Norfloxacin-loaded intraocular lenses loaded by supercritical carbon dioxide impregnation

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Abstract

Cataracts treatment usually involves the extraction of the opaque crystalline lens and its replacement by implanted intraocular lenses (IOLs). A serious problem associated to this procedure is the appearance of a post-surgery infection called endophthalmitis, which is mainly caused by *Staphylococcus epidermidis*, *S. aureus* and *Pseudomonas aeruginosa*. To overcome these issues, acrylate-based IOLs were synthesized in order to load and to release norfloxacin in a controlled way and at efficient therapeutic levels. Different acrylate-based copolymers were prepared using 2-hydroxyethyl methacrylate (HEMA) and 2-butoxyethyl methacrylate (BEM) as comonomers in different proportions (from 100:0 up to 0:100). Ethyleneglycol dimethacrylate (EGDMA) was added as the cross-linker. Norfloxacin was loaded into the prepared polymers using a supercritical solvent impregnation/deposition (SSI) method, at 313 K and at pressures from 15.0 up to 30.0 MPa. Processing/loading time was 14 h, while venting rate was 0.1 MPa min^{-1}. Norfloxacin aqueous immersion loading experiments were also performed for comparison reasons. All prepared and processed samples were characterized by several different techniques. Loading capacities and drug release profiles were obtained, compared and discussed in terms of the copolymer composition and of the employed drug-loading method and operational conditions. Samples BEM composition and SSI operational pressure strongly affected norfloxacin loaded amounts. Additional research work is currently being carried out to clarify these results. Finally, the obtained thermomechanical, water-sorption, wettability and optical properties of prepared and processed samples seemed to be adequate for their potential application as IOL materials.

INTRODUCTION

Cataracts treatment usually involves the extraction of the opaque crystalline lens and its replacement by an implanted intraocular lens (IOL) [1,2]. A serious problem associated to this procedure is the appearance of a post-surgery infection called endophthalmitis which is mainly caused by *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [3,4]. To overcome these issues, acrylate-based IOLs having the ability to load and to release norfloxacin in a controlled way and at efficient therapeutic levels were synthesized.

Supercritical carbon dioxide ($scCO_2$) impregnation/deposition allows the incorporation of $scCO_2$-soluble drugs (usually of the hydrophobic/low polarity type) into most polymeric matrixes and, when properly employed, it will not change and/or damage their most important physical, chemical and mechanical properties, as well as it will not degrade any involved thermally labile materials. Supercritical solvent impregnation (SSI) also permits to have previously prepared polymeric articles or biomedical devices (such as commercial SCLs) and impregnate them later with the desired drugs, taking in

consideration the envisaged therapeutic application and without interfering with the polymeric article/device manufacture and/or processing method. This particular feature is an important advantage of the method that may lead to the development of several other biomedical and pharmaceutical applications [5-9], in order to develop drug delivery systems.

Different acrylate-based copolymers were prepared. Norfloxacin was loaded from aqueous drug solutions as well using a $scCO_2$ impregnation/loading method. After impregnation, the norfloxacin amount released should be above the minimum inhibitory concentration for these microorganisms. Characterization of hydrogels was carried out by different methods. Results were discussed in terms of copolymer composition and of the employed drug-loading method.

MATERIALS AND METHODS

Hydrogels synthesis - Mixtures of 2-hydroxyethyl methacrylate (HEMA) and 2-butoxyethyl methacrylate (BEM) (100:0, 80:20, 60:40, 40:60, 20:80, 0:100) were prepared and ethyleneglycol dimethacrylate (EGDMA) was added as cross-linker (Figure 1). 2,2´-azo-bis(isobutyronitrile) (AIBN) was added as the initiator. Polymerization was carried out at 50ºC for 12 h and at 70ºC for 24 h. Resulting copolymers were boiled in water, cut into 10 mm diameter samples and dried at 70ºC for 12h.

