The Journal of Supercritical Fluids 130 (2017) 63–75

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

journal homepage: www.elsevier.com/locate/supflu

Effect of operational conditions on the supercritical carbon dioxide impregnation of anti-inflammatory and antibiotic drugs in rigid commercial intraocular lenses

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ARTICLE INFO

Chemical compounds studied in this article:
Poly (Methy MethAcrylate) (PubChem CID: 6658)
Dexamethasone 21-phosphate disodium (PubChem CID: 16961)
Ciprofloxacin (PubChem CID: 2764)
Carbon dioxide (PubChem CID: 280)
Ethanol (PubChem CID: 702)
Disodium hydrogenophosphate (PubChem CID: 24203)
Monobasic potassium phosphate (PubChem CID: 516951)

Keywords:
Supercritical fluids
Drug delivery system
Cataract
Rigid IOLs
PMMA
Release study
Experimental design
Dexamethasone 21-phosphate disodium
Ciprofloxacin

ABSTRACT

Drug/lense combinations have proven significant in the field of ocular therapeutics. The development of innovative systems and elaboration processes is an upcoming issue for ocular drug delivery. One challenging issue is the elaboration of drug loaded intraocular lenses (IOLs) to combine cataract surgery and post-operative treatments in a single procedure. In this work, we are studying the elaboration of such systems while using a green process using supercritical fluids for impregnating ophthalmic drugs on commercial IOLs. More particularly, rigid commercial intraocular lenses made from Poly (Methyl MethAcrylate) (PMMA), used in cataract surgery, are loaded with dexamethasone 21- phosphate disodium salt (DXP, an anti-inflammatory drug) and ciprofloxacin (CIP, an antibiotic) in order to prevent short- and mid-term postoperative complications. Supercritical impregnations were carried out in a batch mode and impregnation yields were determined through drug release kinetic studies in a solution simulating the aqueous humor. Before performing an experimental design, preliminary impregnation assays were conducted in order to delimit the operating domain. Transparent IOLs presenting an effective impregnation were obtained. The highest impregnation yields for DXP and CIP in PMMA IOLs were 18.3 and 2.8 $\mu g_{drug}/mg_{IOL}$ respectively. Despite the low solubility of each drug in the fluid phase, homogeneous and in-depth impregnations were successfully obtained with a prolonged drug delivery (about 40 days) for most impregnation experiments.

1. Introduction

Delivering therapeutic compounds to the site of action is the main/a major challenge in the treatment of several diseases. The conventional application of a drug may be characterized by limited effectiveness, poor biodistribution, and lack of selectivity [1]. A relevant solution to overcome those drawbacks could be the use of controlled drug delivery systems (DDS).

Controlled release DDS are designed to improve drug bioavailability by preventing premature degradation and enhancing uptake, to maintain drug concentration within the therapeutic window by controlling the drug release rate, to reduce dosing frequency, and in some cases to reduce side effects by targeting the disease site and cells [2,3].

Among other methods, impregnation processes are used to prepare such systems. The conventional impregnation process requires the use of organic solvents to dissolve and carry the drug components into the impregnation support. In most cases, conventional methods show several drawbacks, like residual solvents present in the final materials, drug/solvents dissolution and compatibility issues, undesired drug reactions, drug photochemical and thermal degradation, low loading yields and heterogeneous drug incorporation/dispersion.

Alternatively, DDS may be prepared using supercritical fluid impregnation. This technique has successfully proved its applicability to the preparation of drug delivery systems [4–9]. The interest of

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http://dx.doi.org/10.1016/j.supflu.2017.07.015
Received 5 April 2017; Received in revised form 13 July 2017; Accepted 15 July 2017
Available online 23 July 2017
0896-8446/ Published by Elsevier B.V.

Nomenclature

$scCO_2$	Supercritical CO_2
IOL	IntraOcular Lens
PMMA	Poly (Methyl Methacrylate)
CIP	Ciprofloxacin
DXP	DeXamethasone 21- Phosphate disodium
T	Temperature
P	Pressure
t	Duration
min	Minute
°C	Celsius degree
D	Diopter
RSM	Response Surface Methodology
ANOVA	ANalysis Of VAriance
bi	Coefficient of the model
NMR	Nuclear Magnetic Resonance
DSC	Differential Scanning Calorimeter
m_{imp}	Impregnated mass
$m_{CIP\ imp}$	Impregnated mass of CIP
$m_{DXP\ imp}$	Impregnated mass of DXP
y_{imp}	Impregnation yield
t_{imp}	Impregnation duration
$t_{release}$	Release duration
T_g	Glass transition temperature
M_t	Cumulative amount of drug released at time t
M_∞	Cumulative amount of drug released at infinite time
k	Kinetic constant
n	Release exponent representing release mechanism
m_{0IOL}	Initial mass of IOL

