SUPERCRITICAL FLUID IMPREGNATION OF POLY(E-CAPROLACTONE) BLENDS FOR OCULAR DRUG DELIVERY

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INTRODUCTION

The two main causes of blindness in adult population are age related macular degeneration and primary open angle glaucoma [1]. Conventional treatment confronts with problems like low drug bioavailability and systemic toxicity, that are caused by impermeability of the cornea, by tear dynamics, by blinking and by nasolachrymal drainage. In the case of eye drops medication, only 5 % of the applied drug actually penetrates the cornea [2]. Several efforts have been made in order to improve the ocular delivery of topically applied drugs and to reduce their side effects, by developing controlled drug delivery systems such as bioadhesive and in situ forming hydrogels, colloidal systems, ocular inserts and implantable devices [3].
One approach for the preparation of controlled release systems is to load drugs into polymeric matrices using supercritical fluids. Impregnation using supercritical fluid technology has proved to be feasible when the pharmaceutical compound is soluble in carbon dioxide and the polymer can be swollen by the supercritical fluid. This process is very appealing due to the mild temperatures involved and the lack of contamination with organic solvents.
Our long term goal is to prepare an implantable (subconjunctival) system for long-term drug delivery, with controlled release and degradation that could deliver timolol maleate for 4-6 months in an attempt to avoid the problem of low bioavailability and systemic toxicity. For the present study, polycaprolactone (PCL) was selected as the main polymer for the preparation of the biodegradable drug matrix because of good biocompatibility and swelling ability in supercritical carbon dioxide [4]. Poly(ethylene-co-vinyl acetate) and poly(oxyethylene-b-oxypropylene) have numerous applications as drug delivery systems because of biocompatibility, processability (i.e. extrusion) and proved long-term release properties [5].
The aim of this work is to evaluate the effects of operational pressure, of blend chemical nature and composition, as well as of cosolvent effects, on the supercritical solvent impregnation process of different poly(ε-caprolactone) blends, in order to determine the best operating conditions to achieve maximum drug loading and optimal drug release profiles.

MATERIALS AND METHODS

The blends (Lu/PCL: 25/75, 50/50 and Lw/PCL: 25/75, 50/50, 75/25, % w/w) were prepared by dissolution in tetrahydrofuran (10 % w/v total polymer solutions), using poly(ε-caprolactone) (PCL, 65000 g/mol, Sigma-Aldrich), Luwax EVA 3 (Lw, poly(ethylene-co-vinyl acetate), 13-15 % vinylacetate, BASF) and Lutrol F 127 (Lu, poly(oxyethylene-b-oxypropylene), 9000-14000 g/mol, 70 % polyoxyethylene, BASF). Films of the blends were

obtained by solvent casting at room temperature. Two operational pressures (110 and 200 bar) and different cosolvents (water, ethanol or none) were used in order to test the best impregnating conditions. Contact angle analysis was performed in order to determine the hydrophilicity/hydrophobicity of the blends, while crystallinity determination using DSC was useful in understanding the release profiles of the different systems.

RESULTS

Supercritical Drug Impregnation Process

In general terms, the obtained results indicate that not just timolol maleate solubility (which is highly dependent on the presence or absence of the cosolvent) in $scCO_2$ plays an important role in the overall impregnation process efficiency, but also all the other specific and complex interactions that may occur between all the involved components of the system: $scCO_2$-polymeric matrices-cosolvent interactions (which determine cosolvent and $scCO_2$ solubility in the polymeric matrix and, consequently, swelling and plasticization effects) and drug-polymeric matrices-cosolvent interactions (which control the entrapment/deposition of the drug in the polymeric network).

It is clear that, for the Lw/PCL blends, the highest impregnation yields (0,018-0,033 g/g) were obtained when using ethanol (at both operational pressures) while for Lu/PCL blends, highest impregnation yields (0,012-0,018 g/g) occurred in the presence of water as cosolvent (also at both employed pressures). For pure PCL samples, best results (0,009 g/g) were achieved when no cosolvent was used and, as observed, water addition decreased the amount of impregnated drug.

These results can be explained by the favourable specific interactions drug-CO_2-cosolvent that may occur, i.e., by the timolol maleate (a water-soluble polar drug) solubility enhancement in the high pressure fluid phase, which was caused by the polarity increase of the mobile phase when the polar cosolvents (ethanol and water) were added [6]. As more drug can be dissolved, more drug can be carried out into the polymeric network by the mobile high pressure phase. In the case of timolol maleate, this ethanol induced solubility enhancement was already measured in our group [7].

