SUPERCRITICAL SOLVENT IMPREGNATION OF ACETAZOLAMIDE IN CONTACT LENSES FOR GLAUCOMA TREATMENT

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ABSTRACT

Therapeutic ophthalmic articles, like drug-loaded contact lenses, are known to improve drug absorption through the cornea and thus, enhancing the therapeutic efficiency for the treatment of several posterior eye diseases, like glaucoma. In this work, we used a Supercritical Solvent Impregnation (SSI) process, employing $scCO_2$+EtOH (5%, molar) solvent mixtures, to impregnate acetazolamide in commercially available silicone hydrogel contact lenses (Balafilcon A, Pure Vision™, Bausch&Lomb®). Contact lenses drug loading/impregnation was studied at 313 K and 323 K, and from 15 up to 20 MPa, and using low depressurization rates to avoid to damage lenses (0.066 MPa/min). *In vitro* kinetic drug release studies were performed and the amount of released drug was quantified spectrophotometrically. Several other analytical techniques (FTIR, contact angle determination and optical microscopy) were employed to characterize processed and non-processed contact lenses. Drug release studies were made *in vitro* at 310 K to simulate the environmental conditions of the eye.
Results demonstrated the feasibility of preparing acetazolamide impregnated therapeutic Balafilcon A contact lenses, using $scCO_2$+EtOH (5%, molar) solvent mixtures. Furthermore, SSI method is a "tunable" process for drug dissolution and drug diffusion into polymeric matrixes and, thus, just by changing operational (*P*, *T*) conditions, it is possible to control the amount of impregnated drug and, consequently, to tune released drug levels into desired therapeutic limits.

INTRODUCTION

Glaucoma is a group of ophthalmic diseases which causes optic nerve damages and loss of retinal cells. Nowadays, it is the leading cause of irreversible blindness in the world. There is no cure for glaucoma but with medication and surgery it is possible to stop further loss of vision. One of glaucoma major risk factors is the increase in intraocular pressure (IOP) as a result of an imbalance between the production (inflow) and drainage (outflow) of aqueous humour [1]. IOP can be decreased using drugs designed to limit aqueous humour production and/or enhance the aqueous humor drainage. One of these drugs is acetazolamide, a carbonic anhydrase inhibitor (Figure 1). Acetazolamide is usually administered orally (as pills) or topically (as eye drops, in conjugation with other anti-glaucoma medications). However, and mainly because of its low bioavailability, these administration routes can induce the occurrence of several systemic side effects.

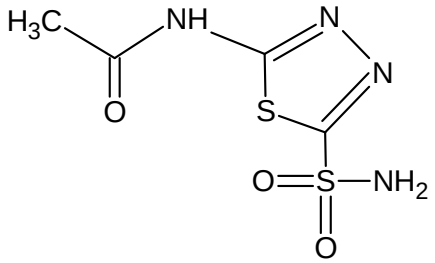

Figure 1 – Chemical structure of acetazolamide ($C_4H_6N_4O_3S_2$), N-5-(Sulfamoyl-1,3,4-thiadiazol-2-yl) acetamide.

To overcome these problems, great research efforts have been made in order to develop different systems to administrate the drug by an efficient and safe ocular route [1]. Acetazolamide controlled drug release systems (CDRS) can be considered as potential good alternative to efficiently treat glaucoma and, simultaneously, to minimize the occurrence of acetazolamide-caused systemic side effects. Therapeutic drug-loaded contact lenses are known to improve drug absorption throughout the cornea since they can promote longer drug residence times in the post-lens tear film. They also may present other advantages such as the reduction of the amount of drug lost by tear drainage and the reduction in the amount of drug needed to produce the desired therapeutic effect, thus minimizing side effects risks. Moreover, contact lenses are comfortable for patients, their use is widely spread and they are biocompatible and already accepted/approved as biomedical devices [2].

