Supercritical carbon dioxide processing of commercial contact lenses: sorption effects on drug loading

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Abstract

The application of soft contact lenses (SCLs) as drug delivery vehicles has been recently fairly studied as it presents a great potential for the treatment of several ophthalmic diseases. Over the last years, our research group has studied the use of supercritical carbon dioxide ($scCO_2$) impregnation/deposition (SSI) methods to load ophthalmic drugs into several different ophthalmic systems, including commercial SCLs. In general terms, the process was found to be feasible, advantageous and "tunable", i.e., it is possible to control the amounts of loaded drugs and consequently to adjust the final drug release levels into the desired therapeutic limits. It is also known that the process efficiency is also controlled by the physicochemical interactions that may be established between all the involved substances in the process: $scCO_2$/drug interactions, drug/water-swollen SCLs interactions and water-swollen SCLs/$scCO_2$ interactions. Therefore, the study of $scCO_2$ sorption/diffusion into SCLs is an important tool for the understanding of the overall impregnation/deposition process and, to the best of our knowledge, no scientific or technical literature covering these phenomena was published so far.

In this work, we employed a gravimetric method to determine the maximum/equilibrium solubility of $scCO_2$ in two commercial SCLs (Hilafilcon B/Soflens® and Balafilcon A/ Purevision®). Experiments were carried out from 308 K up to 328 K, from 10 up to 30 MPa, and employing different exposure periods (from 0.17 h up to 14 h). A Fickian-based diffusion model was applied to study the $scCO_2$ sorption/desorption processes.

Later, flurbiprofen was loaded into the same SCLs using the SSI methodology and at some of the pressure, temperature and exposure periods conditions that were employed for the sorption experiments. In vitro drug release kinetics, oxygen permeability and frictional force studies were performed in order to quantify the drug-loaded amounts and to study the effects of employed operational conditions on some of the final functional properties of SCLs. Obtained impregnation results were discussed in terms of employed experimental conditions and correlated with the previously obtained $scCO_2$ equilibrium sorption data.

INTRODUCTION

The potential application of soft contact lenses (SCLs) as drug delivery vehicles for the posterior segment of the eye is raising much attention as the amount of drug that can reach the therapeutic targets is always superior to that achieved by frequent topical instillation. Moreover, the systemic toxicity risks may be strongly reduced. In addition, the use of supercritical fluid technologies for loading SCLs with pharmaceutical

compounds, namely of supercritical solvent impregnation (SSI), are recent and advantageous innovations for the development of these ophthalmic drug delivery systems [1-6].
In the SSI process, supercritical fluids (SCFs) and in particular supercritical carbon dioxide ($scCO_2$), may act as temporary swelling and plasticizing agents for rubbery polymers thus enhancing the SCF/$scCO_2$ diffusion processes into these materials. Therefore and if a drug is dissolved in this SCF mobile phase, its diffusion into polymeric materials will also be enhanced. Thus, the determination of the best operating SSI conditions to load drugs into polymers must involve the accurate knowledge of the solubility and the diffusion coefficients of $scCO_2$ in the polymeric matrixes (sorption and swelling) as well as the partition coefficient of the drug between the supercritical fluid and the polymeric phases [3-6].
Polymeric $scCO_2$ sorption and polymeric swelling are frequently measured using different methodologies which include simple and quartz-crystal microbalance gravimetric [7,8], calorimetric [9] and spectroscopic methods [10]. Although the strong differences that characterize each of the above referred methods, the accuracy of gravimetric and of spectroscopic methods was recently compared and it was concluded that simple gravimetric methods present quite good data consistency despite the associated simple experimental and calculations procedures [10].
In this work, we employed a simple gravimetric method to determine the equilibrium solubilities of $scCO_2$ in two commercial SCLs (Hilafilcon B/Soflens® and Balafilcon A/Purevision®). A simple Fickian-based diffusion model was applied to study $scCO_2$ sorption/desorption processes. To the best of our knowledge, no scientific or technical literature covering $scCO_2$ sorption on commercial SCLs was published so far. Later, flurbiprofen was loaded (as a model impregnation drug) into the above referred SCLs, using the SSI methodology and at some selected pressure, temperature and exposure periods conditions from those that were employed for the sorption experiments. Obtained impregnation results were discussed in terms of employed experimental conditions and correlated with the previously obtained $scCO_2$ equilibrium sorption data. In vitro drug release kinetics, oxygen permeability and frictional force studies were performed in order to quantify the drug-loaded amounts and to study the effects of employed SSI operational conditions on some of the final functional properties of tested SCLs.