Pressure effects complement the previous discussion about the cosolvent effects on impregnation efficiencies and can also help to explain why impregnation efficiencies are higher at 200 bar for Lu/PCL blends, while Lw/PCL blends and PCL have higher impregnation efficiencies at 110 bar. More effective drug-polymer interactions are expected to take place for Lu/PCL blends because of Lu/PCL blends higher hydrophilicities. Thus, higher pressures will favour drug deposition. For Lw/PCL blends and for PCL samples, drug diffusion into the polymeric samples also takes place but, during depressurization, more drug comes out with the mobile phase, due to the weaker drug-polymer interactions (when compared to the drug-SCF phase interactions). This is also in agreement with other works in which the efficiency of the impregnation decreases at higher pressures [8].

On the other hand, copolymer/polymer chemical structures can strongly affect drug-polymer and polymer-SCF phase interactions, thus controlling the overall impregnation process. Therefore, a hydrophilic drug (like timolol maleate) when is transported by a SCF, or by a SCF-cosolvent mixture, will have a tendency to specifically interact and deposit on the hydrophilic portions of the employed polymeric matrices. The use of a hydrophilic cosolvent will yet increase these interactions with the more hydrophilic parts of the polymeric matrices thus increasing impregnation efficiency. Consequently, we should expect that more timolol maleate would be impregnated in Lu/PCL blends as the composition, in terms of the more

hydrophilic blend compound (Lu), is increased. For Lw/PCL blends, the same effect is observed and as the Lw content is increased (the more hydrophobic component), the impregnation efficiency decreases, but only in the case when ethanol is employed.

In Vitro Drug Release

In vitro kinetics of drug release studies were performed for selected impregnated samples. The cumulative released percentage of timolol maleate was found, after 32 days of release studies, to be higher for Lw/PCL series, followed by Lu/PCL series and PCL (84.6-92.3 %, 79.2-79.9 % and 77.2 %, respectively). All impregnated samples presented almost the same drug release profile, a biphasic release pattern: a burst period with rapid release caused probably by the drug deposited on and near the polymeric surface and a swelling and/or erosion (Lutrol F 127 is soluble in water and polycaprolactone undergoes hydrolytic degradation) phase with constant release (3-10 μg/day after the first day).

The profiles also suggest that timolol maleate is released faster in Lw/PCL series probably because of more drug deposited close to surface. Lu/PCL series and PCL show a more sustained release probably because the drug is deposited inside the polymeric structure (more homogeneously dispersed) as there is more interaction between the drug and the hydrophilic portions of the (co)polymer molecules composing these blends. Crystallinity also controls the drug release rate as the drug is released at a slower rate by Lu/PCL blends and by PCL that present higher percentage of crystalline phase. As a result, less drug and at a lower rate is released during 32 days for Lu/PCL and PCL samples.

It can be seen that, after the initial first day burst release, timolol maleate concentration becomes almost constant (1.2-4 μg/ml/day corresponding to a mass of 3-10 μg/day), which is located above the therapeutic limit of timolol maleate (5 μg/day) [9] and below the maximum recommended human ophthalmic dose (0,42 mg/day, considering a patient weight of 60 kg) [10]. The burst dose, released by the systems during the first day is below the maximum recommended human ophthalmic dose, with two formultions surpassing this value (0.53 mg for 50/50 Lw/PCL and 0.78 mg for 75/25 Lw/PCL). Even these values are well below the maximum recommended daily oral dose, which is 60 mg/day (considering a patient weight of 60 kg) [11]. The knowledge of these values is essential for the development of efficient and safe controlled drug release systems because the released drug concentrations must always be kept between the therapeutic and toxic levels.

CONCLUSIONS

Poly(ε-caprolactone) blends were successfully impregnated with timolol maleate, a drug for the treatment of glaucoma. Different experimental conditions were tested and the impregnation efficiency results suggested that the best impregnating conditions are obtained when a cosolvent is used because the drug solubility is increased and more drug is transported by the mobile phase. Hydrophilicity/hydrophobicity of the blends affect the impregnation because of the specific interactions that are formed between the drug and the more hydrophilic parts of the polymer chains. Pressure can be either a favourable factor through polymer swelling and plasticization (creating more space for the drug loaded mobile phase to reach the inside structure) when the drug and polymer interact so that the drug is entrapped or a unfavourable factor when weaker bonding takes place between drug and polymer (enhanced by the same swelling) and as such the drug leaves the matrix at depressurisation.

Drug loading, heterogeneous/homogeneous dispersion of drug inside the matrix, hydrophilicity, crystallinity seem to influence the drug release rate. The in vitro drug release

results suggest that a sustained drug release rate can be obtained by modulating the composition of blends, as this can be a mean to control crystallinity, hydrophilicity and drug affinity for the polymer matrix.
After a first day burst release, all samples showed a sustained release profile (1.2-4 μg/ml/day) which is between the therapeutic and toxic levels of timolol maleate, during a period of 1 month. These drug-loaded polymeric matrices can be a feasible alternative treatment modality to the conventional repeated daily administration of eye drops.

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