Polymeric-based CDRs (like therapeutic contact lenses) can be prepared in numerous different ways. Dispersing a drug, or therapeutic agent, in biodegradable polymeric matrixes encompasses the majority of all research in this field and there are several methods to incorporate and disperse drugs into polymeric matrixes. However, these conventional methods present several disadvantages, like the use of sometimes toxic organic solvents, drug/solvent dissolution and compatibility issues, undesired drug reactions, drug photochemical and thermal degradation, low incorporation yields and heterogeneous drug dispersion. Drugs may also be impregnated by dissolving them in compressed high volatile fluids (like carbon dioxide) at temperatures and pressures near or above their critical temperatures and pressures, and contacting the resulting mixture with the polymeric matrixes to be infused. In these conditions, the compressed fluid can act also as a swelling and plasticizer agent for polymers, helping drugs' diffusion into them. This recent technique, known as Supercritical Solvent Impregnation (SSI), already proved to be very useful and presents several advantages for the development of drug impregnated polymeric materials which can be used as drug delivery systems for many biomedical applications [3-5]. SSI allows the drug impregnation of most polymeric articles and, when properly employed, without altering and/or damaging their physical, chemical, and mechanical properties and without degrading their constituent drugs, additives and polymers. Furthermore, drug loading and depth penetration can be easily controlled and drugs will be homogeneously dispersed, in short treatment times and leaving no harmful solvent residues.

Finally, SSI also permits to have previously prepared polymeric articles (like contact lenses) and, later, impregnate them with the desired drugs, according to the specific needs of the envisaged therapeutic application, and without interfering with the established conventional method/procedure to produce/process the original polymeric articles. This particular feature can lead to very attractive and useful medical and commercial applications.

In this work, we used a Supercritical Solvent Impregnation (SSI) process, employing $scCO_2$ + EtOH (5%, molar) solvent mixtures, to impregnate acetazolamide in commercially available silicone hydrogel contact lenses (Balafilcon A, Pure Vision™, Bausch&Lomb®).

MATERIALS AND METHODS

Commercial contact lenses were obtained from Bausch&Lomb® (Balafilcon A, 8.6 mm (BC), -4,00 D (PWR)). Acetazolamide was obtained from Sigma-Aldrich. Carbon dioxide (99.995%, Praxair) and ethanol (99.5% purity, Panreac Química) were the employed solvents. Kinetics of drug release experiments were performed in commercial physiological serum (NaCl isotonic solution, pH 6).

The supercritical impregnation apparatus is presented in Figure 2. Experimental procedures were already reported [3-5]. Several experiments were carried out in order to study the effects of operational pressure (from 15 MPa up to 20 MPa) and temperature (313 K and 323 K). Operational conditions were selected based on acetazolamide/CO_2+EtOH 5% solubility data [6]. The impregnation period was kept constant (1 hour) and the depressurization rates were, in average, of 0.066 MPa/min. For release experiments, a lens was placed in a closed vial with 10 ml of physiological serum and placed in a water bath at 310 K. During the 8 hour release experiment, samples of 0.6 ml were taken and replaced by the same volume of fresh serum. Samples were analyzed and quantified by UV Spectroscopy.

Other analytical techniques (FTIR, contact angle determination, and optical observations by microscopy) were employed to characterize processed and non-processed contact lenses with duplicated assays.

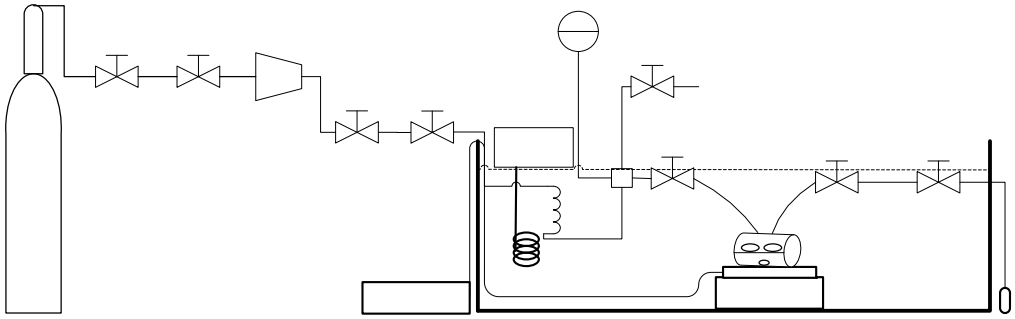

Figure 2 – Schematic diagram of the experimental supercritical solvent impregnation apparatus. C – compressor; PT – high pressure transducer; TC – temperature controller; V – valves; IC – impregnation cell; MS – Magnetic Stirrer; GT – glass trap.

