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Improving sustained drug delivery from ophthalmic lens materials through the control of temperature and time of loading

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ABSTRACT

Although the possibility of using drug-loaded ophthalmic lens to promote sustained drug release has been thoroughly pursued, there are still problems to be solved associated to the different alternatives. In this work, we went back to the traditional method of drug loading by soaking in the drug solution and tried to optimize the release profiles by changing the temperature and the time of loading. Two materials commercially available under the names of CI26Y and Definitive 50 were chosen. CI26Y is used for intraocular lenses (IOLs) and Definitive 50 for soft contact lenses (SCLs). Three drugs were tested: an antibiotic, moxifloxacin, and two anti-inflammatories, diclofenac and ketorolac. Sustained drug release from CI26Y disks for, at least 15 days, was obtained for moxifloxacin and diclofenac increasing the loading temperature up to 60 °C or extending the loading time till two months. The sustained release of ketorolac was limited to about 8 days. In contrast, drug release from Definitive 50 disks could not be improved by changing the loading conditions. An attempt to interpret the impact of the loading conditions on the drug release behavior was done using solid-state NMR and differential scanning calorimetry. These studies suggested the establishment of reversible, endothermic interactions between CI26Y and the drugs, moxifloxacin and diclofenac. The loading temperature had a slight effect on the mechanical and optical properties of drug loaded CI26Y samples, which still kept adequate properties to be used as IOL materials. The *in vivo* efficacy of CI26Y samples, drug loaded at 60 °C for two weeks, was predicted using a simplified mathematical model to estimate the drug concentration in the aqueous humor. The estimated concentrations were found to comply with the therapeutic needs, at least, for moxifloxacin and diclofenac.

1. Introduction

In the last decades, many researchers have investigated the possibility of treating eye diseases through extended drug release provided by therapeutic ophthalmic lenses instead of the inefficient eye drop administration. Delivering the drugs gradually and for an adequate period of time is important in the treatment of many ocular disorders, but it assumes special relevance for elderly patients with problems of memory loss and/or physical disabilities, which may reduce significantly the patient compliance. For example, glaucoma, one of the leading causes of blindness in old age patients, demands the frequent and regular instillation of eye drops, which is difficult to achieve among these patients. Another clinical situation where the substitution of the topical administration of drugs by drug-eluting devices would be extremely convenient is the cataract surgery that consists in the replacement of the natural lens by an intraocular lens (IOL). The most dramatic complication associated with this intervention is endophthalmitis that may occur in the post-surgical period and, eventually, leads to posterior capsule opacification and vision loss. To prevent this, antibiotics and anti-inflammatories are administrated topically through eye drops with a very frequent posology and during a relatively long period of time.

Much effort has been devoted in the last decades to the development of drug-loaded soft contact lenses (SCLs) and IOLs, able to ensure an extended drug release, as described in recent reviews (ElShaer et al., 2014; González-Chomón et al., 2011, 2013; Liu et al., 2013b; Masmoudi et al., 2011; Morrison and Khutoryanskiy, 2014). However, they are not commercially available yet, mainly due to difficulties in achieving

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adequate drug loading as well as prolonged drug release above therapeutic levels. The strategies that have been followed to control the drug release and avoid the initial drug burst from ophthalmic lens materials are based on the introduction of chemical agents that interact reversibly with the drug (Bengani and Chauhan, 2013; Paradiso et al., 2016; Peng and Chauhan, 2011; Xu et al., 2010), on the use of nanocarriers, such as micelles, liposomes or nanoparticles (Danion et al., 2007; Gulsen and Chauhan, 2005; Nasr et al., 2016) and on coatings based on polyelectrolyte multilayers or on the grafting of specific molecules (Shukla et al., 2011; Silva et al., 2016). Improving the drug loading has been another goal of the researchers in this field. Loading the ophthalmic lens materials with drugs is usually achieved by soaking in the drug solution, but other methods have been used to increase the loading capacity, such as, addition of drug to the polymerizing mixture, imprinting, and supercritical impregnation (Alvarez-Lorenzo and Concheiro, 2004; Costa et al., 2010; Patel, 2013; White and Byrne, 2010). All these methods have pros and cons: mixing the drug with the monomers may affect the drug during the polymerization and causes drug loss during the process of lens washing; imprinting implies wasting of the drug used in the first loading; supercritical impregnation demands the set-up of a suitable apparatus. Thus, soaking still remains the most inexpensive and simple method to encapsulate drug inside the ophthalmic lenses.

Here, our goal was to investigate how the traditional method of soaking could be optimized, by playing with the loading conditions, in order to yield a sustained release of an adequate amount of drug. Two materials commercially available under the names of CI26Y and Definitive 50 from Contamac Products (U.K.) were chosen. CI26Y is a hydrophilic material, which is used in the manufacture of IOLs, while Definitive 50 is a silicone hydrogel with very high oxygen permeability, which is suitable for producing a wide range of SCL designs. Three drugs were tested: an antibiotic, moxifloxacin, and two anti-inflammatories, diclofenac and ketorolac. Moxifloxacin is a fourth-generation synthetic fluoroquinolone antibiotic commonly used in the treatment of conjunctivitis, keratitis, keratoconjunctivitis, and bacterial endophthalmitis (Miller, 2008; Vasil'eva et al., 2013). This molecule has a lipophilic character and its protonated form predominates in water at pH 5.6 (Lemaire et al., 2011). Diclofenac and ketorolac are non-steroidal anti-inflammatory drugs (NSAIDs), which are mainly used to treat inflammation and to control pain in the post-operative period. Both are anionic and soluble in water as salts but, in their acidic form, they are hydrophobic drugs (Fini et al., 1993; Gupta, 2000).