supercritical impregnation relies mainly on the opportunity to take advantage of the specific supercritical fluid properties (high density, low viscosity, diffusivity higher than that of liquids, low interfacial tension, *etc.*). Because of those particular properties, the drug to be impregnated may be easily and rapidly trapped inside the impregnation support. Moreover, if carbon dioxide is used, the process of impregnation can be performed at rather moderate temperatures in comparison with the soaking into liquid method. Furthermore, CO_2 is released spontaneously from the final product upon depressurization at the end of the process, hence reducing the number of unitary operations often used in conventional processes for product purification [10,11]. It may then be possible to improve the efficiency of drug loading and release compared to those achievable by conventional preparation techniques, while using a more environmentally friendly technology [12].

Drug delivery systems prepared through the supercritical impregnation process may be applied for the treatment of various diseases using different routes of administration. Among other challenging ocular troubles, cataracts are the most common cause of blindness and severe visual impairment worldwide. The number of patients with cataracts is continuously increasing [13]. Cataracts are conventionally treated through a surgical operation 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. Indeed, IOL implantation is always a concern even with topical drug coverage [14].

The advent of new technologies opens the door to new sustained drug delivery systems to prevent such postoperative complications. Currently, the development of drugs incorporated into polymeric IOLs allows the combination of the cataract surgery and postoperative treatment in a single procedure [14]. It can provide a prolonged intraocular release of anti-inflammatory and antibiotic agents after surgery leading to improved efficacy, reduced toxicity, and better patient compliance [15].

The supercritical impregnation for ocular applications has been widely discussed in the scientific literature and is known to result in enhanced drug loading and the controlled delivery of drugs/the drug. To the best of our knowledge no therapeutic intraocular lenses have yet been approved or commercialized [5,9,16–24]. Furthermore, it is difficult to predict the influence of the operating conditions on the final characteristics (impregnation yield and drug release) since interactions between all the components involved (scCO2/drug/polymeric support) occur during supercritical impregnation. Indeed, the supercritical impregnation process of polymeric devices involves the following three steps: (1) the solubilization of the solute in the $scCO_2$ and swelling of the polymer by CO_2 sorption, (2) drug partition of the solute between the CO_2 rich phase and the polymer and (3) CO_2 release and entrapment of the solutes within the polymer [16,20,23,25]. The different interactions involved in $scCO_2$ impregnation process are detailed in our previous work [16].

The aim of the present work is to study the supercritical impregnation of the commercially available intraocular lenses (rigid IOLs, PMMA) used for cataract surgery with an anti-inflammatory drug (dexamethasone 21-phosphate disodium salt, namely DXP) and an antibiotic (ciprofloxacin, designed CIP). Before impregnation, the influence of pressurization and depressurization conditions was studied in order to understand their effects on the optical properties of PMMA IOLs.

As already described, factors governing supercritical impregnation are complex because of the different interaction mechanisms involved between the drug, the polymer and carbon dioxide [16,20,23,25]. A number of parameters such as pressure, temperature, presence/quantity of co-solvent and impregnation duration were investigated to achieve optimized drug loading of both drugs in PMMA IOLS. The impregnated amount was determined through an *in-vitro* drug release study.

The drug solubility of both drugs in $scCO_2$ were also measured in order to calculate their partition coefficient between the fluid phase and the polymeric matrix.

Lastly, NMR analyses were also carried out on loaded IOLs in order to determine the presence of residual solvent after impregnation.

2. Materials

Supercritical impregnation was performed on commercially available IOLs supplied by “the Fred Hollows Intraocular Lens” (Nepal). IOLs are made from a derivative of Poly (Methyl MethAcrylate) (PMMA): hydrophobic and rigid IOLs at ambient temperature. IOLs with a diopter of +21.0 D were used.

The properties of IOLs as reported by the supplier are summarized in Table 1 and photographs of the IOLs as well as the chemical formula of the polymers are represented in Fig. 1.

Dexamethasone 21- phosphate disodium (DXP) and Ciprofloxacin (CIP) are amongst the most commonly used ophthalmic drugs in postoperative cataract treatment. Both drugs were supplied by Sigma-Aldrich (France).

Dexamethasone 21- phosphate disodium salt ($C_{22}H_{28}FNa_2O_8P$), a synthetic adrenal corticosteroid with potent anti-inflammatory

Table 1
Properties of rigid IOLs.

Polymer	PMMA
Model	FH106
Dioptric power (D)	+21.0
Optical diameter (mm)	6
Overall diameter (mm)	13
Convexity	Biconvex