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Intra-ocular lens optical changes resulting from the loading of dexamethasone

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Abstract: To study the optical changes on hydrogel-silicone intraocular lenses (IOLs) resulting from loading them with dexamethasone. We used prototype hydrogel(pHEMA)-silicone IOLs and loaded the matrices with an anti-inflammatory drug (dexamethasone). The optical properties we analyzed experimentally were a) modulation transfer function (MTF); b) spectral transmission; c) diopter power. These determinations were performed on drug-loaded IOLs, IOLs that had released the drug, and IOLs that had not been drug-loaded. Loading a hydrogel-silicone IOL with dexamethasone results in impairment of its optical qualities, in particular its MTF and spectral transmission, but not dioptric power. However, once the drug has been released, it almost recovers its initial optical properties.

OCIS codes: (170.0170) Medical optics and biotechnology; (330.4460) Ophthalmic optics and devices; (170.4470) Ophthalmology.

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1. Introduction

Cataract surgery is one of the most common operations carried out on the elderly population in developed countries. At present, due to less invasive techniques that reduce surgical risks [1,2], the criteria for surgery indications have been extended, which has made this type of surgery even more usual.

In general, cataract surgery is considered safe and effective, but as in other operations, there are certain effects associated with surgery that include, among others: pain, inflammation, infection, and possible intraocular hemorrhage [3]. Daily administration of anti-inflammatory and anti-infectious agents is often used to prevent or decrease these effects for at least three to four weeks after surgery [4]. Nonetheless, the bioavailability of these drugs, which are usually administered topically, is limited due to the rapid and extensive loss of their properties from the pre-corneal area caused by tear drainage and tear renewal. Moreover, the cornea is a highly effective barrier and it considerably hinders the penetration of the drug administered in this way. Consequently, after instillation of an ophthalmic drop, less than 5% of the drug penetrates the cornea and reaches the intraocular tissue since most of it is absorbed systematically through the conjunctiva and nasolacrimal duct, which in turn can give rise to serious secondary effects. In addition, most people who suffer from cataracts, especially elderly people or those who also suffer from arthritis, find it very difficult to administer eye drops correctly, which makes the effectiveness of the treatment even lower. As a result of all of these factors, many patients do not follow the established therapeutic treatment properly or they discontinue the treatment which considerably increases the risk of ocular complications.

One way of solving this problem is based on developing a new generation of intraocular lenses (IOL) loaded with ophthalmic drugs that release the postoperative treatment into the eye [5–10] in a sustained and controlled way. This could eliminate the need for topical treatment and the risks associated with inadequate treatment compliance; it also increases the effectiveness of the medication as there is a constant and controlled intraocular release of the drugs.

However, a point that has not been taken into account is that the drug-loaded IOL, whether eluting in the mass or on the surface, could modify the optical properties of the lens. The introduction of any type of aberration brought about by modifying its surface could change its capacity to form sharp images. Its spectral transmission could also be modified, causing a

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change in the quantity of total light that reaches the retina and in its spectral composition. Drug-loading a lens can be beneficial, but it should not be detrimental to the main function of a lens, which is to form clear images on the retina.

With a view to analyzing whether drug-loaded IOLs undergo changes in their optical properties, we determined experimentally the optical quality of anti-inflammatory (dexamethasone) loaded lenses by means of measuring the modulation transfer function (MTF) *in vitro*. This measurement has become the internationally accepted standard method for evaluating the performance of IOL image quality [11–13].

Subsequently, after the drug had been released, we again determined its MTF and compared the results. Finally, in order to evaluate the quality level in both cases, i.e., the drug-loaded IOLs and those that had released the drug, we compared their MTFs with the corresponding original IOLs, i.e., the non-treated IOLs. All these measurements were performed on 3 mm pupils to simulate diurnal vision.

Furthermore, we determined the spectral transmission in each of the cases (the drug-loaded IOL, the drug-released IOL, and the non-treated IOL) in order to establish whether there were any variations in intensity or spectral composition of the radiation that reaches the retina. Finally, we also analyzed if the power of the IOL underwent any change when it was drug-loaded.