Drug loading was performed by soaking the lens materials in drug solutions of fixed composition at low and high temperature and different periods of time, which could reach three months. These long times of loading were assessed because the storage of the therapeutic ophthalmic lenses in the drug solution may lead to an increase in the amount of drug loaded if the equilibrium has not been achieved. Drug release profiles were obtained and the effect of loading temperature on the materials properties (swelling, thermotropic behavior, elasticity, transmittance and molecular structure) as well as on the stability of the drugs was evaluated. The concentrations of the drugs released from CI26Y samples in the aqueous humor were estimated using a simplified mathematical model which was presented in a previous work (Galante et al., 2015), and the results were further compared to the therapeutic needs.

2. Experimental

2.1. Materials

Diclofenac sodium salt (DFN) and ketorolac tris salt (KTL) ≥99%, were purchased from Sigma–Aldrich. Moxifloxacin hydrochloride (MXF) was purchased from Carbosynth. Phosphate buffer solution (PBS), pH 7.4, was from Sigma–Aldrich. CI26Y and Definitive 50 (Contamac UK) were supplied by Physiol (Belgium). CI26Y is composed by 80–90% of 2-hydroxyethyl methacrylate (HEMA) and 10–20% of methyl methacrylate (MMA), and contains a blue-light blocker, which is proprietary to Physiol (patent WO2006074843; Yellow chromophore agent composition for intraocular lenses and the thus obtainable lenses). Definitive 50 is a silicone hydrogel with the classification of Filcon V3, composed by a blend of fluorosilicone and hydrophilic monomers. Distilled and deionised (DD) water obtained from a Millipore system was used to prepare all solutions.

2.2. Methods

2.2.1. Preparation of samples

CI26Y and Definitive 50 samples were washed in a soxhlet extractor with DD water, for 60 cycles (each cycle corresponds to 25 min), according to the recommendations of the supplier and cut in the hydrated state, in disks, with a 5 mm diameter cutting punch, or in strips (width ≈ 5 mm and length ≈ 10 mm). The average thickness of the samples is ≈1 mm. All samples were dried for three days at 36 °C and stored inside closed flasks for further experiments. The average weight of the dry disks was ≈20 mg for CI26Y and ≈13 mg for Definite 50.

2.2.2. Swelling tests

Swelling kinetics assays were performed by placing dried disks (at least three replicates each) in 1 mL of DD water or PBS at 4 °C, 25 °C and 60 °C. The samples were weighed at various times after careful wiping of their surface with absorbent paper. The swelling ratio (%*SR*) was estimated using the following expression:

$$\%SR = \frac{W_t - W_0}{W_0} \times 100 \quad (1)$$

where W_t is the weight of the swollen hydrogel at time t, and W_o is the weight of the dry hydrogel.

2.2.3. Drug loading and drug release

Drug loading was done by soaking each dry disk in 1 mL of the drug solutions (5 mg/mL in PBS), at pre-defined temperatures, 4 °C or 60 °C, during different periods of time ranging from four days to three months. After drug incorporation, loaded disks were removed from the drug solution, rinsed with DD water to remove the excess of drug on the surface, and blotted with dry absorbent paper. For the drug release experiments, carried out in static sink conditions, the samples were immersed in 3 mL of PBS and placed in a shaker (Incubating Mini Shaker from VWR) at 36 °C and 180 rpm. To determine the amount of drug release, aliquots of 0.3 mL were collected and replaced with the same volume of fresh PBS solution. The aliquots were taken over time, until the plateau was reached. The drug concentration values were quantified using a spectrophotometer UV–VIS MultiscanGO from ThermoScientific® at wavelengths of 290 nm for moxifloxacin, 275 nm for diclofenac, and 315 nm for ketorolac. All the release experiments were done, at least, in triplicate.

2.2.4. ssNMR experiments

The CI26Y disks for the ssNMR experiments were hydrated in PBS at 4 °C, 25 °C and 60 °C or loaded in the drug solutions, at 4 °C and 60 °C, for two weeks. The concentration of moxifloxacin and ketorolac in the loading solutions was increased to 10 mg/mL to exceed the detection limits of the technique, while the concentration of diclofenac was kept at 5 mg/mL due to solubility problems. The drug loaded samples were rinsed with DD water, blotted with absorbent paper and then packed (four samples) into 7 mm o.d. zirconia rotors, equipped with Kel-F caps. ^{13}C cross polarization/magic angle spinning (CP/MAS) spectra were obtained at 75.49 MHz, on a Tecmag Redstone/Bruker 300WB (Portuguese National NMR Network), with a spinning rate of 3 kHz, unless indicated otherwise. Contact time of 1 ms, 90° RF pulses of about 4 μs and 10 s recycle delays were selected. ^{1}H decoupling was achieved using TPPM (Two Pulse Phase Modulation) (Bennett et al., 1995). The