MATERIALS AND METHODS

Continuous-wear (monthly) Balafilcon A SCLs (36 % water content, Pure Vision™) and daily-wear Hilafilcon B SCLs (59% of water content, Soflens) were kindly supplied by Bausch & Lomb and were used for the $scCO_2$ equilibrium sorption and for the flurbiprofen SSI experiments. Flurbiprofen, CAS [5104-49-4] (97% purity) was obtained from Sigma-Aldrich. Carbon dioxide (99.998%) was obtained from Praxair.
The equilibrium solubilities of $scCO_2$ in the studied commercial SCLs were obtained from 308 K up to 328 K, from 10 up to 30 MPa, employing different exposure periods (from 0.17 h up to 14 h) and using the gravimetric procedure and experimental apparatus already described in the literature [7,8]. In general terms, this procedure comprises a sorption period that is ended by a quick depressurization step, followed by a gravimetric desorption measurement at atmospheric pressure (in a precision balance). Therefore, the depressurization and cell opening rates had to be carefully controlled so that CO_2 did not freeze inside. It is known that, in certain conditions [11], the diffusion of gases into/from rubbery polymers (sorption/desorption processes) can be described simply by the Fick's first law of diffusion. Therefore, the Crank model [11] to describe

the diffusion of gases into/from polymers (of specific shapes) was used in this work just to calculate desorption diffusion coefficients. The sorption diffusion coefficients were then inferred according to the procedures already described in literature [7,8].

The employed supercritical impregnation apparatus and the general impregnation procedures were already described in literature [1,3-6]. SSI assays were carried out in order to load flurbiprofen (as the model impregnation drug) using the operational conditions of pressure and temperature of 20 MPa (the central point of previously performed sorption experiments), at 308 K and 328 K, and for 1.5 h and 14 h of impregnation time). Magnetic stirring was always employed for the drug fast dissolution and the compressed fluid mixture homogenization. Following the pre-established SSI processing time, the system was then slowly depressurized (at approximately 0.06 MPa/min) so that the SCLs were not damaged during this procedure. A single SCL was impregnated in each impregnation batch and all assays were carried out in triplicate.

Drug release kinetics studies were performed in bi-distilled water (20 mL) for all the prepared flurbiprofen-loaded SCLs using a UV-Vis spectrophotometric method (at 247 nm). In order to simulate the envisaged daily-wear ophthalmic use, release experiments were carried out for 8 hours at 37 ºC and under stirring. After this release period and in order to leach out all remaining drug still present in SCLs, a complete renovation of the release medium (20 mL) was daily performed until flurbiprofen was no longer detected in release medium. This occurred after 16 days of flurbiprofen removal. Finally, the total (accumulated) released flurbiprofen from SSI-loaded SCLs was quantified taking in consideration the flurbiprofen amounts released during the previously performed drug release studies and the drug leaching procedures. Therefore, we can consider that the total (accumulated) released flurbiprofen will correspond to the total impregnated/loaded flurbiprofen by the SSI process.

Control (non-processed) and SSI-processed/released SCLs oxygen permeability was measured using a Createch permeometer, model 210T (Rehder Development Company), and a polarographic cell that perfectly fitted lenses curvature. Obtained results are presented as $Dk \times 10^{11}$ $(cm^2/s)(cm^3\ O_2/cm^3\ mmHg)$ and compared with values previously reported in the literature.

The friction force of water-swollen SCLs was measured (at 25 ºC) using a Rheolyst AR1000N rheometer (TA Instruments) equipped with an AR2500 data analyzer and a Peltier plate. Experiments were carried out applying 5 ± 0.1 N normal force (W) for 15 min and a peak hold step with an angular velocity of 0.05 rad/s for other 15 min. The corresponding elasticity moduli were obtained for control (non-processed) and for SSI-processed/released Balafilcon A and for Hilafilcon B SCLs (processed at 20 MPa, at 308 K and 328 K, and for 1.5 h and 14 h of impregnation time). The total friction, *F*, and the coefficient of friction, *l*, were determined according to the procedures reported in literature [2]. All measurements were made in duplicate.

RESULTS

Figure 1 shows the maximum/equilibrium $scCO_2$ sorption degrees obtained for the sorption experiments with Balafilcon A and Hilafilcon B SCLs (carried out at 328 K and at 10.0, 20.0 and 30.0 MPa, and for different exposure times). In this work, the maximum/equilibrium sorption degree was defined to be the percentage ratio between the maximum/equilibrium of the absorbed CO_2 mass in SCLs and the total mass (mass of dry SCLs + absorbed CO_2 mass).