2. Methods

2.1 Drug-loaded IOLs

Non-commercial spherical monofocal intraocular lenses of 21 diopters and 0.24 mm thickness were used for this study. These prototype IOLs were supplied by AJL Ophthalmic S.A. (Vitoria, Spain). The IOLs were made of a hydrogel based on poly(2-hydroxyethylmethacrylate) (pHEMA) and incorporated dexamethasone (DXM), an anti-inflammatory agent, in the matrix. For preparation of the drug-loaded polymer matrix, an appropriate DXM dose was dissolved in a 2-hydroxyethyl methacrylate (HEMA, optical grade) solution under sonication and mild heat (0.005%, corresponding to drug solubility). Subsequently, ethyleneglycol dimethacrylate was incorporated in this solution as the cross-linking agent (100 mM), and the mixture was degassed before the addition of 2,20-azobis(2-methylpropionitrile) (AIBN) as the polymerization initiator. Subsequently, the mixture was injected into a rectangular mold, and thermo-polymerization took place at 60 °C for 1 h, resulting in a solid polymer plate with DXM homogeneously dispersed within the matrix [14]. The lenses were machined from this polymer base. The migration of the drug to the medium that surrounds it is produced by diffusion through the polymer matrix. The process depends on the initial DXM concentration within the IOL, and should extend till complete discharge of the drug.

DXM release in PBS by diffusion through the polymer matrix was monitored by UPLC-UV until complete discharge. For this purpose, a DXM-doped IOL (~20 mg) was introduced in a sterilized dialysis bag (32x20 mm, 12.4 kDa) with 2 mL of PBS. This bag was placed in a 60 mL polypropylene container with 50 mL of PBS and heated in a water bath at 37 °C while shaking. Dialysis medium was completely replaced by fresh PBS at corresponding times for 70 days. The experiment was carried out in triplicate. Afterwards, 10 mL of every dialysis sample were freeze-dried, reconstituted with ethanol and analyzed by reverse-phase high performance liquid chromatography (RP-HPLC) analysis in an Agilent 1220 Infinity LC coupled to a UV detector (λ = 240 nm) with an analytical column (Mediterranean Sea C18, 3µm, 100 x 21 mm). The products were eluted utilizing a constant solvent mixture (CH_3CN/H_2O-TFA pH 4.5 50:50 v/v) at 0.8 mL/min. Triplicate analyses were run for every sample.

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2.2 Modulation transfer function measurements

The MTF measurements have been described by Artigas et al. [11]. Basically, the MTF was calculated from the cross line-spread function recorded with the OPAL Vector System (Image Science Ltd. Oxford, UK) by using fast Fourier transform techniques. The artificial eye model used simulated *in vivo* conditions of the anterior chamber, including an artificial cornea and a wet cell containing physiological solution where the IOL was positioned, following the setup required by EN/ISO 11979-2 [15]. The light source was confined to 546 nm [15]. The detector type used the Reticon K series silicone linear photo diode array 12.8 mm long with 512 pixels. The best focus position was determined by measuring the variation of the MTF with focus at a spatial frequency of 20 c/mm. The MTF values were formed with an average of 16 array scans. The MTF measurements conformed to the requirements of the International Organization for Standardization [16,17]. Three prototype lenses were used to carry out the measurements in this study. Figure 1 shows three cross-line spread functions (LSF) that correspond to a dexamethasone-loaded IOL, the same drug-released IOL, and finally the other original IOL, i.e., non-treated and which is used as a control.

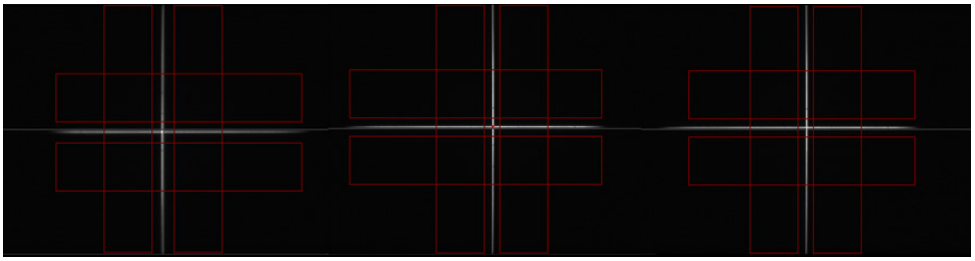

Fig. 1. Cross Line Spread Function (LSF) of a dexamethasone-loaded IOL (left), LSF of a dexamethasone-loaded IOL that had subsequently released this drug (center), compared with the LSF of a similar, but non-treated IOL (right).

