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Full Length Article

Drug-eluting silicone hydrogel for therapeutic contact lenses: Impact of sterilization methods on the system performance

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ABSTRACT

Although contact lenses are promising platforms for ocular drug delivery and have been extensively studied for that purpose, the influence of sterilization methods on these systems remains barely investigated. In this work, a silicone-based hydrogel was produced and loaded with different ophthalmic drugs: levofloxacin, chlorhexidine, diclofenac and timolol. The drug release profiles, along with several material properties, were evaluated before and after sterilization by three different methods steam heat, γ-irradiation and ozone gas. Independently of the sterilization method used, the results of the swelling and mechanical properties tests strongly indicate the occurrence of specific drug-polymer interactions promoted by the sterilization. In general, these interactions led to a decrease on the amount of drug released. It is shown that γ-irradiation and ozone led to significant degradation of all of the drugs used in this study. Thus, it was concluded that steam heat is the sterilization method with less impact on the devices. More importantly, the present work shows that the development of efficient and functional drug delivery devices for ophthalmic purposes cannot be done independently of a careful analysis of the influence of the sterilization procedures and methods on the degradation of these polymeric systems as a whole.

1. Introduction

Hydrogels are three-dimensional polymeric chains with the ability to uptake and retain water or biologic fluids [1]. They are widely used as components for biomedical implants and devices [1,2]. Sterilization is a mandatory step in the production of implants and of many of these devices to ensure their safety for users. However, the effects of sterilization methods on the intrinsic properties of hydrogels remain understudied, which delays the development of new and more effective products. The sensitive nature of these soft biomaterials, renders their sterilization a particularly challenging task for the biomedical industry [3].

There are several terminal sterilization methods that have been used for hydrogel based devices. According to the nature of the sterilizing agent, they can be grouped as physical, chemical, and physicochemical methods [4]. Steam heat and dry heat are the most used within the category of physical methods [5]. They are quite simple and relatively inexpensive. However, their application is limited to heat resistant hydrogels (e.g. silicone based, acrylic based). Sterilization can also be achieved by exposing the hydrogels to radiation, like gamma radiation (GR). GR is highly penetrating, allows operating at low temperature and does not leave any chemical residues [6]. The associated drawbacks are related with the elevated cost and complexity of the process, which requires well-trained staff and special facilities, and with its unsuitability for radio-sensitive materials [7]. Concerning the chemical methods, they are divided in methods that use liquids and gases/vapours [4]. Liquids like alcohols, phenols and aldehydes can be used as sterilizing agents. Alcohols are volatile and do not leave residues, but phenols and aldehydes may be toxic, corrosive and/or irritating [8]. Thus, the Food and Drug Administration (FDA) recommends that the use of those liquids shall be limited to situations where other

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conventional methods cannot be used. Regarding gas sterilization, the most common agents are ethylene oxide (EtO) and hydrogen peroxide (HP). Although EtO is highly efficient and quite adequate for heat and radiation sensitive materials [8], it raises concerns regarding the toxic and carcinogenic nature of EtO residues, which have to be removed, increasing the processing times [8]. In turn, HP is a highly oxidizing agent and its use must be carefully pondered to avoid the material's degradation or harmful changes in properties relevant for the considered application [9]. Recently, new methods have been studied as possible alternatives to the already existent, e.g. plasma, ozone and supercritical fluids have deserved special attention and revealed advantageous in specific cases [10].

Overall, sterilization can lead to degradation of the material, promote further crosslinking of polymers or even induce toxic effects [11–14]. In the case of hydrogels, the presence of water in the structure can aid in the breakdown of chemical bonds and therefore act as a promoter of possible alterations in the material [15].

The development of drug delivery devices using hydrogels has been extensively pursued, which can be easily confirmed by the considerable volume of published work on this topic (e.g. see [16,17] for reviews). Particularly, eye contact lenses (CLs) are hydrogel-based devices that have raised great interest as they are recognized as promising platforms for topical ocular drug delivery, capable of increasing drugs bioavailability in the eye in at least 50% when compared to eyedrops (1–5%) [18]. Because of the close contact with the cornea, these devices are required to be sterile [19]. According to manufacturer's information, the most common methods used at industrial level for the sterilization of these devices are steam heat and gamma irradiation. Other methods, such as plasma, have been used to simultaneously achieve sterilization and treat the surfaces to enhance patient comfort through the decrease of bacterial adhesion, promotion of protein- and cell-repelling properties and improvement of wettability[20–22]. However, there is an evident lack of knowledge in the literature concerning the possible effects of terminal sterilization methods on such type of devices loaded with drugs. For these systems, the sterilization processes become even more critical because, besides being able to compromise the biomaterial integrity, affecting in an adverse way important properties for its performance, phenomena such as drug degradation, loss of activity and changes in the release profile may also occur [23,24].

