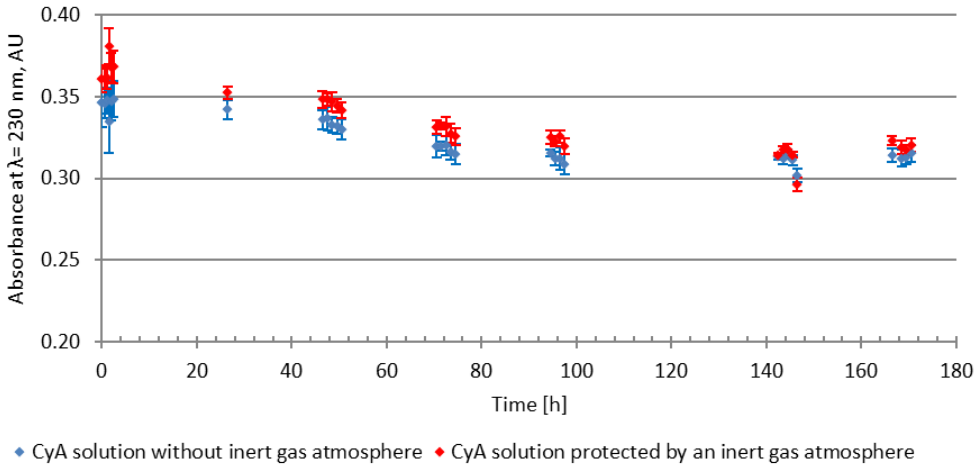

Fig. 1. The absorbance of the CyA in ALF solution. Temperature 5 °C, λ_{max} = 230 nm

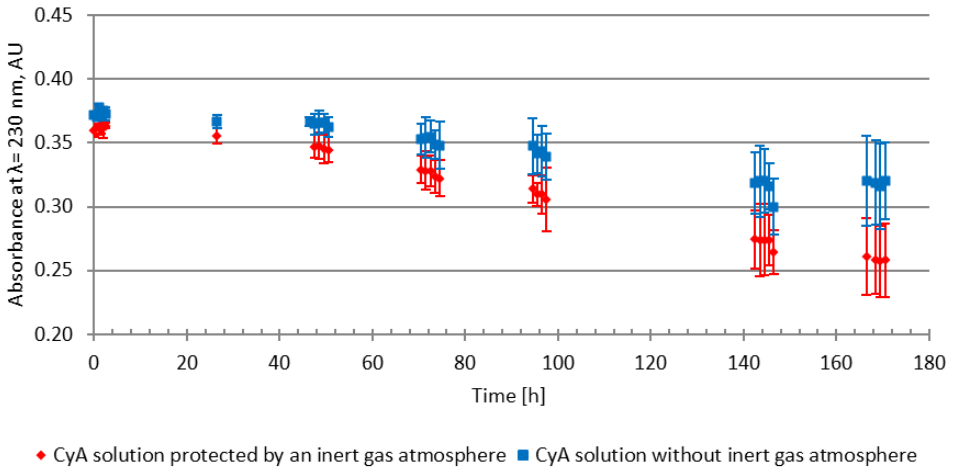

Fig. 2. The absorbance of CyA in ALF solution. Temperature 25 °C, λ_{max} = 230 nm

3.1. Soaking procedure

3.1.1. Weight control of the loading process efficiency

The control of the CLs' weight based on the initial and final mass of the modified lenses was proposed to monitor the loading efficiency.

Before the drug soaking procedure, all lenses were weight. Re-weighting was also conducted after the process with appropriate precautions to avoid contamination or damage to the lenses (Table 5).

The weighing results after loading Vitamin E indicate a high repeatability of the loading process. The difference in lens weights before and after loading was equal to 0.8 to 0.1 mg.

The appearance of the contact lenses after the application of Vitamin E in relation to the control contact lenses did not change. Illustrative photos of the lenses are provided in Fig. 3.