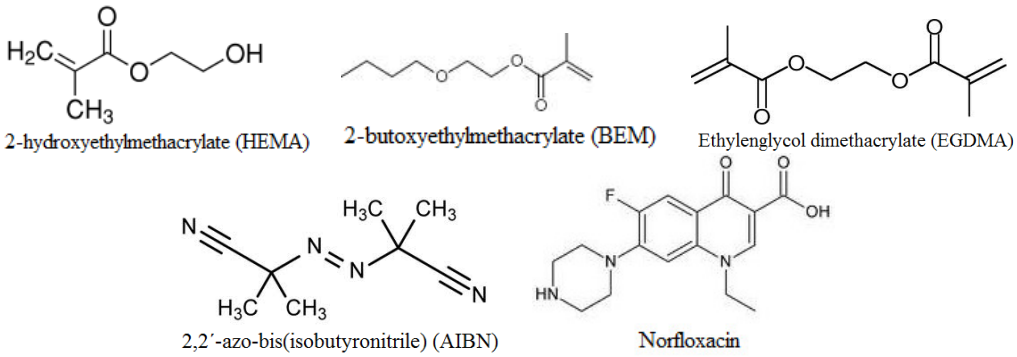

Figure 1. Structures of norfloxacin and of the monomers used in the IOLs synthesis.

Hydrogels characterization - Hydrogels IR spectra were obtained in a FTIR-ATR (Jasco) after being dried at 40 ºC until constant weight. Glass transition temperatures (T_g, ºC) were determined by DSC (TA Instruments). Water contact angles and surface free energy were determined by an OCA20 contact angle apparatus (Dataphysics Instruments). Water sorption capacities (S, %) were obtained by gravimetry. Optical transparency of hydrated hydrogels was also evaluated (at 600 nm).

Norfloxacin loading experiments – Conventional loading from norfloxacin aqueous solutions (0.0096 g/L) was carried out by samples immersion and soaking for 48 hours at 37 ºC. Norfloxacin impregnation with $scCO_2$ was carried out at 40 ºC and at two pressures: 15.0 and 30.0 MPa. SSI processing time was 14 h and depressurization rate was 0.1 MPa min^{-1}. Drug-loaded amounts were spectrophotometrically determined for both drug-loading methods.

Norfloxacin release experiments – Norfloxacin-loaded samples were immersed in artificial lachrymal fluid at 37 ºC, under orbital stirring and release solution absorbance (at 273 nm) was measured continuously for 8h. Other measurements were performed after 48h.

RESULTS

The total amounts of released drug from samples loaded by immersion decreased as the BEM samples compositions were increased until similar HEMA and BEM compositions were employed. Then, and as BEM contents continues to increase, they remain almost constant. For the higher BEM compositions, the total norfloxacin released amounts from those samples impregnated using $scCO_2$ (at both operational pressures) were higher or even much higher than the amounts released from those samples loaded by the soaking method (Figure 2). However and for lower BEM compositions, immersion and SSI methods led to quite similar loading /releasing results (for both employed SSI operational pressures). Finally, the effect of operational pressure on the norfloxacin released amounts from samples impregnated using $scCO_2$ and for all HEMA:BEM compositions it is not completely clear or follows a constant tendency. These results are a consequence of all the physicochemical interactions that may be established between all the involved substances in the SSI process and by their relative magnitudes. In the present case, these substances are the copolymers which are comprised in the prepared samples, the drug (norfloxacin), $scCO_2$ and water (in samples). Thus, in the studied system, the most relevant physicochemical interactions to be considered are the $scCO_2$/norfloxacin interactions (which will determine drug solubility in the $scCO_2$ mobile phase), the water-containing samples/$scCO_2$ interactions (which will control CO_2 sorption and samples swelling/plasticization) and the water-containing samples/norfloxacin interactions (which will control drug "solubility" in samples and its partition between samples and the $scCO_2$ mobile phase). Therefore and by changing samples BEM composition, the relative water-containing samples/$scCO_2$ and water-containing samples/norfloxacin interactions will also change thus leading to the observed distinct SSI results.