In this work, a comparative evaluation of the effects of conventional sterilization methods (steam heat (SH) and γ-irradiation (GI)) and of an alternative method (ozonation (OZ)) was conducted, concerning a hydrogel loaded with drugs, intended for therapeutic soft CLs. For that, a silicone-hydrogel (SiHy) containing hydroxyethyl methacrylate (HEMA) and [tris(trimethylsiloxy)silyl]propyl methacrylate (TRIS) was produced and soaked in different solutions of drugs (levofloxacin, chlorhexidine, diclofenac and timolol) commonly used for the treatment of ocular diseases [25–28]. We show that the development of efficient and functional drug delivery devices for ophthalmic purposes cannot be done independently of the establishment of the adequate sterilization process and procedure.

2. Materials and methods

2.1. Silicone-hydrogel preparation

The SiHy was prepared according to a previously reported method [29]. Briefly, the silicone monomer 3-tris(trimethylsiloxy)silylpropyl 2-methylprop-2-enoate (TRIS, Sigma-Aldrich), the hydrophilic additive N-vinylpyrrolidone (NVP, Merck), 2-hydroxyethyl methacrylate (HEMA, Sigma-Aldrich) and the crosslinker ethylene glycol dimethacrylate (EGDMA, Sigma-Aldrich) were added to prepare a mixture with concentrations of 0.94 M, 3.58 M, 1.53 M, and 30 mM, respectively. The mixture was then degassed by ultra-sounds (5 min) and bubbled with a stream of nitrogen for 15 min, after which the initiator 2,20-azobis(2-methylpropionitrile) (AIBN, Sigma-Aldrich) was added (final concentration 10 mM). The obtained mixture was stirred for additional 10 min to ensure complete homogenization, and then injected into a mold consisting of two silanized glass plates separated by a teflon spacer. The glasses were previously silanized according to the procedure described by Vasquez et al. [30], i.e. immersion in a 2% solution of dimethyldichlorosilane (Fluka) in carbon tetrachloride (Riedel-de Haën) for 1 h, followed by rinsing with dichloromethane (Sigma-Aldrich) and drying with nitrogen. The SiHy was thermopolymerized at 60 °C for 24 h and then washed over 5 days, by soaking in distilled and deionized water (renewed 3 times a day), in order to remove unreacted monomers. The hydrated samples (approx. 0.35 mm in thickness) were cut into discs with 10 mm of diameter or strips with $\sim 11 \times 5\ mm^2$, dried overnight in an oven at 40 °C and kept in a closed recipient until further use.

2.2. Drug loading

The dry SiHy samples were loaded by soaking in the drug solutions (1 mg/mL) for 5 days, at 35 °C: 6 mL in the case of the discs and 4.2 mL for the strips, to keep the ratio sample area/solution volume 0.13. Drug solutions were prepared by dissolving appropriate amounts of levofloxacin (LVF, Sigma-Aldrich), diclofenac sodium (DCF, Sigma-Aldrich) or timolol maleate (TML, kindly provided by Edol) in saline solution (NaCl 0.9%, Sigma-Aldrich). Chlorhexidine diacetate monohydrate (CHX, AppliChem) was dissolved in water due to its limited solubility in saline solution.

2.3. Silicon-hydrogel characterization

2.3.1. Optical transparency

A Thermo Scientific – Multiscan Go spectrophotometer was used for the transparency studies. Measurements of the transmittance of visible light (wavelength range from 400 to 700 nm) through the hydrated hydrogel discs, both in water and drug solutions, were performed before and after the sterilization procedures. For that, the pre-equilibrated hydrated samples were fixed on the surface of a quartz cuvette. Measurements were done in triplicate using as blank the cuvette filled with saline solution.

2.3.2. Swelling capacity

The swelling capacity of the SiHy was measured by placing the dry discs (initial weight, W_0) in test tubes containing 6 mL of distilled and deionized water, NaCl 0.9% solution or the different drug solutions, at 35 °C. At pre-determined time intervals, the samples were taken out, carefully wiped with absorbent paper and immediately weighed (W_t). The procedure was repeated until W_t became constant (final weight). The equilibrium swelling capacity (SC) was then calculated using Eq. (1):

$$SC = \frac{Wt - W_0}{Wt} \times 100 \quad (1)$$

Samples were also weighed immediately after each of the different sterilization procedures, to infer upon their effect on the swelling capacity. The mass of drug present within the loaded SiHy samples was considered negligible (<3.5%) when compared to the mass of absorbed water. All tests were performed at least in triplicate.