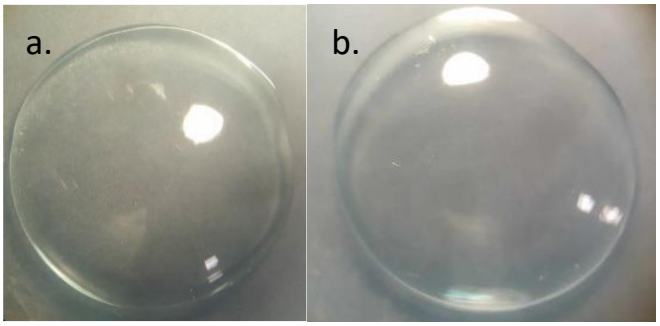

Fig. 3. Contact lens before (a.) and after (b.) Vitamin E modification

However, it should be noted that the assessment of the effectiveness of the CyA application based on the comparison of the lenses' pre-and off-loading weight was impossible. In this case, a decrease in the mass of the lenses was noted,. The observed mass change can be attributed to the water loss from the polymer matrix during the lens drying process.

Therefore, controlling the loading's effectiveness based on the lens mass was considered to be inappropriate.

Table 5. Weight of contact lenses before and after polymer matrices modification

# CL*	CLs weight		
	after removal from the original packaging [mg]	after the VE application [mg]	after the soaking process [mg]
37	17.6	18.2	17.6
38	17.5	18.2	17.5
39	17.7	18.3	17.7
40	17.7	18.3	17.7
41	17.5	18.2	17.9
42	17.3	18.2	17.8
43	17.4	18.2	17.8
44	17.3	18.2	17.3
45	17.6	18.2	17.3
46	17.4	18.2	17.6
47	17.6	18.3	17.6
48	17.7	18.3	17.7

* lens number corresponds to sample number

3.1.2. Spectrophotometric control of drug loading efficiency

The efficiency of the cyclosporine A loading process was monitored spectrophotometrically based on the relationship:

$$W\ \% = \frac{A_0 - A_K}{A_0} \times 100 \tag{3}$$

where A_0 – absorbance before the solutions are deposited with CyA, A_K – absorbance of the post-loading solution. A comparison of the absorbance of the cargo and post-loading solution indicated a loss of CyA, which led to the conclusion that the loading operation was successful. In general, the higher the concentration of the cargo solution, the higher the efficiency of the process was stated.

Thus, the highest deposition efficiency was found for lenses immersed in drug-loading solutions with a CyA concentration of 20 μg/ml. The mean loss of CyA from the cargo solution was approximately 48 %.

In addition to the CyA concentration, the loading time was the second factor affecting the deposition process's efficiency. The highest loading capacity was obtained for 24 h of soaking. Further time extension did not increase the amount of CyA introduced into CL. Moreover, even a decrease in yield (38 %) for 48-hour and about 13 % for 72-hour soaking was observed.

Based on the finding, the following optimal conditions for Hilafilcon B modification with CyA: 24-hour loading process in 20 μg/mg of cargo solution were established.

3.2. Drug release - pharmacokinetics of CyA release

The released amounts of cyclosporine A from individual contact lenses (three lenses correspond to 3 repetitions of one row of the OAD table) associated with specific parameter values are presented in Table 6.

Table 6. Amount of cyclosporine A (μg/ml) released from CLs in dependence on the loading and elution time