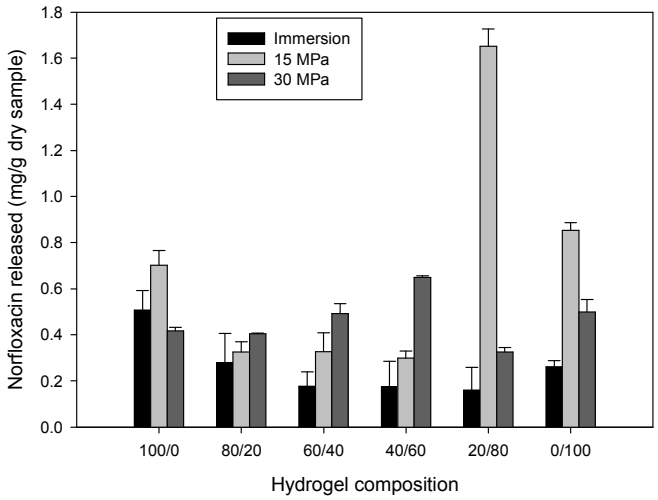

Figure 2. Total norfloxacin released amounts.

In addition, as BEM composition increases the samples hydrophilicity (and thus their water content) will decrease. Finally and as observed, the SSI process is also controlled and affected by the employed operational pressure conditions.

As expected and due to BEM bulkiness, DSC results showed that T_g decreased as the BEM composition was increased. The same trend was observed for samples water sorption capacities (due to the increasing hydrophobicity of samples having higher BEM contents) while water contact angles showed the opposite behaviour (Figure 3). All prepared samples presented a high optical transparency, with transmittance values in the 95-100% range (at 600 nm).

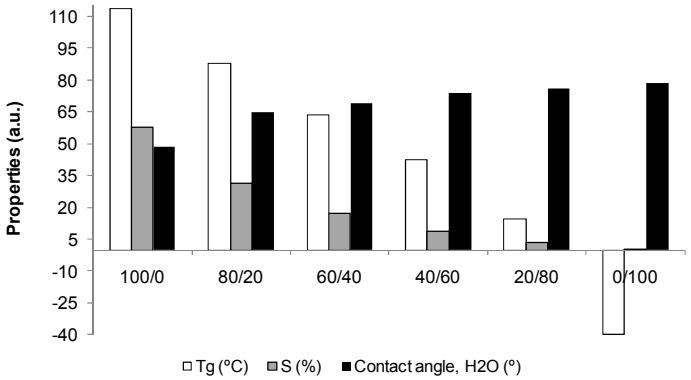

Figure 3. IOLs polymer physical characterization

CONCLUSIONS

Cross-linked HEMA:BEM-based hydrogels were loaded with norfloxacin by soaking in aqueous drug solutions and by a $scCO_2$ SSI loading method. The total amounts of released drug from samples loaded by immersion decreased as the BEM composition was increased until similar HEMA and BEM compositions were employed and were kept constant as BEM contents further increased. For samples with higher BEM compositions, the total norfloxacin released amounts from SSI-processed samples (at both operational pressures) were higher or even much higher than the amounts released from those samples loaded by the aqueous immersion method. However and for lower BEM compositions, immersion and SSI methods led to quite similar loading/releasing results (for both employed SSI operational pressures). Finally, the effect of operational pressure on the norfloxacin released amounts from SSI-processed samples and for all HEMA:BEM compositions it is not yet completely clear. These results are a consequence of the employed operational pressure conditions as well of all the physicochemical interactions that may be established between the involved substances in the SSI process. Additional research work is currently being carried out to clarify these results. Finally, and for most of the prepared and processed samples, the obtained thermomechanical, water-sorption, wettability and optical properties seemed to be adequate for their potential application as IOL materials.

ACKNOWLEDGEMENTS

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