As can be observed and as expected, the maximum/equilibrium sorption degrees increased as pressure and exposure times increased. For both studied SCLs, it was found

that $scCO_2$ sorption equilibria was never completely reached after 14 hours of exposure for both studied contact lenses and for all tested pressure and temperature conditions. This means that the obtained values are just maximum sorption degrees, after a 14 h sorption period and at the employed experimental conditions (and not real sorption equilibria data). After 14 h and for Hilafilcon B SCLs, the higher maximum sorption degree was achieved at 308 K and 30.0 MPa (data not presented) while in the case of Balafilcon A SCLs it was achieved at 328 K and 30.0 MPa. At the lowest temperature (308 K), the effect of operational pressure in the achieved maximum sorption degrees is much more pronounced (for both SCLs). On the other hand, operational temperature presented opposite effects for each tested SCL: as temperature increased, the maximum sorption degree slightly decreased (for Hilafilcon B) and slightly increased (for Balafilcon A). Finally and in general terms, the maximum sorption degrees are always slightly higher for Hilafilcon B than for Balafilcon A SCLs (for the same employed experimental conditions).

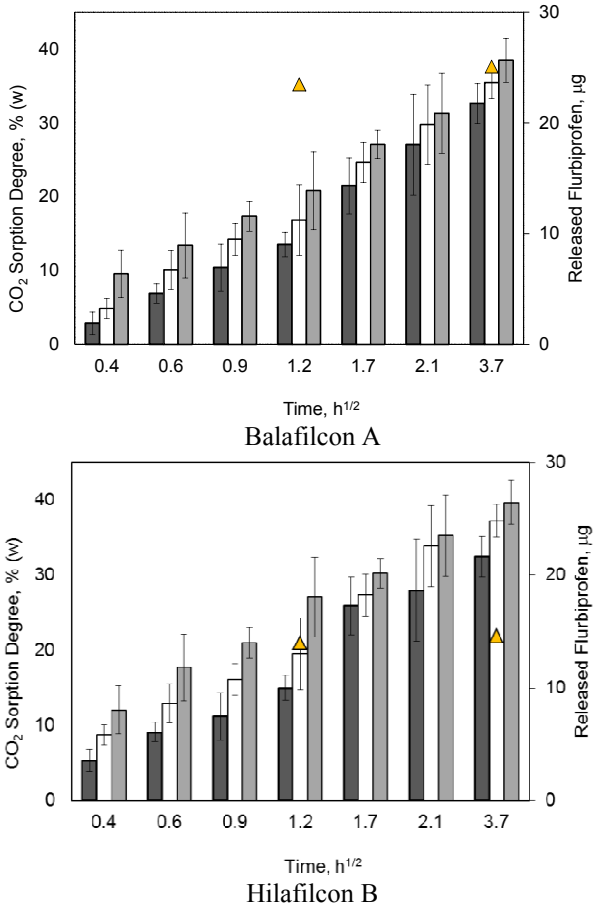

Figure 1. Maximum scCO2 sorption degrees obtained at 328 K, for Balafilcon A and for Hilafilcon B SCLs as a function of $scCO_2$ exposure/sorption time: (■) 10 MPa (□) 20 MPa (■) 30 MPa. Triangles represent the total released flurbiprofen amounts (right axis) from SCLs SSI-processed at 328 K, 20 MPa, processed during 1.5 h and 14.0 h.

The total released flurbiprofen amounts after SSI processing (processed at 328 K, 20 MPa and during 1.5 h and 14.0 h) are also presented in Figure 1 (triangles, right axis): More SSI results are presented in Figure 2. For Balafilcon A, large amounts of loaded drug were still present inside SCLs after the 8 h release period. Moreover, and for most of the SSI-processed samples, the flurbiprofen complete removal (after 16 days) indicated that Balafilcon A SCLs were able to load almost twice the flurbiprofen that

was loaded in Hilafilcon B SCLs (that released almost all loaded flurbiprofen during the 8 h release period). Therefore it is clear that Balafilcon A presents a higher flurbiprofen affinity and loading capacity than Hilafilcon B. These results are certainly due to the most favorable SCLs/flurbiprofen/scCO_2 interactions that were established during the process for Balafilcon A SCLs, namely the enhanced SCLs/flurbiprofen interactions that are the result of their specific constituent comonomers and comonomers composition. Results also show that contact time (and thus scCO_2 sorption) seems to have a slight positive effect on Hilafilcon B loading yields and no effect for Balafilcon A SCLs. This means that scCO_2/SCLs interactions are more favorable for Hilafilcon B than for Balafilcon A (as already discussed in terms of obtained maximum sorption degrees).