Loading time	24 h		48 h		72 h	
CyA loading solution	20 μg/ml		15 μg/ml		10 μg/ml	
	CyA concentration in post-released solution					
Release time [min.]	**Sample number**	**CyA [μg/ml]**	**Sample number**	**CyA [μg/ml]**	**Sample number**	**CyA [μg/ml]**
5	46	2.9	43	4.8	40	1.5
	47	3.6	44	2.2	41	1.9
	48	3.7	45	2.9	42	1.6
15	46	2.1	43	1.8	40	0.9
	47	2.0	44	2.4	41	1.8
	48	2.3	45	2.0	42	< LOD
30	46	2.0	43	1.4	40	< LOD
	47	2.3	44	1.9	41	1.1
	48	2.5	45	1.0	42	0.9
45	46	1.8	43	0.9	40	0.9
	47	2.3	44	0.9	41	1.2
	48	1.7	45	1.1	42	< LOD
60	46	1.3	43	0.9	40	< LOD
	47	1.7	44	< LOD	41	< LOD
	48	2.4	45	2.0	42	1.4
90	46	1.3	43	1.1	40	< LOD
	47	2.2	44	0.9	41	1.1
	48	2.2	45	< LOD	42	0.8
120	46	1.4	43	1.1	40	0.9
	47	1.4	44	1.6	41	0.9
	48	1.5	45	1.7	42	1.1
150	46	1.8	43	1.7	40	< LOD
	47	1.2	44	1.1	41	< LOD
	48	1.6	45	1.1	42	1.4
180	46	< LOD	43	2.0	40	< LOD
	47	1.3	44	1.3	41	< LOD
	48	1.8	45	1.5	42	1.1
240	46	< LOD	43	1.9	40	< LOD
	47	1.0	44	1.0	41	< LOD
	48	1.1	45	2.0	42	< LOD
300	46	< LOD	43	2.0	40	< LOD
	47	1.6	44	1.3	41	< LOD
	48	1.6	45	2.8	42	< LOD

3.3. Effect of loading time on CyA pharmacokinetics

Various time regimes ranging from 24 to 144 hours were used to determine the optimal loading time resulting in a high CyA loading weight and a balanced drug release profile. Figs. 4, 6 and 7 show the release profile of CyA from lenses modified at different loading times. Each graph illustrates CyA's pharmacokinetics based on triplicate experiments for the specified loading time.

3.3.1. 24 hours of loading

For lenses loaded for 24 hours, the total release time was fixed at 5 hours. After this time, the amount of CyA in the post-extraction solution was below the detection limit. The CyA concentration in the first 5

minutes of release was the highest and equal ca. 3 µg/ml. Subsequent doses found in ALF solutions were similar and remained at 1.5 □g/ml. The uniform quantitative transition of the drug to the ALF solution, obtained for indicated parameters (Fig. 4.), is satisfactory and meets the criteria for balanced drug release.

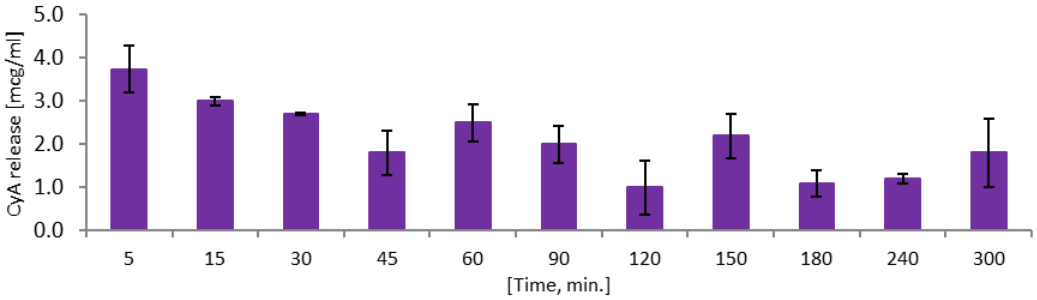

Fig. 4. Amount of CyA (µg/ml) released from CLs. Loading time: 24 hours. CyA cargo solution: 20 µg/ml. Vitamin E: 5 mg/ml

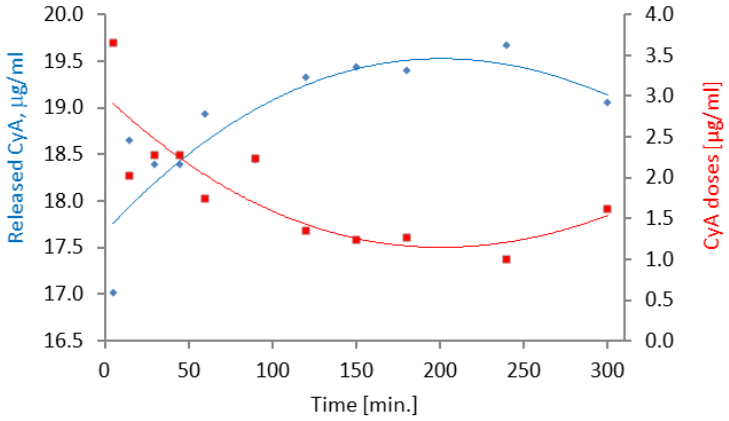

Fig. 5. The exemplary CyA release profile. CyA cargo solution: 20 µg/ml. Loading time: 24 h, VE: 5 mg/ml

