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Drug loading of foldable commercial intraocular lenses using supercritical impregnation

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ABSTRACT

The drug delivery through intraocular lenses (IOLs) allows the combination of cataract surgery act and postoperative treatment in a single procedure. In order to prepare such systems, "clean" supercritical CO_2 processes are studied for loading commercial IOLs with ophthalmic drugs. Ciprofloxacin (CIP, an antibiotic) and dexamethasone 21-phosphate disodium (DXP, an anti-inflammatory drug) were impregnated into foldable IOLs made from poly-2-hydroxyethyl methacrylate (P-HEMA). A first pre-treatment step was conducted in order to remove absorbed conditioning physiological solution. Supercritical impregnations were then performed by varying the experimental conditions. In order to obtain transparent IOLs and avoid the appearance of undesirable foaming, it was necessary to couple slow pressurization and depressurization phases during supercritical treatments. The impregnation yields were determined through drug release studies. For both drugs, release studies showdeep and reproducible impregnation for different diopters.

For the system P-HEMA/CIP, a series of impregnations was performed to delimit the experimental range at two pressures (80 and 200 bar) in the presence or absence of ethanol as a co-solvent for two diopters (+5.0 D and +21.0 D). Increase in pressure in the absence of a co-solvent resulted in improved CIP impregnation. The addition of ethanol (5 mol%) produced impregnation yields comparable to those obtained at 200 bar without co-solvent. A response surface methodology based on experimental designs was used to study the influence of operating conditions on impregnation of IOLs (+21.0 D) in the absence of co-solvent. Two input variables with 5 levels each were considered; the pressure (80–200 bar) and the impregnation duration (30–240 min). CIP impregnation yields ranging between 0.92 and 3.83 $\mu g_{CIP}/mg_{IOL}$ were obtained from these experiments and response surface indicated the pressure as a key factor in the process.

The DXP impregnation in P-HEMA was higher than CIP at all the tested conditions (8.50–14.53 $\mu g_{DXP}/mg_{IOL}$). Furthermore, unlike CIP, highest DXP impregnation yields were obtained in the presence of ethanol as a co-solvent (5 mol%). NMR spectroscopy was performed to confirm complete removal of ethanol in the co-solvent-treated IOLs.

1. Introduction

Cataract is the most common cause of blindness and severe visual impairment worldwide, and its surgery is the most frequently performed ocular procedure. The number of patients with cataract is continuously increasing (Eperon et al., 2013), and currently about 2 million people have their cataractous lenses removed and replaced with an intraocular lens (IOL) each year (Eperon et al., 2008). The surgery involves implantation of an artificial intraocular lens to replace opacified (damaged) natural crystalline lens (Eperon et al., 2013). It is considered safe, however, postoperative infections including endophtalmitis (Parsons et al., 2005; Barry et al., 2006), (rare but potentially devastating condition) and posterior capsular opacification (less serious but common) (Wright et al., 1988; Miyake et al., 2000; Simone and

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Nomenclature

$scCO_2$	Supercritical CO_2
IOL	Intraocular lens
P-HEMA	Poly(2-hydroxyethyl methacrylate)
CIP	Ciprofloxacin
DXP	Dexamethasone 21-phosphate disodium
API	Active pharmaceutical ingredient
Ethanol	EtOH
T	Temperature
P	Pressure
t	Duration
Dep_{rate}	Depressurization rate
min	Minute
°C	Celsius degree
D	Diopter
RSM	Response surface methodology
ANOVA	ANalysis Of Variance
bi	Coefficient of the model
Signif.	Significance (%)
ATR-FTIR	Attenuated total reflectance-Fourier transform infra-red
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 dry IOL

Whitacre, 2001; Yorio et al., 2008) are known to regularly occur in patients.

To prevent short- and long-term complications, a concentrated solution of anti-inflammatory or antibiotic drugs is injected (subconjunctival, topical, intracameral or intravitreal) in the eye after cataract surgery (Parsons et al., 2005). However, the efficacy of this treatment is limited either due to poor drug bioavailability across the blood-ocular barriers (McGhee et al., 2002) or serious side effects (Eperon et al., 2008).

Significant advances have been made in developing new treatments for the prevention of ocular risks following cataract surgery. The advent of new technologies opens the door to new controlled drug delivery systems to prevent postoperative complications. The ability of these systems to deliver drugs at predetermined rates for predefined periods of time in the specific targeted site have been used to overcome the shortcomings of conventional techniques. Most of these proposed ophthalmic drug delivery systems are polymer-based and are either of a reservoir or a matrix type (Yorio et al., 2008).

The development of drug incorporated IOLs allows the combination of the cataract surgery and postoperative treatment in a single procedure (Anderson et al., 2009). 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 (Uhrich et al., 1999).

Several manufacturing processes have been developed to produce polymeric (biocompatible or biodegradable) drug delivery systems including molecular imprinting (Alvarez-Lorenzo and Concheiro, 2004; Venkatesh et al., 2007), ion ligands binding (Uchida et al., 2003; Sato et al., 2005), soaking into liquid (Karlgard et al., 2003; Aqil and Gupta, 2012) among others (Li et al., 2007). Nevertheless, these conventional techniques have some disadvantages such as; high processing temperatures that can deteriorate thermosensitive Active Pharmaceutical Ingredients (API), or the use of organic solvents that must be removed through numerous purification steps to meet FDA's requirements (Champeau et al., 2015a).

To overcome the above-mentioned limitations, the supercritical fluid assisted impregnation has proven to be an alternative green process for pharmaceutical products (Pasquali and Bettini, 2008). The activity of the drug molecules can be preserved notably because supercritical carbon dioxide ($scCO_2$) processing is performed at moderate temperatures (Sun, 2002).

The sorption of $scCO_2$ in a large number of natural and synthetic polymers permits impregnation of hydrophobic molecules without or with a minimal use of a co-solvent. The major advantages of supercritical impregnation include; tunable solute loading and impregnation depth by slight changes in processing conditions. Moreover, residual organic solvent free end-products are obtained since $scCO_2$ is released spontaneously as a gas during depressurization (De Souza et al., 2014).

Supercritical impregnation techniques have been successfully applied to polymer processing among other applications to develop drug delivery systems (Üzer et al., 2006 López-Periago et al., 2009; Kikic and Vecchione, 2003; Masmoudi et al., 2011). Drug impregnation of biocompatible or biodegradable polymers requires the use of a vector phase to solubilize and carry the drug component within the impregnation support (López-Periago et al., 2009). Using $scCO_2$ as impregnation carrier is advantageous since it

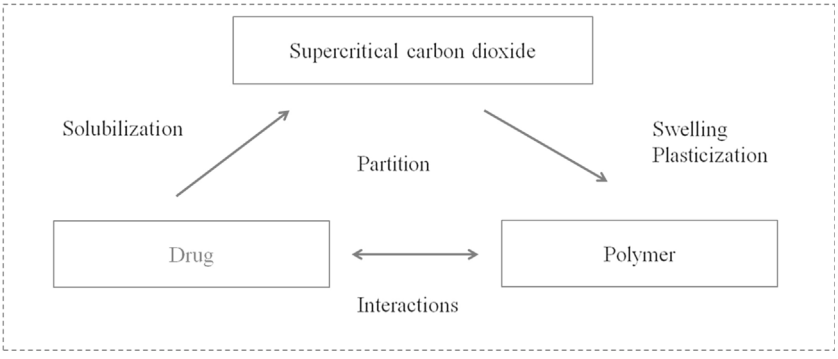

Fig. 1. Interactions governing supercritical impregnation.