2.3 Spectral transmission measurements

The transmission curves were obtained by using a Perkin-Elmer Lambda 35 UV/VIS spectrometer. This apparatus can measure the spectrum from 200 nm onward, which means that spectral transmissions in UVA, UVB, and part of ultraviolet C (UVC) are accurately determined (precision is up to 1 nm). The integrating sphere is used, which means that all radiation that passes through the IOL, both direct and scattered, is collected by the detector. The air was taken as a reference to measure transmittance [18].

2.4 Dioptric power lens measurements

To measure the IOL dioptric power, we used a focimeter with a negative lens and saline solution (0.9% NaCl) [19]. The focimeter is placed in a vertical position with a negative lens (−10D) with its concave surface facing upward and the saline solution inside the lens to make a "wet cell" where the IOL is placed. With this configuration (with no IOL test) if we focus the target on the focimeter, the power reading is −4.50 D instead of zero. The measurements will start centering the target with the divergent lens plus saline solution, then the IOL is introduced and the target is re-centered again by moving the IOL. The real IOL power is the result of subtracting 4.50 D from the focimeter reading.

3. Results

The ISO standards specify that MTF measurements should be performed on 3 mm pupils, which is the average of a human pupil in diurnal vision.

Figure 2 shows the MTFs of the IOLs loaded with dexamethasone together with the MTFs of the same IOLs but which had released the drug, with reference to a perfect optical system, i.e., exclusively limited by diffraction. Each of these curves is the mean of three IOLs of the

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same power and with an equal drug load. Moreover, Fig. 2 shows the MTFs of the drug-released IOLs, compared with the MTF corresponding to a similar, non-treated IOL for a 3 mm pupil. This comparison is for ascertaining whether the drug release makes the IOL reach the optical quality of the original IOL, i.e., non-treated.

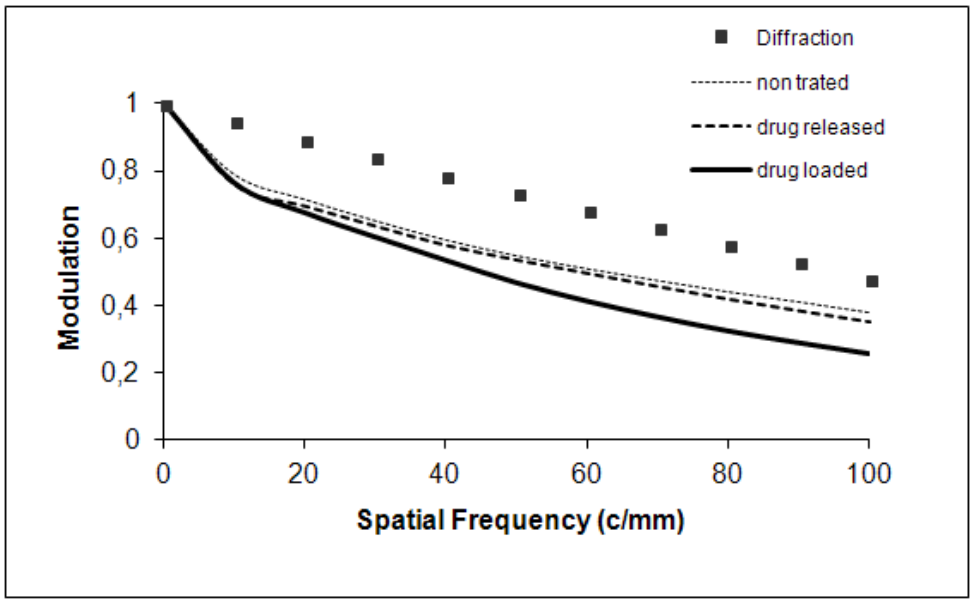

Fig. 2. MTF of a dexamethasone-loaded IOL, and MTF of a dexamethasone-loaded IOL that had subsequently released this drug, for a 3 mm pupil compared with the MTF of a similar, but non-treated IOL. Mean of three lenses.

