Supercritical impregnation of intraocular lenses for the elaboration of controlled drug release systems

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Polymeric drug delivery systems are designed to release the active ingredients in a controlled manner, optimizing thus their bioavailability and decreasing potential side effects, as well as to target a specific site in the body [1]. One route to elaborate such systems is impregnation. Conventional impregnation requires the use of organic solvents to dissolve and carry the drug component into a polymer matrix. Residual solvents are therefore present in the final materials, which can lead to some toxic effects. Supercritical fluid impregnation, using supercritical carbon dioxide ($scCO_2$) as an alternative to organic solvents, can reduce or even eliminate the use of organic solvents. Furthermore, $scCO_2$ plasticizes and swells the polymer matrix. An increase in the free volume of CO_2-swollen polymers is believed to be responsible for the enhanced diffusion of solute molecules in such systems [2].

In the present work, an anti-inflammatory drug (Dexamethasone 21-phosphate disodium) has been impregnated on polymeric intraocular lenses (IOLs) used in cataract surgery to replace the natural crystalline lens of the eye. More particularly, two polymeric IOLs were tested: rigid intraocular lenses made from derivative of Poly-Methyl MethAcrylate (PMMA) and foldable intraocular lenses (hydrated in their original form) made from derivative of Poly 2-Hydroxyethyl Methacrylate (P-HEMA). The influence of experimental conditions (pressure, temperature and use of co-solvent) on the amount of impregnated drug was studied for the both considered IOLs. Transparent IOLs (PMMA and P-HEMA) presenting an effective impregnation were obtained. *In vitro* drug release studies were performed for the most favorable impregnation conditions in order to evaluate the resulting drug release profiles.

INTRODUCTION

A cataract is a clouding of the lens in the eye that affects vision. It is conventionally treated through a surgery consisting in replacing the opacified natural crystalline lens with a synthetic intraocular lens (IOL). It is generally safe but the risk of postoperative endophthalmitis has to be considered and an IOL implantation is always a concern even with topical antibiotic coverage [1]. A relevant solution to overcome those drawbacks could be the use of controlled drug delivery systems (DDS) placed inside the eye. These DDS can allow a slow release of drug over time in the potential infection area [3]. If the DDS is the impregnated IOL, this solution does not require an additional act of the surgeon. As an alternative to conventional impregnation techniques, supercritical fluid impregnation, especially using supercritical carbon dioxide ($scCO_2$) can reduce or even eliminate the use of organic solvents [4].

Furthermore, when applied to polymers, ($scCO_2$) can act as a swelling and/or plasticizing agent promoting therefore the impregnation process.

1 – MATERIALS AND METHODS

1 – 1 CHEMICALS

Two types of IOLs commercially available supplied by "the Fred Hollows Intraoculars Lens" (Nepal) have been studied:

- Rigid IOLs made from derivative of Poly (Methyl MethAcrylate) (PMMA), three dipotres were studied (+8.0 D, +21.0 D and +30.0 D).
- Forldable IOLs made from derivative of Poly 2-Hydroxyethyl Methacrylate (P-HEMA), the dioptre +21.0 D was studied.

The ophthalmic drug used is Dexamethasone 21-phosphate disodium ($C_{22}H_{28}FNa_2O_8P$) an anti-inflammatory drug (≥98%, Sigma-Aldrich, CAS [2392-39-4], China).

The employed solvents were carbon dioxide (99.7%, Air liquide, France) and ethanol (≥99.8% purity, A.P.I.-S.A, France).

1 – 2 EXPERIMENTAL METHOD AND PROCEDURES

A detailed description of the batch impregnation process is described elsewhere [5].

1 – 3 SAMPLE CHARACTERIZATIONS

1 – 3 – 1 IMPREGNATED DRUG AMOUNTS

The amounts of the impregnated drug were determined gravimetrically by double weighing the IOLs before and after supercritical impregnations (Mettler Toledo AK 160 balance, with a precision of 10^{-4} g). The impregnation yield is therefore calculated as follows:

$$Y_{imp}\ (mg_{drug} / mg_{IOLs}) = \frac{mass\ of\ impregnated\ IOLs - mass\ of\ non\ impregnated\ IOLs}{mass\ of\ non\ impregnated\ IOLs} \qquad (1)$$

1 – 3 – 2 ATR – FTIR ANALYSIS

Interaction between the polymer and the drug were analyzed using ATR-FTIR. ATR-FTIR spectra were recorded on a vertex 70 spectrometer with a DLaTGS detector (400-7000 cm^{-1}) (Brucker optics, Ettlingen, Germany). The ATR accessory (Miracle, Pike Technologies, Mandison WI, USA) contained a Germanium crystal (diameter 1.8mm).

2 – RESULTS

The influence of experimental conditions on the amounts of impregnated drug was studied for the both considered implants. For all the experiments, the impregnation duration was set to 2 hours and the depressurization rate was kept constant at 0.2 MPa / min in order to avoid foaming phenomena [5].