RESULTS

Figure 3 shows acetazolamide partition coefficients (between the contact lenses and the supercritical fluid mixture) as a function of mixture density, for the different employed experimental conditions. Acetazolamide solubility is also represented. It is clear that, in general terms, acetazolamide partition coefficient increases with the increase of CO_2 density. This is probably due to the observed drug solubility increment with CO_2 density and to the plausible higher swelling and plasticizing effects promoted by high density supercritical CO_2. There is no experimental published data on swelling and plasticizing effects for Balafilcon A, but these effects are recognized to be very common and important on these processes and are abundantly reported in literature [7-8].

In fact, the global impregnation efficiency will always be the result of the relative specific interactions that may occur in the system: CO_2-drug interactions (which controls drug solubility in CO_2), polymer-CO_2 interactions (which controls CO_2 solubility in the polymer

V1 V2 C

V3 V4 (V)

and, consequently, swelling and plasticization) and drug-polymer interactions (which controls solubility/compatibility of the drug in the polymer). Thus, in this system the predominant effects controlling the impregnation process may be the solubility of the drug in CO_2 as well as the CO_2 swelling and plasticizing effects on contact lenses. Another important operational variable could be the system depressurization rate but it was kept constant for all studied systems.

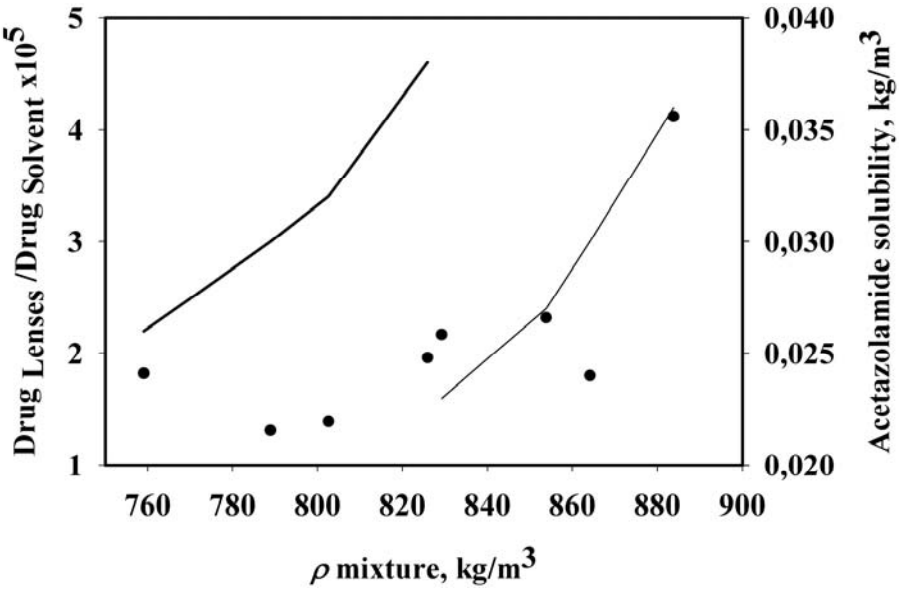

Figure 3 - Partition coefficient of acetazolamide (Drug $_{Lenses}$/Drug $_{Solvent}$ × 10^5) (symbols) and acetazolamide solubility in CO_2+EtOH (5 %, molar) (lines), as a function of mixture density. (●) Experimental partition coefficient; Lines: Acetazolamide solubility at 313 K (—), 323 K (—).