The ISO standards specify that the MTF minimum value for an IOL to have good optical quality is 0.43 for the spatial frequency of 100 c/mm and a 3 mm pupil. However, Felipe et al. [22] and Alarcon et al. [23] emphasize how non-predictive this ISO standard is since it only takes one spatial frequency (100 c/mm) as a parameter. This is why we also determined the Average Modulation (AM) [11,20,21] which is the mean value of the MTF calculated from 0 to 100 c/mm, and the Strehl Ratio which is a parameter used classically for quantifying aberration effects

Figure 3 shows the mean spectral transmissions of the original non-treated, the drug-loaded, and the drug-released IOLs.

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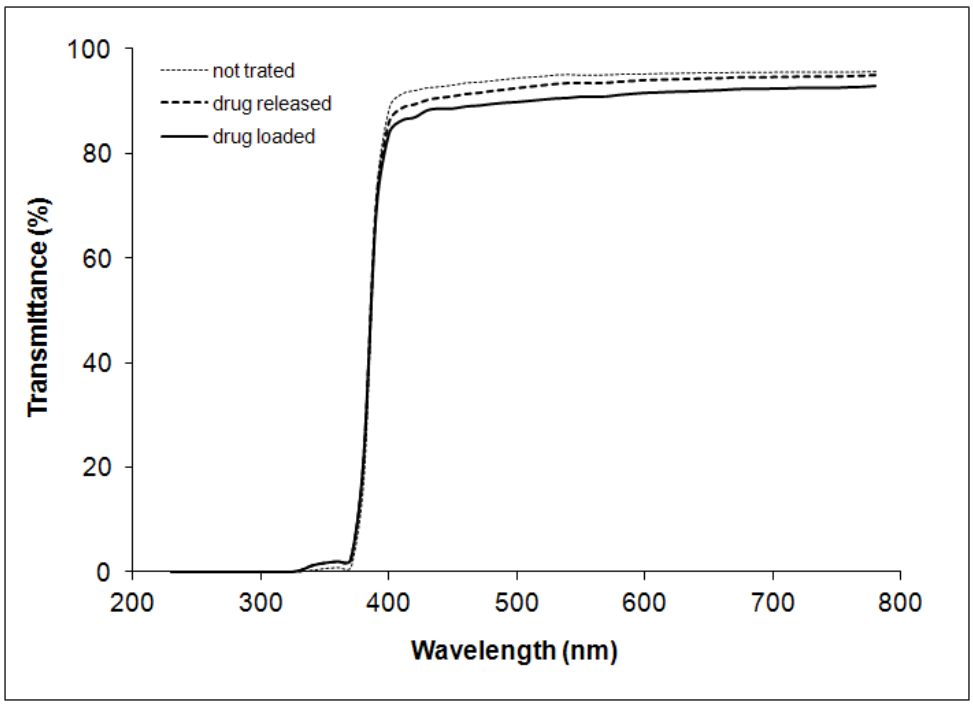

Fig. 3. Spectral transmission of drug-loaded, dexamethasone-released, and non-treated IOLs. Mean of three lenses.

4. Discussion

This study, as its title indicates, focuses exclusively on the optical properties of the lens, since our aim was to test whether loading an IOL with a type of drug (DXM) could impair the main function of a lens, which is to form images.

The MTFs corresponding to the dexamethasone-loaded IOLs and 3 mm pupils (Fig. 2) are quite distant from those of a perfect optical system, i.e., only limited by diffraction, hence their quality is poor.

If we now analyze these same IOLs but after they have released their dexamethasone load, we obtain the MTFs also shown in Fig. 2. In principle, the curves can be seen to draw nearer to the system limited by diffraction, i.e., their optical quality improves. This may mean that the dexamethasone impregnation does indeed affect the optical quality of the IOL.

If we compare the MTFs corresponding to the drug-released IOLs with similar IOLs of the same power and thickness but which have not been drug-loaded (Fig. 2), we can see that the MTF of the drug-released IOLs is practically the same as that of a non-treated IOL.

In order to evaluate these variations numerically, Table 1 shows the MTF values for the spatial frequency of 100 c/mm (ISO standard [15]) and also calculates the Strehl Ratio (SR) and the Average Modulation (AM) for 3 mm pupils and for the drug-loaded IOL, the drug-released IOL, and the non-treated IOL. The dioptric powers measured for the different IOLs we analyzed are also included in Table 1.