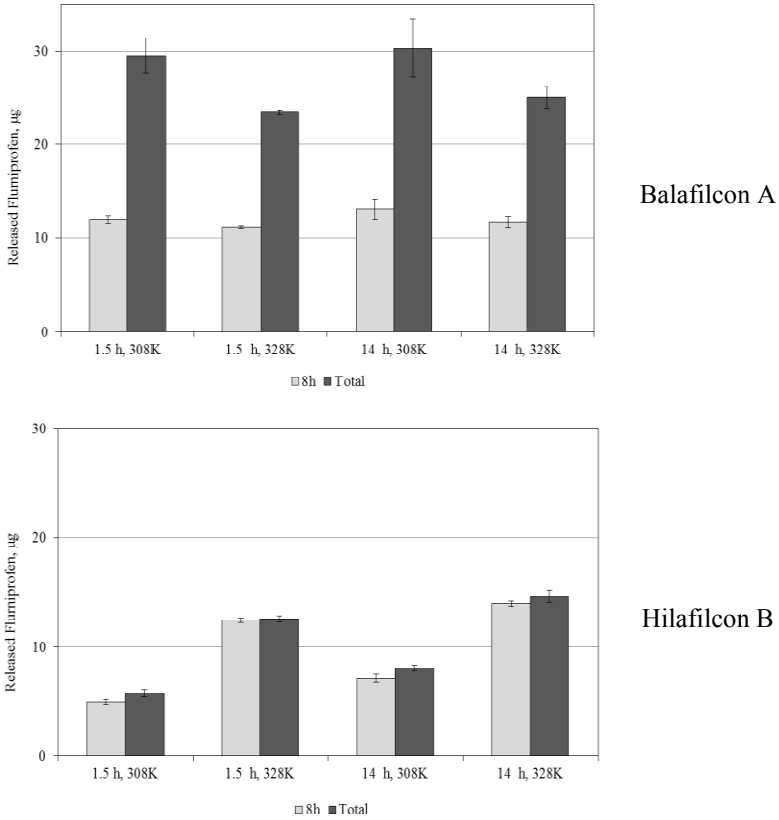

Figure 2. Total released flurbiprofen from SSI-processed Balafilcon A and Hilafilcon B SCLs. Samples were processed at 20 MPa, 308 K and 328 K, and for different impregnation times (■ 1.5 h and ■ 14.0 h).

SCLs should possess adequate O_2 permeability (Dk) properties in order to avoid cornea swelling and hypoxia caused by poor oxygenation. According to supplier (Bausch & Lomb), the oxygen permeability of Balafilcon A is higher than Hilafilcon B (91×10^{-11} and 22 $x10^{-11}$ $(cm^2/s)(cm^3O_2/cm^3$ mmHg), respectively). When compared to the non-processed SCLs, the obtained O_2 permeability results (data not presented) shows a small decrease in the O_2 permeability of Balafilcon A SCLs (higher decrease was obtained for those processed at 308 K during 1.5h). This can be due to the experimental depressurization rate fluctuations which may have promoted SCLs drying or changes in their polymeric structure. However, the employed SSI methodology and the employed experimental conditions did not promote relevant changes in the O_2 permeability of Hilafilcon B SCLs.

SCLs elastic and shear moduli were measured for control (non-processed) and SSI-processed/released Balafilcon A and Hilafilcon B SCLs. For Balafilcon A, results showed that employed methodology did not alter the viscoelastic properties of studied

SCLs (with the exception of those processed at 308 K and for higher $scCO_2$ exposure time (14h). However and for Hilafilcon B SCLs, all SSI-processed SCLs presented G'/G'' values above those obtained for control SCLs, which may be explained by some polymeric changes in the polymeric chain that may occurred during processing.

CONCLUSIONS

It was found that $scCO_2$ sorption equilibria was never completely reached after 14 hours of exposure for both studied SCLs and for all tested experimental conditions. As expected, the maximum sorption degrees increased as pressure and exposure times increased. Maximum sorption degrees were always slightly higher for Hilafilcon B than for Balafilcon A SCLs (for the same employed experimental conditions). Operational temperature presented opposite effects for each tested SCL: as temperature increased, the maximum sorption degree slightly decreased (for Hilafilcon B) and slightly increased (for Balafilcon A). Balafilcon A SCLs were able to load almost twice the flurbiprofen that was loaded in Hilafilcon B SCLs. Results also show that contact time (and thus $scCO_2$ sorption) seems to have a slight positive effect on Hilafilcon B loading yields and no effect for Balafilcon A SCLs. This means that $scCO_2$/SCLs interactions are more favorable for Hilafilcon B than for Balafilcon A (as already found by the sorption experiments). Operational conditions (pressure and temperature) did not greatly affect the O_2 permeability and the rheological properties of the studied SCLs.

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