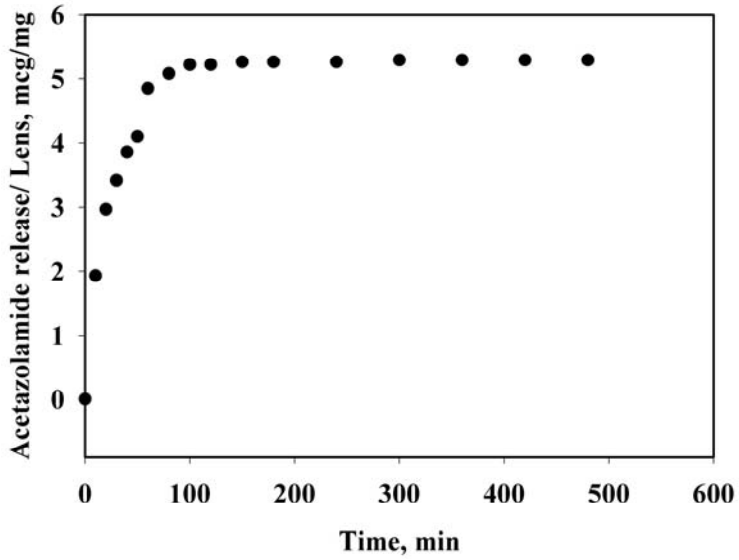

Figure 4 – Accumulated acetazolamide mass released from Balafilcon A contact lens impregnated at 20 MPa and 323 K.

Kinetic release studies were performed to all SSI experiments. Figure 4 shows the accumulated amount of acetazolamide released from a contact lens impregnated at 20 MPa and 323 K. All impregnated lenses presented similar release profiles, with an initial burst period (~ 2 hours) followed by a period in which the amount of released acetazolamide was low. However, and even for these longer periods, the discrete (non-accumulated) released mass of acetazolamide was well above the required therapeutic limit for glaucoma treatment.

Table 1. Reverse sessile drop contact angles of SSI processed Balafilcon A contact lenses.

Pressure, MPa	Temperature, K	Contact Angle, º
Control lenses		106.1 ± 2.7
15	313	115.9 ± 3.4
17		108.4 ± 4.1
18		106.0 ± 1.2
20		90.7 ± 10.1
15	323	103.7 ± 1.3
17		109.9 ± 2.8
18		112.3 ± 2.5
20		106.7 ± 15.5

Reverse sessile-drop water-contact lenses contact angles were measured in order to evaluate lenses surface hydrophilicity/hydrophobicity. Results showed that an increase in processing pressure will increase lenses hydrophilicity (at 313 K) and decrease lenses hydrophilicity (at 323 K), with the exception of lenses processed at 20 MPa.

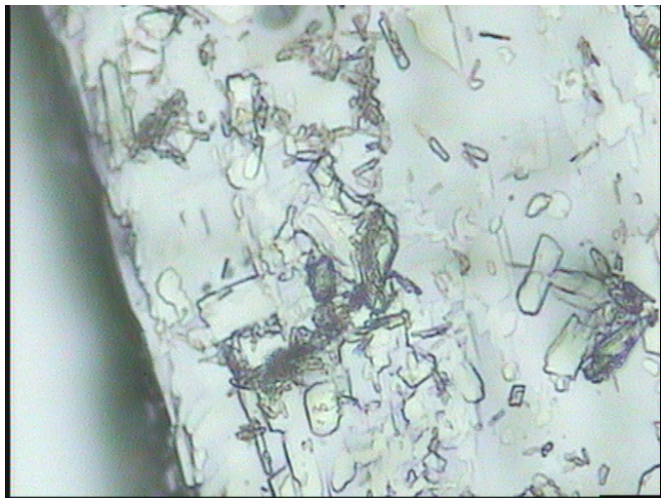

Figure 5. Optical microscopy observations at 400×.

Optical observations, at 400×, by optical microscope (Figure 6) show the presence of impregnated drug particles at the contact lenses cross section.

CONCLUSIONS

The presented results showed the feasibility of preparing acetazolamide impregnated therapeutic Balafilcon A contact lenses, for corneal route glaucoma treatment, using sc-CO_2+EtOH (5%, molar) solvent mixtures. Furthermore, the SSI method is a "tunable" process for drug dissolution and drug diffusion into polymeric matrixes and, thus, just by changing operational (P, T) conditions, it is possible to control the amount of impregnated drug and, consequently, to tune released drug levels into desired therapeutic limits.

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