3.3.2. 48 hours of loading

Fig. 6. shows the drug release curve plotted for lenses soaked in CyA solution (15 □g/ml) for 48 hours. The amount of CyA in post-release ALF was lower than for the 20 µg/ml CyA solution, which is related to the lower concentration of the loading solution. The drug release profile obtained for this set of parameters does not indicate a rapid drug burst in the first 5 minutes. The amount of drug leached from the lens remained constant for 150 minutes of follow-up. After this time, the concentration of CyA in ALF was below the detection limit.

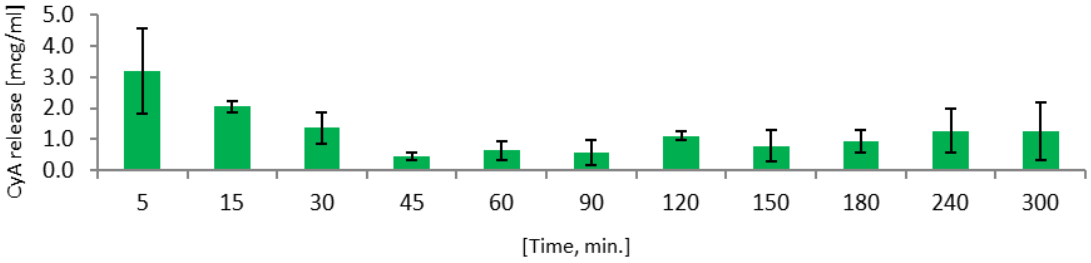

Fig. 6. Amount of Cyclosporine A (µg/ml) released from CLs. Loading time: 48 hours. CyA cargo solution: 15 µg/ml. Vitamin E: 2.5 mg/ ml

3.3.3. 72 hours of loading

The pharmacokinetics of CyA for contact lenses after a 72-hour soaking (CyA = 10 µg/ml) is depicted in Fig. 7. Only in the first 45 minutes was the presence of CyA in the extraction solutions at the ca. 1 to

2 μg/ml level observed. At subsequent time intervals, the amount of CyA was, in most cases, below the detection limit. Nevertheless, it is essential to note that the situation discussed in this context is exceptional due to the low concentration of the loading solution and the absence of Vitamin E, which contributed to the unfavourable release pattern of CyA in this instance.

Error bars in each case were determined from three measurement results. The bars and their values presented in Fig. 6. (for some measurements with large values, e.g. 15, 60 and 150 minutes) result from the varying amounts of cyclosporin A that were released during the measurements. They may be the result of not modifying the contact lenses with vitamin E prior to application of the active substance. The diffusion barrier contributes to balancing the supply of the drug, while its absence may be the cause of uncontrolled fluctuations in the migration of drug molecules from the polymer matrix to the artificial lacrminal fluid (ALF).

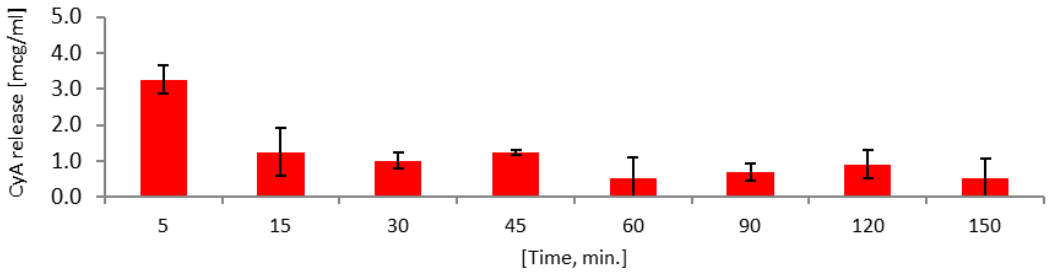

Fig. 7. Amount of cyclosporine A (μg/ml) released from CLs. Loading time 72-hour. CyA loading solution 10 μg/ml. Vitamin E: 0 mg/ ml

3.3.4. 144 hours of loading

Cyclosporin A concentrations released from lenses loaded for 144 hours in 2.5 μg/mL CyA solution (lowest of all concentrations) were below the limit of quantification. Therefore, the release profile of the pharmaceutical could not be determined in this case.