2 – 1 RESULTATS OBTAINED FOR PMMA IOLs

Studies on PMMA IOLs were carried out on samples with different dioptres of +8.0D, +21.0D and +30.0D. The experimental conditions are summed up in Table 1.

Table 1: Gravimetric impregnation yields of PMMA IOLs at 308 K

P (MPa)	ρCO_2 ($Kg.m^{-3}$)	Y imp (mg_{drug} / mg_{IOL}) ± 0.002		
		+8.0 D	+21.0 D	+30.0 D
Without co-solvent				
8	419	/	0.003	/
20	866	0.006	0.004	0.003
With co-solvent				
8	419	0.049	0.045	0.053
20	866	/	0.003	/

For the three dioptres studied, in the absence of cosolvent, low impregnation yields are obtained because of the low drug solubility in supercritical CO_2. When a cosolvent is used and at low pressure (8 MPa), important impregnation yields are obtained. In the presence of a cosolvent, there is an increase in the quantity of drug carried by the fluid phase within the polymeric matrix and the swelling/plasticizing effect of supercritical CO_2 is promoted. Whereas at a higher pressure (20 MPa) the impregnation yield is much lower. It can be considered that by combining the effect of the high pressure and the use of a cosolvent, drug has a relatively higher affinity with the supercritical fluid phase than with the polymer, which could explain the impregnation yields obtained.

A drug release study was performed on the IOLs impregnated under the most favorable impregnation conditions (8 MPa, with a cosolvent) for the three dioptres. Drug release curves exhibit the same profile. The cumulative mass released of the drug is much lower than that impregnated.

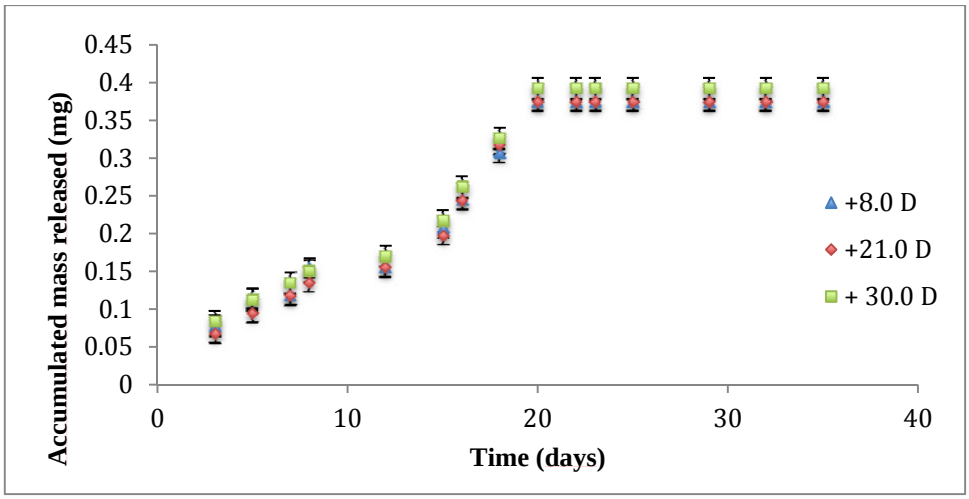

Figure 1: Accumulated release drug from impregnated IOLs at 8 MPa and with cosolvent for the three dioptres

2 – 2 RESULTS OBTAINED FOR P-HEMA IOLS

The P-HEMA implants are initially conditioned in a physiologic solution. Since they are hydrophilic, they absorb a certain quantity of this solution. In order to study the influence of the absorbed solution on the impregnation, a preliminary drying step was carried out.

2 – 2 – 1 Drying

The IOLs were dried using two different drying modes: in the oven and with supercritical CO_2. First, the IOLs were dried in an oven at different temperatures (313, 343, 373 et 393K) and for different durations (from one hour to one week). Under 313 K, a drying duration of 4 hours was necessary for a complete drying of the implants. IOLs were also dried with supercritical CO_2 in a batch mode under a pressure of 20 MPa and a temperature of 308 K for different durations (30, 60 and 120 minutes). A drying duration of 30 minutes was necessary for a complete drying of IOLs.

For the different drying modes, the mass of IOLs after drying was similar (21 % g_{water} / $g_{dried\ IOL}$). This result was confirmed by ATR-FTIR analyzes (Figure 2).