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Table 1. MTF value for drug-loaded, drug-released, and non-treated IOLs for a spatial frequency of 100 c/mm (MTF_100). Strehl Ratio (SR) value. Average Modulation (AM) value. Standard Deviation (SD). All the values for 3 mm pupils. IOL power in diopters (IOL Power).

	Drug-loaded	***Drug-released***	***Non-treated***
	3 mm (SD)	3 mm (SD)	3 mm (SD)
MTF_100	**0.259**(0.027)	**0.353**(0.011)	**0.382**(0.050)
SR	**0.693**(0.043)	**0.820**(0.014)	**0.864**(0.087)
AM	**0.508**(0.023)	**0.562**(0.023)	**0.581**(0.052)
IOL Power	**20.68**(0.14)	**20.75**(0.00)	**20.68**(0.14)

In order to know if these variations in the MTF of the IOL can affect a patient's vision, Felipe et al. [22] demonstrated that for multifocal IOLs the eye's tolerance to MTF decay is approximately 15% of the AM value and it would need to reach a 25% difference in the MTF for it to affect the visual acuity of the patient significantly. Although our case deals with monofocal IOLs, these data can be taken as a reference to ascertain the influence that variations in the MTF can bear on the real vision of the patient. For a 3 mm pupil and a spatial frequency of 100 c/mm the ISO standard [15] gives, as mentioned above, a minimum value of 0.43 for the MTF of a monofocal IOL. The MTF mean value of the IOLs used in our study in these conditions is, however, 0.382, i.e., only 11% lower than the minimum value required, thus its optical quality remains good [21]. Moreover, as we stated above, measuring only one spatial frequency is not very significant [23,23] and in any case, our objective was to compare the optical quality of similar IOLs, some loaded with dexamethasone, others that had released the drug, and finally others that were non-treated which were used as controls.

Then, when the IOL was loaded with dexamethasone its mean MTF was 0.259, i.e., 31% lower than the non-treated IOL, therefore the visual acuity of the patient may be compromised. When this IOL releases all the drug, its MTF value for 100 c/mm increases up to 0.353, i.e., only 8% less than for a non-treated IOL, which means that its optical quality reaches a similar level to that of the original IOL. The SR and AM values follow a similar pattern, as the Strehl Ratio gives a 20% lower MTF value for the loaded IOL than for the non-treated IOL, but this MTF value increases when the drug is released up to a 5% lower value than the original IOL. With regard to the Average Modulation, these MTF values are 13% lower for the doped IOL than for the original and this value increases when the drug is released up to only 3% less than the original IOL.

It seems logical to think that scattering causes the decrease in the MTF, which increases when the drug is released. On the other hand, since the dexamethasone incorporated in the polymer matrix is of a molecular nature and it is two or three orders lower than the wavelength used for measuring the MTF, λ = 546 nm (ISO standard), the scattering that is brought about cannot be excessive. This agrees with the experimental fact that the decrease in the MTF when the IOL is loaded, it is not very great. However, this hypothesis should be confirmed in future studies.

The spectral transmission is hardly affected by the action of the drug load (Fig. 3). This Figure shows that the IOL incorporates a perfect cut-off filter [18], which totally filters out ultraviolet radiation, only a slight uniform decrease (approximately 3%) in the transmission in the visible spectrum when the IOL is drug-loaded can be observed. When the IOL releases the drug this small decrease is practically recovered. The difference between an unloaded IOL and a non-treated IOL is approximately 1%, which enters in the measurement error of the spectrophotometer.

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In our study and as can be observed in Table 1, the dioptric powers of the IOLs are not affected by drug-loading as the measurements in drug-loaded, drug-released, and non-treated IOLs are always within the tolerated margin of error (± 0.4 D) [15] for IOLs.

To sum up, when the matrix of a hydrophobic silicone-hydrogel IOL is loaded with dexamethasone its optical quality is affected because its MTF values for a 3 mm pupil (photopic vision) drop significantly. However, this optical quality is practically recovered when it releases the drug and almost reaches the values of that of a non-treated IOL. This would mean that the patient could have a lower visual acuity that would be restored in days as soon as the drug was released. The spectral transmission is hardly affected by dexamethasone loading, just a slight, uniform decrease in the visible spectrum is observed, which is recovered when the drug is released. Likewise, the power of the IOL is not affected by the drug-loading and its value always remains within the tolerable margin of error.

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Disclosure

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