3.4. Effect of vitamin E on the cyclosporin A release profile

The effect of Vitamin E built in the lens matrix on the drug loading and release profile was studied by designing procedures carried out on VE pre-modified lenses. The purpose of the modification was to create a diffusion barrier, slowing down the hydrophobic drug's migration along the polymer network's transport channels. To achieve the goal, different amounts of antioxidant was placed in the matrix during the soaking process (Table 2). Based on experiments, it was found that introducing the drug into not pre-modified lenses was less effective, and drug release was much faster than in lenses containing VE. CLs with no diffusion barrier (VE = 0 mg/ml) were characterised by relatively short elution time (2.5 h, Fig. 7). The opposite effect was obtained for matrices with enclosed VE where prolonged drug, up to 5-hour supply, took place (Fig. 4, Fig. 7). In addition, the cyclosporin release profile from the pre-modified polymer network was approximately even and, therefore, more satisfying.

4. Conclusions

In this work, cyclosporin A was loaded on drugstore-available soft contact lenses. Prior to the procedure, the stability of CyA was evaluated across a broad range of concentrations (which encompassed therapeutic dosages) and temperatures (5 and 25 °C) in an artificial lacrimal fluid that imitates the properties of tears. It was also ascertained that there was no necessity to safeguard CyA solutions against air exposure.

The findings showed that the 24-hour soaking process is sufficient for the successful deposition of CyA in the Hilafilcon B polymer material, and prolonging the exposure time does not enhance the loading effectiveness.

The release procedure was carried out to ALF in a human-specific secreted amount. The most satisfactory drug release profile was achieved when lenses were pre-modified with Vitamin A, and the concentration of the CyA loading solution was twice as high as the therapeutic dose of the drug

(20 μg/ml). Lack of VE results in lower deposition of the drug, which results in its low supply in the release process. In both instances, the release pattern resembled the secondary profile, with the drug being administered uniformly in divided doses (approximately 1.5 μg/ml) for durations ranging from 5 minutes to 5 hours. This was preceded by a drug burst that was one and a half times larger than subsequent doses.

The purpose of drug delivery systems (DDS) such as presented drug-modified contact lenses is that the rate of the drug release does not decrease over time. This is related to the use of Vitamin E, which prolongs the elution of the drug.

Thus, we suggest that the process of depositing Vitamin E should be incorporated into the Hilafilcon B CyA modification protocol. This is not only because it enhances the efficacy of drug loading and delivery but also because of its safeguarding (UV-Vis) and antioxidant characteristics.

Employing contact lenses as drug delivery systems (DDS) presents an opportunity to augment the bioavailability of the active ingredient while also mitigating the possible side effects of drugs introduced into the body. By properly selecting loading parameters, such as the type of polymer matrix, soaking duration, temperature, the addition of vitamin E to the polymer matrix, and the concentration of the active ingredient in the loading solution, a safe and convenient device can be created as a reservoir for ophthalmic drugs with the desired release profile, which meets therapeutic requirements and patient expectations.

The orthogonal matrix approach was employed to develop therapeutic contact lenses using pre-existing Hilafilcon B polymer lenses to determine the optimal parameters. This study is a component of a multivariate orthogonal analysis. The data presented here enable us to identify the most critical parameters that affect the effectiveness of the chosen polymer material's modification process. These parameters comprise of the loading time, the concentration of the CyA loading solution, and the requirement of loading assistance using Vitamin E. The qualitative assessment of these parameters will be feasible upon completion of the ongoing research.

In the future, studies on changes in optical and physical properties of contact lenses after application of active substances are planned. After passing preliminary laboratory tests and safety tests, it will be possible to attempt in vitro tests.

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