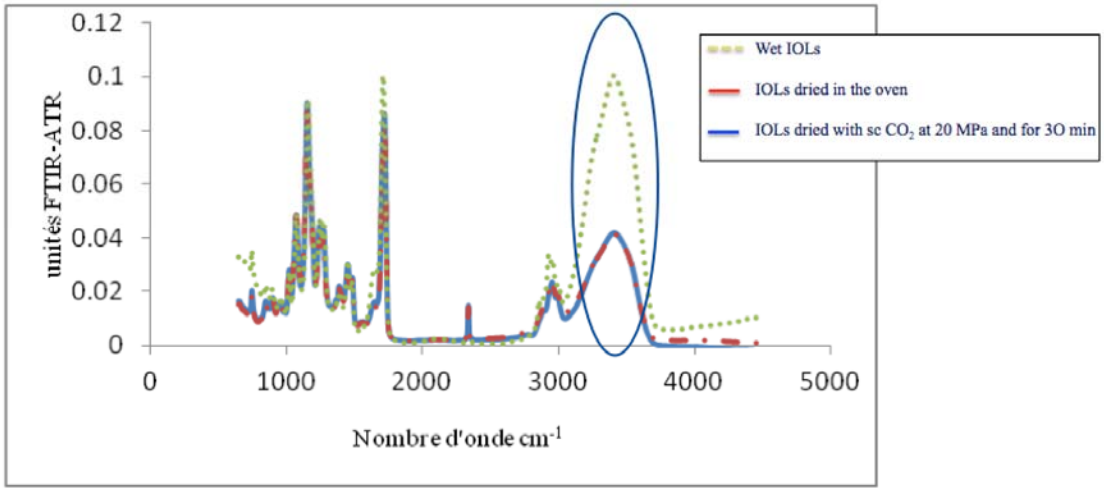

Figure 2: ATR – FRIT analysis

2 – 2 – 2 SUPERCRITICAL IMPREGNATION

Supercritical impregnation of implants (diopter +21.0 D) having undergone a drying step in the oven and wet implants have been carried out in a batch mode at a temperature of 308 K and a pressure of 20 MPa for 2 hours. The corresponding impregnation yields are summarized in Table 2.

Table 2: Impregnation yields of P-HEMA

Initial state implants before impregnation	$Y_{imp} \pm 0.002$ mg $_{drug}$ / mg $_{IOL}$)
Wet implants	0.021
Implants dried in oven	0.079

For implants dried in the oven, the obtained impregnation yield is relatively high (0.079 mg $_{drug}$ / mg $_{IOL}$). Whereas for the wet implants, the impregnation yield is lower. It can be considered that the presence of water promotes the drug partition towards the fluid phase. ATR-FTIR analysis confirms the presence of the drug on the surface of the impregnated IOLs.

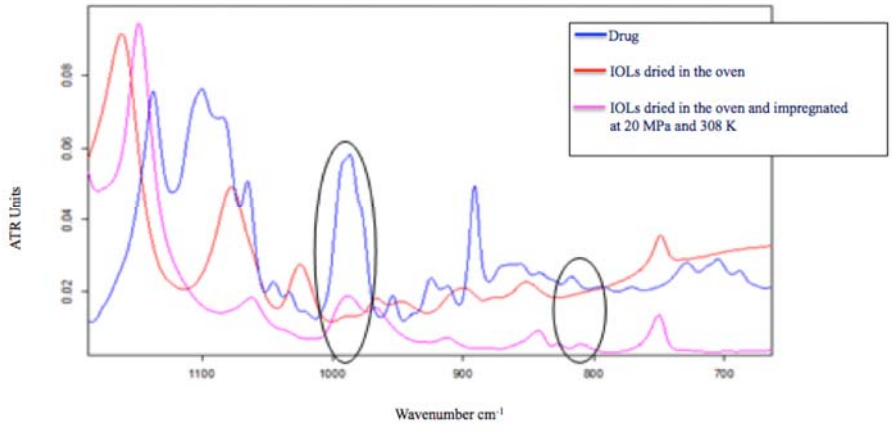

Figure 3: ATR – FRIT analysis

CONCLUSION

This work aims to elaborate therapeutic IOLs using supercritical technique. Two commercial intraocular implants (PMMA and P-HEMA) were impregnated with Dexamethasone 21 phosphate disodium. For both IOLs an effective impregnation was obtained. For the experiments carried out with PMMA IOLs, in presence of co-solvent and at low pressure (8 MPa), the obtained impregnation yield was relatively high. Drug release of impregnated PMMA IOLs shows a low cumulative mass released compared to that impregnated (lower than 5.5%). For P-HEMA implants, a high impregnation yield (0.079 (g $_{drug}$ / g $_{IOL}$)) was obtained for implants dried in the oven compared to that obtained for wet IOLs. The elimination of water allows a higher impregnation rate. The presence of the drug within the

IOLs was confirmed by ATR-FTIR analysis. An impregnation study of implants dried with supercritical CO_2 is now in progress in order to have a compact impregnation process. Other impregnation experiments are also being conducted on PMMA and P-HEMA implants with dexamethasone, in order to further study the influence of several parameters such as the pressure, the temperature, the use of a co solvent and the impregnation duration.

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